Delfini

Systematic Safety Reviewof Five Biologic Antirheumatic Drugs

Agent	Abbrev	Rheumatoid Arthritis (RA)	Psoriasis	Psoriatic Arthritis (PsA)
Adalimumab (Humira)	**ADA**	Adults with moderately to severely active RA	Adults with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy	Active PsA in adults
Certolizumab (Cimzia)	**CZP**	Adults with moderately to severely active RA		
Etanercept (Enbrel)	**ETN**	Adults with moderately to severely active rheumatoid arthritis	Adults with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy	Active PsA in adults, alone or in combination with MTX
Golimumab (Simponi)	**GLM**	Adults with moderately to severely active RA ,in combination with MTX		Active PsA in adults, alone or in combination with MTX
Infliximab (Remicade)	**IFX**	Adults with moderately to severely active RA, in combination with MTX	Adult patients with chronic severe (i.e., extensive and /or disabling) plaque psoriasis who are candidates for systemic therapy and when other systemic therapies are medically less appropriate	Active PsA in adults
Ustekinumab (Stelara)	**UST**		Adult patients (18 or older) with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy	Active PsA in adults

Michael E. Stuart MD
Sheri Ann Strite

June 2011

NAVIGATION NOTE: **Microsoft Word Navigation Pane** or **Contents** can used be to actively navigate the document online in .doc format.

CONTENTS

HOW TO READ THIS REPORT

Synthesized scientific information is presented with increasing level of detail.

- **Executive Summary Conclusions:** Highlights of evidentiary findings
- **Details of Evidence Findings:** Further details

Critical appraisals of individual studies and detailed search documentation are produced in appendices below titled—

- **Safety of Selected Agents: Search Documentation**
- **Safety of Selected Agents: Critical Appraisal Documentation**

Because this review addresses safety, research at high-risk of bias, such as evidence from observational studies and registries, is included along with higher quality evidence from clinical trials, systematic reviews and meta-analyses of randomized controlled trials. Important issues concerning risk of bias in registries is included in the **Appendices** under **General Risk of Bias Considerations for Registries**.

DISCLAIMERS & LEGAL NOTICES

FUNDING

- Funding for this review was provided by Amgen, Inc.
- Authors had complete control over all aspects of the review except for the choice of agents and conditions selected for review which were chosen by Amgen, Inc. Amgen, Inc. was provided with the opportunity to review and comment. All final decisions were made by authors.

ABBREVIATIONS USED IN THIS REPORT

Other abbreviations, with their explanations, are found, at times in individual critical appraisals and study reviews.

Table 1. Abbreviations

Abbreviation	Definition
ADA	Adalimumab (Humira)
AE	Adverse event
AERS	Adverse Event Reporting System of the US Food and Drug Administration
AHRQ	Agency for Healthcare Research and Quality
AIDS	Acquired immune deficiency syndrome
Anti-TNF agents	Agents targeting tumor necrosis factor (TNF). TNF promotes the inflammatory response which is thought to be causally related to clinical conditions such rheumatoid arthritis, psoriasis and psoriatic arthritis. See related terms "anti-TNF mAb, TNF, TNFa, TNFI."
anti-TNF mAb	Anti-tumor necrosis factor monoclonal antibody. This specific term applies to agents that both target TNF and are monoclonal antibodies. See related more general terms " Anti-TNF agents, TNF, TNFa, TNFI."
ARR	Absolute risk reduction
AS	Ankylosing spondylitis
BIW	Twice weekly
BSRBR	British Society of Rheumatology Biologics Register
CD	Crohn's disease
CI	Confidence interval
CLTR	Cumulative lifetime risk
CVD	Cardiovascular disease
CZP	Certolizumab (Cimzia)
DMARD	Disease-modifying antirheumatic drug
EHCP	Effective Health Care Program
ERA	Early rheumatoid arthritis
ETN	Etanercept (Enbrel)
FDA	US Food and Drug Administration
GLM	Golimumab (Simponi)
GVHD	Graft versus host disease
HR	Hazard ratio
I^2	Inconsistency statistic: The I^2 statistic is a test of heterogeneity. The range of I^2 values is between 0% and 100%. I^2 provides an estimate of the percentage of variability in results across studies that is likely due to true differences in treatment effect as opposed to chance. When the I^2 is 0%, chance provides a satisfactory explanation for the variability in the individual study point estimates, and clinicians can be comfortable with a single pooled estimate of treatment effect in a valid study. As the I^2 increases, bias becomes more likely. A rule of thumb characterizes an I^2 of less than 25% as small heterogeneity, 25% to 50% as moderate and more than 50% as large heterogeneity.
IFI	Invasive fungal infection
IFX	Infliximab (Remicade)
IR	Incidence rate: the number of events divided by the person-time at risk.
IRR	Incidence rate ratio is the ratio of two incidence rates. The incidence rate is defined as number of events divided by the person-time at risk. To calculate the IRR, the incidence rate among the exposed proportion of the population, divided by the incidence rate in the unexposed portion of the population, gives a relative measure (IRR) of the effect of a given exposure and approximates the relative risk or the odds ratio if the occurrences are rare.

Abbreviation	Definition
JIA	Juvenile idiopathic arthritis
LOE	Level of evidence
LRA	Long-standing RA
MS	Multiple sclerosis
NNH	Number-needed-to-harm
NNT	Number-needed-to-treat
NR	Not reported
NS	Not significant
OI	Opportunistic infection
ON	Optic neuritis
OR	Odds ratio
PCP	Pneumocystis pneumonia
PMID	The PMID (PubMed identifier or PubMed unique identifier) is a unique number assigned to each PubMed citation of life sciences and biomedical scientific journal articles. Full citations can be retrieved from PubMed by entering the PMID number into the search window.
PsA	Psoriatic arthritis
PY	Patient-years
RA	Rheumatoid arthritis
RATIO	Research Axed on Tolerance of Biotherapies
RR	Relative risk
RRR	Relative risk reduction
SAE	Serious adverse event
SEER database	US National Cancer Institute SEER (Surveillance, Epidemiology, and End-Results) database
SIR	Standardized incident ratio: the ratio of observed occurrences to expected occurrences. Expected occurrences for SIR calculations are based on selected data sources e.g., the National Cancer Institute (NCI) Surveillance Epidemiology and End Results (SEER) database. For example, a SIR of 150 is interpreted as 50% more cases than the expected number; a SIR of 90 indicates 10% fewer cases than expected.
SMR	Standardized mortality ratio: the ratio of observed deaths to expected deaths calculated using the expected rates (e.g., based on country-specific age and sex matched general population data from the World Health Organization).
SR	Systematic review
TNF	Tumor necrosis factor is a class of cytokines (molecules secreted by the immune system). TNF is frequently used to refer to TNF-alpha, a member of this class that is involved in the inflammatory response. See related terms “anti-TNF agents, TNF, anti-TNF mAb, TNFa and TNFI.”
TNFa	Shortened version of TNF-alpha (see TNF)
TNFI	Tumor necrosis factor inhibitor. Synonym for “anti-TNF agent” and “TNFI.”
USPSTF	United States Preventive Services Task Force
UST	Ustekinumab (Stelara)

EXECUTIVE SUMMARY

1. BACKGROUND

Optimal management of rheumatoid arthritis, psoriatic arthritis and psoriasis has increasingly included the use of biologic agents for therapeutic success. New agents have recently become available and recent evidence has prompted earlier institution of biologic agents. (Smolen 10). With the increasing use of these agents, it is important to review the relative safety of the available agents.

2. AIM

The aim of this project is to systematically review, critically appraise and analyze research evidence regarding the comparative safety ofselected agents used in the treatment of rheumatoid arthritis, psoriasis and psoriatic arthritis. Specifically, this project systematically reviews safety outcomes for the following agents commonly used in the conditions below—

Condition	Abbrev	adalimumab (Humira) ADA	certolizumab pegol (Cimzia) CZP	etanercept (Enbrel) ETN	golimumab (Simponi) GLM	infliximab (Remicade) IFX	ustekinumab (Stelara) UST
Active rheumatoid arthritis	RA	x	x	x	x	x	
Psoriasis		x		x		x	x
Active psoriatic arthritis	PsA	x		x	x	x	x

3. KEY QUESTION

What is the evidence regarding the comparative safety of the following antirheumatic agents as used in the treatment of rheumatoid arthritis (RA), psoriasis and psoriatic arthritis?

1. adalimumab (Humira) (ADA)
2. certolizumab pegol (Cimzia) (CZP)
3. etanercept (Enbrel) (ETN)
4. golimumab (Simponi) (GLM)
5. infliximab (Remicade) (IFX)
6. ustekinumab (Stelara) (UST)

4. CONCLUSIONS

Comparative safety of the various antirheumatic agents is complicated by the lack of head-to-head studies, relatively small study size and substantial heterogeneity in the study populations, study designs and multiple other contextual differences. For example, there are differences in disease activity, previous and concomitant treatments, co-interventions, study settings and study duration. In some cases, there may be differences between agents that are not apparent because of the relative rarity of adverse events and lack of power to determine true differences. However, certain compelling patterns emerge. Table 2 reflects our estimates of risk and risk differences for the agents of interest based on this review. The estimates are based on patterns of safety data from clinical trials and observational studies. The estimates should be seen as tentative and suggestive of differences because of the methodological limitations mentioned above. Additional studies are needed in order to draw firm comparative safety conclusions.

We conclude that patients with rheumatoid arthritis treated with ETN compared to ADA and IFX are at lower risk for serious infections, tuberculosis, opportunistic infections and lymphoma. There is somewhat weaker evidence that patients treated with ADA, ETN, GLM and IFX may be at lower risk for serious infections than those receiving CZP. We found consistent evidence from RCTs and observational data that patients receiving ETN are at lower risk for withdrawals from clinical trials due to adverse events than patients receiving ADA and IFX, but there are substantial differences in estimates of effect. There is inconclusive evidence from RCTs that patients receiving ADA and GLM may be at lower risk for withdrawal from clinical trials than patients receiving IFX.

Table 2. Comparative Safety Estimates From Evidence Review of The Agents of Interest

Safety Issue	The evidence is suggestive that…
Serious Infections in RA	ETN compared to the pooled risk for the monoclonal antibodies IFX and ADA *Estimated risk difference: between 1 and 2 fewer serious infections per 100 patients treated with ETN treatment for 3 to 12 months than with the monoclonal antibodies.* *Estimated risk:* • *IFX: 3.9 to 4.6 serious infections/100 pt-years;* • *ADA: 3.8 to 4.3 serious infections/100 pt-years* • *ETN: 2.6 to 3. 8 serious infections/100 pt-years.*
Serious Infections in RA	ADA, ETN, GLM and IFX compared to CZP *Estimated risk difference: between 4 and 6 fewer serious infections per 100 patients treated with* ADA, ETN, GLM or IFX *for 6 to 12 months than with CZP.* *Estimated risk:* • *CZP: 8.6 serious infections/100 patients treated for 6 months* • *ADA: 2.9 serious infections/100 patients treated for 6 months to 4.3 serious infections/100 pt-years* • *ETN: 2.5 to 3.8 serious infections/100 pt-years* • *GLM: 3.3 serious infections/100 patients treated for 6 months* • *IFX: 3.7 to 3.9 serious infections/100 pt-years*
Tuberculosis in Studied Populations	ETN compared to the pooled risk for the monoclonal antibodies IFX and ADA *Estimated risk difference: 1 less case of tuberculosis per 1000 patient-years with ETN treatment than with the monoclonal antibodies.* *Estimated risk:* • *IFX: 1.4 TB cases/1000 pt-years* • *ADA: 1.4 TB cases/1000 pt-years* • *ETN: 0.4 TB cases/1000 pt-years.*
Non-TB Opportunistic Infections in Studied Populations	ETN compared to the pooled risk for the monoclonal antibodies IFX and ADA *Estimated risk difference: 1 less case of opportunistic infection per 1000 patient-years with ETN treatment than with the monoclonal antibodies.*

	Estimated risk: • *IFX: 2.9 opportunistic infections /1000 pt-years* • *ADA 0.61 opportunistic infections/1000 pt-years* • *ETN: 0.07 opportunistic infections/1000 pt-years*
Lymphoma in Studied Populations	ETN compared to the pooled risk for the monoclonal antibodies IFX and ADA *Estimated risk difference: 1 less case of lymphoma per 1000 patient-years with ETN treatment than with the monoclonal antibodies.* *Estimated risk:* • *IFX and ADA: 0.62 to 2.91lymphomas/1000 pt-years* • *ETN: 0.07 lymphomas/1000 pt-years*
Withdrawals and Withdrawals due to Adverse Events in RA	ETN compared to ADA and IFX *Estimated risk difference in withdrawal rates is 2 fewer withdrawals per 100 patients per year with ETN compared to ADA and 6 fewer withdrawals per 100 patients per year compared to IFX.*
Serious Infections in Psoriasis or PsA	Insufficient evidence to determine the relative risk of the five agents (ADA, ETN, GLM, IFX, UST)
Malignancy in RA, Psoriasis and PsA	Insufficient evidence to determine the relative risk of the agents; The evidence suggests that RA patients treated with ADA, ETN, GLM and IFX are not at increased risk for mortality compared to patients taking synthetic DMARDs.
Mortality in RA, Psoriasis and PsA	Insufficient evidence to determine the relative risk of the agents
Demyelinating Disease in RA, Psoriasis and PsA	Insufficient evidence to determine the relative risk of the agents
Infusion Reactions	• *Approximately 18% of RA patients treated with IFX will experience an infusion reaction. Most will be mild (e.g., headache, dizziness, nausea, pruritus, chills, or fever).* • *However, severe acute reactions resembling acute anaphylactic conditions or associated with convulsions have been reported in 0.5% to 3.7% of patients receiving IFX.*
Injection Site Reactions	• *ETN range 8.5% to 36.3%* • *ADA range 5.2% to 27.9%* • *UST range <1% to 25%* • *GLM range 5% to 20%* • *CZP range 1.6% to 4.5%*

:: END OF EXECUTIVE SUMMARY ::

5. EVIDENCE GRADING

Safety outcomes from all included primary and secondary studies were assessed for validity and clinical meaningfulness. Individual studies were evaluated for quality, and the body of evidence was rated for overall quality of the evidence using a modified version of the Agency for Healthcare Research and Quality and the Effective Health Care Program (AHRQ-EHCP) system as summarized below (Owens 09). All included studies were rated as of uncertain validity and clinical usefulness for safety.

AHRQ-EHCP System, Delfini Modified—Overall Evidence Quality

Overall quality of the safety findings was rated by using a version of the quality assessment system developed by the **AHRQ-EHCP** group and modified by Delfini.

AHRQ-EHCP System Overall Evidence Quality	AHRQ-EHCP System, Delfini Modified—Overall Evidence Quality
High: High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.	**High:** Same as AHRQ
Moderate: Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.	**Moderate:** Same as AHRQ
Low: Low confidence that the evidence reflects the true effect. Further research is likely to change the confidence in the estimate of effect and is likely to change the estimate.	**Borderline***: The evidence may be reliable enough to be useful in informing decisions but caution is urged and further evidence is needed.
Insufficient: Evidence either is unavailable or does not permit a conclusion.	**Inconclusive****: The evidence may be absent, conflicting, sparse, or weak and conclusions based on evidence cannot be drawn.

*For this review, we modified the AHRQ-EHCP grading system for overall LOE by changing AHRQ'S fourth category of "low" to "borderline" to increase clarity as we believe "moderate" and "low" are not precise enough to address evidence of borderline usefulness.
**We substituted the term "inconclusive" for the AHRQ term "insufficient" because we believe "inconclusive" is a better summary term when the evidence does not permit a conclusion, i.e, is absent, conflicting, sparse, or weak.

Critical appraisals of individual studies and search documentation are produced in two appendices below titled—

- **Safety of Selected Agents: Search Documentation**
- **Safety of Selected Agents: Critical Appraisal Documentation**.

6. EVIDENCE SYNTHESIS

This review includes evidence generated after the original pivotal trials were completed. It should be noted that the pivotal trials of the agents were designed to show statistically significant differences in efficacy outcomes—not safety outcomes. Therefore, it is important to note that the pivotal trials included in the meta-analyses summarized below were not powered to detect statistically significant differences in outcomes such as serious infections, malignancies, lymphomas, withdrawals and other adverse events included in this review.

6a. SERIOUS INFECTIONS, TUBERCULOSIS (TB) AND NON-TB OPPORTUNISTIC INFECTIONS

Serious Infections, TB and Non-TB Opportunistic Infections in Patients Receiving IFX, ADA or ETN

The evidence from randomized, controlled trials (RCTs) and observational studies is sufficient to conclude that, in rheumatoid arthritis (RA) patients treated with the monoclonal antibodies IFX and ADA, there is an increased risk of serious infections compared to patients treated with ETN or placebo with or without traditional disease-modifying antirheumatic drugs (DMARDs) (LOE: borderline).

Although inconclusive, evidence from RCTs suggests that CZP is associated with a higher risk of serious infections when compared to ADA, ETN, GLM and IFX. Larger, high quality studies with longer follow-up are needed to more fully assess the relative safety of these agents compared to other antirheumatic agents (LOE: inconclusive).

The evidence from randomized, controlled trials and observational studies is sufficient to conclude that the monoclonal antibodies IFX and ADA are associated with an increased risk of developing or reactivating TB compared to ETN or placebo with or without traditional disease-modifying antirheumatic drugs (DMARDs) in patients being treated for rheumatoid arthritis and possibly other conditions (LOE: borderline).

Weak signals suggest that there may be an increased risk for developing or reactivating TB in RA patients receiving GLM, CZP or UST compared to patients receiving traditional DMARDs and placebo. However, larger, high quality studies with longer follow-up are needed in order to confirm these findings and assess the comparative safety of these agents compared to other antirheumatic agents (LOE: inconclusive).

There are potential weak signals from observational studies suggesting that the monoclonal antibodies IFX and ADA are associated with an increased risk of non-TB opportunistic infections compared to the soluble TNF receptor therapy ETN in some populations (LOE: inconclusive).

The evidence is insufficient to determine the relative risk of serious infections with GLM, CZP and UST compared to each other and to other antirheumatics agents in the treatment of RA, psoriasis and PsA. There are potential weak signals from randomized, controlled trials of increased risk of serious infection in RA and PsA patients treated with GLM, CZP and UST compared to patients treated with traditional DMARDs or placebo, but larger, high quality studies with longer follow-up are needed in order to confirm these findings and assess the risk of TB, fungal infections and other non-TB opportunistic infections (LOE: inconclusive).

6b. MALIGNANCY AND LYMPHOMA

Malignancy

The evidence from randomized, controlled trials and observational studies is insufficient to determine the relative risks of malignancies in patients with RA, psoriasis or PsA receiving the agents included in this review (ADA, CZP, ETN, IFX, GLM, UST) (LOE: inconclusive).

Malignancy rates in patients receiving IFX, ADA and ETN are not statistically higher than in RA patients treated with placebo with or without MTX or than in the general population (LOE: borderline).

There is insufficient evidence to determine the risk of malignancy in patients with RA receiving CZP or GLM compared to each other and other agents (LOE: inconclusive).

There is insufficient evidence to determine the risk of malignancy in patients with psoriasis or PsA receiving UST compared with each other and to other antirheumatic agents (LOE: inconclusive).

Lymphoma

There is insufficient evidence from RCTs to determine the relative risk of lymphoma in RA patients treated with IFX, ADA and ETN. However evidence from a recently published French registry study (Mariette 10) suggests that the risk of lymphoma in patients treated with IFX or ADA for any indication may be greater than in patients treated with ETN (LOE: inconclusive).

There is insufficient evidence to determine the risk of lymphoma in RA patients, psoriasis patients or patients with PsA receiving GLM, CZP or UST compared to each other and to other antirheumatic agents. (LOE: inconclusive).

There is insufficient evidence to determine the relative risk of lymphoma in patients with psoriasis or PsA treated with any of the agents of interest (LOE: inconclusive).

6c. WITHDRAWALS AND WITHDRAWALS DUE TO ADVERSE EVENTS

Withdrawals Due To Adverse Events in Patients with RA, Psoriasis And Patients Receiving IFX, ADA, ETN, GLM, CZP or UST

The evidence from randomized, controlled trials and observational studies is sufficient to suggest that RA patients receiving the monoclonal antibodies IFX or ADA are at increased risk of withdrawing from clinical trials due to adverse events or other reasons compared to patients receiving ETN or placebo with or without synthetic DMARDs (LOE: borderline).

There is insufficient evidence to accurately estimate the risk of withdrawing from trials due to adverse events or other reasons in patients receiving GLM, CZP or UST compared to each other or to the other agents of interest; however, there are signals from one recent meta-analysis that the risk of withdrawal may be lower with ADA or GLM when compared to IFX (LOE: inconclusive).

6d. MORTALITY

The evidence from randomized, controlled trials and observational studies is insufficient to reliably determine the relative risks of mortality in patients with RA, psoriasis or PsA who receive ADA, CZP, ETN, GLM, IFX or UST (LOE: inconclusive).

Indirect evidence from randomized, controlled trials and observational studies suggests that RA patients receiving IFX, ADA, ETN or GLM are not at increased risk for mortality compared to patients receiving standard non-biologic agents therapy (LOE: borderline).

The evidence is insufficient to determine risk of mortality in patients receiving CZP or UST (LOE: inconclusive).

High quality studies with extensive follow-up periods are needed in order to accurately determine the relative risk of mortality in patients receiving these antirheumatic agents.

6e. DEMYELINATING DISEASE

There is insufficient evidence to determine the relative risk of developing demyelinating disease in patients receiving the agents (LOE: inconclusive).

High quality studies of sufficient duration are needed to determine the relative risks for demyelinating disease in RA patients, PsA patients and patients with psoriasis receiving various antirheumatic agents.

6f. INFUSION REACTIONS

The evidence is sufficient to conclude that the risk of mild infusion reactions in patients treated with IFX is higher than in patients treated with placebo (LOE: borderline).

6g. INJECTION SITE REACTIONS

The evidence is sufficient to conclude that the risk of mild injection site reactions is higher in patients treated with ADA and ETN than in patients treated with placebo (LOE: borderline).

The evidence is insufficient for determining the relative risk of injection site reactions in patients treated with ADA, CZP, ETN, GLM and UST (LOE: inconclusive).

7. EVIDENCE REVIEW: DETAILS

It should be noted that the pivotal trials of biologic agents were designed to show statistically significant differences in efficacy outcomes—not safety outcomes. Therefore, it is important to understand that the pivotal trials included in the meta-analyses summarized below were not powered to detect statistically significant differences in outcomes such as serious infections, malignancies, lymphomas, withdrawals and other adverse events included in this review.

7a. SERIOUS INFECTIONS, TUBERCULOSIS (TB) AND NON-TB OPPORTUNISTIC INFECTIONS

7a1. Serious Infections

Rheumatoid Arthritis: Meta-analyses and RCTs of Serious Infections in Patients Treated with ADA, IFX ETN and CZP (Tables 3a-3d)

In a recent meta-analysis of 5,619 RA patients being treated with biologic agents, investigators evaluated serious infections (defined as adverse events requiring prolonged hospitalization, adverse events leading to the risk of death or resulting in death or classified as serious by investigators) (Wien 10). Comparators were placebo with or without MTX. The relative risk for serious infection was lower in patients treated with ETN compared to patients treated with the monoclonal antibodies ADA and IFX; however, the differences were not statistically significant.

Three relevant trials totaling 1,785 RA patients from three RCTs (Fleischhmann 09, Keystone 08a, Smolen 09), reported signals of increased serious infection rates for patients treated with CZP compared to placebo with or without MTX. The trials were potentially underpowered to detect statistically significant differences between the groups in rates of severe infection. A meta-analysis of 4 trials of CZP (N=1929), which included the above 3 trials and one trial conducted in patients with Crohn's disease, reported that CZP was associated with a significantly higher risk of serious infections compared to control treatments (OR 3.51 (95% CI 1.59 to 7.79, NNH = 17 (95% CI 7 to 68) (Singh 11). CZP was also associated with significantly higher odds of serious infections compared to ETN, ADA and IFX: ETN OR 3.32 (95%CI 1.43 to 7.75), ADA OR 3.15 (95%CI 1.31 to 7.52), IFX OR 2.42 (95% CI 1.05 to 5.60).

Table 3a. Risk of Serious Infections in RA Patients Receiving ADA, IFX and ETN Compared to Placebo +/- MTX (Wien 10)

Drug	Trials Reporting Serious Infection Data	N	Relative Risk (95% CI)	P-value
ADA	Keystone 04, Kim 07, Miyasaka 07, Furst 03, van de Putte 03, Breedveld 06	2300	2.22 (0.83 to 5.99)	0.11
IFX	Lipsky 00, Maini 99, St Clair 04, Westhovens 06, Schiff 08	2017	0.96 (0.39 to 2.38)	0.93
ETN	Klareskog 04, Emery 08, Lan 04	1302	0.89 (0.54 to1.48)	0.66

In a previous meta-analysis, the risk of serious infection in RA patients was also lowest with ETN and highest with IFX, but the RRs were also not statistically significant (Alonso Ruiz 08). Respective relative risks compared to placebo for IFX, ADA and ETN were 1.8 (95% CI 0.9 to 3.4), 1.2 (95% CI 0.6 to 2.8) and 0.9 (95% CI 0.4 to 2.3).

In an earlier meta-analysis of nine trials that included 3,493 patients who received anti-TNF antibody treatment and 1512 patients who received placebo, the authors pooled serious infection rates in patients receiving both monoclonal antibodies (IFX and ADA) and compared the rates of serious infection to placebo with or without MTX (Bongartz 06). The pooled odds ratio (OR) for the combination of IFX and ADA was statistically significant, OR 2.0 (95% CI 1.3 to 3.1). One out of 59 patients (95% CI 39 to 125) taking IFX or ADA for 3 to 12 months would experience an additional serious infection that would not have occurred if the patient had received placebo with or without MTX.

Table 3b. Risk of Serious Infections in RA Patients Receiving ADA or IFX Compared to Placebo +/- MTX (Bongartz 06)

Drug	Trials Reporting Serious Infection Data	N	Pooled Odds Ratio* ADA and IFX (95% CI)	P-value
ADA	Keystone 04, Furst 03, van de Putte 03, van de Putte 04, Breedveld 06, Weinblatt 03, Keystone 04	5,005	2.01 (1.31 to 3.09)	0.002
IFX	Lipsky 00, Maini 98, St Clair 04, Westhovens 04			

* Absolute difference within 3-12 months: 1.7% (95% CI 0.8 to 2.6); * NNH within 3-12 months: 59 (95% CI 39 to 125)

Table 3c. Risk of Serious Infections CZP Compared To Controls (3 RA trials, 1 Crohn's Disease Trial) (Singh 11)

Intervention	Comparison	Risk Comparator	Risk With Agent (95% CI)	Relative Effect	N	Quality Rating (GRADE)	NNH (95% CI)
CZP	Control	26 per 1000	86 per 1000 (41 to 172)	OR 3.51 (95% CI 1.59 to 7.79)	1929 (4 studies)	Moderate	17 (7 to 68)

Table 3d. Risk of Serious Infections CZP Compared To ADA, ETN, GLM, IFX and Placebo (3 RA trials, 1 Crohn's Disease Trial) (Singh 11)

Agent	Comparator	Odds Ratio (95% CI)
ADA*	**CZP**	0.32 (95% CI 0.13 to 0.76)
CZP*	**ETN**	3.32 (95% CI 0.1.43 to 7.75)
CZP*	**GLM**	2.73 (95% CI 1.04 to 7.13)
CZP*	**IFX**	2.42 (95% CI 1.05 to 5.60)
CZP*	**Placebo**	3.51 (95% CI 1.59 to 7.79)

*Statistically significant

Rheumatoid Arthritis: Observational Studies of Severe Infections in Patients Treated with IFX, ADA and ETN (Tables 3e-3f)

In the largest observational study based on registry data done to date, using data from the British Society for Rheumatology Biologics Register (BSRBR), investigators compared the risk of serious infections (defined as those requiring intravenous antibiotics or hospitalization, or those resulting in death) in 11,798 anti-TNF-treated patients and 3,598 patients treated with traditional DMARDs (Galloway 10). The incidence rate for serious infection in the combined anti-TNF group was 42/1,000 patient-years of follow-up (95% CI 40 to 44) and in the traditional DMARDs group was 32/1,000 patient-years of follow-up (95% CI 28 to 36). For IFX the rate was 46/1,000 patient-years of follow-up (95% CI 42 to 50). For ADA the rate was 43/1,000 patient-years (95% CI 39 to 47). For ETN the rate was 38/1,000 patient-years (95% CI 35 to 42). The differences in hazard ratios among the three agents were not statistically significant.

In a large retrospective cohort study of serious infections comparing IFX, ADA and ETN to MTX in RA patients, the incident rate ratio (IRR) for IFX +ADA (N=850) in the first 6 months was 2.4 (95% CI 1.4 to 5.2). For ETN (N= 1412) compared to MTX, the IRR was not statistically significant at 1.2 (95% CI 0.5 to 2.5). ADA was excluded from the analysis because of a small N (118) (Curtis 07). After 6 months, there were no significantly increased risks in either of the groups compared to MTX. The authors state that the reduction in infection rates seen with both IFX and ETN after 6 months of therapy could be due to a change in the study cohort where patients who experience a serious infection early in the course of therapy discontinue the drug, resulting in a less susceptible cohort later in time.

In a retrospective cohort study which utilized registry data from a German biologics registry of RA patients comparing severe adverse events and infection rates in patients taking biologic agents to non-biologic DMARDS, the RR of lower respiratory infection for IFX was 4.82 (95% CI 1.4 to 20.8) (Listing 05). For patients receiving ETN, the RR was 2.66 (95% CI 0.7 to 11.8). RRs for skin and subcutaneous infections were similar for ETN and IFX. The respective RRs for bone and joint infections were not statistically significantly different for patients taking the biologic agents and patients taking conventional DMARDs. The RR for IFX was 1.75 (95% CI 0.1 to 28.0). The RR for ETN was 5.91 (95% CI 0.7 to 50.7).

In a retrospective cohort study examining safety in the first 36 months of biologic agent usage based on data from the Italian Lombardy Rheumatology Network (LORHEN) registry which included 1,114 patients with long-standing RA (519 treated with IFX, 303 with ADA, and 242 with ETN), the incidence rate (IR) for serious infections defined as the number of events per 1,000 patient-years was higher in patients receiving monoclonal antibodies (Favalli 09). The IR was 38.91 (95% CI 27.14 to 50.67) in the IFX patients, 38.17 (95% CI 21.44 to 54.90) in patients receiving ADA and 25.58 (95% CI 10.46 to 40.69) in patients receiving ETN.

Table 3e. Risk of Serious Infections in RA Patients Receiving ADA or IFX
Registries and Observational Study (Galloway 10, Favalli 09, Curtis 07, Listing 05)

SOURCE	COMPARATORS	OUTCOMES	COMMENTS
Galloway 10 British Society for Rheumatology Biologics Register (BSRBR)	IFX ADA ETN Non-biologic DMARDs	INCIDENCE RATES PER 1,000 PATIENT-YRS 46/1,000 (95% CI 42 to 50) 43/1,000 (95% CI 39 to 47) 38/1,000 (95% CI 35 to 42) 32/1,000 (95% CI 28 to 36)	• 11,798 anti-TNF-treated RA patients • 3,598 patients treated with traditional DMARDs • Largest registry study to date
Favalli 09 Italian Lombardy Rheumatology Network (LORHEN) registry	IFX ADA ETN	INCIDENCE RATES PER 1,000 PATIENT-YRS 38.91 (95% CI 27.14 to 50.67) 38.17 (95% CI 21.44 to 54.90) 25.58 (95% CI 10.46 to 40.69)	• 1,114 patients with RA • 519 treated with IFX • 303 with ADA • 242 with ETN
Curtis 07 Retrospective Cohort	IFX + ADA ETN MTX	INCIDENCE RATE RATIO (COMPARATOR IS MTX) 2.4 (95% CI 1.4 to 5.2) 1.2 (95% CI 0.5 to 2.5) Reference Agent	• ADA N=850 • ETN N=1,412 • Rates are for first six months on agent • No statistically significant increase after 6 months
Listing 05 German biologics registry	IFX ETN Non-biologic DMARDs	RR OF LOWER RESPIRATORY INFECTION 4.82 (95% CI 1.4 to 20.8) 2.66 (95% CI 0.7 to 11.8) Reference Agent	• Rates for bone, joint, skin and subcutaneous infections not statistically different from non-biologic DMARDS

Data from the British RA Registry (Dixon 07) was used to calculate the relative differences in rates of serious infections (defined as those that led to death or hospitalization or required intravenous antibiotics) in RA patients receiving IFX, ADA and ETN compared to patients receiving conventional DMARDs (Table 3d), adjusted for the timing of starting and stopping therapy and duration of therapy. The investigators reported that in the ever-received IFX analysis, but not the ADA or ETN analyses, there was a statistically significant increased IRR. The calculations were based on data from 8,659 patients treated with biologic agents and 2,170 patients treated with traditional DMARDs. Examination of the confidence levels suggests that, for IFX, the increased risk for infection could be increased by approximately 2% to 97% (relative increase in risk) whereas in the ADA and ETN groups, the difference between the biologic agent and conventional DMARDs was not statistically significant. These investigators postulate that a clinician's assessment of risk of infection following an initial infection and subsequent prescribing changes may seriously compromise interpretation of infection rates in registry studies of biologic agents because patients allowed to continue a biologic agent following an infection may result in a "healthy drug continuers" or "depletion of susceptibles" effect, where those patients who are allowed to continue the drug are at the lowest risk for infection.

Table 3f. Incidence Rate Ratios (IRR) of Serious Infections in RA Patients Receiving ADA, ETN and IFX (Comparator is Traditional DMARDs) (Dixon 07)

CATEGORY	IFX	ADA	ETN
Infections per patient year	Receiving Agent Analysis: 317/5,034=6.3% Receiving Agent + 90 days: 354/5,226=6.8% Ever-received Agent: 405/5,874=6.9% Average 6.7%	Receiving Agent Analysis: 112/2,221=5.0% Receiving Agent + 90 days: 127/2,323=5.5% Ever-received Agent : 138/2,548=5.4% Average=5.3%	Receiving Agent Analysis: 308/6,021=5.1% Receiving Agent + 90 days: 361/6,274=5.1% Ever-received Agent: 432/6,998=6.2% Average=5.5%
Adjusted IRR (receiving Rx)	1.28 (95% CI 0.91 to 1.81)	1.17 (95% CI 0.81 to 1.69)	1.15 (95% CI 0.82 to 1.61)
Adjusted IRR (receiving Rx plus 90 day window lag)	1.35 (95% CI 0.97 to 1.89)	1.24 (95% CI 0.87 to 1.78)	1.26 (95% CI 0.91 to 1.74)
Adjusted IRR (ever received Rx)	1.41 (95% CI 1.02 to 1.97)	1.25 (95% CI 0.88 to 1.77)	1.34 (95% CI 0.97 to 1.86)

In summary, indirect evidence from RCTs and observational studies regarding serious infections in RA patients being treated with IFX, ADA and ETN is of borderline strength and suggestive that ETN is associated with a lower risk of serious infections when compared to the pooled risk for IFX and ADA. High quality, direct comparison studies with extensive follow-up periods are needed in order to confirm these findings and more accurately determine the comparative risks of serious infections in patients receiving these three biologic agents. Inconclusive evidence from RCTs (Singh 11) suggests that CZP is associated with a higher risk of serious infections when compared to ADA, ETN, GLM and IFX: ETN OR 3.32 (95% CI 1.43 to 7.75), ADA OR 3.15 (95% CI 1.31 to 7.52), infliximab (OR 2.42, 95% CI 1.05 to 5.60).

Rheumatoid Arthritis: RCTs Evaluating Risk of Serious Infections with GLM

Two recent RCTs (Keystone 08b, Kremer 10) totaling 1,087 RA patients, reported more frequent severe infections in the GLM + MTX groups than in the placebo + MTX groups. A third RCT (Kavanaugh 09), which included 405 patients, reported similar rates in the study groups (P-values not provided). In a meta-analysis of safety data from 1,231 patients in 6 RCTS (Emery 09, Kay 08, Keystone 08b, Smolen 09, Keystone 10, Kremer 10), a statistically significant increase in serious infections with GLM compared to placebo was not found (Singh 10). Long-term surveillance studies and larger RCTs with safety outcomes are needed to provide reliable data regarding the risk of serious infections in patients treated with GLM.

Psoriasis: Meta-analyses, RCTs and Observational Studies Evaluating Risk of Serious Infection in Patients Treated With ADA, ETN, IFX and UST

Comparative safety data for serious infections in psoriasis patients treated with ADA, ETN, IFX and UST are sparse, and the comparative safety of these agents for severe infections is inconclusive**.** Rates of severe infection in published studies are approximately 1%. A recent safety review of clinical trials, observational studies, registries and databases reporting safety outcomes in studies of ETN and UST in the previous 20 years summarized the data on severe infections and reported that, in 8 clinical trials, the rates of serious infections in patients receiving ETN were not statistically higher than those in the placebo groups. Significant differences between UST and placebo groups for serious adverse events were not found (Uhlenhake 10). We found 4 RCTs with relevant published safety data for UST in moderate to severe psoriasis, totaling 3,219 patients (Leonardi 08, Papp 08, Krueger 07, Griffiths 10). The studies were potentially underpowered to detect statistically significant differences between the groups in rates of severe infection. In one trial, 766 patients were studied for 76 weeks with findings of similar serious infection rates of less than 1% in the UST and placebo groups (Leonardi 08). In a 40-week trial (Papp 08), severe infection rates were <2% in the placebo group and the combined UST groups. In a trial of 320 patients with a mean follow-up of 19 weeks (Krueger 07), there were no statistically significant differences in rates of severe infections in the UST and placebo groups. A meta-analysis of these three trials (Tan 10) reported that differences in rates of serious AEs including infection compared to placebo in the UST 45mg group and 90 mg group were not statistically different with respective relative risks of 1.17 (95% CI 0.98 to 1.38) and 1.06 (95% CI 0.89 to 1.27).

In a trial of 903 patients comparing UST 45mg and 90mg to ETN 50mg twice weekly (64 weeks of safety data) (Griffiths 10), the serious infection rate for infections of common bacterial or viral origin was 1.2% in the ETN group, 1% in the group that received 45 mg of UST and 2.9% in patients receiving 90 mg of UST. A systematic review that included three of these RCTs, totaling 2,316 patients, reported a serious infection rate of less than 1% for placebo, UST 45mg and UST 90 mg groups for up to 12 weeks (Scanlon 09).

We found one meta-analysis comparing severe infection rates in ADA-treated patients with RA to rates in patients with PsA and psoriasis (Burmester 09). Data were taken from 36 trials of ADA, 19 in RA (N=12,345), 3 in PsA (N=837), 3 in ankylosing spondylitis, 1 in juvenile inflammatory arthritis, 5 in Crohn's disease and 5 in psoriasis (N=1,819). The meta-analysis included randomized controlled trials, open-label trials and long-term extension studies. The rate of serious infections per 100 patient-years was 1.32 in the psoriasis group and 4.65 in the RA group. P-values were not provided.

We found five RCTs reporting safety outcomes for IFX in the treatment of psoriasis (Chaudhari 01, Gottlieb 04, Reich 05, Menter 06, Antoni 08), but only one reported serious infection rates. In an RCT reporting safety outcomes over 30 weeks in 445 patients treated with IFX versus placebo, the percent of patients with severe infections was 0% in the placebo group and 0.5% in the combined IFX groups. P-values were not reported (Gottlieb 04).

Psoriatic Arthritis (PsA): RCTs Evaluating Risk of Serious Infections with ADA, ETN, GLM, IFX and UST
In one meta-analysis (Burmester 09), the rate of serious infections per 100 patient-years was lower in PsA patients than in RA patients with rates of 2.81 in PsA patients and 4.65 in RA patients. P-values were not reported.

Studies of PsA patients treated with ADA, ETN, GLM, IFX and UST are small, and estimates of effect need confirmation from larger clinical trials. A 12-week trial with 12 weeks of additional open-label extension comparing ETN 50 mg weekly to 50 mg twice weekly in patients with psoriasis and PsA (N=752) reported serious infection rates of less than 1% in ETN and placebo groups (Sterry 10). A trial of ADA reported similar rates of less than 1% with both ADA and placebo (N=298) in a 24-week trial. In a two year open-label extension including only ADA, the rate of serious infection was 5% (Mease 09). In a 16-week trial with an open-label extension to 98 weeks (N=104), the rate of severe infections was 2.6% (Antoni 08). In a 24-week trial comparing 343 patients treated with GLM to 113 patients treated with placebo, the rate of serious infection was 4% in the placebo group and less than 1% in the GLM group (Kavanaugh 09). In a 36 week cross-over trial of 146 patients receiving UST, the rate of serious infections was less than 1% (Gottlieb 09). We found no useful registry information on the biologic agents of interest in the treatment of PsA.

In summary, safety data for serious infections in psoriasis and PsA patients treated with ADA, ETN, GLM, IFX and UST are sparse, and the comparative safety of these agents for severe infections is inconclusive.

7a2. Risk of Tuberculosis (TB) in RA Patients Receiving IFX, ADA and ETN (Tables 4-5f)
The risk for developing or reactivating TB or other granulomatous diseases in RA patients receiving IFX, ADA or ETN appears to be low. However, the evidence suggests that the risk may be lower in patients receiving ETN than in those treated with the monoclonal antibodies. For example, in a meta-analysis of 9 RCTs which included 3,493 patients who received anti-TNF antibody treatment with ADA or IFX and 1,512 patients who received placebo, only 12 of the 126 serious infections could be identified as granulomatous: 10 cases of tuberculosis, 1 case of histoplasmosis, and 1 case of coccidiomycosis (Bongartz 06).

In a study of 4,322 subjects (3,399 average subject-years of exposure) enrolled in 18 RA trials, 2 PsA trials, and 2 ankylosing spondylitis trials that assessed long term safety outcomes of ETN, there were no cases of tuberculosis (Fleischmann 06). The rates of TB in patients receiving IFX, ADA or ETN reported in RCTs and observational studies conducted after recommendations for routine TB screening were less than 1% in another study (Schiff 06). However, individual RCTS have reported increased rates of tuberculosis in patients receiving IFX compared to

those receiving traditional DMARDs (St. Clair 04, Breedveld 04, Westhovens 06 reviewed in Nams 10), and observational studies have reported higher rates of TB in patients receiving IFX and ADA than in patients receiving ETN (Dixon 10, Schiff 06, Tubach 09, Dixon 06, Asking 05, Seong 07, Gomez-Reino 07, Mohan 04, Wolfe 04).

Based on safety data for ADA-treated patients from RCTs, open-label extensions and 2 phase IIIb open-label trials (10,050 patients, representing 12,506 patient-years (PY) of ADA exposure), one systematic review reported the incidence of tuberculosis prior to routine TB screening in patients receiving ADA to be 7 cases of TB in 534 patient-years (PY) of ADA exposure (1.3/100 PY), but the incidence was only 23 cases in 7,058 PY (0.27/100 PY) beginning in 1999 when trial protocols called for tuberculosis screening. Following the initiation of TB screening, 5/866 patients receiving tuberculosis prophylaxis (0.6%) developed active tuberculosis (Schiff 06).

The most recent prospective observational study using data from the British Society for Rheumatology Biologics Register (BSRBR) (Dixon 10) (Table 4) reported rates of tuberculosis to April 2008 in 10,712 anti-TNF treated RA patients (3,913 receiving ETN, 3,295 receiving IFX and 3,504 receiving ADA) and 3,232 patients treated with traditional disease-modifying antirheumatic drugs. Forty cases of TB were reported, all in the anti-TNF cohort. The rate of TB was higher for the monoclonal antibodies, ADA and IFX. For ADA there were 11 cases (144 events/100,000 person-years) and for IFX there were also 11 cases (136/100,000 person-years). In patients receiving ETN, there were 5 cases (39/100,000 person-years). After adjustment, the incidence rate ratio (IRR) compared with ETN-treated patients was 3.1 (95% CI 1.0 to 9.5) for IFX and 4.2 (1.4 to 12.4) for ADA. The median time-to-event was lowest for IFX (5.5 months) compared with ETN (13.4 months) and ADA (18.5 months). 13/40 cases (32.5%) occurred after stopping treatment and 25/40 (62%) cases were extrapulmonary. Eleven cases were disseminated. Patients of non-white ethnicity had a six-fold increased risk of TB compared with white patients treated with anti-TNF therapy.

Table 4. Observational Studies of Tuberculosis in RA Patients Treated with IFX, ADA and ETN (Dixon 10)

Drug (N)	Cases	Rate TB	IRR (Compared To ETN)
ADA (3,504)	11	144/100,000	3.1 (95% CI 1.0 to 9.5)
IFX (3259)	11	136/100,000	4.2 (95% CI 1.4 to 12.4)
ETN (3913)	5	39/100,000	Reference Agent

Registry studies from other countries have also reported lower rates of TB in patients treated with ETN than in patients treated with monoclonal antibodies (Tubach 09, Asking 05, Seong 07, Gomez-Reino 07). The difference in rates of TB between monoclonal antibodies and ETN is estimated to be approximately 100 events/100,000 person-years.

In a French registry study (Tubach 09), investigators conducted an incidence study and case-control analysis to determine the risk of newly diagnosed TB associated with the use of monoclonal anti-TNF agents received for any indication. Data from the French Research Axed on Tolerance of Biotherapies (RATIO) registry was used. For the incidence study, the investigators estimated the annual incidence rate of TB in patients treated with anti-TNF monoclonal antibody therapy, adjusted for age and sex, compared with the incidence of TB in the French population. Data was prospectively collected for all cases of TB occurring from February 1, 2004 to January 1, 2007 in patients who were receiving anti-TNF monoclonal antibody therapy. In the case-control study, for each case of TB occurring in patients receiving IFX or ADA, 2 patients treated with anti-TNF agents served as control subjects.

Seventy-five cases of TB were identified and 69 cases were validated: 40 in rheumatoid arthritis patients, 18 in patients with spondylarthritides, 9 in patients with inflammatory colitis, and 1 each in patients with psoriasis and Behcet's disease. Thirty-six patients had received IFX, 28 had received ADA and 5 had received ETN. Among the 58 patients receiving only 1 anti-TNF agent, 34 (58.6%) had received IFX, 23 (39.7%) had received ADA and 1 (1.7%) had received ETN. The standardized incidence ratios (SIR) and odds ratios are provided in Tables 5a and 5b. The authors conclude that the risk of TB is higher for patients receiving anti-TNF monoclonal antibody therapy than for those receiving soluble TNF receptor therapy. They also point out that the numerous registries which were set up in multiple countries to investigate the safety of anti-TNF agents after the FDA alert regarding the risk of TB associated with the use of IFX (with the exception of the French registry) are cohort studies. A concern with cohort

studies is that they involve only a part of the population of interest and are not likely to be sufficiently powered to demonstrate very rare events or investigate risk differences between anti-TNF agents. For example, an early British registry reported an incidence of TB of 1.5 per 1,000 patient-years with IFX and 0.5 per 1,000 patient-years in patients treated with ETN, but the numbers of cases were only 7 and 2, respectively (Dixon 06). In a Swedish registry, the incidence rates were 1.5 per 1,000 patient-years with IFX and 0.8 per 1,000 patient-years with ETN. Nine cases were treated with IFX alone, and 4 cases were treated with ETN alone (Asking 05). In a Korean study, 2 cases of TB were observed among 90 patients receiving IFX, and no cases were observed among 103 patients receiving ETN (Seong 07). The French investigators concluded that difference in risk between the types of anti-TNF agents was only suggested in the earlier registry studies, but that their study has demonstrated the increased risk of TB in patients treated with the monoclonal antibodies (Tubach 09). The problem of failure to demonstrate differences in outcomes between agents if they exist because of lack of power also exists in the currently available RCTs and meta-analyses. Larger clinical trials and registry studies are needed to confirm these findings.

Table 5a. TB In 68 Patients Receiving Biologic Agents Compared To 136 Control Subjects Without TB Receiving Anti-TNF Therapy RATIO French Registry (Tubach 09)

Last anti-TNF Agent Received	Odds Ratio	P-Value
ETN	1	n/a
ADA	17.08 (95% CI 3.62 to 80.59)	<0.001
IFX	13.29 (95% CI 2.56 to 69.04)	0.002

Table 5b. Risk of TB by Biologic Agent Standardized Incidence Ratios (SIR) of IFX, ADA and Odds Ratio of IFX and ADA Versus ETN (Tubach 09)

Agent	N	SIR with French Population as Reference	Odds Ratio of Agent Compared to ETN
Only IFX	34	18.6 (95% CI 13.4 to 25.8)	13.3 (95% CI 2.6 to 69.0)
Only ADA	23	29.3 (95% CI 20.3 to 42.4)	17.1 (95% CI 3.6 to 80.6)
Only ETN	1	1.8 (95% CI 0.7 to 4.3)	Reference agent
All Anti-TNF	69	12.2 (95% CI 9.7 to 15.5)	Not reported

A Spanish registry study (Gomez-Reino 07) evaluated new cases of active tuberculosis after March 2002 in patients treated with tumor necrosis factor antagonists for rheumatic disease included in the national registry BIOBADASER (Base de Datos de Productos Biologicos de la Sociedad Espanola de Reumatologia) after the dissemination of recommendations to prevent reactivation of latent tuberculosis infection. The risk of TB was reported in patients receiving ADA, ETA and IFX. The risk of TB was greater in patients treated with IFX and ADA than in patients receiving ETN (Table 5c).

Table 5c. Risk of TB by Biologic Agent after March 2002 (Gomez-Reino 07)

Agent	Cases/Subjects (Time-to-Develop)	Incidence per 100,000/yr
IFX	5/1303 (1.2 to 8.7 mos)	383 (95% CI 159 to 921)
ADA	1/565 (14 mos)	176 (95% CI 24 to 1,245)
ETN	2/1740 (<2.5 mos)	114 (95% CI 28 to 459)

In a study based on data from the Korean National Tuberculosis Association (KNTA), investigators used 1,285 patients with RA not exposed to TNF blockers as a control and reviewed medical records of 90 and 103 patients with RA treated with IFX or ETN between the years 2001 and 2005 (Seong 07). The estimated mean risk of TB in the Korean population was 67.2 per 100,000 PY. In the IFX RA group, 2 cases of TB developed during 78.17 patient-years (PY) of follow-up (incidence of 2,558 per 100,000 PY), and there were no cases of TB during 73.67 PY of follow-up in the ETN group. The risk of TB in RA patients receiving IFX was approximately 30 times higher than

the risk in the general Korean population. There was no increased risk found with ETN compared to the Korean population (Table 5d).

Table 5d. Risk of TB by Biologic Agent (Seong 07)

Agent	Cases/Subjects	Sex- And Age-adjusted Risk Ratio (Compared to Korean Population)
IFX	2/90	30.1 (95% CI 7.4 to 122.3)
ETN	0/103	1

In a Swedish registry study (Askling 05), the incidence of reported TB in RA-patients treated with TNF antagonists from 1999 through 2004 was 118 (95% CI 58 to 210) per 100,000 person-years among RA patients during treatment, and 105 (95% CI 56 to 180) per 100,000 person-years among RA patients who had ever been treated with a TNF antagonist. Among RA patients who had received only IFX, the incidence of TB during treatment was 145 (95% CI 58 to 299) per 100,000 person-years; among RA patients who had received only ETN, the incidence was 80 (95% CI 16 to 232) per 100,000 person-years; and, among patients who had received both IFX and ETN, the incidence was 129 (95% CI 3.3 to 719) per 100,000 person years. The relative risk for TB in patients treated with ETN compared to IFX was 0.5 (95% CI 0.1 to 2.4).

Table 5e. Risk of TB by Biologic Agent (Askling 05)

Agent	Incidence of TB / 100,000 PY	Relative Risk For TB Compared to IFX
IFX Only	145 (95% CI 58 to 299)	n/a
ETN Only	80 (95% CI 16 to 232)	0.5 (95% CI 0.1 to 2.4)

In a small, retrospective observational study of TB following the use of ETN based on data reported to the Adverse Event Reporting System (AERS) of the US Food and Drug Administration (FDA) through March 2002, the estimated number of TB cases reported to the FDA for each person-year of treatment with ETN in patients with RA was approximately 10 cases/100,000 patient-years of exposure (Mohan 04). In contrast, in a prospective cohort study there was an eightfold higher rate of tuberculosis in patients treated with IFX than in patients in a historic control group who had been treated with synthetic DMARDs. The TB rates were 6.2 cases (95% CI 1.6 to 34.4) per 100,000 patient-years in the control group and 52.5 cases (95% CI 14.3 to 134.4) per 100,000 patient-years in patients treated with IFX (Wolfe 04).

Table 5f. Risk of TB by Biologic Agent(Mohan 04, Wolfe 04)

Agent	Reference	Incidence of TB / 100,000 PY
ETN	Mohan 04, FDA reports between Nov 1998 and March 2002	10 cases (95% CI not provided)
IFX	Wolfe 04, Prospective cohort study 2 Yrs N=6,460	52.5 cases (95% CI 14.3 to 134.4)

In summary, weak, indirect, but consistent evidence from RCTs and observational studies regarding TB in RA patients and larger populations treated with IFX, ADA and ETN is suggestive that ETN is associated with a decreased risk of serious infections when compared to IFX and ADA. High quality, direct comparison studies with extensive follow-up periods are needed in order to confirm these findings and more precisely define the comparative risks of TB in patients receiving these three biologic agents.

7a3. Fungal and Non-TB Opportunistic Infections Associated With ADA, IFX, ETN in RA (Table 6)

Fungal infections and other opportunistic infections have been reported in RA patients taking ADA, IFX and ETN, but the incidence rates are low and the evidence regarding comparative safety differences between ADA, IFX and ETN is inconclusive (Tsidodras 08).

In a three year French registry study (Salmon-Ceron 10), investigators conducted an incidence study and case-control study to determine the risk of non-tuberculosis opportunistic infections (OIs) associated with IFX, ADA and ETN. The French RATIO registry was designed by a multidisciplinary expert group to prospectively collect all cases of OI occurring from 1 February 2004 to 1 February 2007 in France, in patients who were receiving or had received anti-TNF treatment before the occurrence of the OI. Annual incidence rate of OIs in patients receiving anti-TNF treatment was determined, adjusted for age and sex, with the French population used as the reference. A case–control study was performed using cases from the RATIO registry. Controls were patients treated with anti-TNF agents (current treatment or stopped for <24 months), for a labeled indication, in whom no OI had ever developed. Three controls for each case were randomly selected from that database, matched to cases by sex and underlying inflammatory disease. A consensus-based validation process for all OI cases was carried out by 3 infectious disease specialists. Cases for which diagnosis was uncertain or possible as opposed to certain were excluded.

The diagnosis of the 45 validated infections (out of 67 reported cases) in 43 patients was as follows:

- 15 bacterial infections (4 listeriosis, 4 nocardiosis, 4 atypical mycobacteriosis and 3 non-typhoid bacteremic salmonellosis);
- 18 severe viral infections (8 severe herpes zoster, 3 varicella with visceral involvement, 3 extensive herpes simplex infection and 4 disseminated cytomegalovirus (CMV) infection);
- 10 fungal infections (5 pneumocystis infections , 3 invasive aspergillosis and 2 cryptococcosis); and,
- 2 parasitic infections (2 leishmaniasis).

Twenty-six (60.5%) patients with OIs had been diagnosed with RA. Three cases (7%) occurred in patients with psoriatic arthritis or ankylosing spondylitis. There were 8 cases (18.6%) of Crohn's disease or ulcerative colitis and 1 case (2.3%) of psoriasis. 22 cases were excluded because of lack of microbiological/histological confirmation (n=17) or because they were not considered to be an OIs (n=5).

For the 34 patients who had received only one anti-TNF agent, 25 had received IFX, 7 had received ADA and 2 had received ETN. For the 2 patients with 2 OIs, 1 received IFX for RA and presented with aspergillosis. IFX was later resumed, and the patient secondarily developed listeriosis. The second received IFX for inflammatory colitis and presented concomitantly a disseminated cytomegalic virus infection and a pneumocystis infection. Six patients were thought to have had another cause of immunosuppression other than anti-TNF (1 diabetes mellitus, 1 history of cancer, 1 AIDS and 3 chronic obstructive pulmonary disease).

The main analysis relied on a total number of 57,711 patient-years of use of anti-TNF therapy in France during the 2004 through 2006 study period, with 18% receiving ADA, 51% ETN and 31% IFX. The annual adjusted incidence rates of OIs were lowest for ETN (Table 6). In the case–control study, factors predictive of OI were treatment with IFX versus ETN, treatment with ADA versus ETN and treatment with steroids (Table 6). Multiple sensitivity analyses gave similar results, suggesting that the risk of non-TB OIs may be higher with monoclonal anti-TNF antibody therapy rather than with soluble TNF receptor therapy.

As in all observational studies, numerous biases may have distorted results. For example, there may have been over-reporting or under-reporting, and patients may have received other immunosuppressive drugs. These biases appear to have been minimized by the methodology of the study. Important aspects of this study include the validation of infections and the sensitivity analyses. Reporting of all severe drug-related adverse events is mandatory in France. All cases of OI reported to the 31 French pharmacovigilance regional centers were collected along with reports to individual drug companies. Reminders were sent to physicians 4 times each year. OI definition was based on the list of OIs used to identify B and C stages of HIV infection with the addition to the list of other severe infections usually considered as opportunistic in immunosuppressed patients. TB and legionellosis were excluded because they were analyzed in other French registry studies. In almost half the cases, the OI was due to an intracellular multiplying organism. It is important to note that many of the patients developing OIs reported in this study experienced severe clinical courses. 26% of patients required hospitalization in the intensive

care unit and 9% died from the OI. This study appears to have addressed some concerns about lack of severity of reported OIs and selective reporting which may have been present in previous studies.

Table 6. Non-TB Opportunistic Infections With ADA, IFX, ETN (Salmon-Ceron 10)

Agent	Annual Rate OI/100,000 Patient-years
IFX	290.9 (95% CI 0.0 to 835.8)
ADA	61.8 (95% CI 0.0 to 162.5)
ETN	7.1 (95% CI 0.0 to 24.2)
Odds Ratio (Comparator was patients receiving TNFIs without previous OI)	
Treatment with IFX versus treatment with ETN	17.6 (95% CI 4.3 to 72.9)
Treatment with ADA versus treatment with ETN	10.28 (95% CI 2.35 to 44.94)
Treatment with steroids >10 mg/day or intravenous boluses during the previous year	10.0 (95% CI 2.3 to 44.4)
Sensitivity Analysis: OIs per 100,000 patient-years with 95% confidence interval for all the TNFIs, according to the last anti-TNF agent received and according to each drug in patients having received only one TNFI	
Category; N	**Incidence Rate OIs per 100,000 PT YR**
All TNFIs; N=45	151.6 (95% CI 0 to 468.3)
Last TNFI IFX; N=31	290.9 (95% CI 0 to 835.8)
Last TNFI ADA; N=10	61.8 (95% CI 0 to 162.5)
Last TNFI ETN; N=4	7.1 (95% CI 0 to 24.2)
Only IFX; N=27	245.2 (95% CI 0 to 728.7)
Only ADA; N=7	50.1 (95% CI 0 to 144.5)
Only ETN; N=2	4.5 (95% CI 0 to 20)

In a review of case reports of invasive fungal infections (IFI) in any condition associated with IFX, ADA and ETN (Tsiodras 08), the authors grouped fungal infections by major category, i.e., molds, yeasts and IFIs caused by endemic and dimorphic fungi. Pneumocystis jiroveci pneumonias (PCPs) were excluded. The authors reported that, of 281 cases of IFI obtained in a search of PubMed and MEDLINE databases (based on National Library of Medicine filing dates from January 1, 1966, to June 1, 2007), 226 cases (80%) were associated with IFX, 44 (16%) with ETN and 11 (4%) with ADA. Histoplasmosis (n = 84), candidiasis (n = 64), and aspergillosis (n = 64) were the most frequently observed fungal infections in the study.

- The authors identified 84 cases of histoplasmosis: 72 (86%) were associated with IFX, 8 (10%) with ETN, and 4 (5%) with ADA. Most cases for which data were available occurred in areas endemic for the fungus, and all patients received concomitant immunosuppressant medication.
- Candida Infections: 64 of cases of Candida infection were identified in patients receiving TNFI therapy—54 (84%) were associated with IFX, 9 (14%) with ETN, and 1 (2%) with ADA. The affected patients ranged in age from 28 to 74 years. The number of infusions of anti–TNF-α agent was noted for only 3 patients, all of whom received infliximab; the range was 2 to 35 infusions. The pattern of underlying disease was Graft Versus Host Disease in 11 of 17 cases (5, *Candida glabrata*; 5, other species; all but 1178 received infliximab), inflammatory bowel disease in 5 cases, and rheumatoid arthritis in 2 cases. The site of infection was reported in 8 cases and included bloodstream or endovascular infection (n=3), abscess (n=1), and oropharyngeal infection or esophagitis (n=4). Final outcome data were available for only 8 patients, and 4 (50%) of them died: 2 with inflammatory bowel disease, 1 with rheumatoid arthritis, and 1 with GVHD. Thus, cases of minor infections such as candida vaginosis do not appear to have been included in this study. Aspergillosis: 64 cases of aspergillosis associated with the use of TNFIs were identified—48 (75%) were associated with IFX, 14 (22%) with ETN, and 2 (3%) with ADA. All but one of the patients were exposed to other immunosuppressant medications, such as corticosteroids or methotrexate.

- Cryptococcus Infections: 28 cases of Cryptococcus infection associated with TNFIs were identified—17 (61%) were associated with IFX, 10 (36%) with ETN, and 1 (3%) with ADA. Of 8 patients with data available for review, 6 with rheumatoid arthritis had received IFX after a median of 3 infusions (interquartile range (IQR) 3-10).
- There were 3 tinea corporis and 3 pityriasis versicolor cases of patients receiving anti-TNF-[alpha] inhibitors, in which 13 of the 35 had new onset of cutaneous infections. Three patients had received IFX (range of infusions, 2-7; all for ankylosing spondylitis), 1 ETN (for rheumatoid arthritis), and 2 ADA (range of infusions, 26-36; both for rheumatoid arthritis).
- Coccidioidomycosis: 29 cases were identified. 27 (93%) were associated with IFX and 2 (7%) were associated with ETN. All patients were concomitantly taking either corticosteroids or MTX. All had pneumonia and 4 had evidence of disseminated infection.
- Of the entire group of 281 patients who developed fungal infection in association with TNF-[alpha] blockade, 226 (80%) had received IFX, 44 (16%) received ETN, and 11 (4%) received ADA.
- One hundred and two of the 104 (98%) patients for whom data were available received at least 1 other immunomodulating medication (e.g., corticosteroids, MTX) during the course of the fungal infection.Pneumonia was the most common pattern of infection.

Of the 90 (32%) of 281 cases for which outcome information was available, 29 fatalities (32%) were recorded. Because this study is based on anecdotal reporting, it is not possible to reliably estimate comparative OI rates.

In a review of open-label extension studies of RCTs, which also included results from the parent trials of ETN (Weinblatt 10), the authors reported the incidence of OIs. The definition of OI was based on that provided for patients with human immunodeficiency virus by the Centers for Disease Control and Prevention Wonder online database (1992).

- A total of 194 ERA and 217 LRA patients were treated with 25 mg ETN twice weekly over 10 years.
- Five opportunistic infections were reported in 1,272 patients (0.39% over the study period): 1 Candida septicemia, 1 herpes zoster, 1 atypical mycobacterium infection, 1 meningoencephalitis (unspecified) and 1 fungal sepsis (unspecified).

In summary although reliable evidence from RCTs regarding the comparative rates of OIs in patients with RA, psoriasis and PsA is lacking, indirect but consistent RCT evidence regarding differences in rates of serious infections and TB in patients treated with IFX, ADA and ETN together with consistent observational studies reporting differences in rates for serious infections and TB suggest that patients treated with ETN may be at lower risk of OIs than patients treated with IFX and possibly with ADA.

7a4. Fungal and Non-TB Opportunistic Infections Associated With CZP, GLN, and UST

We found no useful evidence to determine the relative risk of fungal and non-TB opportunistic infections in patients treated with CZP, GLN or UST.

In summary, the evidence is inconclusive, but suggestive that the risk of fungal and non-TB opportunistic infections may be higher in patients treated with monoclonal antibody therapy that with ETN.

7b. MALIGNANCY (Tables 7a-7b)

Some individual RCTs (Maini 99, Klareskog 04, Smolen 07, Keystone 08a) and meta-analyses (Bongartz 06, Bongartz 09) have reported higher rates of malignancy in RA patients receiving biologic agents compared to patients receiving placebo with or without MTX. A meta-analysis that included 9 trials (Bongartz 06) totaling 3,493 patients treated with IFX or ADA and 1,512 patients who received placebo, reported a statistically significant increased risk with the monoclonal antibodies with a pooled odds ratio for malignancy of 3.3 (95% CI 1.2 to 9.1) compared to placebo with or without MTX. The NNH was estimated to be 154 (95% CI 91 to 500) (Table 7a).

A meta-analysis comparing 2,244 RA patients who received ETN (contributing 2484 person-years of follow-up) and 1,072 who received control therapy (1,051 person-years) found malignancies in 26 patients in the ETN group (incidence rate 10.47/1000 person-years) and 7 patients in the placebo group with or without MTX (in one study the comparison group was placebo plus sulfasalizine) (IR 6.66/1000 person-years) with a hazard ratio of 1.84 (95% CI, 0.79 to 4.28) for the ETN group compared with the control group (Bongartz 09) (Table 7a).

In a meta-analysis that included 21 trials (8 ADA trials totaling 1,524 patients, 7 IFX trials totaling 1,116 patients and 6 ETN trials totaling 1,029 patients) malignancy rates were not statistically higher in patients treated with standard doses of the three biologic agent groups than in the placebo groups with or without MTX. The relative risks for the three agents assessed individually were 0.55 (95% CI 0.14 to 2.11) for ADA, 1.64 (95% CI 0.30 to 8.89) for IFX and 0.98 (95% CI 0.32 to 3.02) for ETN (Wiens 10) (Table 7a).

In an earlier meta-analysis of 13 trials totaling 7,087 RA patients treated with IFX, ETN and ADA, malignancy rates were also not statistically different from placebo with or without MTX. The incidence of malignancy was less than 0.5% in all groups. The relative risks for the three agents were 1.42 (95% CI 1.01 to 1.99) for ADA, 2.6 (95% CI 0.6 to 11.6) for IFX and 1.9 (95% CI 0.6 to 5.7) for ETN (Alonso-Ruiz 08) (Table 7a).

In a meta-analysis of several populations (19,041 patients exposed to ADA in 36 global clinical trials in RA, PsA, ankylosing spondylitis, Crohn's disease, psoriasis and juvenile idiopathic arthritis), the overall malignancy rates for ADA-treated patients were as expected for the general population. Standardized incidence rates were calculated for malignancies using national and state-specific databases. The rate of malignancies (excluding lymphoma) per 100 patient-years was 0.76 in patients being treated for RA, 0.49 in patients with psoriasis and 0.30 in patients being treated for psoriatic arthritis (Burmester 09).

Table 7a. Risk of Malignancy in RA, Psoriasis and PsA With IFX, ADA, ETN—Results From 5 Meta-Analyses

Reference	Agents and Population (N)	Outcomes
Bongartz 06	IFX or ADA in RA versus Placebo with or without MTX (1,512)	OR 3.3 (95% CI 1.2 to 9.1) ARI 0.65 (95% CI 0.2 to 1.1) 6 to 12 mos NNH 154 (95% CI 91 to 500) 6 to 12 mos
Bongartz 09	ETN versus Placebo with or without traditional DMARD (3,316)	IR 10.47/1000 person years ETN group (26 malignancies) IR 1.84/1000 person years control group (7 malignancies)
Wiens 10	IFX, ADA, ETN in RA versus Placebo with or without MTX (2,145)	IFX: RR 1.64 (95% CI 0.30 to 8.89) ADA: RR 0.55 (95% CI 0.14 to 2.11) ETN: RR 0.98 (95% CI 0.32 to 3.02)
Alonso-Ruiz 08	IFX, ADA, ETN in RA versus Placebo with or without MTX (7,087)	IFX: RR 2.6 (95% CI 0.6 to 11.6) ADA: RR 1.42 (95% CI 1.01 to 1.99) ETN: RR 1.9 (95% CI 0.6 to 5.7)
Burmester 09	ADA in RA, PsA, AS, Crohn's disease versus general population (19,041)	Rate of malignancy per 100 patient years • 0.76 in RA • 0.49 in psoriasis • 0.30 in PsA

Observational Studies of Malignancy in RA Patients Treated with IFX, ADA and ETN

A recent systematic review (Nam 10) comparing malignancy rates for RA patients using general population data and those for RA patients not receiving biologic agents as the controls reported no increased malignancy risk with IFX,ADA and ETN compared with traditional DMARDs. The review summarized 2 registry-based studies reporting malignancy rates for ETN (Klareskog 08) and ADA (Burmester 08). These studies reported no statistically significant increase in malignancies compared to general population data derived from SEER data (data from US National Cancer Institute Surveillance, Epidemiology, and End-Results database). Respective standardized incidence ratios

(SIR) and 95% CIs for ETN (N=2,054) and ADA (N=3,421) were 0.98 (95% CI 0.8 to 1.12) and 0.89 (95% CI 0.68 to 1.13)

A previous registry study (Wolfe 07) reported odds ratios for malignancy in 13,001 RA patients during approximately 49,000 patient-years of observation in the years 1998–2005 using population malignancy rates from the SEER database for comparison (Table 7b). Odds ratios for individual agents compared to US population cancer rates (excluding non-melanoma skin cancer) were IFX OR 1.0 (95% CI 0.8 to 1.3), P=0.820; ADA OR 0.7 (95% CI 0.3 to 1.6), P=0.393; ETN OR 1.0 (95% CI 0.8 to 1.3), P=0.962.

Table 7b. Risk of Malignancy Associated With IFX, ADA, ETN—Registry Studies of RA Patients

Reference	Agents and Population (N) SEER Data	Outcomes^
Burmester 08	ADA in RA versus general population (3421)	ADA: SIR 0.89 (95% CI 0.69 to 1.13)
Klareskog 08	ETN versus general population (2054)	ETN: SIR 0.98 (95% CI 0.69 to 1.12)
Wolfe 07	IFX, ADA, ETN versus general population (13,001)	IFX: OR 1.0 (95% CI 0.8 to 1.3) ADA: OR 0.7 (95% CI 0.3 to 1.6) ETN: OR 1.0 (95% CI 0.8 to 1.3)

^SIR: standardized incidence rate with US population used as comparator; OR: odds ratio

RCTs of Malignancy in RA Patients Treated with GLM, CZP and UST

In a recent review that included 6 RCTs totaling 1,404 patients (Emery 09, Kavanaugh 09, Kay 08, Keystone 08b, Kremer 10, Smolen 08), investigators provided estimates of malignancy risk in patients receiving GLM (Zidi 10). The incidence of lung adenocarcinoma was 3.1%, basal cell and squamous cell carcinoma 1%, breast, ovarian and bladder carcinoma 0.8% and lung cancer and prostate cancer 0.7%. The incidence of malignancy in the trials was not statistically different from placebo groups with or without methotrexate. The authors state that there is "no major and evident risk" of malignancy associated with GLM in the current scientific literature. A previous Cochrane review, based on 4 of the same studies, concluded that there was no difference in malignancy rates between GLM and placebo (Singh 10).

We found three RCTs reporting safety results for CZP in patients with RA. One 6-month trial of 220 patients reported no cases of cancer in either group (Fleischmann 09). A second 12-month trial of 982 patients reported 11 cases of cancer in the CZP group (2.3 per 100 patient-years) and 1 case in the placebo + MTX group (1.1 per 100 patient-years) (Keystone 08a). A third 6-month trial of 619 patients reported 1 case of malignant melanoma in the placebo + MTX group and 2 in the CZP group.

Four RCTs have reported rates of malignancy in trials of UST. Three of the trials compared UST to placebo (Leonardi 08, Papp 08, Krueger 07) and one trial compared UST to ETN (Griffiths 10). In all four trials, malignancy rates were not statistically different from placebo with or without MTX and occurred in less than 1% of patients.

RA: Observational Studies Evaluating Malignancy in Patients Treated with GLM, CZP and UST
We found no registry or observational studies reporting useful evidence regarding the relative risk of malignancy in RA patients receiving GLM, CZP or UST.

Psoriasis and PsA: RCTs Evaluating The Risk of Malignancy in Patients Treated with ADA, ETN, GLM, IFX and UST
We found no RCTs, registry or observational studies reporting useful evidence regarding the relative risk of malignancy in psoriasis in patients receiving ADA, ETN, IFX or UST. CZP and GLM are not FDA-approved for the treatment of psoriasis. We found no useful evidence regarding relative malignancy rates in psoriatic arthritis patients receiving ADA, ETN, GLM, IFX or UST. One RCT reporting safety data on 627 patients found a 1.9% malignancy rate in patients receiving IFX compared to no malignancies in the placebo group (Menter 06). CZP is not FDA-approved for the treatment of psoriatic arthritis.

7c. LYMPHOMA (Table 8-9)
RA: Meta-analyses and RCTs Evaluating Lymphoma in Patients Treated with ADA, ETN and IFX
A recent meta-analysis reported the number of lymphomas per 100 patient-years in patients treated with ADA. The rate in RA (19 trials) was 0.12 lymphomas per 100 PT YR (N=12,345). The rate in PsA (3 trials) was 0.20 per 100 PT YR (N=837). The rate in psoriasis (5 trials) was 0 (N=1819). The standardized incidence ratio (SIR) for RA was 2.98 (95% CI 1.89 to 4.47). Expected occurrences for SIR calculations are based on data from the National Cancer Institute (NCI) Surveillance Epidemiology and End Results (SEER) database (1993–2001) and from an NCI survey of eight locations in the USA (1977-1978) (Burmester 09) (Table 8).

Ten cases of lymphoma were reported in a meta-analysis of 9 RCTs totaling 3,493 patients receiving IFX or ADA for treatment of RA. Six additional cases were detected in follow-up after the trials ended (Bongartz 06). The calculated incidence for the trials was 0.29% (mean duration of trials 34 weeks).

Table 8. Risk of Lymphoma in RA, Psoriasis and PsA With IFX, ADA—Results From 2 Meta-Analyses (Burmester 09, Bongartz 06)

Burmester 09 (19 RA Trials) N=12,345		
Agent	**Number Lymphomas per 100 PT YR**	**SIR (Comparator SEER and NCI data)**
ADA in RA (19 trials, N=12,345)	0.12	2.98 (95% CI 1.89 to 4.47)
ADA in PsA (3 trials, N=837)	0.20	Not reported
ADA in psoriasis (5 trials, N=1819)	0	Not reported
Bongartz 06 (9 RA Trials) N=3493		
Agent	**Number of Cases**	**Incidence (Up to 34 Weeks)**
IFX or ADA	10 per 3493 Patients	0.29%

RA and Psoriasis Patients: Meta-analyses and RCTs of Lymphoma in Patients Treated with GLM, CZP and UST
In a recent review that included 6 RCTs totaling 1,404 patients (Emery 09, Kavanaugh 09, Kay 08, Keystone 08b, Kremer 10, Smolen 08), investigators reported an incidence of lymphoma in patients treated with GLM (5 trials in RA, 1 trial in PsA) of 0.6% (Zidi 10).

In a 6-month trial of 220 patients with RA comparing CZP with MTX to placebo with MTX, there were no cases of lymphoma in either group (Fleischmann 09). In a 12-month trial of 982 patients with RA comparing CZP with MTX to placebo with MTX, 1 case of lymphoma occurred in the CZP group and no cases occurred in the placebo group (Keystone 08a). In a 6-month trial of 619 patients with RA comparing CZP with MTX to placebo with MTX, 1 case of lymphoma occurred in the CZP group and no cases occurred in the placebo group (Smolen 09).

In 4 RCTs of psoriasis patients totaling 3,219 patients receiving UST, there were no cases of lymphoma (Leonardi 08, Papp 08, Krueger 07, Griffiths 10).

RA: Observational Studies Evaluating Lymphoma in Patients Treated with ADA, ETN and IFX

In the French RATIO registry cohort and case-control study of patients receiving anti-TNF agents without restriction for underlying disease, the standardized incidence ratios (French population was used for comparison) in the cohorts receiving ADA or IFX were higher than for those treated with ETN (Mariette 10). Standardized incidence ratio (SIR) were 4.1 (95% CI 2.3 to 7.1) and 3.6 (95% CI 2.3 to 5.6) for ADA and IFX compared to 0.9 (95% CI 0.4 to 1.8) for ETN. The exposure to ADA or IFX versus ETN was found to be an independent risk factor for lymphoma in the included case-control study. The odds ratios compared to ETN were 4.7 (95% CI 1.3 to 17.7) for ADA and 4.1 (95% CI 1.4 to 12.5) for IFX. The authors concluded that the risk of lymphoma is higher with monoclonal-antibody therapy than with soluble-receptor therapy. Previous observational cohort studies (e.g., Wolfe 07a, Wolfe 07b, Askling 09 and Wolfe 04) failed to demonstrate a higher risk of lymphoma in patients receiving ADA or IFX. The lack of difference may be due to insufficient power in the previous studies.

Table 9. Risk of Lymphoma by Biologic Agent French RATIO Registry Study*
Standardized Incidence Ratios (SIR) of IFX, ADA and Odds Ratio of IFX and ADA Versus ETN (Mariette 10)

Agent	N	SIR (95% CI) with French Population as Reference	Odds Ratio of Agent Compared to ETN
IFX		3.6 (95% CI 2.3 to 5.6)	4.1 (95% CI 1.4 to 12.5)
ADA		4.1 (95% CI 2.3 to 7.1)	4.7 (95% CI 1.3 to 17.7
ETN		0.9 (95% CI 0.4 to 1.8)	Reference agent
All Anti-TNF		12.2 (9.7 to 15.5)	Not reported

*Population French subjects without restriction for underlying disease

RA, Psoriasis and PsA: Observational Studies Evaluating Lymphoma in Patients Treated with GLM, CZP and UST

We found no or observational studies reporting useful lymphoma evidence for GLM, CZP or UST.

In summary, although the evidence is inconclusive, observational studies suggest there may be an increased risk of lymphoma in some patients treated with the monoclonal antibodies, IFX and ADA, compared to patients treated with ETN (LOE: inconclusive). The evidence is insufficient to determine the relative risk for lymphoma in patients receiving CZP, GLM or UST compared to each other and to other agents for the treatment of RA, psoriasis and PsA (LOE: inconclusive)

7d. WITHDRAWAL FROM CLINICAL TRIALS AND WITHDRAWAL DUE TO ADVERSE EVENTS (Table 10)

RA: Meta-analyses Evaluating Withdrawals in RA Patients Receiving ADA, IFX and ETN

Four meta-analyses (Singh 11, Wiens 10, Singh 09, Alonso-Ruiz 08) provide signals suggestive that the risk of withdrawing from trials due to adverse events is higher for IFX and ADA compared to placebo A recent meta-analysis (Wiens 10) included 21 trials: 8 ADA trials, 7 IFX trials and 6 ETN trials. For IFX, the relative risk (RR) for withdrawing from the study due to adverse events compared to controls was 2.05 (95% CI 1.33 to 3.16). For ADA, the RR was 1.56 (95% CI 1.04 to 2.35). For ETN, the RR was 0.86 (95% CI 0.63 to 1.16). A Cochrane meta-analysis (Singh 09) included 8 ADA trials (2944 subjects with safety evaluations), 4 ETN trials (1248 subjects with safety evaluations) and 4 IFX trials (835 subjects with safety evaluations). ADA was more likely to lead to withdrawals compared to ETN, with a ratio of OR of 1.89 (95% CI 1.18 to 3.04), P = 0.009. ETN was less likely than IFX to result in withdrawals than placebo with a ratio of odds ratios of 0.37 (95% CI 0.19 to 0.70), P=0.002, compared to controls. The Cochrane investigators estimated the NNH (withdrawal due to adverse event) and 95% confidence interval (CI) compared to placebo as follows (studies were of 6 to 12 months duration): 39 (95% CI 19 to 162) for ADA and 18 (95% CI 8 to 72) for IFX. The NNH for ETN was not significant. In updated safety meta-analysis, ADA, ETN and GLM were all significantly less likely than IFX to result in withdrawals (Singh 11). Compared to IFX, ADA (OR 0.50 (95% CI 0.32 to 0.78), ETN (OR 0.63 (95% CI 0.41 to 0.95) and GLM (OR 0.55 (95% CI 0.30 to 0.99) were associated with significantly fewer withdrawals. Odds ratios for withdrawals for the three agents compared to controls were 1.02 (95% CI 0.70 to 1.48), N=7622 (22 studies) for ADA, 1.28 (95% CI 0.92 o 1.78), N= 8113 (33

studies) for ETN and 2.04 (95% CI 1.43 to 2.91), N=7559 (33 studies) for IFX. The data for GLM were drawn from 7 trials (5 trials in patients with RA, 1 trial in patients with ankylosing spondylitis and 1 trial in patients with PsA. In an earlier meta-analysis (Alonso-Ruiz 08), which included 13 trials and 7,087 subjects, patients receiving IFX were more likely to drop out because of side effects than controls, with a number-needed-to-harm (NNH) of 24. The authors did not consider differences in lengths of the trials in calculating NNHs. Patients receiving ADA were also more likely than controls to drop out because of side effects (NNH 47). Patients receiving ETN were less likely than controls to drop out because of side effects (NNH favoring ETN 26).

Table 10. Risk of Withdrawal by Biologic Agent
4 Meta-analyses (Singh 11, Wiens 10, Singh 09, Alonso-Ruiz 08)

Reference	Agents and Population (N)	Outcomes
Singh 11	ADA Compared to IFX ETN Compared to IFX GLM Compared to IFX	OR of Compared Agents (Mean Duration 6 months) 0.5 (95% CI 0.32 to 0.78) 0.63 (95% CI 0.41 to 0.950) 0.55 (95% CI 0.30 to 0.99)
Singh 11	IFX Compared to Control ADA Compared to Control ETN Compared to Control	OR of Agents Compared to Controls 2.04 (95% CI 1.43 to 2.91)(N=7559 (33 studies) • Risk with IFX: 181 per 1000 (95% CI 134 to 240) • Risk with Comparator: 98 per 1000 1.02 (95% CI 0.70 to 1.48) N=7622 (22 studies) 1.28 (95% CI 0.92 o 1.78) N= 8113 (33 studies)
Wiens 10	IFX (7 trials) ADA (8 trials) ETN (6 trials)	RR of Withdrawal Due To Adverse Events Compared to Controls 2.05 (95% CI 1.33 to 3.16) 1.56 (95% CI 1.04 to 2.35) 0.86 (95% CI 0.63 to 1.16).
Singh 09	ADA Compared to ETN ETN Compared to IFX	OR of Compared Agents (6 to 12 Months) 1.89 (95% CI 1.18 to 3.04), P = 0.009 0.37 (95% CI 0.19 to 0.70), P = 0.002
Singh 09	ADA (8 trials) IFX (4 trials) ETN (4 trials)	NNH (Withdrawal due to AE Versus Controls) 39 (95% CI 19 to 162) 18 (95% CI 8 to 72) NS
Alonso-Ruiz 08	13 Trials ADA IFX ETN	NNH (Withdrawal due to AE Versus Controls) 47 24 26

RA: Observational Studies Evaluating Withdrawals in Patients Receiving ADA, IFX and ETN (Table 11)
Two registry studies (Hetland 09, Marchesoni 09) reported lower withdrawal rates with ETN than with ADA or IFX consistent with the 3 meta-analyses. A Danish registry study reported the comparative risk for drug withdrawal of IFX, ADA and ETN. The risk for withdrawal, compared to ETN, was 1.98 for IFX (95% CI 1.63 to 2.40), 1.35 for IFX versus ADA (95% CI 1.15 to 1.58), and 1.47 for ADA versus ETN (95% CI 1.20 to 1.80) (Hetland 09). A study using data from an Italian registry (Marchesoni 09) reported that, after 36 months, the likelihood of continuing on the drug (referred to as "survival") on ETN was 62.5% which was significantly higher than the likelihood of survival on IFX (49.1%) or ADA (53.6%). The risk of ETN discontinuation was lower than for the other two agents beginning at

6 months and was 37.5% by month 36, when the risk of discontinuing ADA was 46.4% and the risk of discontinuing IFX was 50.9% (P = 0.027).

Table 11. Risk of Withdrawal by Biologic Agent
Registry Studies (Hetland 09, Marchesoni 09)

Reference	Agents	Outcomes
Hetland 07		RR of Withdrawal
	IFX Compared to ETN	1.98 (95% CI 1.63 to 2.40)
	IFX Compared to ADA	1.35 (95% CI 1.15 to 1.58)
	ADA Compared to ETN	1.47 (95% CI 1.20 to 1.80)
Marchesoni 09	36 Months Study	Likelihood of Continuing Agent ("Survival")
	ETN	62.5%*
	ADA	53.6%
	IFX	49.1%

*P<0.05 for difference between ETN and other agents

RA: RCTs Evaluating Withdrawals in Patients Receiving CZP

The evidence is inconclusive for determining the relative risk of withdrawal in RA patients receiving CZP compared to placebo, non-biologic DMARDs or other biologic agents. We found 3 relevant trials totaling 1,785 patients, and in all 3 trials there were potential weak signals of increased withdrawal rates (approximately 2% higher) for patients taking CZP compared to placebo with or without MTX. The trials were potentially underpowered to detect statistically significant differences. (Fleischmann 09, Keystone 08a, Smolen 09).

Psoriasis: Meta-analyses Evaluating Withdrawals in Patients Receiving ADA, IFX and ETN

The evidence is inconclusive for risk of withdrawals in psoriasis patients receiving ADA, IFX and ETN. A meta-analysis comparing withdrawals for any reason in trials of IFX, ADA and ETN (Schmitt 08) reported a lower average monthly withdrawal rate for patients receiving ETN than for patients receiving IFX or ADA. The average incidence of monthly withdrawals in patients receiving ADA (N=814) was 2.9% (CIs not provided). The respective rate for IFX (N= 711) was 2.5% (95% CI 1.8 to 3.0). The rate for patients receiving ETN 25 mg twice weekly (N=253) was 1.3% (95% CI 1.0 to 2.5) and for patients receiving 50mg twice weekly (N=505) was 0.6% (95% CI 0.6 to 0.8).

RA and PsA: RCTs Evaluating Withdrawals in Patients Receiving GLM

The evidence is inconclusive for risk of withdrawals in RA and PsA patients receiving GLM. In a meta-analysis of safety data (Singh 10) from 1,231 RA patients from 4 RCTS (Emery 09, Kay 08, Keystone 08b [recorded as Keystone 09 in Singh 10]), Smolen 09), investigators reported similar rates for withdrawals due to adverse events in the GLM group and placebo (with or without MTX) group. The odds ratio for withdrawals due to adverse events in GLM-treated RA patients was 0.80 (95% CI 0.26 to 2.42) compared to placebo. Two recent RCTs (Keystone 10, Kremer 10), totaling 1087 patients, did not report withdrawals due to adverse events, but severe adverse event rates were slightly higher in the GLM groups than in the placebo with MTX group with severe adverse events rates per year of 6% and 4.2% (P-values not reported) in the two GLM groups and 3.7% in the placebo group (Keystone 10). The severe adverse event rates in another trial were 1.9% and 0.8% in the combined GLM group and placebo group (Kremer 10). A third RCT (Kavanaugh 09), which included 405 PsA patients, reported a higher rate of serious adverse events (P-values not reported) in the placebo group (6%) than in the combined GLM groups (2%).

Psoriasis: RCTs Evaluating Withdrawals in Patients Receiving UST

The evidence is inconclusive for risk of withdrawals in psoriasis patients receiving UST. We found 4 RCTs with published safety data addressing patient withdrawals (Krueger 07, Papp 08, Leonardi 08, Griffiths 10). The 4 trials included 3,219 patients with moderate to severe psoriasis. In the first 12 weeks of a 76-week trial, withdrawals due to adverse events occurred in 2.4% of patients in the placebo group, 0.4 % in the 45 mg UST group and 1.6% in the 90mg UST group (P-values not reported) (Leonardi 08). In a 40-week trial (Papp 08,) similar rates of withdrawals occurred in all groups. In the third trial of 320 patients with a mean follow-up of 19 weeks (Krueger 07), there were also similar withdrawal rates in the groups. In the fourth trial of 903 patients (Griffiths 10)

comparing UST 45mg and 90mg to ETN 50mg twice weekly (64 weeks of safety data), withdrawals were also similar in the three groups: 1.9%, 1.2% and 2.3% respectively (P-values not reported).

PsA: Meta-analyses and RCTs Evaluating Withdrawals in Patients Receiving ADA, IFX and ETN (Table 12)
The evidence is inconclusive for risk of withdrawals in PsA patients receiving ADA, IFX and ETN (Saad 08). A meta-analysis of 5 RCTs comparing risk of withdrawal in patients receiving the 3 agents to placebo found that the risk of withdrawal was similar with the 3 agents, but was lowest with ETN (Table 12). In an RCT reporting withdrawals up to week 98 in PsA patients receiving IFX, the withdrawal rate due to AEs was 6.4% in the ADA group (Antoni 08). In a 24-week trial, the withdrawal rate for ADA was 4% (Mease 08). The withdrawal rate for UST in a 24-week trial was 3% and in another 36-week trial was 7.5% (Gottlieb 09). In a 12-week trial comparing severe AEs in ETN 50 mg twice weekly to 25mg twice weekly, the respective rates were 4% and 2.9%.

Table 12. Risk of Withdrawal in PsA Relative Risks of Withdrawal in PsA Patients Associated With ADA, IFX and ETN Compared to Placebo
Meta-analysis of 5 Trials (Saad 08)

Withdrawal For Any Reason	Withdrawals Due To AEs
IFX: 1.50 (95% CI 0.26 to 8.61)	IFX: 2.90 (95% CI 0.60 to 13.96)
ADA: 0.83 (95% CI 0.39 to 1.74)	ADA: 1.98 (95% CI 0.35 to 11.28)
ETN: 0.24 (95% CI 0.12 to 0.49)	ETN: 1.03 (95% CI 0.07 to 16.24)

In summary, the evidence from randomized, controlled trials and observational studies suggests that patients with RA, psoriasis and PsA receiving IFX or ADA are at increased risk of withdrawing from clinical trials due to adverse events or other reasons compared to patients receiving (ETN) or placebo with or without traditional disease-modifying antirheumatic drugs (DMARDs). We estimate that an additional 5 to 6 patients out of 100 treated with IFX and an additional 2 to 3 patients treated with ADA will withdraw compared to ETN. Based on recent RCT data (Singh 11) it also appears that ADA, ETN and GLM are significantly less likely than IFX to result in withdrawals due to adverse events. The evidence regarding the relative risk of withdrawing from studies in patients treated with CZP, GLM and UST compared to each other or to other antirheumatic agents is inconclusive.

7e. MORTALITY (Table 13a-14)
RA: Systematic Reviews and RCTs Evaluating Risk of Mortality with ADA, IFX and ETN
In a recent systematic review and meta-analysis of 21 randomized, placebo controlled trials (8 ADA trials, 7 IFX trials, 6 ETN trials) of adults with rheumatoid arthritis, mortality rates in patients receiving the 3 biologic agent groups (mean duration of 4 years) were not statistically different from controls (placebo with or without MTX) (Wiens 10).

Table 13a. Relative Risk Of Mortality in RA Patients Receiving ADA, ETN and IFX Compared To Controls (Placebo With Or Without MTX)
Meta-analysis (Wiens 10)

Drug	N	Relative Risk	P-Value
ADA	2428	2.52 (95% CI 0.72 to 8.86)	0.15
ETN	1178	1.54 (95% CI 0.19 to 12.48)	0.68
IFX	1042	0.71 (95% CI 0.11 to 4.85)	0.73

In another recent meta-analysis of RA patients (19 trials) treated with ADA, the standardized mortality ratio was less than one, i.e., the number of deaths observed during treatment with adalimumab was less than what would be expected in the general population. The standardized mortality ratio (SMR), the ratio of observed deaths to expected deaths, for each disease was calculated using the expected rates based on country-specific age and sex matched general population data from the World Health Organization to 2002. (Burmester 09).

In a previous meta-analysis that included 13 trials in RA patients receiving IFX, ADA and ETN, mortality rates in patients receiving the 3 drugs were not statistically different from controls (placebo with or without MTX) (Alonso-Ruiz 08).

Table 13b. Relative Risk of Mortality in RA Patients Receiving ADA, ETN, IFX Compared To Controls – Meta-analysis (Placebo With Or Without MTX) (Alonso-Ruiz 08)

Drug	Events/Total DMARD PTS	Events/Total Control PTS	Relative Risk (95% CI)	I^2
ADA	10/1922	3/947	1.3 (0.4 to 4.7)	0
ETN	4/1082	1/555	1.5 (0.2 to 9.5)	0
IFX	9/1822	5/759	0.5 (0.2 to 1.4)	0

RA: Observational Studies Reporting Mortality Rates in RA Patients Treated with IFX, ADA and ETN

In a recent registry study utilizing data from participants in the British Society for Rheumatology Biologics Register (BSRBR) (Lunt 10), after adjusting for baseline differences, investigators found no overall difference in mortality rates between IFX, ADA and ETN and the non-biologic DMARD cohort (weighted HR 0.86 (95% CI 0.64 to 1.16))(Table 14). Comparative mortality data for the three agents was not provided. 12,672 patients with RA were recruited to the anti-TNF cohort (4,420 ETN, 4,161 IFX, 4,091 ADA). The findings in this study are in contrast to 2 earlier registry studies reviewed by Nam et al. (see Nam 10). In the earlier registry studies, investigators reported decreased mortality rates in patients receiving anti-TNF therapy compared to patients receiving traditional DMARDs. Both the BIOBADASER study in Spain (Carmona 07) and a Swedish study (Jacobsson 05) from the South Swedish Arthritis Treatment Group (SSATG), found a substantial reduction in mortality in anti-TNF treated patients compared to those receiving standard DMARD therapy. There were 20 deaths in the Spanish study and 51 deaths in the Swedish study. Neither previous study provided comparative mortality data for the three agents.

Table 14. Relative Risk of Mortality in RA Patients Receiving ADA, ETN, IFX Compared To Controls (Non-biologic DMARDs) Registry Studies (Lunt 10, Carmona 07, Jacobsson 05)

Reference	Agents	Mortality Compared to PTs Receiving Non-biologic Agents
Lunt 10 British Registry	ADA (N=4091) ETN (N=4420) IFX (N=4161)	No overall difference in mortality rates between the biologic agent and the non-biologic DMARD cohort: HR 0.86 (95% CI 0.64 to 1.16)
Carmona 07 Spanish Registry	Not specified	Mortality Rate Ratio in RA Pts Receiving Biologic Agents Versus RA Pts Receiving Non-biologic DMARDS: 0.32 (95% CI 0.20 to 0.53)
Jacobsson 05 Swedish Registry	ETN or IFX	3 deaths (2 CVD, one lymphoma) in patients receiving biologic agents and 29 deaths (12 CVD) in those not receiving biologic agents

RA, Psoriasis and Psoriatic Arthritis: Systematic Reviews, RCTs and Observational Studies Evaluating Risk of Mortality In Patients Receiving ADA, IFX, ETN, GLM, CZP and UST

In a systematic review and meta-analysis that included 19,041 patients exposed to ADA in 36 global clinical trials in RA, PsA, ankylosing spondylitis, Crohn's disease, psoriasis and juvenile idiopathic arthritis, standardized mortality rates (SMR) were calculated for each disease using data from the World Health Organization for estimating risk in the general population. The standardized mortality ratio was 1.07 (95% CI 0.75 to 1.49), with 35 deaths observed compared with 32.6 deaths expected in the general population (Burmester 09).

In a recent Cochrane review of 4 RCTs which included 1,231 RA patients treated with GLM and 483 patients treated with placebo (with or without MTX), no significant mortality differences were noted between GLM and the placebo groups (Singh 10). We found no RCTs reporting useful mortality data for GLM in PsA.

Several RCTs have reported increased mortality in RA patients taking CZP compared to placebo groups (with or without MTX) (Keystone 08a, Smolen 09), but the numbers were small. We found no systematic review or meta-analyses reporting mortality rates for CZP.

We found no RCTS, systematic reviews or observational studies reporting useful mortality data in RA, psoriasis or PsA for UST.

In summary, the evidence from randomized, controlled trials and observational studies is insufficient to determine the relative risks of mortality in patients with RA, psoriasis or PsA who receive ADA, CZP, ETN, GLM, IFX or UST. The evidence suggests that RA patients treated with ADA, ETN, GLM and IFX are not at increased risk for mortality compared to patients taking synthetic DMARDs. Large, high quality studies with extensive follow-up periods are needed in order to accurately determine the relative risk of mortality in patients receiving these agents.

7f. DEMYELINATING DISEASE (Tables 15a-15b)

RA: RCTs and Observational Studies Evaluating Risk of Demyelinating Disease in Patients Receiving ADA, IFX, ETN, CZP, GLM and UST

In a recent review (Dharamsi 09), investigators sought risk data from 3 general types of study design—controlled and open-label clinical trials, cohort studies and post-marketing surveillance database studies of studies that included RA patients receiving ADA, IFX and ETN. Analysis of adverse events from cohort studies was limited to those that compared a cohort of patients treated with TNF inhibitors to a cohort of general patients or, preferably, patients with RA not treated with TNF inhibitors, with at least 300 patients per group. If any study did not report exposure time in patient-years, attempts were made to contact the authors, and if the information could not be obtained, the study was excluded. One exception to this rule was for post-marketing surveillance data on demyelinating disease with IFX, where 1 year of exposure time was assumed. The control groups used varied depending on the study design. The investigators used RA rates as the control cohort assuming similar rates to the general population. For clinical trials and post-marketing surveillance studies, the control group was patients with RA in the general population and, when data were available, those known to have been unexposed to TNF inhibitors. The relative risk of demyelinating disease derived from clinical trials is higher than for relative risks derived from post-marketing surveillance studies (Table 15b) but 95% CIs were not provided. Precise estimates of the risk of demyelinating disease with the agents of interest is not possible. There is insufficient evidence to determine the comparative risk of the agents of interest (LOE: inconclusive).

Table 15a. Relative Risk Of Demyelinating Disease In Controlled And Open-label Clinical Trials of RA Patients Receiving IFX, ADA and ETN (Dharamsi 09)

Reference	Population	Experimental Incidence/100,000 (Actual Cases)	Control* Incidence/100,000	RR^
Magnano 04	IFX in RA	36.7 (2 of 5443)	8.0	4.6
Fleischmann 06	ETN in RA	92.6 (6 of 6479)	8.0	11.6
Schiff 06	ADA in RA	80 (10 of 12,506)	8.0	10.1

* From Incidence of Multiple Sclerosis and Optic Neuritis in US population

^95% CI not reported

Table 15b. Relative Risk Of Demyelinating Disease In Post-Marketing Surveillance Studies Of RA Patients Receiving IFX, ADA and ETN (Dharams 09)

Reference	Population	Experimental Incidence/100,000 (Actual Cases)	Control* Incidence/100,000	RR^
Magnano 04	IFX in RA	2.54 to 5.49 (27 of 492,000)*	8.0	0.7
Magnano 04	ETN in RA	8.28	8.0	1.0

Schiff 06	ADA in RA	~7.0 (of 78,522)	8.0	1.3

* From Incidence of Multiple Sclerosis and Optic Neuritis in US population
^95% CI not reported

We found no systematic reviews, meta-analyses or registry studies reporting risk of demyelinating disease in patients receiving CZP. In an RCT of 220 patients randomized to CZP or placebo with MTX, there were no cases of demyelinating disease in either group (Fleischmann 09). Demyelinating disease was not reported in other RCTs of CZP (Keystone 08a, Smolen 09).

We found no systematic reviews, meta-analyses or registry studies reporting risk of demyelinating disease in psoriasis patients receiving UST. No cases were reported in published RCTs (Leonardi 08, Papp 08, Krueger 07, Griffiths 10).

In summary, there is insufficient evidence to determine the relative risk of demyelinating disease for RA, psoriasis patients or patients with PsA treated with ADA, ETN, CZP, GLM, IFX or UST.

7g. INJECTION SITE REACTIONS AND INFUSION REACTIONS (Table 16)
The evidence regarding risk of injection site reactions and infusion reactions, as with other safety outcomes, is limited, and risk estimates vary greatly. The reason for the lack of preciseness in the estimates of effect may be due to numerous methodological issues such as heterogeneity of study designs, study duration, populations studied, inconsistent reporting and differences in definitions of infusion and injection site reactions.

RA, Psoriasis and PsA: Injection Site Reactions and Infusion Reactions in Patients Receiving The Agents of Interest (Table 16)
In a meta-analysis of 7 RCTs in RA patients, the crude incidence of infusion reactions in patients receiving IFX was 17.9% (Alonso-Ruiz 08). Details regarding severity were not provided. In a RCT of 249 patients with severe plaque psoriasis, the incidence of infusion reactions through week 30 in patients receiving IFX was 18% in patients receiving 3mg/kg and 22% in patients receiving 5mg/kg compared to 2% in the placebo group (Gottlieb 04). In this trial, infusion reactions were classified as mild (easily tolerated), moderate (discomfort that interferes with usual activity) or severe (significant impairment of function or incapacitation). The most common infusion reactions in patients treated with IFX were chills, headache, flushing, nausea, dyspnea, injection site infiltrations and taste perversion. The majority of infusion reactions were mild or moderate in severity. There were no serious or life-threatening infusion reactions. In a meta-analysis reporting infusion reaction rates (2 trials) in patients with PsA, infusion reactions occurred in 7.4% of patients receiving IFX (Saad 08).

The FDA labeling document states that, in RA patients, infusion reactions are approximately 20% in patients receiving IFX compared to 10% in patients receiving placebo. Infusion reactions associated with IFX appear to be mild (e.g., headache, dizziness, nausea, pruritus, chills or fever) in the majority of instances. However, severe acute reactions (e.g., reactions resembling anaphylactic conditions or associated with convulsions) have been reported in 0.5% to 3.7% of patients (Gartlehner 06).

In a recent meta-analysis of RA patients, the crude incidence of injection site reactions for ADA based on 7 RCTs was 17.5% (95% CI 7.1 to 27.9). The rate for ETN, based on 5 RCTs, was 22.4% (95% CI 8.5 to 36.3) (Thaler 09). In a meta-analysis of PsA patients, injection site reactions occurred in 5.2% of patients receiving ADA (2 trials) and 32% in patients receiving ETN (2 trials) (Saad 08). The FDA labeling documents for ADA and ETN state that, in placebo-controlled trials, 20% of patients treated with ADA developed injection site reactions (e.g., erythema and/or itching, pain or swelling), compared to 14% of patients receiving placebo and that, in rheumatologic indications, approximately 37% of patients treated with ETN developed injection site reactions (e.g., pain, itching or swelling) during the first 3 months of treatment.

RCTs reporting injection site reactions in RA patients receiving CZP have reported rates from 1.6% to 4.5% (Smolen 09, Keystone 08a, Fleischmann 09). The FDA labeling document does not provide CZP injection site data.

RCTs have reported injection site reactions in psoriasis and psoriatic arthritis patients treated with GLM from 5% to 20% (Keystone 10, Kavanaugh 09). The FDA labeling document states that, in controlled Phase 3 trials in RA, PsA and ankylosing spondylitis, 6% of the GLM-treated patients experienced injection site reactions compared with 2% of control-treated patients (16 weeks of trial data). The majority of the injection site reactions were mild, and the most frequent manifestation was injection site erythema.

RCTs assessing injection site reactions in psoriasis patients receiving UST have reported rates from less than 1% to 24.8% (Leonardi 08, Papp 08, Krueger 07, Griffiths 10). The FDA labeling document states that, based on 2 trials, injection site erythema occurred in 2% of patients.

Table 16. Risk of Injection Site and Infusion Reactions in 6 Agents Included in This Review

Reference	Agent	Condition	Type of Reaction	Crude Incidence or Range
Saad 08 Meta-analysis	IFX	PsA	Infusion	7.4%
Alonso-Ruiz 08 Meta-analysis	IFX	RA	Infusion	17.9%
Gottlieb 04 RCT	IFX	Psoriasis	Infusion	18% to 22%
Thaler 09 Meta-analysis	ADA	RA	Injection	17.5% (95% CI 7.1 to 27.9)
Saad 08 Registry	ADA	PsA	Injection	5.2%
Thaler 09 Meta-analysis	ETN	RA	Injection	22.4% (95% CI 8.5 to 36.3)
Saad 08 Meta-analysis	ETN	PsA	Injection	32%
Smolen 09, Keystone 08a, Fleishman 09 RCTs	CZP	RA	Injection	1.6% to 4.5%
Keystone 10, Kavanaugh 09	GLM	Psoriasis and PsA	Injection	5% to 20%
Leonardi 08, Papp 08, Krueger 07, Griffiths 10 RCTs	UST	Psoriasis	Injection	<1% to 24.8%

8. DISCUSSION

Making optimal decisions regarding therapeutic interventions requires knowledge about available options and the relative benefits and risks of each option together with other considerations such as patient preference, availability of agents, etc. This review provides a synthesis of evidence regarding six agents and important adverse events which should be considered when making treatment decisions in patients with rheumatoid arthritis, psoriasis and psoriatic arthritis. The review also demonstrates the need for additional safety studies to more precisely define the comparative safety of these agents used to treat patients with rheumatoid arthritis, psoriasis and psoriatic arthritis.

In our review, we found consistent evidence from clinical trials and observational studies suggesting that there may be meaningful differences between ADA, ETN and IFX in some safety outcomes. Specifically, we found evidence that patients with rheumatoid arthritis treated with ETN compared to ADA and IFX appear to be at lower risk for serious infections, tuberculosis, opportunistic infections and lymphoma. In addition, we found somewhat weaker evidence that patients treated with ADA, ETN, GLM and IFX may be at lower risk for serious infections than those receiving CZP. We found consistent evidence from RCTs and observational data that patients receiving ETN are at lower risk for withdrawals from clinical trials due to adverse events than patients receiving ADA and IFX. We found evidence from RCTs that patients receiving ADA and GLM may be at lower risk for withdrawal from clinical trials than patients receiving IFX.

There may be other important safety differences between CZP, GLM and UST and between these agents and other antirheumatic agents, but further research is required to define them.

As in all systematic reviews, our review has potential limitations. Available RCTs, meta-analyses and observational studies used to inform our evidence synthesis were not designed to directly compare available agents, and our findings were based on indirect comparisons. Indirect comparisons increase the risk of bias because of differences in study populations, study designs and study methodologies. Bias is likely when combining results from studies involving different populations with different co-morbidities, treatment histories and other prognostic variables, different medication dosages, co-interventions and other care experiences. In many clinical trials, safety outcomes are not pre-specified and, when evaluating multiple safety outcomes, some significant differences are likely to be due to chance. On the other hand, statistically non-significant differences between groups may be due to small study size and true differences may be found with larger studies. Other problems include inconsistent reporting of outcomes, switching of agents, different half-lives of agents, loss to follow-up and unblinded or biased assessments. It is possible that only observational studies of sufficient duration will be available to address some safety questions.

Observational studies and open-label phases of clinical trials are also at risk for bias. Differences in study populations may represent important confounders in observational studies. For example, RA patients receiving biologic agents may have had more active disease and more disability than patients receiving traditional DMARDS. Disease severity may be associated with the decision to prescribe a biologic agent. Thus, increased severity of disease in patients selected to receive biologic agents may result in increased reported mortality rates. It may be equally possible that clinicians choose to withhold biologic agents from patients with multiple co-morbidities due to concerns about adverse events. In this situation, mortality rates might be higher in patients not receiving biologic agents. Results of studies may also be biased because of differences in dosages, adherence, co-interventions, length of follow-up, attrition and assessment of outcomes. For example, in registry studies, physicians' decisions to switch treatments after patients experience an adverse event may affect the results reported later in the study because of resulting differences in the study population such as a decreased risk of experiencing an adverse outcome in the cohort over time Other biases may also occur over time. For example, if adverse events are reported and recognized as potential risks by clinicians, increased awareness may result in changes in prescribing and future reporting of adverse events. Although investigators frequently try to adjust for differences between groups, it is not possible to adjust for unknown confounders in observational studies, and bias created by the multiple choices and contextual differences present in all observational studies cannot be eliminated.

Because of the possibility of confounding described above, we rated all studies as inconclusive for validity and clinical usefulness of safety data. We considered consistency of results across various populations, study designs and study methodologies in drawing our conclusions. For example, multiple meta-analyses in RA patients conducted by different authors, one meta-analysis conducted in patients with psoriasis and one meta-analysis conducted in patients with PsA have consistently reported lower withdrawal rates in patients treated with ETN than with the monoclonal antibodies IFX and ADA. Our conclusions about differences in comparative safety are further strengthened by multiple observational studies reporting consistent differences in withdrawal rates.

Without direct comparisons between antirheumatic agents, the reliability of any conclusions is limited. However, we believe this review and our findings from the available indirect comparisons will provide useful information for professionals faced with therapeutic decisions. Large, well-designed and conducted RCTs with direct comparisons between agents in patients with rheumatoid arthritis, psoriasis and psoriatic arthritis are needed. The trials should be designed with attention to inclusion and exclusion criteria such as stage and severity of disease, prior treatments and co-morbidities. The studies should be conducted with rigorous methodology and with consistency of all patient treatments and experiences except for the interventions being studied. Registry studies will continue to play an important role in providing comparative safety information.

APPENDICES CONTENTS

All included studies were rated as of uncertain validity and clinical usefulness for safety.

I. METHODS

Searching and Filtering

We conducted a systematic literature search to identify relevant studies published in peer-reviewed publications, critically appraised, documented and synthesized the evidence from the obtained literature. We searched for systematic reviews and meta-analyses of RCTS and observational studies reporting safety outcomes of interest as described below.

The following electronic databases were searched to identify relevant peer-reviewed studies:

- PubMed (includes MEDLINE, OLDMEDLINE, HealthStar) and Cochrane Databases (including Systematic Reviews, Registry of Clinical Trials, Database of Reviews of Effectiveness)
- AHRQ
- Relevant FDA documentation or reports
- Selected studies from bibliographies of retrieved studies

Searches were conducted using standard MeSH terms (controlled vocabulary) as well as specific free-text terms and combinations of terms related to the key question. The search terms and results are provided in **V. Search Documentation**.

Inclusion & Exclusion Criteria of Studies Included in the Review

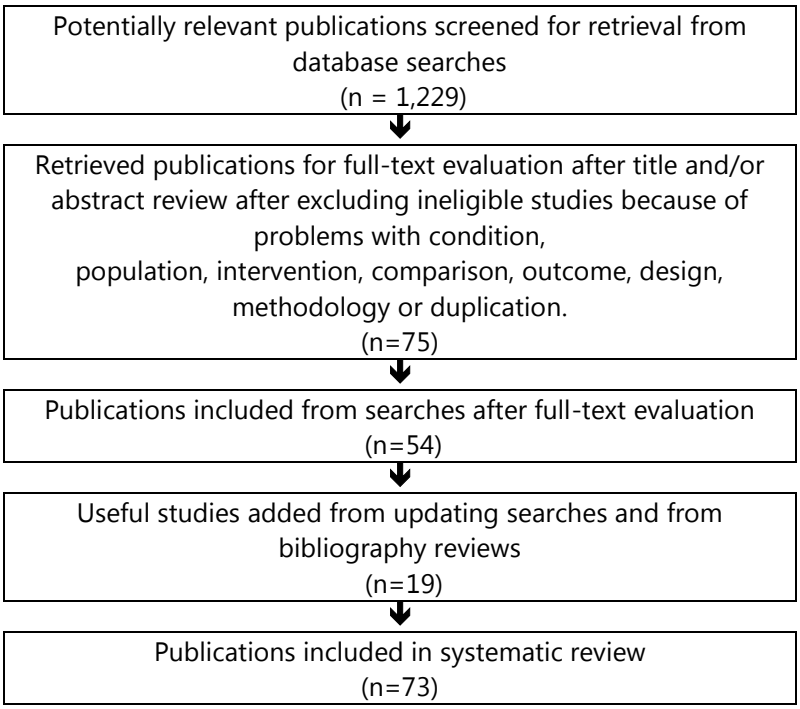
Study Component	Inclusion	Exclusion
Participants	▪ Adults treated for rheumatoid arthritis, psoriasis and psoriatic arthritis	▪ Children ▪ Adults treated for other conditions
Intervention	▪ The following six agents–adalimumab (Humira), certolizumab pegol (Cimzia), etanercept (Enbrel), golimumab (Simponi), infliximab (Remicade), and ustekinumab (Stelara)	▪ Other traditional DMARDs or biologic agents
Comparators	▪ Determined by available studies ▪ Clinical trials: Appropriate control group ▪ Observational studies: Report of population-based expected incidences	
Outcomes	▪ Demyelinating disease ▪ Infusion reactions ▪ Injection-site reactions ▪ Lymphoma ▪ Malignancy ▪ Mortality ▪ Serious infections, tuberculosis (tb) and non-tb opportunistic infections ▪ Withdrawals and withdrawals due to adverse events	
Study Design	▪ Systematic reviews, meta-analyses, relevant RCTs and relevant observational studies (including registries) providing safety data	▪ Case reports ▪ Meta-analyses providing only an estimate of effect for tumor necrosis factor inhibitors as a class
Publication	▪ Studies published in the English language in peer reviewed journals or publicly available FDA reports	▪ Studies not reported in the English language ▪ Studies available only as abstracts, editorials, opinion pieces, poster presentations unless the documents contain sufficient detail for quality assessment. ▪ Duplicate publications of the same subjects which do not report on different outcomes

		▪ Studies which have been superseded by updating studies that have added data from additional patients ▪ Most post-hoc analyses from clinical trials ▪ White papers ▪ Most narrative reviews (exceptions for background information) ▪ Articles identified as preliminary reports when results are published in later versions

1. Multiple searches were performed applying various search terms and limits to maximize potentially relevant studies. Limits included none, systematic reviews, reviews, meta-analysis, clinical trials, randomized controlled trials.
2. Search terms for the PubMed searches dealing included the following terms:
3. "DMARD" and "biologic disease modifying antirheumatic drug" and "tumor necrosis factor" and "TNF" and "inhibitor" and "adalimumab" and "certolizumab" and "CDP870" and "etanercept" and "golimumab" and "infliximab" and " ustekinumab" and "rheumatoid" and "arthritis" and "psoriasis" and "psoriatic" and "demyelinating" and "multiple sclerosis" and "infusion reaction" and "injection site reaction" and " lymphoma" and "malignancy" and "carcinoma" and "mortality" and "serious" and "infection" and "communicable" and "tuberculosis"" and opportunistic" and "fungal" and "withdrawal" and "adverse" and "event" and "health technology" and "technology assessment" and "register" and "registry."
4. Search dates in some cases were based on search dates of systematic reviews or meta-analyses obtained from our initial searches. Details of the search include search date, search terms, limits (e.g., randomized controlled trial (RCT) or systematic review (SR)) and PubMed query translation were documented, as were the number of hits.
5. Titles and abstracts were evaluated to determine relevancy. Studies found to be irrelevant in terms of condition, intervention, comparator and outcomes reported and those seen to have fatal flaws identifiable by title or abstract review were excluded and the remaining studies were selected for retrieval and recorded.
6. Full text review of retrieved studies was used to exclude studies that contained no relevant or useful safety information.
7. During the full text review other studies of interest were noted, retrieved and reviewed utilizing reference lists provided in the studies. The flow diagram below quantifies the studies considered and included in this review.
8. Searches were repeated periodically up to March 1, 2011 looking for useful new studies.

Flowchart Summarizing Search and Application of Relevance and Inclusion Criteria

We screened 1,229 potentially relevant publications from our 24 database searches. We retrieved 75 studies for further abstract and/or full text evaluation after excluding ineligible studies because of problems with topic, condition, intervention, comparison, outcome, design, methodology or duplication. We included 54 studies obtained from searches and 19 from useful studies published after search dates and from bibliography reviews. We included 73 publications in our systematic review.



Study Selection, Quality Assessment and Rating of the Body of Evidence

One or two Delfini reviewers assessed the methodological quality of studies selected for critical appraisal after examining titles, abstracts and, in some cases, full text for relevance.

Studies selected for further review were evaluated for selection, performance, attrition and assessment bias along with other threats to validity. Individual studies were assessed for validity and usefulness. References lists were examined for other relevant studies. All studies were rated as of uncertain validity and clinical usefulness because of study size, design or methodological problems.

A description of the rating system is provided above in **Section 5. Evidence Grading**.

II. GENERAL RISK OF BIAS CONSIDERATIONS FOR REGISTRIES

There are many potential opportunities for bias to distort outcomes in registries. Common to many of the registries are the following issues—

1. No mention of how switching was handled between therapeutic agents.
2. Potential for double-counting of outcomes.
3. Unblinded assessment,
4. It is possible that differences are chance effects or are due to differences in care experiences between agents (e.g., frequency of visits).
5. More follow-up time may be needed for outcomes to occur.
6. Patients on the agents of interest may have been more or less at risk for the development of outcome of interest due to channeling.
7. Differences in outcomes may be reflective of detection and not causation.

8. Patients on the agents of interest may have been more at risk for overdiagnosis bias due to potential of care differences between other patients due to pretreatment evaluations, which also may have varied between agents.
9. Registries are longitudinal databases; therefore differences in baseline characteristics in the groups, lack of blinding, different co-interventions and other clinical management decisions and assessment differences may confound results.
10. Different behaviors and choices made by clinicians and patients choosing different antirheumatic agents could be confounders.
11. Possible undocumented co-interventions and other differences in management and differing patient experiences may be causally associated with outcomes.
12. In addition to administration of different TNFIs, differences in antirheumatic agent dosing, route of administration, frequency of administration, half-life of agents, immunogenic differences in agents, etc. could explain the results.
13. Findings of no difference raise questions of sufficient power to detect differences.

These issues apply to all of the studies based on registries utilized in this review unless specifically noted in individual study critiques.

III. PROJECT TEAM

Delfini Group comprises Michael E. Stuart MD and Sheri Ann Strite, two experts in evidence-based clinical improvement methods and in evidence-based scientific reviews.

IV. CRITICAL APPRAISALS

Safety of Biologic Agents: Critical Appraisal Documentation

The following should be considered working documents only and repository of working notes used to help create the report, entitled **Systematic Safety Review of Five Biologic Antirheumatic Drugs**. The systematic review should be considered the repository of all pertinent information to answer the question, "What is the evidence regarding the comparative safety of the following six agents as used in the treatment of rheumatoid arthritis (RA), psoriasis and psoriatic arthritis: adalimumab (Humira) (ADA), certolizumab pegol (Cimzia) (CZP), etanercept (Enbrel) (ETN), golimumab (Simponi) (GLM), infliximab (Remicade) (IFX), ustekinumab (Stelara) (UST)?" Important information from this document is summarized in the systematic review.

We have included in the review a discussion of the general reliability of the studies reviewed. A detailed list of bias considerations for registries is also included in the review under, **GENERAL RISK OF BIAS CONSIDERATIONS FOR REGISTRIES.** Because of these issues and various commonalities, we have not prepared detailed critical appraisals of each of the included studies nor graded individual studies, but rather here document additional information specific to each study. Some studies appear more than once in order to document inclusion in a systematic review or to make comparisons with other studies.

ALONSO-RUIZ meta RA ifx ada etn 08 FINAL

AUTHOR YR: Alonso-Ruiz 08

Citation: Alonso-Ruiz A, Pijoan JI, Ansuategui E, Urkaregi A, Calabozo M, Quintana A. Tumor necrosis factor alpha drugs in rheumatoid arthritis: systematic review and metaanalysis of efficacy and safety. BMC Musculoskelet Disord2008;9:52. PMID: 18419803

Study Type: SR and Meta-analysis

Manufacture Involvement: No information

Abstract

Background: To analyze available evidence on the efficacy and safety of anti-TNFα drugs (infliximab, etanercept and adalimumab) for treating rheumatoid arthritis (RA).

Methods: We searched systematically for randomised controlled clinical trials on treatment of RA with anti-TNFα drugs, followed by a systematic review with metaanalysis. Trials were searched from MEDLINE, EMBASE and Cochrane Library databases. The American College of Rheumatology (ACR) efficacy response criteria were used. Safety parameters provided by the trials were also assessed. Positive and undesired effects were estimated using combined relative risks (RR), number needed to treat (NNT) and number needed to harm (NNH). Heterogeneity was evaluated by Cochrane's Q and I2 statistics.

Safety Results: Thirteen trials (7087 patients) met the inclusion criteria. Side effects were more common among patients receiving anti-TNFα drugs than controls (overall combined NNH 27). Patients receiving infliximab were more likely to drop out because of side effects (NNH 24) and to suffer severe side effects (NNH 31), infections (NNH 10) and reactions (NNH 9). Patients receiving adalimumab were also more likely to drop out because of side effects (NNH 47) and to suffer injection site reactions (NNH 22). Patients receiving etanercept were less likely to drop out because of side effects (NNH for control versus etanercept 26) but more likely to experience injection site reactions (NNH 5).

Conclusion: Anti-TNFα drugs are effective in RA patients, with apparently similar results irrespective of the drug administered. Doses other than those recommended are also beneficial. The main factor influencing therapeutic efficacy is the prior response to DMARD treatment. The effect of treatment with etanercept or adalimumab does not differ from that obtained with MTX. The published safety profile for etanercept is superior but the fact that no patients are treated with higher than recommended doses requires explanation.

Reviewer Comments

- Compared agents to placebo with or without MTX.
- Prespecified safety outcomes included serious adverse events (those adverse events that required prolonged hospitalization, led to the risk of death, resulted in death, or were classified as serious by the investigator), serious infections (infections that required treatment with parenteral antibiotics or led to hospitalization or the risk of death), malignancy, or death. Withdrawals from treatment due to lack of efficacy or adverse events were also evaluated.
- Inclusion/Exclusion Criteria: Clinical trials had to be of at least 6 months duration and were excluded if they either used administration routes other than recommended or included no treatment arm or did not use recommended doses.
- Search dates: Information from the MEDLINE, EMBASE and Cochrane Library databases up to October 2006
- Methodological quality by applying Jadad Scale – included trials with scores of 3-5 (Jadad 96). Jadad Scale ratings of 3 or higher do not assure that study quality is medium or high. The Jadad scale consists of three items for which points are awarded: randomization, double blinding, and reporting of withdrawals or dropouts. However, the scale does not address these items adequately. For instance, in the domain of randomization, the scale addresses the sequence generation, but not concealment of allocation of the sequence. Other methodological flaws are also not assessed when using the Jadad scale. For example, a low quality study found to have numerous flaws such as no concealment of allocation, a large number of dropouts that are well-described, a per-protocol analysis, and myriad other biases such as multiple differences in care delivered to the study groups could receive five points and be judged to be a study of the highest quality. The Jadad scale has therefore been criticized by several authors as being inadequate for assessing bias in RCTs (Juni 99, Lundh 08). Meta-analyses that employ the Jadad scale as the sole instrument for assessing quality may therefore include trials that are distorted by bias and confounding.
- Heterogeneity for some outcomes was moderate to high.
- **Conclusion:** This meta-analysis of RCTs reported that patients treated with anti–TNF drugs demonstrated a significantly higher frequency of adverse events compared to placebo (RR 1.02 [95% CI 1.00–1.04]). The three biologic drugs also demonstrated statistically significant differences in terms of withdrawal due to adverse events compared with the placebo group, but in the etanercept group withdrawal due to adverse events was higher in the placebo group. The meta-analysis reported similar data regarding serious adverse events, malignancy, and deaths for the three biologic drugs compared with the placebo group, and the data were not statistically significant. Data about serious infections were only statistically significant for infliximab. This finding differs from a later (Wien 10) meta-analysis which reported nonsignificant results for all the safety parameters when compared with the placebo group.

Results (Controls: Placebo With Or Without MTX)

Withdrawals Due To Adverse Events

Drug and Trials	Events/Total DMARD	Events/Total Control	Relative Risk	NNH	I^2
Adalimumab Weinblatt 03, van de Putte 04, Furst 03, Keystone 04, Breedveld 06.	131/1922	44/947	1.42 (95% CI 1.01 to 1.99)	47	0
Etanercept Moreland 99, Weinblatt 99, Bathon 00, van der Heijde 06, Lipsky 00.	103/1082	75/555	0.70 (95% CI 0.53 to 0.92)	-26 (favors ETN)	0
Infliximab Lipsky 00, St Clair 04, Quinn 05, Westhovens 06.	138/1822	24/759	2.04 (95% CI 1.34 to 3.12)	24	0

Serious Adverse Events

Lipsky 00, St Clair 04, Quinn 05, Westhovens 06, van der Heijde 06, van de Putte 04, Furst 03, Keystone 04,

Drug and Trials	Events/Total DMARD	Events/Total Control	Relative Risk	NNH	I^2
Adalimumab	167/1171	75/628	1.0 (95% CI 0.7 to 1.4)	**NS**	**25**
Etanercept	64/454	37/228	0.9 (95% CI 0.5 to 1.6)	**NS**	**0**
Infliximab	217/1610	77/759	1.4 (95% CI 1.0 to 2.0)	31 (17–167)	**52**

Injection-site Reactions

Lipsky 00, St Clair 04, Quinn 05, Westhovens 06, van der Heijde 06, van de Putte 04, Furst 03, Keystone 04,

Drug and Trials	Events/Total DMARD (%)	Events/Total Control	Relative Risk	NNH	I^2
Adalimumab	241/1380 (17.5%)	88/690 (12.8%)	1.7 (95% CI 1.0 to 3.0)	22 (13–67)	72
Etanercept	303/1074 (28.2%)	32/555 (5.8%)	5.1 (95% CI 2.9 to 8.8)	5 (4–6)	0

Infusion Reactions

Lipsky 00, St Clair 04, Quinn 05, Westhovens 06, van der Heijde 06, van de Putte 04, Furst 03, Keystone 04,

Drug and Trials	Events/Total DMARD	Events/Total Control	Relative Risk	NNH	I^2
Infliximab	136/761 (17.9%)	20/308 (6.5%)	2.7 (95% CI 1.7 to 4.2)	9 (7 to 14)	0

Serious Infections

Drug and Trials	Events/Total DMARD	Events/Total Control	Relative Risk	NNH	I^2
Adalimumab	44/1922	14/947	1.2 (95% CI 0.6 to 2.8)		**31**
Etanercept	47/454	25/28	0.9 (95% CI 0.4 to 2.3)		**0**
Infliximab	90/1812	19/726	1.8 (95% CI 0.9 to 3.4)		**26**

Malignancy

Drug and Trials	Events/Total DMARD	Events/Total Control	Relative Risk	NNH	I^2
Adalimumab	16/1922	5/947	1.1 (95% CI 0.4 to 2.7)	NS	0
Etanercept	15/1082	4/555	1.9 (95% CI 0.6 to 5.7)	NS	0
Infliximab	13/1822	1/759	2.6 (95% CI 0.6 to 11.6)	NS	0

Mortality

Drug	Events/Total DMARD	Events/Total Control	Relative Risk	NNH	I^2
Adalimumab	10/1922	3/947	1.3 (95% CI 0.4 to 4.7)		**0**
Etanercept	4/1082	1/555	1.5 (95% CI 0.2 to 9.5)		**0**
Infliximab	9/1822	5/759	0.5 (95% CI 0.2 to 1.4)		**0**

RR was not statistically significantly different from control for all 3 agents.

ANTONI AEs psoriasis 08 FINAL

AUTHOR YR: Antoni 08

Citation: Antoni CE, Kavanaugh A, van der Heijde D, Beutler A, Keenan G, Zhou B, Kirkham B, Tutuncu Z, Burmester GR, Schneider U, Furst DE, Molitor J, Keystone E, Gladman DD, Manger B, Wassenberg S, Weier R, Wallace DJ, Weisman MH, Kalden JR, Smolen JS. Two-year efficacy and safety of infliximab treatment in patients with active psoriatic arthritis: findings of the Infliximab Multinational Psoriatic Arthritis Controlled Trial (IMPACT). J Rheumatol. 2008 May;35(5):869-76. Epub 2008 Mar 15. PubMed PMID: 18381786.

Study Type: RCT

Manufacture Involvement: unrestricted grant from Centocor, Inc.

Abstract

Objective. To investigate longterm efficacy/safety of infliximab over 2 years in patients with active psoriatic arthritis (PsA).

Methods. Initially, 104 patients were randomized to receive blinded infusions of infliximab 5 mg/kg or placebo at Weeks 0, 2, 6, and 14. At Week 16, all patients received infliximab 5 mg/kg every 8 weeks throughWeek 46. Seventy-eight of the 87 patients completing the first year continued into the open-label longterm extension and received infliximab 5 mg/kg at Weeks 54, 62, 70, 78, 86, and 94. The primary efficacy endpoint for the study extension was the proportion of patients with at least 20% improvement in the American College of Rheumatology response criteria (ACR20) at Week 98. Radiographic progression was assessed by the PsA-modified van der Heijde-Sharp score in patients with radiographs available at baseline and Week 98 (n = 43).

Results. At Week 98, 62% (48/78) of infliximab-treated patients achieved an ACR20 response; 45% (35/78) and 35% (27/78) of patients achieved ACR50 and ACR70 responses, respectively. Among patients with baseline Psoriasis Area and Severity Index scores ≥2.5, 64% (16/25) achieved > 75% improvement from baseline to Week 98. The average estimated annual radiographic progression with infliximab treatment was significantly reduced versus the estimated baseline rate of progression. No new safety issues were observed during the second year of the study.

Conclusion. Therapy with infliximab 5 mg/kg through Week 94 produced sustained improvement in joint and skin symptoms, inhibited radiographic progression, and continued to exhibit a favorable benefit- risk ratio in this population with treatment-refractory PsA. (First Release Mar 15 2008; J Rheumatol 2008;35:869–76)

Reviewer Comments

- The withdrawal rate due to AEs was 6.4% in the ADA group.
- The rate of severe infections was 2.6%.

ASKLING TB SWEDISH REGISTRY RA 05 final

AUTHOR YR: Askling 05

Citation: Askling J, Fored CM, Brandt L, Baecklund E, Bertilsson L, Cöster L, Geborek P, Jacobsson LT, Lindblad S, Lysholm J, Rantapää-Dahlqvist S, Saxne T, Romanus V, Klareskog L, Feltelius N. Risk and case characteristics of tuberculosis in rheumatoid arthritis associated with tumor necrosis factor antagonists in Sweden. Arthritis Rheum. 2005 Jul;52(7):1986-92. PubMed PMID: 15986370.

Study Design: Registry

Manufacture Involvement: Supported by the Swedish Cancer Society, AFA Insurance Company, Wyeth-Ayerst, Schering-Plough, Abbott Immunology, and Bristol-Myers Squibb.

Abstract

Objective. Because treatment with tumor necrosis factor (TNF) antagonists may increase the risk of tuberculosis (TB), and because knowledge of the risk of TB in rheumatoid arthritis (RA) not treated with biologics is scarce and of uncertain generalizability to low-risk populations, this study sought to determine the risk of TB among Swedish patients with RA.

Methods. Using data from Swedish nationwide and population-based registers and data from an ongoing monitoring program of TNF antagonists, the relative risks of TB in patients with RA (versus the general population) and of TB associated with TNF antagonists (versus RA patients not treated with biologics) were determined by comparing the incidence of hospitalization for TB in 3 RA cohorts and 2 general population cohorts from 1999 to 2001. We also reviewed the characteristics of all reported cases of TB in RA patients treated with TNF antagonists in Sweden and calculated the incidence of TB per type of TNF antagonist between 1999 and 2004.

Results. During 1999–2001, RA patients who were not treated with TNF antagonists were at increased risk of TB versus the general population (relative risk 2.0, 95% confidence interval [95% CI] 1.2–3.4). RA patients treated with TNF antagonists had a 4-fold increased risk of TB (relative risk 4.0, 95% CI 1.3–12) versus RA patients not treated with TNF antagonists. The reported TB cases during 1999–2004 in RA patients exposed to TNF antagonists (9 infliximab, 4 etanercept, 2 both) were predominantly pulmonary. TB occurred up to 3 years following the start of treatment.

Conclusion. Irrespective of whether TNF antagonists are administered, Swedish patients with RA are at increased risk of TB. During 1999–2001, TNF antagonists were associated with an increased risk of TB, up to 4-fold in magnitude. This increased risk may persist over time during treatment and is related to both infliximab and etanercept.

Reviewer Comments

- The incidence of reported TB in RA-treated with TNF antagonists from 1999 through 2004 was 118 (95% CI 58 to 210) per 100,000 person-years among RA patients during treatment, and 105 (95% CI 56 to 180) per 100,000 person-years among RA patients who had ever been treated with a TNF antagonist.
- Among RA patients who had received only IFX, the incidence of TB during treatment was 145 (95% CI 58 to 299) per 100,000 person-years
- Among RA patients who had received only ETN, the incidence was 80 (95% CI 16 to 232) per 100,000 person-years
- Among patients who had received both IFX and ETN, the incidence was 129 (95% CI 3.3 to 719) per 100,000 person years
- The relative risk for TB in patients treated with ETN compared to IFX was 0.5 (95% CI 0.1 to 2.4)

Risk of TB by Biologic Agent (Askling 05)

Agent	Incidence of TB / 100,000 PY	Relative Risk For TB Compared to IFX
IFX Only	145 (95% CI 58 to 299)	n/a
ETN Only	80 (95% CI 16 to 232)	0.5 (95% CI 0.1 to 2.4)

ASKLING09_Registry_Swedish_Cancer_LYMPHOMA 09

AUTHOR YR: Askling 09

Citation: Askling J, Baecklund E, Granath F, Geborek P, Fored M, Backlin C, Bertilsson L, Cöster L, Jacobsson LT, Lindblad S, Lysholm J, Rantapää-Dahlqvist S, Saxne T, van Vollenhoven R, Klareskog L, Feltelius N. Anti-tumour necrosis factor therapy in rheumatoid arthritis and risk of malignant lymphomas: relative risks and time trends in the Swedish Biologics Register. Ann Rheum Dis. 2009 May;68(5):648-53. Epub 2008 May 8. PubMed PMID: 18467516.

Study Type: Registry

Manufacture Involvement: Financial support for this study was obtained from the Swedish Cancer Society and from Wyeth-Ayerst, Schering-Plough, Abbott Immunology and Bristol-Myers Squibb.

ABSTRACT

Background: Tumour necrosis factor (TNF) antagonists have proved effective as treatment against rheumatoid arthritis (RA), but the unresolved issue of whether the use of anti-TNF therapy increases the already elevated risk of lymphoma in RA remains a concern.

Methods: Using the Swedish Biologics Register (ARTIS), the Swedish Cancer Register, pre-existing RA cohorts and cross-linkage with other national health and census registers, a national RA cohort (n = 67 743) was assembled and patients who started anti-TNF therapy between 1998 and July 2006 (n = 6604) were identified. A general population comparator (n = 471 024) was also assembled and the incidence of lymphomas from 1999 to 31 December 2006 was assessed and compared in these individuals.

Results: Among the 6604 anti-TNF-treated RA patients, 26 malignant lymphomas were observed during 26 981 person-years of follow-up, which corresponded to a relative risk (RR) of 1.35 (95% CI 0.82 to 2.11) versus anti-TNF-naive RA patients (336 lymphomas during 365 026 person-years) and 2.72 (95% CI 1.82 to 4.08) versus the general population comparator (1568 lymphomas during 3 355 849 person-years). RA patients starting anti-TNF therapy in 1998–2001 accounted for the entire increase in lymphoma risk versus the two comparators. By contrast, RR did not vary significantly by time since start of first treatment or with the accumulated duration of treatment, nor with the type of anti-TNF agent.

Conclusion: Overall and as used in routine care against RA, TNF antagonists are not associated with any major further increase in the already elevated lymphoma occurrence in RA. Changes in the selection of patients for treatment may influence the observed risk.

Reviewer Comments

- Agents of Interest: Adalimumab, etanercept , infliximab, in RA
- Authors assessed risks in relation to the time since starting the first anti-TNF agent (irrespective of treatment discontinuation), the duration of anti-TNF therapy, and the specific anti-TNF agent received.
- Swedish registries described as nationwide; population-based; mandatory and semi-automated participation; described as “virtually complete.”
- Population patients hospitalized with (not necessarily because of) RA, between 1964 and 2005; outpatient visits for patients with RA listed as a diagnosis; and, incident RA cases diagnosed from 1995 through 2007.
- Various quality control measures taken including previous validation surveys for accuracy of diagnosis with good results.
- Consistent with prevalence estimates.
- Anti-TNF therapy in the national RA cohort: “Since 1998, patients with RA (or other rheumatologic diseases) who are older than 16 years and are starting treatment with TNF antagonists have been entered into, and followed up in, Anti-Rheumatic Therapy in Sweden (ARTIS), the practice-based national Swedish Biologics Register. For each initiated treatment, information on the underlying rheumatologic condition, including the date of onset, date of treatment initiation (and discontinuation), type and dose of biologic agent, scores and the Health Assessment Questionnaire (HAQ), concomitant disease-modifying antirheumatic drugs (DMARDs), steroids, nonsteroidal antiinflammatory drugs, and analgesics, is recorded by the treating rheumatologist at the start of treatment as well as at prespecified followup visits. By linking the above-mentioned national cohort of 67,743 RA patients to the Swedish Biologics Register, we identified those who were starting anti-TNF therapy, including their dates of starting/ stopping.”
- Patients were described as similar except for a higher proportion of methotrexate use among patients starting infliximab.
- A total of 6604 patients with RA started a first TNF antagonist treatment between 1998 and 31 July 2006 (table 1); 51% were first treated with infliximab, 34% with etanercept and 14% with adalimumab; 25% had been treated with more than one anti-TNF drug.
- Linkage to the Swedish Cancer Register, to which reporting of all malignant neoplasms is mandatory both for the treating physician and for the pathologist since 1958, identified all registered malignant lymphomas and other cancers between 1958 and December 2006 for all unique individuals in the study. Previous reclassification of some 400 RA lymphomas identified through this method indicates a diagnostic correctness greater than 95% with respect to the lymphoma diagnosis.9 For RA patients exposed to TNF antagonists, we also searched for lymphomas among the adverse events reported within the framework of the Swedish Biologics Register (no additional cases were detected), and verified all lymphomas through scrutiny of the medical records and reclassification of the tissue specimens.
- RR did not vary significantly by time since start of first treatment or with the accumulated duration of treatment, nor with the type of anti-TNF agent. Authors state, “We did not note any major difference in RR for each of the three anti-TNF drugs (RR for etanercept, infliximab, adalimumab and for switchers all fell between 1.2 and 1.5, not shown) although precision was limited.

BONGARTZ 06_Metaanalysis_INFECTIONS_ADA_IFX RA_FINAL

AUTHOR YR: Bongartz 06

Citation: Bongartz T, Sutton AJ, Sweeting MJ, Buchan I, Matteson EL, Montori V. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. JAMA2006 May 17;295(19):2275-85.PMID: 16705109

Study Type: Meta-analysis

Manufacture Involvement: Additional data were provided by Abbott and Centocor and were subject to a confidentiality agreement. Abbott and Centocor received the manuscript 4 weeks prior to submission but did not have any role in the design and conduct of the study. Dr Bongartz and Dr Matteson report having been paid consultants for Abbott for work unrelated to this study.

Abstract

Context

Tumor necrosis factor (TNF) plays an important role in host defense and tumor growth control. Therefore, anti-TNF antibody therapies may increase the risk of serious infections and malignancies.

Objective

To assess the extent to which anti-TNF antibody therapies may increase the risk of serious infections and malignancies in patients with rheumatoid arthritis by performing a meta-analysis to derive estimates of sparse harmful events occurring in randomized trials of anti-TNF therapy.

Data Sources

A systematic literature search of EMBASE, MEDLINE, Cochrane Library, and electronic abstract databases of the annual scientific meetings of both the European League Against Rheumatism and the American College of Rheumatology was conducted through December 2005. This search was complemented with interviews of the manufacturers of the 2 licensed anti-TNF antibodies.

Study Selection

We included randomized, placebo-controlled trials of the 2 licensed anti-TNF antibodies (infliximab and adalimumab) used for 12 weeks or more in patients with rheumatoid arthritis. Nine trials met our inclusion criteria, including 3493 patients who received anti-TNF antibody treatment and 1512 patients who received placebo.

Data Extraction

Data on study characteristics to assess study quality and intention-to- treat data for serious infections and malignancies were abstracted. Published information from the trials was supplemented by direct contact between principal investigators and industry sponsors.

Data Synthesis

We calculated a pooled odds ratio (Mantel-Haenszel methods with a continuity correction designed for sparse data) for malignancies and serious infections (infection that requires antimicrobial therapy and/or hospitalization) in anti-TNF– treated patients vs placebo patients. We estimated effects for high and low doses separately. The pooled odds ratio for malignancy was 3.3 (95% confidence interval [CI], 1.2-9.1) and for serious infection was 2.0 (95% CI, 1.3-3.1). Malignancies were significantly more common in patients treated with higher doses compared with patients who received lower doses of anti-TNF antibodies. For patients treated with anti-TNF antibodies in the included trials, the number needed to harm was 154 (95% CI, 91- 500) for 1 additional malignancy within a treatment period of 6 to 12 months. For serious infections, the number needed to harm was 59 (95% CI, 39-125) within a treatment period of 3 to 12 months.

Conclusions

There is evidence of an increased risk of serious infections and a dose dependent increased risk of malignancies in patients with rheumatoid arthritis treated with anti-TNF antibody therapy. The formal meta-analysis with pooled sparse adverse events data from randomized controlled trials serves as a tool to assess harmful drug effects.

Reviewer Comments

NOTE: Most studies included in the meta-analysis are reported individually in NAM critical appraisal.

- Individual trials have shown inconsistent associations between TNF inhibitors and serious infections and malignancy.
- Post hoc meta-analysis of RCT data.
- Included RCTs of 12 week duration or more in RA patients on IFX or ADA. Study participants had to be randomized to receive treatment with an anti-TNF antibody vs placebo (or anti- TNF antibody plus traditional DMARD vs placebo plus traditional DMARD) for at least 12 weeks.
- Heterogeneity in trial populations and concomitant drug use. However inconsistency statistic for malignancy was 0% (95% CI 0% to 25%). For infection the statistical inconsistency statistic was 24% (95% CI 0% to 66%).
- Published data in the 9 included randomized controlled trials reported 24 malignancies in 3493 patients who received at least 1 dose of an anti-TNF antibody (0.8%) and 2 malignancies in 1512 control patients (0.2%).
- Safety data from these trials as reported to the FDA included 37 malignancies in the treatment groups and 3 malignancies in the control groups. After contacting the sponsors and principal investigators for verification of the retrieved numbers and clarification of discrepancies between published and FDA data, 29 malignancies in the treatment groups and 3 malignancies in the placebo groups were used for analysis. Seven malignancies not reported in the published data were skin cancers (2 squamous cell carcinoma and 5 basal cell carcinoma) and 6 malignancies were malignant lymphoma that occurred in the anti- TNF study arms during follow-up, after the actual trial period had ended. The latter were not included in this meta-analysis. Two malignancies, which occurred in 2 anti-TNF–

treated patients who had already developed a first malignancy during the study period, were censored and not included into the analysis.

Risk of Serious Infections in RA Patients Receiving ADA or IFX Compared to Placebo +/- MTX (Bongartz 06)

Drug	Trials Reporting Serious Infection Data	N	Pooled Odds Ratio ADA and IFX	P Value
ADA	Keystone 04, Furst 03, van de Putte 03, van de Putte 04, Breedveld 06, Weinblatt 03, Keystone 04	5005	2.01 (95% CI 1.31 to 3.09)	0.002
IFX	Lipsky 00, Maini 98, St Clair 04, Westhovens 04			

Risk of Malignancy in RA, Psoriasis and PsA With IFX, ADA, ETN

Reference	Agents and Population (N)	Outcomes
Bongartz 06	IFX or ADA in RA versus Placebo with or without MTX (1,512)	OR 3.3 (95% CI 1.2 to 9.1) ARI 0.65% (95% CI 0.2% to 1.1%) 6 to 12 mos NNH 154 (95% CI 91 to 500) 6 to 12 mos

Risk of Lymphoma in RA, Psoriasis and PsA With IFX, ADA

Bongartz 06 (9 RA Trials) N=3493		
Agent	Number of Cases	Incidence (Up to 34 Weeks)
IFX or ADA	10 per 3493 Patients	0.29%

BONGARTZ 09_Metaanalysis_Malignancy_Etanercept_FINAL

AUTHOR YR: Bongartz 09

Citation: Bongartz T, Warren FC, Mines D, Matteson EL, Abrams KR, Sutton AJ. Etanercept therapy in rheumatoid arthritis and the risk of malignancies: a systematic review and individual patient data meta-analysis of randomised controlled trials. Ann Rheum Dis. 2009 Jul;68(7):1177-83. Epub 2008 Nov 19. Review. PubMed PMID: 19019889.

Study Type: Meta-analysis

Manufacture Involvement: Funded by Wyeth and Amgen. Companies provided data for analysis and had opportunity to comment on study design and manuscript. All final decisions rested with the authors. However, some authors are company employees (including one with reported stock), and many other relationships were disclosed.

Abstract

PURPOSE

Tumour necrosis factor (TNF) plays an important role in inflammation and may affect tumour growth control. To assess the risk of malignancy with etanercept, a fusion protein that inhibits TNF action, a meta-analysis was performed using individual patient data from randomised controlled trials (RCT) in patients with rheumatoid arthritis (RA).

METHODS

A search was conducted of bibliographic databases, abstracts from annual meetings and any unpublished studies on file with manufacturers of etanercept to December 2006. Only RCT of etanercept used for 12 weeks or more in patients with RA were included. Nine trials met the inclusion criteria. To adjudicate endpoints, the case narratives of potential cases were reviewed. Patient-level data were extracted from the clinical trials databases.

RESULTS

The nine trials included 3316 patients, 2244 who received etanercept (contributing 2484 person-years of follow-up) and 1072 who received control therapy (1051 person-years). Malignancies were diagnosed in 26 patients in the etanercept group (incidence rate (IR) 10.47/1000 person-years) and seven patients in the control group (IR 6.66/1000 person-years). A Cox's proportional hazards, fixed-effect model stratified by trial yielded a hazard ratio of 1.84 (95% CI 0.79 to 4.28) for the etanercept group compared with the control group.

CONCLUSION

In this analysis, the point estimate of malignancy risk was higher in etanercept-treated patients, although the results were not statistically significant. The approach of obtaining individual patient data of RCT in cooperation with trial sponsors allowed important insights into the methodological advantages and challenges of sparse adverse event data meta-analysis.

Reviewer Comments

NOTE: Most studies included in the meta-analysis are reported individually in NAM critical appraisal.

- Control groups: placebo with or without MTX (in one study control group was placebo plus sulfasalazine)
- Non-significant findings could be a result of insufficient power. Authors indicate that the HR cannot exclude a clinically meaningful association.

Meta-analysis comparing 2,244 RA patients who received ETN (contributing 2484 person-years of follow-up) and 1,072 who received control therapy (1,051 person-years) malignancies in 26 patients in the ETN group (incidence rate 10.47/1000 person-years) and 7 patients in the placebo group with or without MTX (in one study the comparison group was placebo plus sulfasalizine) (IR 6.66/1000 person-years) with hazard ratio of 1.84 (95% CI, 0.79 to 4.28) for the ETN group compared with the control group.

Reference	Agents and Population (N)	Outcomes
Bongartz 09	ETN versus Placebo with or without traditional DMARD (3,316)	IR 10.47/1000 person years ETN group (26 malignancies) IR 1.84/1000 person years control group (7 malignancies)

BURMESTER 09 META-ANALYSIS SAFETY AND MORTALITY RA, PSORIASIS AND PsA_FINAL

AUTHOR YR: Burmester 09

Citation: Burmester GR, Mease P, Dijkmans BA, et al. Adalimumab safety and mortality rates from global clinical trials of six immune-mediated inflammatory diseases. Ann Rheum Dis 2009;68:1863-9.PMID: 1914761
Study Type: SR and Meta-analysis

Study Type: Systematic Review

Safety Outcomes: Withdrawals and withdrawals due to serious adverse events

Manufacture Involvement: NO

RELEVANT INFORMATION FROM PUBLISHED ABSTRACT AND TEXT

AIM: To assess the safety of adalimumab in rheumatoid arthritis (RA) over time and across five other immune-mediated inflammatory diseases and to compare adalimumab malignancy and mortality rates with data on the general population.
METHODS: This analysis included 19,041 patients exposed to adalimumab in 36 global clinical trials in RA, psoriatic arthritis (PsA), ankylosing spondylitis (AS), Crohn's disease (CD), psoriasis and juvenile idiopathic arthritis (JIA) to 15 April 2007. Events per 100 patient-years were calculated using SAE reported after the first dose to 70 days after the last dose. Standardised incidence rates were calculated for malignancies using national and state-specific databases. Standardised mortality rates (SMR) were calculated for each disease using data from the World Health Organization.
RESULTS: Cumulative rates of SAE of interest in RA have remained stable over time. Rates of SAE of interest for PsA, AS, CD, psoriasis and JIA were similar to or lower than rates for RA. Overall malignancy rates for adalimumab-treated patients were as expected for the general population. SMR across all six diseases indicated that no more deaths occurred with adalimumab than expected in the general population.
CONCLUSIONS: Based on 10 years of clinical trial experience across six diseases, this safety report and the established efficacy of adalimumab in these diseases provide the foundation for a better understanding of its benefit-risk profile.

Reviewer Comments

- Agents of Interest: Adalimumab in 3 conditions of interest: RA, psoriatic arthritis and psoriasis
- Search quality: uncertain—few details.
- Data from 36 trials of adalimumab, 19 in RA, three in PsA, three in AS, one in JIA, five in CD and five in psoriasis, including randomised controlled trials, open-label trials and long-term extension studies to 15 April 2007.
- A total of 19 041 patients received adalimumab. Of these, 12 345 were patients with RA, of whom 1472 received adalimumab therapy for at least 5 years. Rates of SAE of interest for the three diseases of interest are listed below.
- For each disease, SAE rates were reported as events per 100 patient-years (number of events divided by the total patient-years of exposure and multiplied by 100).
- SIR used for cancer (based on NCI data for denominator).
- SMR (standardized mortality rate) use WHO data for denominator. Deaths during clinical trials, whether related to the study drug or not, were included in the analysis.
- Suggestive that the SAE of interest in patients receiving ADA for PsA, psoriasis and JIA were similar to rates for RA for most outcomes. Overall malignancy rates for adalimumab-treated patients were similar to those for the general population. SMR across all six diseases indicated that no more deaths occurred with adalimumab than expected in the general population. The risk of serious infections was higher in RA.

RESULTS

Significant Adverse Events/100 Patient-Years (As of April 2007)

Category	RA (19 Trials)	Psoriatic Arthritis (3 Trials)	Psoriasis (5 trials)
N	12,345	837	1819
Serious Infections	4.65	2.81	1.32
Tuberculosis	0.29	0.30	0.12
Opportunistic Infections	0.09	0	0
Malignancy excluding Lymphoma	0.76	0.30	0.49
Lymphoma	0.12	0.20	0

Mortality: SMR for patients treated with adalimumab for each of the six diseases, regardless of sex, were all less than 1.0 (ie, the number of deaths observed during treatment with adalimumab was less than what would be expected in the general population. SMRs were reported in graphic without numerical data. The standardized mortality ratio was less than 1, i.e., the number of deaths observed during treatment with adalimumab was less than what would be expected in the general population. The standardized mortality ratio (SMR), the ratio of observed deaths to expected deaths, for each disease was calculated using the expected rates based on country-specific age and sex matched general population data from the World Health Organization to 2002.

Risk of Malignancy in RA, Psoriasis and PsA With ADA

Burmester 09	ADA in RA, PsA, AS, Crohn's disease versus general population (19,041)	Rate of malignancy per 100 patient years: 0.76 in RA Rate of malignancy per 100 patient years: 0.49 in psoriasis Rate of malignancy per 100 patient years: 0.30 in PsA

Risk of Lymphoma in RA, Psoriasis and PsA With IFX, ADA – Results From 2 Meta-Analyses (Burmester 09, Bongartz 06)

Burmester 09 (19 RA Trials) N=12,345		
Agent	**Number Lymphomas per 100 PT YR**	**SIR (Comparator SEER and NCI data)**
ADA in RA (19 trials, N=12,345)	0.12	2.98 (95% CI 1.89 to 4.47)
ADA in PsA (3 trials, N=837)	0.20	Not reported
ADA in psoriasis (5 trials, N=1819)	0	Not reported
Bongartz 06 (9 RA Trials) N=3493		
Agent	Number of Cases	Incidence (Up to 34 Weeks)
IFX or ADA	10 per 3493 Patients	0.29%

CARMONA SPANISH REGISTRY MORTALITY RA 07 FINAL

AUTHOR YR: Carmona 07

Citation: Carmona L, Descalzo MA, Perez-Pampin E, Ruiz-Montesinos D, Erra A, Cobo T, Gómez-Reino JJ; BIOBADASER and EMECAR Groups. All-cause and cause-specific mortality in rheumatoid arthritis are not greater than expected when treated with tumour necrosis factor antagonists. Ann Rheum Dis. 2007 Jul;66(7):880-5. Epub 2007 Feb 26. PubMed PMID: 17324968.

Study Type: Registry

Safety Outcomes: Mortality

Manufacture Involvement: supported by grants of similar quantity from Schering-Plough, Wyeth, Abbott Immunology, Roche Farma and Bristol-Myers Squibb, Spain. The EMECAR cohort was supported by Aventis.

ABSTRACT

Background: Mortality is increased in rheumatoid arthritis (RA), mainly because of cardiovascular (CV) events, cancer and infections. Recent data suggest that treatment with tumour necrosis factor (TNF) antagonists may affect this trend.

Objective: To assess whether treatment with TNF antagonists is associated with reduction in CV events, cancer and infection rates, and in mortality in patients with RA treated and not treated with TNF antagonists.

Methods: BIOBADASER is a registry for active long-term follow-up of safety of biological treatments in patients with RA. It includes 4459 patients with RA treated with TNF antagonists. EMECAR is an external RA cohort (n = 789) established to define the characteristics of the disease in Spain and to assess comorbidity. The incidence density (ischaemic heart disease) of CV events, cancer and infections was estimated and compared. The standardised mortality ratio was compared with the rate in the general population. A propensity score was used to match cohorts by the probability of being treated. Results: Rates of CV and cancer events are significantly higher in EMECAR than in BIOBADASER (RR 5–7 for different CV events, and RR 2.9 for cancer), whereas the rate of serious infections is significantly higher in BIOBADASER (RR 1.6). Mortality ratio of BIOBADASER by EMECAR is 0.32 (0.20–0.53) for all causes of death, 0.58 (0.24–1.41) for CV events, 0.52 (0.21–1.29) for infection and 0.36 (0.10–1.30) for cancer related deaths.

Conclusion: Morbidity, other than infection, and mortality are not higher than expected in patients with RA treated with TNF antagonists.

Reviewer Comments

- Agents of Interest: ETN, IFX
- Reported decreased mortality rates in patients receiving anti-TNF therapy compared to patients receiving traditional DMARDs: Mortality ratio of BIOBADASER was 0.32 (0.20–0.53) for all causes.
- Conflicting evidence in Lunt 10. Differences in mortality results are most likely due to confounding.

CHAUDHARI AEs psoriasis RCT 01 FINAL

AUTHOR YR: Chaudhari 01

Citation: Chaudhari U, Romano P, Mulcahy LD, Dooley LT, Baker DG, Gottlieb AB. Efficacy and safety of infliximab monotherapy for plaque-type psoriasis: a randomised trial. Lancet. 2001 Jun 9;357(9271):1842-7. PubMed PMID: 11410193.

Study Type: RCT

Manufacture Involvement: Funding was provided by Centocor Inc and a COSAT grant from the Johnson and Johnson Focused Giving Program.

Abstract

Background

Currently available treatments for moderate to severe psoriasis are either incompletely effective in some patients, or are associated with toxic effects. Since tumour necrosis factor alpha (TNF-alpha) is thought to have a role in the pathogenesis of psoriasis, we did a double-blind, randomised trial to assess the clinical benefit and safety of infliximab—a monoclonal antibody against TNF alpha.

Methods

33 patients with moderate to severe plaque psoriasis were randomly assigned intravenous placebo (n=11), infliximab 5 mg/kg (n=11), or infliximab 10 mg/kg (n=11) at weeks 0, 2, and 6. Patients were assessed at week 10 for the primary endpoint (score on the physician's global assessment [PGA]). Analysis was by intention to treat. Findings Of the 33 patients enrolled, three dropped out. Nine of 11 (82%) patients in the infliximab 5 mg/kg group were responders (good, excellent, or clear rating on PGA), compared with two of 11 (18%) in the placebo group (difference 64% [95% CI 20–89], p=0·0089), and ten of 11 (91%) patients in the infliximab 10 mg/kg group were responders (difference from placebo 73% [30–94], p=0·0019). The median time to response was 4 weeks for patients in both infliximab groups. There were no serious adverse events, and infliximab was well tolerated.

Interpretation
In this controlled trial, patients receiving the anti-TNF-_ agent infliximab as monotherapy experienced a high degree of clinical benefit and rapid time to response in the treatment of moderate to severe plaque psoriasis compared with patients who received placebo. These findings suggest that TNF-alpha has a pivotal role in the pathogenesis of psoriasis. Lancet 2001; 357: 1842–47

Reviewer Comments

- Small N
- Data not included in review

CURTIS 07 RA IFX ETN FINAL

AUTHOR YR: Curtis 07

Citation: Curtis JR, Patkar N, Xie A, Martin C, Allison JJ, Saag M, Shatin D, Saag KG. Risk of serious bacterial infections among rheumatoid arthritis patients exposed to tumor necrosis factor alpha antagonists. Arthritis Rheum2007 Apr;56(4):1125-33. PMID: 17393394

Study Type: Retrospective Cohort

Manufacture Involvement: None

Abstract

In a previous study by our group (1), we observed a significantly increased risk of being hospitalized with a serious bacterial infection among patients with rheumatoid arthritis (RA) who were treated with tumor necrosis factor α (TNFα) antagonists compared with patients with RA who received methotrexate (MTX). Although we showed that this risk was increased during the entire study period (median duration of followup 17 months), the risk was highest within the first 6 months after beginning treatment with the TNFα antagonist. Given our further interest in characterizing drug-specific risks, we evaluated the comparative effects of antibody-based and non–antibody-based TNFα antagonists on the risk of being hospitalized with a bacterial infection. Extending our previously published analysis (1), we defined cohorts of patients with RA who had at least 2 International Classification of Diseases, Ninth Revision, Clinical Modification diagnosis codes for RA (714.x, excluding 714.3) and were receiving either infliximab or adalimumab, etanercept, or MTX without a TNFα antagonist.

Because the number of patients receiving adalimumab (n = 118) was insufficient to permit meaningful conclusions, these patients were excluded from this analysis.

All patients exposed to TNFα antagonist were new users, defined as having at least 6 months of nonexposure to these drugs prior to the first filled prescription. Patients were considered at risk of infection within 90 days of the most recent filled prescription for the drug of interest. Patients who were exposed to multiple TNFα antagonists during the same window of risk were excluded. In a sensitivity analysis, shorter risk windows were used (i.e., 30 days for etanercept and MTX, and 60 days for infliximab). Given our previously observed increased risks within the first 6 months of starting a biologic agent, we separately considered exposure time within and beyond 6 months. Using methods previously described (1), serious bacterial infections were initially identified through administrative claims data. Following nationwide medical record abstraction of hospital records, infections were confirmed independently by infectious disease physicians who were blinded to the medication lists for each hospitalization. Incidence rates, crude and adjusted incidence rate ratios, and 95% confidence intervals were computed for patients who received infliximab and etanercept compared with those who received MTX. Among the patients with RA who were exposed to TNFα antagonists, 850 were exposed to infliximab, and 1,412 were exposed to etanercept. The unexposed comparator cohort included 2,933 patients with RA who were treated with MTX. Etanercept users were younger (mean age 47.8 years; P <0.0001 versus MTX users) than infliximab users (mean age 53.4 years; P < 0.05 versus MTX users) and MTX users (mean age 54.9 years). Infliximab users had more physician encounters in the 6 months prior to therapy (mean 8.2; P < 0.0001 versus MTX users) compared with etanercept users (mean 7.0; P nonsignificant versus MTX users) and MTX users (mean 6.9 months). The pattern of glucocorticoid usage and burden of comorbidity were similar or greater in the unexposed cohort than in the TNFα-exposed cohorts. The absolute number of cases of bacterial infection, person-time, incidence rates, and incidence rate ratios are presented in Table 1. As shown, the incidence of a serious bacterial infection was highest during the first 6 months after initiation of a TNFα antagonist, and this finding was significant only among patients exposed to inflix-imab. There were no significantly increased risks of infection in either the infliximab or etanercept group after the first 6 months following initiation. In our sensitivity analysis using shorter exposure windows, results were similar.

Incidence rates, crude and adjusted incidence rate ratios, and 95% confidence intervals for bacterial infection in patients treated with infliximab and etanercept compared with MTX

Category	IFX	ETN
Adjusted incidence rate ratio < 6 Months Since Initiation (compared to MTX)	2.40 (95% CI 1.23 to 4.68)	1.61 (95% CI 95% 0.75 to 3.47)
Adjusted incidence rate ratio > 6 Months Since Initiation (compared to MTX)	1.14 (95% CI 0.55 to 2.24)	1.37 (95% CI 0.74 to 2.53)

Incidence Rates Compared to MTX (IRRs)

Curtis 07 Retrospective Cohort	IFX + ADA ETN MTX	INCIDENCE RATE RATIO (COMPARATOR IS MTX) 2.4 (95% CI 1.4 to 5.2) 1.2 (95% CI 0.5 to 2.5) Reference Agent	• ADA N=850 • ETN N=1412 • Rates are for first six months on agent • No statistically significant increase after 6 mos

Dharamsi CRITIQUE SR ADAL INFLIX ETN 09_FINAL

NOTE: The title states this information is FOR patients with severe psoriasis but utilized data from RA patients.

AUTHOR YR: Dharamsi 09

Citation: Dharamsi JW, Bhosle M, Balkrishnan R, Yentzer BA, Feldman SR. Using 'number needed to treat' to help conceptualize the magnitude of benefit and risk of tumour necrosis factor-alpha inhibitors for patients with severe psoriasis. Br J Dermatol 2009;161:605-16. PMID: 19438475

Study Type: Systematic Review

Agents of Interest: Adalimumab, etanercept, infliximab in RA

Safety Outcomes: tuberculosis, lymphoma and demyelinating disease

Manufacture Involvement: This study was funded by a grant from Abbott Laboratories. The Center for Dermatology Research is supported by an unrestricted educational grant from Galderma Laboratories, L.P. The sponsors had no role in the design and conduct of the study, in the collection, analysis and interpretation of data, or approval of the manuscript.

Study Abstract or Details

Objectives: To illustrate the risks and benefits of TNFalpha inhibitors in relation to risks that patients understand. METHODS: Authors performed a number needed to treat analysis for patients with psoriasis on TNFalpha inhibitors following a Medline and Embase search. They determined the number needed to benefit and the number needed to harm with TNFalpha inhibitor treatment and compared the risk of serious adverse events from treatment with a TNFalpha inhibitor to the risk of death from driving a car. The risk analyses were limited to the risks of tuberculosis, lymphoma and demyelinating disease.

Search: Investigators performed a variety of Medline and Embase searches from inception to April 2007, imposing no language restrictions, combining terms for adverse events ('safety', 'risks', 'adverse events', 'lymphoma', 'tuberculosis', 'infection', 'demyelinating disease', and 'multiple sclerosis') with the words 'rheumatoid arthritis' and 'psoriasis' and the list of TNFa antagonists and their respective trade names. Reviewed reference lists from pertinent articles and retrieved relevant studies. Obtained the latest FDA-approved prescribing information from the three pharmaceutical company websites, performed internet searches using Google, and accessed the FDA website (http://www.fda.gov accessed 26 January 2009) for additional information.

Methods: Investigators obtained data from three general types of study design -- controlled and open-label clinical trials, cohort studies, and postmarketing surveillance database studies. The most up to date published data on adverse events in controlled and uncontrolled clinical trials were abstracted from FDA-approved prescribing information for each drug, as well as from two studies of integrated clinical trial databases and one review article. Post marketing surveillance data were obtained from publications that reported adverse events from the U.S. FDA Adverse Events Reporting Database. Every time that a drug manufacturer receives a report of an adverse event, the manufacturer is required by law to submit the report to the FDA. Authors compared all articles reporting post marketing data and included only those with the most up-to-date information for each adverse event and drug. Analysis of cohort studies of adverse events was limited to those that compared a cohort of patients treated with TNFa inhibitor to a cohort of general patients or, preferably, patients with RA not treated with TNFa inhibitor, with at least 300 patients per group. If any study did not report exposure time in patient-years, attempts were made to contact the authors, and if the information could not be obtained, the study was excluded. One exception to this rule was for post marketing surveillance data on demyelinating disease with infliximab, where 1 year of exposure time was assumed.

In the equation for number needed to harm (NNTH), the experimental group event rate is the incidence of a particular adverse event in patients with RA taking a TNFa inhibitor, while the control group event rate was the incidence of that adverse disease process in patients with RA not taking the TNFa inhibitor. The control groups used varied depending on the study design. For cohort studies, the assembled control cohorts of general patients or patients with RA not treated with TNFa were used as the control groups. For clinical trials and postmarketing surveillance studies, they designated the control group to be patients with RA in the general population, preferably, when data was available, those known to have been unexposed to TNFa inhibitors. Authors included safety data from both controlled and open-label extension portions of trials to take into account events that occurred over increased exposure time. To provide the most reliable estimate of the control group event rate, authors considered the most recent and largest study that followed subjects for the longest period of time out of several population-based cohort studies that report the risk of lymphoma in patients with RA. The incidence of TB among U.S. patients with RA was determined from the National Data Bank of Rheumatic Diseases. The incidence of TB in European patients with RA was obtained from a cohort study based on data from the U.K.-based General Practice Research Database. The current literature was stated to lack data to suggest that RA is associated with a higher rate of demyelinating disease, and thus the control event rate was considered to be its incidence in the general population.

Re Schiff 06: Up to 15 April 2005, the date of the analysis, 10 050 patients (12 506 PYs) had participated in adalimumab RA clinical trials and more than 300 of subjects had at least 5 years of exposure to adalimumab. Four of the adalimumab RCTs were published pivotal trial. Patients in the pivotal trials had moderately or severely active, long standing disease (average duration of approximately 11 years), and the majority had failed treatment with prior DMARDs.

Authors' Conclusions

The risks of serious adverse events are relatively rare and comparable to the risk of death patients take on a regular basis such as driving a car. For many patients with severe psoriasis, the benefits of TNFalpha inhibitors may greatly outweigh the risks. Depending on the adverse event and study design, the numbers needed to harm ranged from **380 to 360,000 treated patients per year**. Screening prior to the initiation of TNFalpha inhibitor therapy reduces risk of tuberculosis.

Reviewer Comments

- Authors combined open-label trials with blinded trials.
- Formal assessment of study quality was not conducted – selection, performance attrition, assessment biases were not addressed.
- Lack of preciseness in data; NNHs vary depending upon study type; i.e., risk estimates of ADA, IFX, ETN from post-marketing surveys differ from those from clinical trials which may be due to differing populations, reporting differences or other factors.

Studies and Documents Utilized by Review

Amgen and Wyeth Pharmaceuticals. Enbrel_ (etanercept) for SubcutaneousInjection [product information]. Amgen and WyethPharmaceuticals, Thousand Oaks, CA, U.S.A., 2008. Available at:http://www.enbrel.com/pdf/enbrel_pi.pdf (accessed by authors 7 February 2009).

Askling J, Fored CM, Brandt L et al. Risk and case characteristics of tuberculosis in rheumatoid arthritis associated with tumor necrosis factor antagonists in Sweden. Arthritis Rheum 2005; 52:1986–92.

Centocor, Inc. Remicade_ (infliximab) for IV Injection [product information]. Centocor, Inc., Malvern, PA, U.S.A., 2008. Available at: http://www.remicade.com/remicade/assets/HCP_PPI.pdf (accessed by authors 7 February 2009).

Fleischmann R, Baumgartner SW, Weisman MH et al. Long term safety of etanercept in elderly subjects with rheumatic diseases. Ann Rheum Dis 2006; 65:379–84.

Keystone EC. Safety of biologic therapies–an update. J Rheumatol Suppl 2005; 74:8–12

Magnano MD, Robinson WH, Genovese MC. Demyelination and inhibition of tumor necrosis factor (TNF). Clin Exp Rheumatol 2004; 22 (Suppl.):S134–40.

Schiff MH, Burmester GR, Kent JD et al. Safety analyses of adalimumab (HUMIRA) in global clinical trials and US postmarketing surveillance of patients with rheumatoid arthritis. Ann Rheum Dis 2006; 65:889–94.

Wolfe F, Michaud K, Anderson J et al. Tuberculosis infection in patients with rheumatoid arthritis and the effect of infliximab therapy. Arthritis Rheum 2004; 50:372–9.

Wolfe F, Michaud K, Anderson J et al. Tuberculosis infection in patients with rheumatoid arthritis and the effect of infliximab therapy. Arthritis Rheum 2004; 50:372–9.

STUDY RESULTS

STUDY RESULTS: LYMPHOMA CONTROLLED AND OPEN-LABEL TRIALS UNITED STATES

Reference	Population	Experimental Incidence	Control Incidence	RR	NNH
Centocor, Inc. 08	Infliximab in RA	80	73.2	1.1	15,000
Amgen and Wyeth 08	Etanercept in RA	90 (9 of 10,000)		1.2 (95% CI 0.6 to 2.4)	5900
Schiff 06	Adalimumab in RA	120 (15 of 12,506)		1.6 (95% CI 1.0 to 2.7)	2100

Amgen and Wyeth Pharmaceuticals. Enbrel_ (etanercept) for SubcutaneousInjection [product information]. Amgen and Wyeth Pharmaceuticals, Thousand Oaks, CA, U.S.A., 2008. Available at:http://www.enbrel.com/pdf/enbrel_pi.pdf (last accessed 7 February2009).

Centocor, Inc. Remicade_ (infliximab) for IV Injection [product information]. Centocor, Inc., Malvern, PA, U.S.A., 2008. Available at: http://www.remicade.com/remicade/assets/HCP_PPI.pdf (last accessed 7 February 2009).

Schiff MH, Burmester GR, Kent JD et al. Safety analyses of adalimumab (HUMIRA) in global clinical trials and US postmarketing surveillance of patients with rheumatoid arthritis. Ann Rheum Dis 2006; 65:889–94.

LYMPHOMA POST-MARKETING SURVEILLANCE

Reference	Population	Experimental Incidence	RR	NNH (NNT)
Schiff 06	Adalimumab in RA	40 (~31 of 78,522)	0.6 (95% CI 0.4 to 0.8)	-3000 favors ADA

Schiff MH, Burmester GR, Kent JD et al. Safety analyses of adalimumab (HUMIRA) in global clinical trials and US postmarketing surveillance of patients with rheumatoid arthritis. Ann Rheum Dis 2006; 65:889–94.

TUBERCULOSIS CONTROLLED AND OPEN-LABEL TRIALS EUROPE

Reference	Population	Experimental Incidence	RR	NNH
Schiff 06	Adalimumab in RA (prior to 1999)	1300 (7 of 534)	57.0	78
Schiff 06	Adalimumab in RA (after 1999)	325.9 (23 of 7058)	14.2	330

Schiff MH, Burmester GR, Kent JD et al. Safety analyses of adalimumab (HUMIRA) in global clinical trials and US postmarketing surveillance of patients with rheumatoid arthritis. Ann Rheum Dis 2006; 65:889–94.

TUBERCULOSIS COHORT STUDIES

Reference	Population	Experimental Incidence/100,000	RR	NNH (NNT)
Wolfe 04	Infliximab in RA	52.5 (4 of 7621)	8.5 (95% CI 1.3 to 56.5)	2100
Askling 05	Infliximab in RA	145	4.2	900
Askling 05	Etanercept in RA	80	2.3	2200

Askling J, Fored CM, Brandt L et al. Risk and case characteristics of tuberculosis in rheumatoid arthritis associated with tumor necrosis factor antagonists in Sweden. Arthritis Rheum 2005; 52:1986–92.

Wolfe F, Michaud K, Anderson J et al. Tuberculosis infection in patients with rheumatoid arthritis and the effect of infliximab therapy. Arthritis Rheum 2004; 50:372–9.

TUBERCULOSIS POST-MARKETING SURVEILLANCE

Reference	Population	Experimental Incidence	RR	NNH (NNT)
Keystone 05	Infliximab in RA	30.2 (90 of 298,240)	4.9 (95% CI 0.9 to 27.9)	4200
Keystone 05	Etanercept inRA	6.83 (26 of 380,700)	1.1	160,000
Schiff 06	Adalimumab in RA	20 (~16 of 78 522)	3.2 (95% CI 0.5 to 19.1)	7200

Keystone EC. Safety of biologic therapies–an update. J Rheumatol Suppl 2005; 74:8–12

Schiff MH, Burmester GR, Kent JD et al. Safety analyses of adalimumab (HUMIRA) in global clinical trials and US postmarketing surveillance of patients with rheumatoid arthritis. Ann Rheum Dis 2006; 65:889–94.

Reviewer Comments

- The risk of TB in patients taking adalimumab is increased approximately 3-fold compared to the general population.
- The risk of TB in patients taking infliximab is increased approximately 5-fold compared to the general population.
- The risk of TB in patients taking etanercept is not increased when compared to the risk in the general population.

DEMYELINATING DISEASE CONTROLLED AND OPEN LABEL CLINICAL TRIALS

Reference	Population	Experimental Incidence/100,000	Control Incidence/100,000 8.0 (from Incidence of MS and ON in US population)	RR	NNH (NNT)
Magnano 04	Infliximab in RA	36.7 (2 of 5443)	8.0	4.6	3500
Fleischmann 06	Etanercept in RA	92.6 (6 of 6479)	8.0	11.6	1200
Schiff 06	Adalimumab in RA	80 (10 of 12,506)	8.0	10.1	50,000

Abbreviations: 0N= optic neuritis, MS=multiple sclerosis

Fleischmann R, Baumgartner SW, Weisman MH et al. Long term safety of etanercept in elderly subjects with rheumatic diseases. Ann Rheum Dis 2006; 65:379–84.

Magnano MD, Robinson WH, Genovese MC. Demyelination and inhibition of tumor necrosis factor (TNF). Clin Exp Rheumatol 2004; 22 (Suppl.):S134–40.

Schiff MH, Burmester GR, Kent JD et al. Safety analyses of adalimumab (HUMIRA) in global clinical trials and US postmarketing surveillance of patients with rheumatoid arthritis. Ann Rheum Dis 2006; 65:889–94.

DEMYELINATING DISEASE POST-MARKETING SURVEILLANCE

Reference	Population	Experimental Incidence/100,000	Control Incidence/100,000 8.0(from Incidence of MS and ON in US population)	RR	NNH (NNT)
Magnano 04	Infliximab in RA	2.54 to 5.49 (27 of 492,000)*	8.0	0.7	40,000 (NNT)
Magnano 04	Etanercept in RA	8.28	8.0	1.0	360,000
Schiff 06	Adalimumab in RA	~7.0 (of 78,522)	8.0	1.3	50,000

Abbreviations: 0N= optic neuritis, MS=multiple sclerosis
*Assumed 1 year of exposure

Magnano MD, Robinson WH, Genovese MC. Demyelination and inhibition of tumor necrosis factor (TNF). Clin Exp Rheumatol 2004; 22 (Suppl.):S134–40.

Schiff MH, Burmester GR, Kent JD et al. Safety analyses of adalimumab (HUMIRA) in global clinical trials and US postmarketing surveillance of patients with rheumatoid arthritis. Ann Rheum Dis 2006; 65:889–94.

Dixon 10 BRIT TB REGISTRY FINAL

AUTHOR YR: Dixon 10

Citation: Dixon WG, Hyrich KL, Watson KD, Lunt M, Galloway J, Ustianowski A, Symmons DP. Drug-specific risk of tuberculosis in patients with rheumatoid arthritis treated with anti-TNF therapy: results from the British Society for Rheumatology Biologics Register (BSRBR). Ann Rheum Dis 2010 Mar;69(3):522-8. PMID: 19854715

Study Type: Registry Cohort and Case-Control

Manufacture Involvement: DPMS and KLH are principal investigators on the BSRBR. BSR receives restricted income from UK pharmaceutical companies, presently Abbott Laboratories, Amgen, Schering Plough and Wyeth Pharmaceuticals. This income finances a wholly separate contract between the BSR and the University of Manchester which provides and runds the BSRBR data collection, management and analysis services.

Abstract

BACKGROUND: The risk of tuberculosis (TB) in patients with rheumatoid arthritis (RA) is thought to be increased following anti-tumour necrosis factor (anti-TNF) therapy, with a proposed differential risk between the anti-TNF drugs etanercept (ETA), infliximab (INF) and adalimumab (ADA). OBJECTIVE: To compare directly the risk between drugs, to explore time to event, site of infection and the role of ethnicity.

METHODS: Data from the British Society for Rheumatology Biologics Register (BSRBR), a national prospective observational study, were used to compare TB rates in 10 712 anti-TNF treated patients (3913 ETA, 3295 INF, 3504 ADA) and 3232 patients with active RA treated with traditional disease-modifying antirheumatic drugs.

RESULTS: To April 2008, 40 cases of TB were reported, all in the anti-TNF cohort. The rate of TB was higher for the monoclonal antibodies ADA (144 events/100,000 person-years) and INF (136/100,000 person-years) than for ETA (39/100,000 person-years). After adjustment, the incidence rate ratio compared with ETN-treated patients was 3.1 (95% CI 1.0 to 9.5) for INF and 4.2 (1.4 to 12.4) for ADA. The median time to event was lowest for INF (5.5 months) compared with ETA (13.4 months) and ADA (18.5 months). 13/40 cases occurred after stopping treatment. 25/40 (62%) cases were extrapulmonary, of which 11 were disseminated. Patients of non-white ethnicity had a sixfold increased risk of TB compared with white patients treated with anti-TNF therapy.

CONCLUSION: The rate of TB in patients with RA treated with anti-TNF therapy was three- to fourfold higher in patients receiving INF and ADA than in those receiving ETA. “We have confirmed that the monoclonal antibodies INF and ADA are associated with a three- to fourfold higher rate of TB compared with ETA. Although no direct comparison with the DMARD cohort was possible, the expected number of cases (n=10) in the DMARD cohort based on the rate seen in the anti-TNF cohort versus the observed (n=0) suggests that anti- TNF therapy confers a significant risk in patients with active RA.”

Reviewer Comments

- Agents of Interest: Adalimumab, etanercept, infliximab in RA
- Large national prospective registry to study long-term safety of exposure to biologic agents in patients with RA.
- Assumably a voluntary registry as, in 2001 it was “recommended” that patients “should be registered.”
- Patients were recruited to the ETA and INF cohorts from 2001 onwards. Recruitment to the ADA cohort started later because of its more recent launch date. Recruitment targets of 4000 patients for the ETA cohort were met in 2005, for INF in 2007 and for ADA in 2008.
- Authors state that they estimate that the registry includes over 80% of anti-TNF treated patients; however, they provide no details of how this estimate was made.
- Analysis was restricted to patients with a doctor’s diagnosis of RA. All patients had to have at least one returned consultant follow-up questionnaire before 31 March 2008. The anti-TNF cohort comprised patients starting an anti-TNF drug as their first biological drug. A comparison cohort of biologic-naıve patients with active RA was recruited in parallel (patients with active disease despite current treatment with a traditional DMARD and biologic naıve).
- Followup data: 6-monthly rheumatologist questionnaire, 6-monthly patient diary and by ‘‘flagging’’ with the UK Office for National Statistics which provided information on mortality, including cause of death. If active TB was reported from any source, further information, including site of infection and supporting evidence for diagnosis (clinical/radiological/microbiological/histopathological), was requested from the rheumatologist. Patient-reported cases of TB were only included in the analysis if later verified by a consultant.
- Baseline characteristics varied in the groups. Analyses examining the influence of ethnicity were performed after adjustment for age, gender and calendar year and after exclusion of patients with missing ethnicity data. Multiple variable regression was performed with additional confounders identified from an *a priori* list of possible confounders, including smoking, diabetes, chronic obstructive pulmonary disease/asthma, prior TB, disease severity (Health Assessment Questionnaire, DAS28 and disease duration as continuous variables), number of prior DMARDs, baseline steroid use, and methotrexate use (as a time varying covariate). Authors state they identified true confounders by sequentially including each confounder in the regression model, and including in the multiple variable regression those confounders that individually changed the estimation after adjustment by more than 10%.
- Assessors were not blinded.

- Comparison patients also contributed person-years from their registration date until their most recent completed consultant follow-up or death, whichever came sooner. Patients in the comparison cohort who switched to an anti-TNF drug contributed person-years to the comparison cohort up to the date the anti-TNF drug was started and subsequent follow-up to the anti-TNF cohort. Conversely, patients initially registered in the anti-TNF cohort could not subsequently contribute person-years to the comparison cohort after stopping anti-TNF therapy.
- Sensitivity analyses were conducted excluding time after the first diagnosis of TB, and restricting analyses to the first anti-TNF drug. Between-drug comparisons led to a statistically significantly increased rate of TB for both monoclonal antibodies compared with ETA, using the ''most recent drug'' model. Seven cases of TB occurred after treatment with a second or third anti-TNF drug. Of these, two occurred with ADA, one with ETA, three after discontinuing ADA and one after discontinuing ETA. When sensitivity analyses were performed excluding time periods following switching the between-drug adjusted IRRs were largely unchanged.

Observational Studies of Tuberculosis in RA Patients Treated with IFX, ADA and ETN (Dixon 10)

Drug (N)	Cases	Rate TB	IRR (Compared To ETN)
ADA (3,504)	11	144/100,000	3.1 (95% CI 1.0 to 9.5)
IFX (3259)	11	136/100,000	4.2 (95% CI 1.4 to 12.4)
ETN (3913)	5	39/100,000	Reference Agent

Dixon BRIT infection ra REGISTRY 06 and 07 FINAL

AUTHOR YR: Dixon 07

Citation: Dixon WG, Symmons DP, Lunt M, Watson KD, Hyrich KL, Silman AJ. Serious infection following anti-tumor necrosis factor alpha therapy in patients with rheumatoid arthritis: lessons from interpreting data from observational studies. Arthritis Rheum2007 Sep;56(9):2896-904. PMID: 17763441

Study Type: Registry Cohort (the British Society for Rheumatology Biologics Register[BSRBR]), Serious Infection, Mortality

Manufacture Involvement: DPS and KLH are principal investigators on the BSRBR. BSR receives restricted income from UK pharmaceutical companies, presently Abbott Laboratories, Amgen, Schering Plough and Wyeth Pharmaceuticals. This income finances a wholly separate contract between the BSR and the University of Manchester which provides and runs the BSRBR data collection, management and analysis services.

Abstract

Objective. In a recent observational study, we found that the risk of serious infection following anti– tumor necrosis factor alpha (anti-TNFi) therapy in patients with rheumatoid arthritis (RA) was not importantly increased compared with the background risk in routinely treated RA patients with similar disease severity (Dixon 06 –see below). Observational data sets are, however, subject to a number of important biases related to selection factors for the timing of starting and stopping therapy. Infection risk is also likely to vary with duration of therapy. This study was undertaken to examine the influences of these biases and of the method of analysis on the risk of infection.
Methods. We compared the risk of serious infection in 8,659 patients treated with anti-TNF_ with that in 2,170 patients treated with traditional disease modifying antirheumatic drugs (DMARDs) recruited to the British Society for Rheumatology Biologics Register. We applied a number of statistical models in which we varied the length of the followup period by using different definitions of the date of discontinuation of treatment and different lag periods of risk following drug cessation.
Results. When the at-risk period was defined as "receiving treatment", the adjusted incidence rate ratio comparing patients receiving anti-TNF therapy with patients receiving DMARD therapy was 1.22 (95% confidence interval [95% CI] 0.88–1.69). Limiting followup to the first 90 days, however, revealed an adjusted incidence rate ratio of 4.6 (95% CI 1.8–11.9). Rates of infection were increased in the 90 days immediately following drug discontinuation and beyond, explained by selection factors for drug discontinuation.
Conclusion. These findings show that overall, the way in which UK rheumatologists select patients for starting and discontinuing anti-TNF therapy explains our previous finding of no increase in risk. However, there may be important increases in true risk, notably early in the course of treatment, that would become more evident depending on the definition of at-risk period. [See IRR table below.]

Reviewer Comments

- Agents of Interest: Adalimumab, etanercept, infliximab in RA
- Large national prospective registry to study long-term safety of exposure to biologic agents in patients with RA.
- Patients were recruited to the ETA and INF cohorts from 2001 onwards. Recruitment to the ADA cohort started later because of its more recent launch date. Recruitment targets of 4000 patients for the ETA cohort were met in 2005, for INF in 2007 and for ADA in 2008.
- All patients are followed up using 3 parallel methods. First, consultants are sent a questionnaire every 6 months, requesting details of all changes in therapy and all adverse events that have occurred in that period. Second, patients are sent a 6-month diary in which to document all hospital admissions, new medications, and new hospital referrals. Third, all patients are flagged with the UK General Register Office, which provides the BSRBR with information on deaths.
- Serious infections, reported from any of these 3 sources, are defined as those that led to death or hospitalization or required intravenous antibiotics.
- There were 10,755 patients included in the analysis (8,659 treated with anti-TNF alpha and 2,170 treated with DMARDs only). Seventy four patients switched from the DMARD cohort to the anti-TNFcohort and were included in both groups. The DMARD cohort included proportionally more men, and patients in this cohort were older and, as expected, had less severe disease.
- Risk of infection while receiving therapy. There were 1,089 serious infections in total: 114 in the comparison cohort and 975 in the anti-TNF cohort, 737 occurring while the patients were receiving therapy. Using the "receiving treatment" model of analysis, the crude rate of serious infection was 39.2 per 1,000 person-years in the DMARD cohort and 55.5 per 1,000 person-years in the anti-TNF cohort, ranging from 50.4 to 63.0 events per 1,000 person-years in the 3 anti- TNF drug cohorts. Baseline characteristics of the anti-TNFcohort were compared with those of the DMARD cohort, using Wilcoxon's rank sum tests for continuous variables and chi-square tests for categorical outcomes.
- Rates of serious infection per 1,000 person-years were calculated using a large series of assumptions relating to the issues of starting and stopping drugs and duration of therapy. Assessors were not blinded. Patients in the comparison cohort who switched to an anti-TNF drug contributed person-years to the comparison cohort up to the date the anti-TNF drug was started and subsequent follow-up to the anti-TNF cohort. Conversely, patients initially registered in the anti-TNF cohort could not subsequently contribute person-years to the comparison cohort after stopping anti-TNF therapy.
- Three models of serious infection rates in patients receiving IFX, ADA and ETN appear in the table below with IFX demonstrating a statistically significant increased IRR in model C. Plausible models of risk over time include increased risk of an adverse event on initial exposure, constant risk with ongoing drug exposure, or increasing risk with cumulative exposure to the drug. The pattern of risk is likely to differ according to the adverse event considered. An infusion reaction may be more likely to occur early in the course of therapy, whereas a malignancy may be related to cumulative drug exposure. For any given adverse event, the overall risk pattern may

be a composite of multiple patterns. For example in patients who have a serious infection while receiving anti-TNF therapy, clinicians may decide whether treatment should be resumed, based on their opinion of further infection risk. Thus, there could be a "healthy drug continuers" or "depletion of susceptibles" effect, and restricting analysis to those who continue the drug selectively retains those at the lowest risk. The authors state that although it is important to be specific about aspects such as time period of interest during therapy, the choice of stop date, selection factors for both starting and discontinuing therapy may seriously compromise interpretation in registry studies.

Incidence Rate Ratios (IRR) (Comparator is Traditional DMARDs Group) with 3 Models

Category	IFX	ADA	ETN
Infections per patient years in models A,B,C	317/5,034, 354/5,226 405/5,874	112/2,221 127/2,323 138/2,548	308/6,021 361/6,274 432/ 6,998
Adjusted IRR (95% CI) model A (receiving Rx)	1.28 (95% CI 0.91 to 1.81)	1.17 (95% CI 0.81 to 1.69)	1.15 (95% CI 0.82 to 1.61)
Adjusted IRR (95% CI) model B (receiving Rx plus 90 day window lag)	1.35 (95% CI 0.97 to 1.89)	1.24 (95% CI 0.87 to 1.78)	1.26 (95% CI 0.91 to 1.74)
Adjusted IRR (95% CI) model C (ever received Rx)	1.41 (95% CI 1.02 to 1.97)	1.25 (95% CI 0.88 to 1.77)	1.34 (95% CI 0.97 to 1.86)

Abstract Dixon 06: Updated Above

Objective. To determine whether the rate of serious infection is higher in anti–tumor necrosis factor (anti-TNF)–treated rheumatoid arthritis (RA) patients compared with RA patients treated with traditional disease-modifying antirheumatic drugs (DMARDs).

Methods. This was a national prospective observational study of 7,664 anti-TNF–treated and 1,354 DMARD-treated patients with severe RA from the British Society for Rheumatology Biologics Register. All serious infections, stratified by site and organism, were included in the analysis.

Results. Between December 2001 and September 2005, there were 525 serious infections in the anti-TNF– treated cohort and 56 in the comparison cohort (9,868 and 1,352 person-years of followup, respectively). The incidence rate ratio (IRR), adjusted for baseline risk, for the anti-TNF–treated cohort compared with the comparison cohort was 1.03 (95% confidence interval 0.68–1.57). However, the frequency of serious skin and soft tissue infections was increased in anti-TNF–treated patients, with an adjusted IRR of 4.28 (95% confidence interval 1.06–17.17). There was no difference in infection risk between the 3 main anti-TNF drugs. Nineteen serious bacterial intracellular infections occurred, exclusively in patients in the anti-TNF–treated cohort.

Conclusion. In patients with active RA, anti-TNF therapy was not associated with increased risk of overall serious infection compared with DMARD treatment, after adjustment for baseline risk. In contrast, the rate of serious skin and soft tissue infections was increased, suggesting an important physiologic role of TNF in host defense in the skin and soft tissues beyond that in other tissues.

EMERY GOL RCT 09 FINAL

AUTHOR YR: Emery 09

Citation: Emery P, Fleischmann RM, Moreland LW, Hsia EC, Strusberg I, Durez P, Nash P, Amante EJ, Churchill M, Park W, Pons-Estel BA, Doyle MK, Visvanathan S, Xu W, Rahman MU. Golimumab, a human anti-tumor necrosis factor alpha monoclonal antibody, injected subcutaneously every four weeks in methotrexate-naive patients with active rheumatoid arthritis: twenty-four-week results of a phase III, multicenter, randomized, double-blind, placebo-controlled study of golimumab before methotrexate as first-line therapy for early-onset rheumatoid arthritis. Arthritis Rheum2009 Aug;60(8):2272-83. PMID: 19644849

Study Type: RCT

Agents of Interest: Golimumab in Rheumatoid Arthritis

Safety Outcomes: Reported adverse events

Manufacture Involvement: Supported by Centocor Research and Development (a subsidiary of Johnson & Johnson) and Schering-Plough Research Institute. Data were collected by the investigators and entered into a Centocor database. Centocor statisticians and programmers conducted the analyses, and members of the steering committee, with the assistance of a medical writer, prepared the manuscript.

RELEVANT INFORMATION FROM PUBLISHED ABSTRACT AND TEXT

Objective. To assess the safety and efficacy of golimumab in methotrexate (MTX)–naive patients with active rheumatoid arthritis (RA).

Methods. MTX-naive patients with RA (n _ 637) were randomized to receive placebo plus MTX (group 1), golimumab 100 mg plus placebo (group 2), golimumab 50 mg plus MTX (group 3), or golimumab 100 mg plus MTX (group 4). Subcutaneous injections of golimumab or placebo were administered every 4 weeks. The dosage of MTX/placebo capsules started at 10 mg/week and escalated to 20 mg/week. The primary end point, the proportion of patients meeting the American College of Rheumatology 50% improvement criteria (achieving an ACR50 response) at week 24, required significant differences between groups 3 and 4 combined (combined group) versus group 1 and significant differences in a pairwise comparison (group 3 or group 4 versus group 1).

Results. Serious adverse events occurred in 7%, 3%, 6%, and 6% of patients in groups 1, 2, 3, and 4, respectively.

- Serious infections (percent) were 3 (1.9), 2 (1.3) 2 (1.3) 7 (4.4) in groups 1,2,3,4 respectively.
- Discontinuations of study agent due to adverse events (percent) in subcutaneous study agent occurred in 2 (1.3) 1 (0.6) 6 (3.8) 7 (4.4) in groups 1,2,3,4 respectively.
- Numbers of malignancies, serious adverse event totals were small and similar in the groups.

Conclusion. The incidence of serious adverse events and serious infections was low and similar across treatment groups, with the exception of a seemingly higher incidence of serious infections with golimumab 100 mg plus MTX (4.4%) versus the other treatments (1.3–1.9%). It is noteworthy that the relatively small number of patients evaluated and the lack of power to detect treatment group differences in individual safety events preclude drawing definitive conclusions regarding these safety findings.

Reviewer Comments

- All subjects included in safety analysis
- Interactive voice system for randomization
- Reported safety outcomes
- Underpowered for detecting safety differences if they existed.

FAVALLI 09 infection registry Italy 3 drugs_FINAL

AUTHOR YR: Favalli 09

Citation: Favalli EG, Desiati F, Atzeni F, Sarzi-Puttini P, Caporali R, Pallavicini FB, Gorla R, Filippini M, Marchesoni A. Serious infections during anti-TNFalpha treatment in rheumatoid arthritis patients. Autoimmun Rev2009 Jan;8(3):266-73.PMID: 19022409

Study Type: Retrospective Cohort Study from: Italian Lombardy Rheumatology Network (LORHEN) Registry Infection

Manufacture Involvement: No information

Abstract

The objective was to estimate the incidence of serious infections in the patients treated with anti-TNFα agents for rheumatoid arthritis (RA) recorded in the Lombardy Rheumatology Network (LORHEN) registry. The study inclusion criteria were met by 1064 of the 1114 patients with long-standing RA, 519 treated with infliximab, 303 with adalimumab, and 242 with etanercept; their mean age was 55.8 years and the mean duration of RA 9.4 years.

Seventy-three patients (6.9%) experienced a total of 74 serious infections, an incidence rate for all treatment courses of 35.9 per 1000 patient-years (95% confidence interval [95% CI] 27.66– 44.13). Most were lower respiratory tract (34.2%) or skin and soft tissue infections (20.5%). Of the 1064 patients, the 790 treated with anti-TNFα after March 2002 underwent screening tests for LTBI; five patients developed active tuberculosis. Three patients died of septic shock. The type of anti-TNFα agent did not seem to affect the incidence or site of the infections.

Both univariate and multivariate analyses identified age at the start of anti-TNFα treatment (p=0.008), baseline erythrocyte sedimentation rate ([ESR] p=0.014), and the concomitant use of corticosteroids (p=0.029) as significant predictors of infections.

There was no statistically significant difference in risk between the anti-TNFα agents.

Reviewer Comments

- Infectious adverse events are common in patients with rheumatic diseases and it has been reported that the rate of infections in the RA population is nearly twice as high as that observed in matched non-RA controls [8] Doran MF, Crowson CS, Pond GR, O'Fallon WM, Gabriel SE. Frequency of infection in patients with rheumatoid arthritis compared with controls. A population-based study. Arthritis Rheum 2002;9:2287–93.
- LORHEN is a regional population-based registry that was established with the aim of examining the efficacy and safety of TNFα blockers in the everyday treatment of RA. LORHEN contains a cohort of all of the RA patients treated with anti- TNFα agents in four major Rheumatology Units in Lombardy (Italy) since 1999.
- This analysis covers the first 36 months from the date of the first administered dose (median follow-up: 23.22 months for etanercept, 21.26 months for adalimumab, 29.88 months for infliximab, and 24.21 months for the patients as a whole). Total exposure to anti-TNF treatment was 2033.62 person/ years (430.09 for etanercept, 524.00 for adalimumab, and 1079.53 for infliximab).
- The patients were considered at risk of serious infection from the date of the start of the first anti-TNFα drug (baseline) to the date of the first occurrence of the event or the last date of follow-up within 36 months, regardless of any treatment discontinuation or switch.
- Fifty patients were lost to follow-up during the first six months of treatment, and so 1064 patients (83.2% women) were considered for the safety analysis.
- Recorded infections were categorised as “serious” (defined as life-threatening, requiring hospitalization and/or intravenous antibiotic therapy, or leading to significant disability/ incapacity or a comparable significant risk)

RESULTS	**Infliximab**	**Adalimumab**	**Etanercept**
	N= 519 (48.8%)	N=303 (28.5%)	N=242 (22.7%)
	Incidence rate (IR): number of events per 1000 patient-years		
Any serious infection	38.91 (95% CI 27.14 to 50.67)	38.17 (95% CI 21.44 to 54.90)	25.58 (95% CI 10.46 to 40.69)

FLEISCHMANN 09_SMOLEN 09_KEYSTONE 08a_CZP

AUTHORs YR: **FLEISCHMANN 09, SMOLEN 09, KEYSTONE 08a**

Citations: Fleischmann R, Vencovsky J, van Vollenhoven RF, Borenstein D, Box J, Coteur G, Goel N, Brezinschek HP, Innes A, Strand V. Efficacy and safety of certolizumab pegol monotherapy every 4 weeks in patients with rheumatoid arthritis failing previous disease-modifying antirheumatic therapy: the FAST4WARD study. Ann Rheum Dis. 2009 Jun;68(6):805-11. Epub 2008 Nov 17. PubMed PMID: 19015206; PubMed Central PMCID: PMC2674555.

Smolen J, Landewé RB, Mease P, Brzezicki J, Mason D, Luijtens K, van Vollenhoven RF, Kavanaugh A, Schiff M, Burmester GR, Strand V, Vencovsky J, van der Heijde D. Efficacy and safety of certolizumab pegol plus methotrexate in active rheumatoid arthritis: the RAPID 2 study. A randomised controlled trial. Ann Rheum Dis. 2009 Jun;68(6):797-804. Epub 2008 Nov 17. PubMed PMID: 19015207.

Keystone E, Heijde D, Mason D Jr, Landewé R, Vollenhoven RV, Combe B, Emery P, Strand V, Mease P, Desai C, Pavelka K. Certolizumab pegol plus methotrexate is significantly more effective than placebo plus methotrexate in active rheumatoid arthritis: findings of a fifty-two-week, phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Arthritis Rheum. 2008 Nov;58(11):3319-29. Erratum in: Arthritis Rheum. 2009 May;60(5):1249. PubMed PMID: 18975346.

Study Type: RCTs

Manufacture Involvement
Fleischmann 09: UCB contributed to the design, conduct and reporting of the study.

Smolen 09: The RAPID 2 study was fully funded by UCB, Inc. 2 authors were employees of UCB.

Keystone 08a: “Supported by UCB Inc.”

Abstracts not included here.

Reviewer Comments
Based on 3 relevant trials totalling 1785 patients from searches up to 11/15/10: Trials provide weak signals of increased serious infection including tuberculosis, increased injection-site reactions, malignancy and increased withdrawal due to adverse events in patients taking CZP compared to placebo. The trials were underpowered to detect statistically significant differerences.

Results

Reference	Population and N	Intervention	Safety Findings	Reviewer Comments
Fleischmann 09 FAST4WARD	Fleischmann 09 Months:6 N:220 Age: ~54 Duration: ~9.5 years Incomplete responders to DMARDs % on steroids: 59/56 % on NSAIDs:NR HAQ score:1.6/1.4	Placebo + MTX N=109 CZP 400mg 4 weekly N-111	PNEUMONIA: 1 TB:0 LYMPHOMA:0 MALIGNANCY:0 DEMYELINATING:0 DEATH: 0 WITHDRAWAL ADVERSE: 2 (1.8%) SERIOUS INFECTION: 0 OPPORTUNISTIC INFECTION: 0 REACTIONS AT INJECTION SITE: NR SERIOUS AEs: 2.8% PNEUMONIA: 1 TB:0 LYMPHOMA:0 MALIGNANCY:0 DEMYELINATING:0 DEATH: 0 WITHDRAWAL ADVERSE: 5 (4.5%) SERIOUS INFECTION: 2 (4 cases per 100 pt years) OPPORTUNISTIC INFECTION:0 REACTIONS AT INJECTION SITE:4.5% SERIOUS AEs: 7.2%	• No P values

Keystone 08a RAPID 1	Keystone 2008(RAPID1) [25]/ Strand ACR 2007 946[26] Months:12 N:982 Age: ~52 Duration: ~6 years Incomplete responders to MTX % on steroids: NR % on NSAIDs: NR HAQ score:~1.7	Placebo + MTX N=199	PNEUMONIA: NR TB:0 INFUSION RXN:NR LYMPHOMA:0 MALIGNANCY:1 (1.1 per 100 patient-years) DEMYELINATING:NR DEATH: 1 WITHDRAWAL ADVERSE: (3.3) SERIOUS INFECTION: (2.2) REACTIONS AT INJECTION SITE: 0 SERIOUS AEs: 12%	Generation Sequence: No details Concealment Alloc: No details Blinding: Yes for assessor reading radiographs; No other details N Safety Placebo + MTX: 190/199 N Safety CZP + MTX: 781/783
		CZP 200mg to 400mg 2 weekly sc. +MTX N=783	PNEUMONIA: NR TB (0.85) INFUSION RXN:NR LYMPHOMA:1 MALIGNANCY:11 (2.3 per 100 patient-years) DEMYELINATING:NR DEATH: 7 WITHDRAWAL ADVERSE: (6.3) SERIOUS INFECTION:(6.3) REACTIONS AT INJECTION SITE:(0.8 and 2.3%) SERIOUS AEs: 15%	Potential weak signal of increased malignancy, serious infection, withdrawal due to adverse events.
Smolen 09 RAPID 2	Smolen EULAR 2009(RAPID2)[27]/ Landewe ACR 2009[28]/ Strand Months:6 N:619 Age: ~52 Duration: ~6 years Incomplete responders to MTX % on steroids: 59 % on NSAIDs: NR HAQ score:1.6	Placebo + MTX N=127	PNEUMONIA: NR TB:0 INFUSION RXN:NR LYMPHOMA:0 MALIGNANCY:1 DEMYELINATING:NR DEATH: 1 WITHDRAWAL ADVERSE: 2 (1.6) SERIOUS INFECTION: 0 REACTIONS AT INJECTION SITE: 0 SERIOUS AEs: 3.2%	Generation Sequence: No details Concealment Alloc: No details Blinding: No details N Safety Placebo + MTX: 125/127 N Safety CZP + MTX: 492/492
		CZP 200mg 2 weekly sc. + placebo; N=246 CZP 400mg 2 weekly sc. + placebo; N=246	PNEUMONIA: NR TB:5 INFUSION RXN:NR LYMPHOMA:1 MALIGNANCY:2 DEMYELINATING:NR DEATH: 2 WITHDRAWAL ADVERSE: 15(3.45) SERIOUS INFECTION:14 (2.2) REACTIONS AT INJECTION SITE:8 (1.6) SERIOUS AEs: 7.3%	Potential weak signal of serious infections including tuberculosis, withdrawal due to adverse events.

Reviewer Comments

- Search: NLM, Cochrane, Embase. Following the search, a total of three full papers were included in the evidence base, one phase II trial and two phase III trials. The search on PubMed was updated on June 1st, 2009.
- Delfini search detected one additional RCT (Smolen 09).
- Underpowered to reliably demonstrate safety differences in groups if one existed.

GALLOWAY 10_Registry_British_Infection_3Agents_FINAL

AUTHOR YR: Galloway 10

Citation: Galloway JB, Hyrich KL, Mercer LK, Dixon WG, Fu B, Ustianowski AP, Watson KD, Lunt M; BSRBR Control Centre Consortium, Symmons DP; on behalf of the British Society for Rheumatology Biologics Register. Anti-TNF therapy is associated with an increased risk of serious infections in patients with rheumatoid arthritis especially in the first 6 months of treatment: updated results from the British Society for Rheumatology Biologics Register with special emphasis on risks in the elderly. Rheumatology (Oxford). 2010 Jul 31. [Epub ahead of print] PubMed PMID: 20675706.

Study Type: Registry Cohort

Manufacture Involvement: The registry receives financial support from a variety of manufacturers; however, there is no other manufacturer involvement.

Abstract

Objectives

To evaluate the risk of serious infections (SIs) in patients with RA treated with anti-TNF therapy with emphasis on the risk across different ages.

Methods

Using data from the British Society for Rheumatology Biologics Register, a prospective observational study, we compared the risk of SI between 11,798 anti-TNF-treated patients and 3,598 non-biologic DMARD (non-biologic DMARD)-treated patients.

Results

A total of 1808 patients had at least one SI (anti-TNF: 1512; non-biologic DMARD: 296). Incidence rates were: anti-TNF 42/1000 patient-years of follow-up (95% CI 40, 44) and non-biologic DMARD 32/1000 patient-years of follow-up (95% CI 28, 36). The adjusted hazard ratio (adjHR) for SI in the anti-TNF cohort was 1.2 (95% CI 1.1, 1.5). The risk did not differ significantly between the three agents adalimumab, etanercept and infliximab. The risk was highest during the first 6 months of therapy [adjHR 1.8 (95% CI 1.3, 2.6)]. Although increasing age was an independent risk factor for SI in both cohorts, there was no difference in relative risk of infection in patients on anti-TNF therapy in the older population. There was no difference in hospital stay for SI between cohorts. Mortality within 30 days of SI was 50% lower in the anti-TNF cohort [odds ratio 0.5 (95% CI 0.3, 0.8)]. Conclusions. These data add to currently available evidence suggesting that anti-TNF therapy is associated with a small but significant overall risk of SI. This must be balanced against the risks associated with poor disease control or alternative treatments.

Reviewer Comments

- Agents of Interest: Adalimumab, etanercept, infliximab in RA
- Large national prospective registry to study long-term safety of exposure to biologic agents in patients with RA.
- Assumably a voluntary registry as, in 2001 it was “recommended” that patients “should be registered.”
- Authors state that they estimate that the registry includes over 80% of anti-TNF treated patients; however, they provide no details of how this estimate was made.
- Difference in length of time data between agents evaluated. Patients were recruited to etanercept (ETN) and infliximab (INF) cohorts from 2001 onwards; recruitment to adalimumab (ADA) cohort began in 2003.
- Comparison cohort of biologic-naïve patients with active RA were recruited in parallel.
- Difference in location of patients and care centers between study and comparison group. Study group was recruited across the whole of the United Kingdom (UK) in over 250 hospitals. Controls were recruited from 29 centers. However, those centers were distributed across the UK and included a mix of secondary and tiertiary care rheumatology units in both urban and rural settings and in affluent and deprived areas.
- Data was collected via questionnaires to care providers and patients and via death registries. Serious infections (Sis) were defined as those requiring i.v. antibiotics or hospitalization, or those resulting in death. This analysis was confined to cases that were reported or verified by the patient’s rheumatologist. Thus, patient-reported SIs were only included in the analysis if later verified by a consultant. Events were ascribed to the anti-TNF agent if they occurred while the patient was receiving anti-TNF therapy or within 90 days of the first missed dose. Events were attributed to the most recent drug in patients who switched anti-TNF therapy. Patients were censored from this analysis after their first episode of SI.
- 3366 (22%) of patients switched biologics during the follow-up period.
- Disease activity was higher in the anti-TNF cohort.
- Authors state characteristics were similar across the three anti-TNF agents at baseline.
- Missing baseline data were filled in using multiple imputations. Authors do not report the amount of missing data.
- Baseline steroid exposure was different between the study cohort and comparison cohort, rising with increasing age with 18% of non-biologic DMARD cohort and 40% of anti-TNF cohort aged <55 years receiving steroid at baseline, compared with 36% of the non-biologic DMARD cohort and 55% of the anti-TNF cohort aged > 75 years.
- The highest crude SI rate was seen with INF [46/1000 (95% CI 42 to 50)], followed by ADA [43/1000 (95% CI 39 to 47)] and ETN [38/1000 (95% CI 35 to 42)]. However, in the adjusted analysis, there was no significant difference in SI rates between the three anti-TNF agents. The analysis was also performed excluding patients who switched biologic (censoring them at the time of first switch):

adjHR 1.2 (95% CI 1.0 to 1.4).

- Authors point out that, "Patients who commence and respond to anti-TNF are likely to require less steroids during their follow-up period (and the converse may be true with the non-biologic DMARD cohort). If this is the case, our adjusted model may be underestimating the effect of anti-TNF."
- Authors point out that presenting a single estimate for risk of SI is misleading as the risk is not consistent over time. This may be due to patients being taken off an anti-TNF agent when experiencing an outcome, with the end result that the remaining pool contains patients at reduced risk.
- Authors found no significant difference in risk between the three agents for overall SIs, either in first 6 months or overall.
- The risk did not differ significantly between the three agents: adalimumab, etanercept and infliximab. Rate/1000 patient years was 32 (95% CI 28 to 36) for non-biological DMARDs, 38 (95% CI 35 to 42) for ETN, 46 (95% CI 42 to 50) for IFX and 43 (95% CI 39 to 47) for ADA. The risk was highest during the first 6 months of therapy [adjHR 1.8 (95% CI 1.3 to 2.6)].

Risk of Serious Infections in RA Patients Receiving ADA or IFX

SOURCE	COMPARATORS	OUTCOMES	REVIEWER COMMENTS
Galloway 10 British Society for Rheumatology Biologics Register (BSRBR)	 IFX ADA ETN Non-biologic DMARDs	INCIDENCE RATES PER 1000 PATIENT-YRS 46/1,000 (95% CI 42 to 50) 43/1,000 (95% CI 39 to 47) 38/1,000 (95% CI 35 to 42) 32/1000 (95% CI 28 to 36)	• 11,798 anti-TNF-treated RA patients • 3,598 patients treated with traditional DMARDs • Largest registry study to date

GARTLEHNER 06 meta IFX ETN FINAL

AUTHOR YR: Gartlehner 06

Citation: Gartlehner G, Hansen RA, Jonas BL, Thieda P, Lohr KN. The comparative efficacy and safety of biologics for the treatment of rheumatoid arthritis: a systematic review and metaanalysis. J Rheumatol. 2006 Dec;33(12):2398-408. Review. PubMed PMID: 17225293.

Study Type: Meta-analysis

Manufacture Involvement: None

Abstract

Objective. Biologics are an important therapeutic option for treating patients with rheumatoid arthritis (RA). However, they are associated with rare but severe adverse events such as serious infections, lymphoma, or chronic heart failure. In addition, dosing regimens and routes of administration differ substantially among biologics. In a systematic review, we assessed the comparative efficacy and safety of biologic agents for RA.

Methods. We searched electronic databases up to May 2006. We limited evidence to controlled trials for efficacy but included observational evidence for safety. Outcomes of interest were clinical response, radiographic progression, and quality of life. Given the paucity of head-to-head evidence, we conducted adjusted, indirect comparisons of placebo-controlled trials.

Results. Twenty-six controlled trials provided efficacy data; 18 additional studies assessed safety. The only evidence directly comparing 2 biologic agents was a nonrandomized, open-label trial that found no differences in effectiveness and safety between etanercept and infliximab. Adjusted indirect comparisons indicate no significant differences in efficacy between anti-tumor necrosis factor (TNF) drugs. However, anti-TNF drugs appear to be more efficacious than anakinra, although not all comparisons reached statistical significance. Because of the lack of sound longterm safety data, evidence is insufficient to draw firm conclusions about the comparative safety of biologics.

Conclusion. Anti-TNF drugs appear to be more efficacious than anakinra but do not differ significantly among each other. Clinical considerations such as comorbidities, route of administration, dosing regimens, and specific side effect profiles may guide the choice of an anti-TNF drug. (First Release Nov 1 2006; J Rheumatol 2006;33:2398–408)

Reviewer Comments

Injection Site Reactions Percent based on data from 26 controlled trials and 18 additional studies; 5 ADA trials; 4 ETN trials

- ADA: 18.98 (95% CI 9.21 to 28.76)
- ETN: 24.67 (95% CI 11.21 to 38.13)
- Superseded by Thaler 09 with 7 RCTs
- Most infusion reactions associated with IFX will be mild (e.g., headache, dizziness, nausea, pruritus, chills, or fever). However, severe acute reactions (e.g., reactions resembling anaphylactic conditions or associated with convulsions) have been reported in 0.5% to 3.7% of patients.

Gomez-Reino 07 TB 3 drugs FINAL

AUTHOR YR: Gomez-Reino 07

Citation: Gomez-Reino JJ, Carmona L, Angel Descalzo M. Risk of tuberculosis in patients treated with tumor necrosis factor antagonists due to incomplete prevention of reactivation of latent infection. Arthritis Rheum2007 Jun 15;57(5):756-61. PMID: 17530674

Agents of Interest: Adalimumab, etanercept , infliximab

Study Type: Registry Cohort

Manufacture Involvement: Authors have received consultancy fees from relevant manufacturers which had no role in the study. The RATIO Registry support includes unrestricted industry grant funding from mixed sources.

Abstract

Objective. To evaluate the causes of new cases of active tuberculosis (ATB) in patients treated with tumor necrosis factor (TNF) antagonists included in the national registry BIOBADASER (Base de Datos de Productos Biologicos de la Sociedad Espanola de Reumatologıa) after the dissemination of recommendations to prevent reactivation of latent tuberculosis infection (LTBI). *Methods.* Incidence rate of ATB per 100,000 patient-years and 95% confidence intervals (95% CIs) were calculated in patients entering BIOBADASER after March 2002 and were stratified by compliance with recommendations (complete or incomplete). ATB rates in BIOBADASER were compared with the background rate and the rate in the rheumatoid arthritis cohort EMECAR (Estudio de la Morbilidad y Expresio´n Clı´nica de la Artritis Reumatoide) not treated with TNF antagonists. In addition, rates of ATB among patients treated with adalimumab, etanercept, and infliximab were estimated and compared only for treatments started after September 2003, when all 3 drugs became fully available.

Results. Following March 2002, a total of 5,198 patients treated with a TNF antagonist were registered in BIOBADASER. Fifteen ATB cases were noted (rate 172 per 100,000 patient-years, 95% CI 103–285). Recommendations were fully followed in 2,655 treatments. The probability of developing ATB was 7 times higher when recommendations were not followed (incidence rate ratio 7.09, 95% CI 1.60–64.69). Two-step tuberculosis skin test for LTBI was the major failure in complying with recommendations. *Conclusion.* New cases of ATB still occur in patients treated with all available TNF antagonists due to lack of compliance with recommendations to prevent reactivation of LTBI. Continuous evaluation of recommendations is required to improve clinical practice.

Notes on the Registry

A detailed description of BIOBADASER has been previously published (3) and is also available at http:// biobadaser.ser.es/. In brief, BIOBADASER is a registry established in February 2000 for active long-term followup of the safety of biologic response modifiers. The registry, which is supported by the SER and funded, in part, by the Spanish Medicines Agency, notes relevant adverse events occurring during and after treatment. BIOBADASER registers patients with rheumatic diseases being treated with any of the currently approved biologic response modifiers, and comprises ~50% of this group of patients in Spain. Patients treated with adalimumab, etanercept, infliximab, anakinra, and rituximab have been included up to the present. The following data are collected systematically: 1) patient data including sex, date of birth, diagnosis, and date of diagnosis; 2) data on treatment, including type, start date, and discontinuation date together with reason for discontinuation, if applicable; and 3) data regarding adverse events, such as type, date of occurrence, outcome, comorbid conditions, and concomitant medication. Starting March 1, 2002, when recommendations regarding prevention of reactivation of LTBI in patients treated with TNF antagonists were issued, results from TST, chest radiograph, and therapy for LTBI were also registered. Incompleteness and agreement of data with patient charts are assessed on site by annual audits of random samples of 10% of all registered patients. A total of 665 clinical records from 82 centers were reviewed in the last audit before the present analysis; 14% of the records contained errors. All errors were corrected accordingly, yielding an expected underreporting of 11% of discontinuations or adverse events. Data on 12 centers that did not report relevant data actively in the last 2 years and that were detected after random monitoring were censored at the last valid data entry. For the purpose of the present analysis, full compliance was considered when 1) INH treatment was started in patients with a TST result >/=5 mm (either the first test or the retest); 2) INH treatment was started in patients with a chest radiograph compatible with past tuberculosis; and 3) TST retest was performed following a negative TST result, or chest radiograph was performed despite negative TST and TST retest results. In all other cases, recommendations were considered to be incompletely followed. Recording of adverse events is done online. An ATB compliance with recommendations (complete or incomplete). ATB rates in BIOBADASER were compared with the rate in Spain (4) and the rate in a previously described cohort of patients with RA not exposed to TNF. In any case, rates were compared to estimate the relative risk of ATB. Incidence rate ratio (IRR) was calculated as IR of the exposed group divided by IR of the nonexposed group. In addition, the rate of ATB among patients treated with adalimumab, etanercept, and infliximab was estimated and compared only for treatments started after September 2003, when all 3 drugs became fully available.

Summary

In a Spanish registry study (Gomez-Reino 07) that evaluated new cases of active tuberculosis after March 2002 in patients treated with tumor necrosis factor (TNF) antagonists included in the national registry BIOBADASER (Base de Datos de Productos Biologicos de la Sociedad Espanola de Reumatologıa) after the dissemination of recommendations to prevent reactivation of latent tuberculosis infection (LTBI), the risk of TB ADA, ETA and INF were:

Agent	Cases/subjects (time to develop)	Incidence per 100 000/yr (95% CI)
INF	IFX: 5/1303 (1.2 to 8.7 mos)	383 (159 to 921)
ADA	ADA: 1/565 (14 mos)	176 (24 to 1245)
ETA	ETN: 2/1740 (<2.5 mos)	114 (28 to 459)

The authors reported an IRR of developing active tuberculosis for the nonadherent group of 5.346 (95% CI 1.29 to 22.21).

GOTTLIEB UST PsA RCT 04 FINAL

AUTHOR YR: Gottlieb 04

Citation: Gottlieb AB, Evans R, Li S, Dooley LT, Guzzo CA, Baker D, Bala M, Marano CW, Menter A. Infliximab induction therapy for patients with severe plaque-type psoriasis: a randomized, double-blind, placebo-controlled trial. J Am Acad Dermatol. 2004 Oct;51(4):534-42. PubMed PMID: 15389187.

Study Type: RCT

Agents of Interest: IFX in psoriasis

Safety Outcomes: Reported adverse events

Manufacture Involvement: Drs Gottlieb and Menter have received research support from and served as consultants for Centocor Inc. Drs Baker, Bala, Dooley, Evans, Guzzo, and Marano, and Ms Li, are employees of Centocor Inc.

RELEVANT INFORMATION FROM PUBLISHED ABSTRACT AND TEXT

Background: Tumor necrosis factor is a key mediator in the pathogenesis of psoriasis. Infliximab is a monoclonal antibody that specifically binds to tumor necrosis factor-a, blocking its biologic activity.

Objective: The purpose of this study was to access the efficacy and safety of infliximab induction therapy for patients with severe plaque psoriasis.

Methods: In this multicenter, double-blind, placebo-controlled trial, 249 patients with severe plaque psoriasis were randomly assigned to receive intravenous infusions of either 3 or 5 mg/kg of infliximab or placebo given at weeks 0, 2, and 6. The primary end point was the proportion of patients who achieved at least 75% improvement in Psoriasis Area and Severity Index score from baseline at week 10. At week 26, patients whose Physician Global Assessment indicated moderate or severe disease were eligible for a single intravenous infusion of their assigned treatment to assess the safety of retreatment after a 20-week, treatment-free interval.

Results: At week 10, 72% of patients treated with infliximab (3 mg/kg) and 88% of patients treated with infliximab (5 mg/kg) achieved a 75% or greater improvement from baseline in Psoriasis Area and Severity Index score compared with 6% of patients treated with placebo (P<.001). Improvement was observed in both infliximab groups as early as 2 weeks. Overall, 63%, 78%, and 79% of patients in the placebo, 3-, and 5-mg/kg groups, respectively, reported one or more adverse events. Conclusions:

Infliximab treatment resulted in a rapid and significant improvement in the signs and symptoms of psoriasis. Infliximab was generally well tolerated. (J Am Acad Dermatol 2004;51:534-42.)

Reviewer Comments

- Outcomes over 30 weeks in 445 patients treated with IFX versus placebo: the percent of patients with severe infections was 0% in the placebo group and 0.5% in the combined IFX groups. P-values were not reported.
- The incidence of infusion reactions through week 30 in patients receiving IFX was 18% in patients receiving 3mg/kg and 22% in patients receiving 5mg/kg compared to 2% in the placebo group.

.

GRIFFITHS RCT USTEK VS ETN 10 FINAL

AUTHOR YR: Griffiths 10

Citation: Griffiths CE, Strober BE, van de Kerkhof P, Ho V, Fidelus-Gort R, Yeilding N, Guzzo C, Xia Y, Zhou B, Li S, Dooley LT, Goldstein NH, Menter A. Comparison of ustekinumab and etanercept for moderate-to-severe psoriasis. N Engl J Med2010 Jan 14;362(2):118-28.

Study Type: RCT

Agents of Interest: ustekInumab, (UST) etanercept(ETN) in psoriasis.

Safety Outcomes: Serious infections, cancer, reactions at injection site, ≥1 Serious adverse event, adverse events leading to withdrawal

Manufacture Involvement: Sponsored by Centocor

ABSTRACT OR STUDY SAFETY DATA

Background
Biologic agents offer a range of new therapeutic options for patients with psoriasis; however, the relative benefit–risk profiles of such therapies are not well known. We compared two biologic agents, ustekinumab (an interleukin-12 and interleukin-23 blocker) and etanercept (an inhibitor of tumor necrosis factor α), for the treatment of psoriasis.

Methods
Investigators randomly assigned 903 patients with moderate-to-severe psoriasis to receive subcutaneous injections of either 45 or 90 mg of ustekinumab (at weeks 0 and 4) or high-dose etanercept (50 mg twice weekly for 12 weeks). 67 sites world wide. The primary end point was the proportion of patients with at least 75% improvement in the psoriasis area-and severity index (PASI) at week 12; a secondary end point was the proportion with cleared or minimal disease on the basis of the physician's global assessment. Assessors were unaware of the treatment assignments. The efficacy and safety of a crossover from etanercept to ustekinumab were evaluated after week 12.

Safety Results
One or more adverse events occurred through week 12 in 66.0% of patients who received 45 mg of ustekinumab and 69.2% of patients who received 90 mg of ustekinumab and in 70.0% who received etanercept; 1.9%, 1.2%, and 1.2%, respectively, had serious adverse events. Safety patterns were similar before and after crossover from etanercept to ustekinumab.

(ClinicalTrials.gov number, NCT00454584.)

Reviewer Comments

- 12 week study, but safety results also at 64 weeks
- Safety was evaluated by assessing adverse events and routine hematologic and laboratory values. Possible major cardiovascular events (cardiovascular death, myocardial infarction, and stroke) were adjudicated by an independent panel of academic cardiologists. In addition, serum samples were evaluated for antibodies to ustekinumab. Adverse events reported at 12 weeks and at 64 weeks.
- Data analysis by Centocor
- Medical writer employed by Centocor
- No details regarding co-interventions or differences in care experiences
- N=903 randomized
    - 209 patients to 45 mg of ustekinumab, 347 patients to 90 mg of ustekinumab, and 347 patients to high-dose etanercept.
- Analyzed
    - 209 patients to 45 mg of ustekinumab, 347 patients to 90 mg of ustekinumab, and 347 patients to high-dose etanercept.
    - 347 crossover to 90 mg before crossover UST; 295 crossover to UST after crossover.
- Randomization: adaptive randomization scheme; no details regarding generation sequence or concealment of allocation.
- Safety data were summarized according to the actual treatment received.
- Inclusion criteria: Patients were eligible for the study if they were adults (≥18 years of age) who had received a diagnosis of plaque psoriasis at least 6 months earlier, were candidates for phototherapy or systemic treatment, had a score on the psoriasis area-and-severity index (PASI) of 12 or higher (on a scale of 0 to 72, with higher scores indicating more severe disease), had a score of at least 3 on the physician's global assessment (on a scale of 0 to 5, with 0 indicating no disease and 5 severe disease), and had involvement of at least 10% of body-surface area at baseline. Additional eligibility criteria were an inadequate response, intolerance, or contraindication to at least one conventional systemic agent for the treatment of psoriasis (i.e., methotrexate, cyclosporine, or psoralen plus ultraviolet A) and no previous treatment with ustekinumab or etanercept.
- Exclusion criteria: nonplaque (i.e., pustular, guttate, or erythrodermic) or drug-induced forms of psoriasis, a recent serious infection or a history of chronic or recurrent infectious disease, or a known malignant condition (with the exception of treated basal-cell or squamous-cell skin cancer or cervical cancer in situ with no evidence of recurrence for ≥5 years). Patients could not have received conventional systemic therapy or phototherapy within 4 weeks before enrollment, topical psoriasis agents within 2 weeks, investigational drugs within 4 weeks or five half-lives, whichever was longer, or biologic agents within 3 months or five half-lives, whichever was longer.
- Blinding: Patients were aware of their treatment assignment, although patients who were randomly assigned to ustekinumab

received double injections (one injection of active treatment and one injection of placebo) to maintain blinding for the dose. All study personnel, except those who dispensed or administered a study agent, remained unaware of the treatment assignments throughout the study. Assessors were unaware of the treatment assignments.

Safety Results

During the first 12 weeks of the trial, the proportions of patients who had at least one adverse event were similar in the etanercept group (70.0%) and both ustekinumab groups (66.0% in the group that received 45 mg of ustekinumab and 69.2% in the group that received 90 mg) and similar proportions of patients discontinued treatment because of adverse events (2.3% of patients in the etanercept group, as compared with 1.9% of those who received 45 mg of usteki numab and 1.2% of those who received 90 mg of ustekinumab). The greatest disparity in adverse events was observed in the proportions of patients who reported injection-site reactions (24.8% of patients who received etanercept as compared with 4.3% of patients who received 45 mg of ustekinumab and 3.7% of patients who received 90 mg of ustekinumab); the majority of these reactions were mild, and no anaphylaxis or serum sickness–like reactions were reported.

Through week 12, serious adverse events occurred in four patients in each treatment group. In the etanercept group, one patient each had upper abdominal pain, bacterial meningitis, nephrolithiasis, and the rotator-cuff syndrome. In the group of patients who received 45 mg of ustekinumab, one patient each had pancreatitis, psychotic disorder, and hypertension with chest pain, and one patient with a family history of breast cancer received a diagnosis of breast cancer at week 7 of the study. In the group of patients who received 90 mg of ustekinumab, one patient each had appendicitis, gastrointestinal infection due to food poisoning, and uvulitis, and one patient was hospitalized twice: initially for urosepsis complicated by acute renal failure, gastritis, peptic-ulcer hemorrhage, nosocomial pneumonia, and chest pain (reported as a myocardial infarction by the investigator but determined not to be a myocardial infarction by adjudication) and subsequently for angina. Infections occurred at similar rates in the three treatment groups (29.1%, 30.6%, and 29.7% in the groups that received etanercept, 45 mg of ustekinumab, and 90 mg of ustekinumab, respectively). Nonmelanoma skin cancers occurred in two patients in the group that received 45 mg of ustekinumab and in one patient in the group that received 90 mg of ustekinumab; all cases occurred in areas of cleared psoriatic plaques. See table below.

Note: actual numbers of serious adverse events was low.

Adverse Events
(All randomized subjects included to before crossover)
Number of patients (%)

Category	Week 0-12			Week 0-64	
	ETN (n=347)	UST 45 mg (n=209)	UST 90 mg (n=347)	Crossover to 90 mg UST (before) (n=347)	Crossover to 90 mg UST (after) (n=295)
Injection Site Reaction	86 (24.8)	9 (4.3)	13 (3.7)	86 (24.8)	5 (1.7)
Adverse event leading to withdrawal of study	8 (2.3)	4 (1.9)	4 (1.2)	11 (3.2)	2 (0.7)
≥1 Serious adverse event	4 (1.2)	4 (1.9)	4 (1.2)	12 (3.5)	10 (3.4)
Infection requiring treatment	34 (9.8)	18 (8.6)	33 (9.5)	56 (16.1)	33 (11.2)
Malignant condition other than nonmelanoma skin cancer†	0	1 (0.5)	0	0	1 (0.3)

†Malignant conditions other than nonmelanoma skin cancer included breast cancer in one patient and an oral neoplasm in one patient in the group of patients who received 45 mg of ustekinumab, chronic lymphocytic leukemia in one patient and mycosis fungoides in one patient in the group of patients who received 90 mg of ustekinumab, and prostate cancer in one patient who received etanercept followed by crossover to 90 mg of ustekinumab.

HETLAND 09_Registry_Danish_General_3Agents_FINAL

AUTHOR YR: Hetland 09

Citation: Hetland ML, Christensen IJ, Tarp U, Dreyer L, Hansen A, Hansen IT, Kollerup G, Linde L, Lindegaard HM, Poulsen UE, Schlemmer A, Jensen DV, Jensen S, Hostenkamp G, Østergaard M; All Departments of Rheumatology in Denmark. Direct comparison of treatment responses, remission rates, and drug adherence in patients with rheumatoid arthritis treated with adalimumab, etanercept, or infliximab: results from eight years of surveillance of clinical practice in the nationwide Danish DANBIO registry. Arthritis Rheum. 2010 Jan;62(1):22-32. PubMed PMID: 20039405.

Study Type: Registry Cohort (Denmark)

Manufacture Involvement: The registry receives financial support from a variety of manufacturers; however, there is no other manufacturer involvement. Authors have received consultancy fees from various manufacturers.

Abstract

OBJECTIVE

To compare tumor necrosis factor alpha inhibitors directly regarding the rates of treatment response, remission, and the drug survival rate in patients with rheumatoid arthritis (RA), and to identify clinical prognostic factors for response.

METHODS

The nationwide DANBIO registry collects data on rheumatology patients receiving routine care. For the present study, we included patients from DANBIO who had RA (n = 2,326) in whom the first biologic treatment was initiated (29% received adalimumab, 22% received etanercept, and 49% received infliximab). Baseline predictors of treatment response were identified. The odds ratios (ORs) for clinical responses and remission and hazard ratios (HRs) for drug withdrawal were calculated, corrected for age, disease duration, the Disease Activity Score in 28 joints (DAS28), seropositivity, concomitant methotrexate and prednisolone, number of previous disease-modifying drugs, center, and functional status (Health Assessment Questionnaire score).

SAFETY RESULTS

At 48 months, the HRs for drug withdrawal were 1.98 for infliximab versus etanercept (95% 1.63-2.40), 1.35 for infliximab versus adalimumab (95% CI 1.15-1.58), and 1.47 for adalimumab versus etanercept (95% CI 1.20-1.80).

CONCLUSION

Older age, low functional status, and concomitant prednisolone treatment were negative predictors of a clinical response and remission. Infliximab had the lowest rates of treatment response, disease remission, and drug adherence, adalimumab had the highest rates of treatment response and disease remission, and etanercept had the longest drug survival rates. These findings were consistent after correction for confounders and sensitivity analyses and across outcome measures and followup times.

Reviewer Comments

- All registry studies are observational studies without control groups and are subject to confounding.
- Agents of Interest: Adalimumab, etanercept, infliximab in RA
- DANBIO registry described as Danish web-based registry since October 2000. It is sponsored by hospital owners and pharmaceutical companies manufacturing products for RA (without their influence). Patients were followed until April 3, 2009 or until they withdrew from treatment, whichever came first.
- Population diagnosed for RA by their treating rheumatologist. All patients had been treated with >/=1 conventional disease-modifying antirheumatic drug (DMARD), but treatment failed to such an extent that therapy with either adalimumab, etanercept, or infliximab was initiated as the first biologic agent. The treatment regimens reflected routine care: concomitant MTX (or other DMARD) and prednisolone were administered according to the decision of the treating rheumatologist. The TNF alpha inhibitors were prescribed in standard doses unless the rheumatologist decided otherwise. The rheumatologist recorded information on the type of drug, start and stop dates (date of first missed dose), reasons for withdrawal, and patient assessment. The patient completed the Danish version of the Health Assessment Questionnaire (HAQ) together with the patient's global and pain assessment, either by touch screen or using paper forms. Patients were registered at least twice yearly.
- No comparison group.
- Various comparisons were undertaken as sensitivity analyses. Authors report that "…results were very robust in a variety of sensitivity analyses."
- Authors state, "However, the possibility cannot be excluded that differences in the timing of clinical assessments may potentially have biased the treatment outcomes, because infliximab-treated patients were often scored on the day of infusion (at trough drug levels), whereas the subcutaneously treated patients were scored independently of the day of injection. It cannot be ruled out that the infliximab dosage was insufficient in some patients, and that higher dosages would have improved the outcome. However, the patients were treated according to standard recommendations, and the dose of infliximab had been increased by 69% compared with the standard dose in the majority of patients who withdrew due to lack of efficacy. Furthermore, the adjusted HR for drug withdrawal was highest for infliximab compared with adalimumab and etanercept, and this ratio was independent of differences in the timing of the clinical assessment."
- No mention of how switching was handled between agents.

Registry Study (Hetland 09) Risk of Withdrawal

Reference	Agents	Outcomes
Hetland 07		RR of Withdrawal
	IFX Compared to ETN	1.98 (95% CI 1.63 to 2.40)
	IFX Compared to ADA	1.35 (95% CI 1.15 to 1.58)
	ADA Compared to ETN	1.47 (95% CI 1.20 to 1.80)

Key findings

The risk for withdrawal, compared to ETN, was 1.98 for IFX (95% CI 1.63 to 2.40), 1.35 for IFX versus ADA (95% CI 1.15 to 1.58), and 1.47 for ADA versus ETN (95% CI 1.20 to 1.80).

JACOBSSON SWEDISH REGISTRY MORTALITY RA 05 FINAL

AUTHOR YR: Jacobsson 05

Citation: Jacobsson LT, Turesson C, Gülfe A, Kapetanovic MC, Petersson IF, Saxne T, Geborek P. Treatment with tumor necrosis factor blockers is associated with a lower incidence of first cardiovascular events in patients with rheumatoid arthritis. J Rheumatol. 2005 Jul;32(7):1213-8. PubMed PMID: 15996054.

Study Type: Registry

Agents of Interest: TNFIs (etanercept, infliximab)) and Mortality in RA

Safety Outcomes: Mortality

Manufacture Involvement: No.

ABSTRACT

Objective. To investigate the risk of cardiovascular disease (CVD) in patients with rheumatoid arthritis (RA) treated with tumor necrosis factor (TNF) inhibitors, compared to a standard RA population.

Methods. Patients were recruited from a regional register, which includes over 90% of patients with RA started on TNF blockers in 1999 or later, and a local community based cohort of RA patients, established in 1997. Of a total of 983 patients in the combined cohort, 531 received treatment with etanercept or infliximab during the study period. The total cohort (n = 983) was linked with national registers for inpatient care and cause of death through December 31, 2001. CVD was defined as the first inpatient care or death from CVD without inpatient care for CVD prior to study entry. First CVD events in those treated versus not treated with TNF blockers were estimated, using age and sex adjusted incidence density computations with treatment and disease severity markers as time dependent covariates.

Results. In the anti-TNF-treated patients, the age-sex adjusted incidence rate of first CVD event was 14.0/1000 person-years at risk (95% CI 5.7–22.4), compared with 35.4/1000 person-years (95% CI 16.5–54.4) in those not treated. Controlling for disability, the age-sex adjusted rate ratio was 0.46 (95% CI 0.25–0.85, p = 0.013) in anti-TNF-treated versus not treated.

Conclusion. These findings suggest that the risk of developing CVD is lower in patients with RA treated with TNF blockers. This is compatible with the hypothesis that inflammation contributes to the development of cardiovascular events. (J Rheumatol 2005;32:1213–8)

Reviewer Comments

- Reported decreased mortality rates in patients receiving anti-TNF therapy compared to patients receiving traditional DMARDs.
- Conflicting evidence in Lunt 10

KEYSTONE GOL RA TRIAL 10 FINAL

AUTHOR YR: Keystone 10

Citation: Keystone E, Genovese MC, Klareskog L, Hsia EC, Hall S, Miranda PC, Pazdur J, Bae SC, Palmer W, Xu S, Rahman MU. Golimumab in patients with active rheumatoid arthritis despite methotrexate therapy: 52-week results of the GO-FORWARD study. Ann Rheum Dis2010 Jun;69(6):1129-35.

Study Type: RCT

Agents of Interest: Golimumab in rheumatoid arthritis.

Safety Outcomes: reported adverse events

Funding: Centocor

ABSTRACT OR STUDY SAFETY DATA

Objective
To evaluate the efficacy and safety of golimumab to 52 weeks in patients with active rheumatoid arthritis despite methotrexate.

Methods
Patients were randomly assigned to receive placebo plus methotrexate (group 1), golimumab 100 mg plus placebo (group 2), golimumab 50 mg plus methotrexate (group 3) and golimumab 100 mg plus methotrexate (group 4). At week 16, patients in groups 1, 2 and 3 who had less than 20% improvement in tender and swollen joints entered early escape. At week 24, patients in group 1 who had not entered early escape crossed over to 50 mg golimumab plus methotrexate.

Results
At week 16, 31%, 27% and 17% of patients in groups 1, 2 and 3, respectively, entered early escape. Patients in group 4 appeared to have an increased risk of serious adverse events and serious infections. The exposure-adjusted rate of adverse events in each of the golimumab groups appeared to be similar to the placebo group. However, patients who received the 100 mg dose of golimumab with or without methotrexate appeared to have greater rates of serious adverse events and serious infections compared with patients who received 50 mg with methotrexate.

Conclusion
The results of various outcome measures showed that the response rates achieved by patients receiving golimumab to 24 weeks were sustained to 52 weeks. The safety profile appeared to be consistent with the known safety profile of tumour necrosis factor inhibitors.

Reviewer Comments

- Complex trial with relatively small numbers (see below) underpowered to reliably demonstrate statistically significant differences in safety outcomes between multiple groups.
- Funded by Centocor
- No details regarding randomization
- No details regarding co-interventions or differences in care experiences
- N=444 randomized
    - 209 patients to 45 mg of ustekinumab, 347 patients to 90 mg of ustekinumab, and 347 patients to high-dose etanercept.
- Analyzed
    - See table below: total is unclear.
- Safety data were summarized according to the actual treatment received.
- Blinding: No details except authors state injections provided in blinded fashion.
- Increased rate of adverse events (serious infection, injection site reaction, malignancy) with GLN compared to MTX; no P-values

Safety Results: Small groups; see table below.

Category	Group 1: placebo+MTX → GLM 50 mg+MTX*		Group 2: GLM 100mg+Placebo		Group 3: GLM 50 mg + MTX		
	Early escape (weeks 16–52)	Crossover (weeks 24–52)	100 mg + placebo only	Early escape (weeks 16–52) 100 mg → 100 mg+MTX	50 mg+MTX only	Early escape (weeks 16–52) 50 mg+ MTX → 100 mg+MTX	Group 4: golimumab 100 mg+MTX
Patients treated with golimumab	41	82	133	36	89	15	89
Patients with one or more serious infections (%)	2 (4.9)	0 (0)	5 (3.8)	3 (8.3)	2 (2.2)	0 (0)	7 (7.9)
Patients with one or more injection-site disorders (%)	1 (2.4)	2 (2.4)	15 (11.3)	2 (5.6)	7 (7.9)	3 (20.0)	8 (9.0)
Patients with one or more malignancies (%)	0 (0)	1 (1.2)	1 (0.8)	0 (0)	1 (1.1)	0 (0)	3 (3.4)

* Only included patients who took at least one dose of GLM.

KREMER 10_KAVANAUGH 09 GLM INFECTION

AUTHOR YR: Kremer 10 and Kavanaugh added to Singh 10 review—see below

Citation: Singh JA, Noorbaloochi S, Singh G. Golimumab for rheumatoid arthritis: a systematic review. J Rheumatol. 2010 Jun;37(6):1096-104. Epub 2010 May 1. Review. PubMed PMID: 20436075.

Study Type: SR and Meta-analysis

Agents of Interest: Golimumbab (GLM) Simponi in RA

Safety Outcomes: serious adverse events, infections, serious infections, lung infections, tuberculosis, cancer, withdrawals due to adverse events and deaths.

Manufacture Involvement: No.

PUBLISHED ABSTRACT WITH RELEVANT SAFETY DATA COCHRANE

Background
Golimumab is a humanized inhibitor of tumor necrosis factor-alpha, recently approved by the Food and Drug Administration (FDA) for the treatment of Rheumatoid arthritis (RA).
Objectives
The objective of this systematic review was to compare the efficacy and safety of golimumab (alone or in combination with DMARDs or biologics) to placebo (alone or in combination with DMARDs or biologics) in randomized or quasi-randomized clinical trials in adults with RA.
Search strategy
An expert librarian searched six databases for any clinical trials of golimumab in RA, including the Cochrane Central Register of Controlled Trials (CENTRAL), OVID MEDLINE, CINAHL, EMBASE, Science Citation Index (Web of Science) and Current Controlled Trials databases.
Selection criteria
Studies were included if they used golimumab in adults with RA, were randomized or quasi-randomized and provided clinical outcomes. Data collection and analysis Two review authors (JS, SN) independently reviewed all titles and abstracts, selected appropriate studies for full review and reviewed the full-text articles for the final selection of included studies. For each study, they independently abstracted study characteristics, safety and efficacy data and performed risk of bias assessment. Disagreements were resolved by consensus. For continuous measures, we calculated mean differences or standardized mean differences and for categorical measures, relative risks. 95%confidence intervals were calculated.
Main results
Four RCTs with 1,231 patients treated with golimumab and 483 patients treated with placebo were included. Of these, 436 were treated with the FDA-approved dose of golimumab 50 mg every four weeks. No significant differences were noted between golimumab and placebo regarding serious adverse events, infections, serious infections, lung infections, tuberculosis, cancer, withdrawals due to adverse events and deaths.

Reviewer Comments

Authors state that randomized controlled trials included in the review are limited in their ability to assess safety. They searched U.S. Food and Drug Administration (FDA) web site for labels and warnings and other similar regulatory agency's web sites to summarize warnings related to golimumab.

- 148 relevant studies, 4 included in review
- Cochrane N=1231
- Search quality: high
- Search dates: 1966 to June Week 3, 2009
- Additional safety searches: FDA web site for warnings and adverse events related to golimumab use on 09/01/2009.
- Inclusion criteria: Studies were included if they used golimumab in adults with RA, were randomized or quasi-randomized and provided clinical outcomes.
- Intervention: golimumab 50 mg and 100 mg every four weeks plus methotrexate verus placebo plus methotrexate.
- Quality assessment
    - The following were assessed: blinding of participant, care provider and outcome assessor in the studies, allocation concealment, random sequence generation, incomplete outcome data, and selective outcome reporting. Each trial was assessed as being at high, low or unclear risk of bias. All studies reported adequate methods of randomization, allocation concealment and blinding.
    - The overall possibility of bias rated as low.
- Heterogeneity: moderately high and statistically significant heterogeneity in the golimumab 50 mg and 100 mg every four weeks plus methotrexate verus placebo plus methotrexate groups with I2 values of 76% and 77% (P-values of 0.005 for each).
- Studies were relatively small and of relatively short duration.
- Golimumab (50mg every 4-weeks) was not associated with statistically significant higher risk of infections, serious infections, tuberculosis, lung infections, cancer or death in Cochrane review.
- Withdrawals due to adverse events not statistically significantly different in groups.

- None of the RCTs had safety as the primary outcome.
- High likelihood of being underpowered to detect differences between groups if they exist.

Additional Information From Delfini Updated Search and Review of Additional Studies

- Keystone 10: Patients who received the 100 mg dose of golimumab with or without methotrexate appeared to have greater rates of serious adverse events and serious infections compared with patients who received 50 mg with methotrexate.
- Kremer 10 reported increased serious adverse events and serious infections with GLM compared to placebo.

Conclusions

- Based on safety data from 2723 patients, there are weak signals of increased serious adverse events and serious infections with GLM compared to placebo and a suggestion of higher rates with 100mg doses. Long-term surveillance studies and RCTs with safety as primary outcome are needed to provide reliable safety data.
- LOE: Inconclusive differences between golimumab and placebo regarding serious adverse events, infections, serious infections, lung infections, tuberculosis, cancer, withdrawals due to adverse events and deaths.

Primary Studies Included in Cochrane Review

Emery P, Fleischmann RM, Moreland LW, Hsia EC, Strusberg I, Durez P, et al. Golimumab, a human anti-tumor necrosis factor alpha monoclonal antibody, injected subcutaneously every four weeks in methotrexate-naive patients with active rheumatoid arthritis: Twenty-four-week results of a phase III, multicenter, randomized, double-blind, placebo-controlled study of golimumab before methotrexate as first-line therapy for early-onset rheumatoid arthritis. *Arthritis Rheum* 2009;**60**(8):2272–83.

Kay J, Matteson EL, Dasgupta B, Nash P, Durez P, Hall S, et al. Golimumab in patients with active rheumatoid arthritis despite treatment with methotrexate: a randomized, double-blind, placebocontrolled, dose-ranging study. *Arthritis Rheum* 2008;**58**:964–75.

Keystone EC, Genovese MC, Klareskog L, Hsia EC, Hall ST, Miranda PC, et al. Golimumab, a human antibody to tumour necrosis factor {alpha} given by monthly subcutaneous injections, in active rheumatoid arthritis despite methotrexate therapy: the GO-FORWARD Study. *Ann Rheum Dis* 2009;**68**:789–96.

Smolen JS, Kay J, Doyle MK, Landewe R, Matteson EL, Wollenhaupt J, et al. Golimumab in patients with active rheumatoid arthritis after treatment with tumour necrosis factor alpha inhibitors (GO-AFTER study): a multicentre, randomised, double-blind, placebo-controlled, phase III trial. *Lancet* 2009;**374**(9685):210–21.

UPDATED SEARCH 11/15/10

Keystone E, Genovese MC, Klareskog L, Hsia EC, Hall S, Miranda PC, Pazdur J, Bae SC, Palmer W, Xu S, Rahman MU. Golimumab in patients with active rheumatoid arthritis despite methotrexate therapy: 52-week results of the GO-FORWARD study. Ann Rheum Dis2010 Jun;69(6):1129-35.

Kremer J, Ritchlin C, Mendelsohn A, Baker D, Kim L, Xu Z, Han J, Taylor P. Golimumab, a new human anti-tumor necrosis factor alpha antibody, administered intravenously in patients with active rheumatoid arthritis: Forty-eight-week efficacy and safety results of a phase III randomized, double-blind, placebo-controlled study. Arthritis Rheum2010 Apr;62(4):917-28.

Kavanaugh A, McInnes I, Mease P, Krueger GG, Gladman D, Gomez-Reino J, Papp K, Zrubek J, Mudivarthy S, Mack M, Visvanathan S, Beutler A. Golimumab, a new human tumor necrosis factor alpha antibody, administered every four weeks as a subcutaneous injection in psoriatic arthritis: Twenty-four-week efficacy and safety results of a randomized, placebo-controlled study. Arthritis Rheum2009 Apr;60(4):976-86.PMID: 19333944

From Cochrane

Golimumbab with MTX to Placebo for Withdrawals Due to Adverse Events

- All four studies provided data from 1231 patients (Emery 2009, Kay 2008, Keystone 2009, Smolen 2009).
- The odds ratio for withdrawals due to adverse events in golimumab-treated RA patients was 0.80 (95% CI 0.26 to 2.42), compared to placebo.
- Authors comment: The safety profile of golimumab was similar to that of methotrexate with regards to number of adverse events, serious adverse events, infections, serious infections and cancer. Withdrawals rates overall and due to adverse events were similar.

Golimumab 100 mg every four weeks + methotrexate versus placebo + methotrexate

- Number and type of adverse effects (AEs) and serious adverse events (SAEs):
- There was no significant difference between the number of adverse events and serious adverse events occurring for golimumab treated patients compared to placebo treated patients with (P= 0.14) and (P=0.9) respectively.

Golimumab 50 mg every two weeks + methotrexate versus placebo + methotrexate

- Number and type of adverse effects (AEs) and serious adverse events (SAEs): There was no significant difference between the number of adverse events and serious adverse events occurring for golimumab treated patients compared to placebo treated patients with (P=0.3) and (P=0.6) respectively.

Delfini Update 11/15/10

Keystone 2010

52 week study: 444 patients. Patients were randomly assigned to receive placebo plus methotrexate (group 1), golimumab 100 mg plus placebo (group 2), golimumab 50 mg plus methotrexate (group 3) and golimumab 100 mg plus methotrexate (group 4). At week 16, patients in groups 1, 2 and 3 who had less than 20% improvement in tender and swollen joints entered early escape. At week 24, patients in group 1 who had not entered early escape crossed over to 50 mg golimumab plus methotrexate. See Keystone 10 above for results.

Kremer 2010

- Phase III, multicenter, randomized, double-blind, placebo-controlled, 48-week study of 643 patients to assess the efficacy and safety of intravenous administration of golimumab (with and without MTX) in patients in whom RA remained active despite treatment with MTX.
- Eligible patients were randomly assigned (1:1:1:1:1), using an interactive voice-response system, to receive blinded intravenous infusions of placebo plus MTX, 2 mg/kg golimumab with or without MTX, or 4 mg/kg golimumab with or without MTX.
- Golimumab and placebo were supplied as sterile liquid (aqueous medium of histidine, sorbitol, polysorbate 80, pH 5.5, with or without golimumab) ready for intravenous infusion. Active and placebo MTX were supplied as matching opaque capsules (microcrystalline cellulose filled with or without MTX; those with MTX were overencapsulated and provided the stable prescreening dose).
- Safety evaluations through week 48 included assessment for adverse events, including infusion site reactions, routine laboratory analyses, and determination of antibodies to golimumab.
- Higher proportions of golimumab-treated patients than placebo plus MTX–treated patients had serious adverse events (63 [10%] of 626 patients and 7 [5%] of 129 patients, respectively)
- Serious infections (23 [4%] of 626 GLM-treated patients and 2 [2%] of 129 placebo patients,) through week 48**.**
- Two cases of TB occurred between week 24 and week 48 in patients who initially tested negative for TB at the time of screening (1 patient each from Argentina and Mexico, and 1 each receiving 4 mg/kg golimumab plus placebo and 4 mg/kg golimumab plus MTX).

Kavanaugh 2009

- 24 week placebo-controlled, double blind trial: 405 patients were randomized in a blinded manner (1:1.3:1.3) by a centralized interactive voice response system (113, 146, 146 patients to placebo, golimumab 50mg + stable dose of MTX, corticosteroids and NSAIDs and golimumab 100mg + stable doses as above.
- Safety evaluations included adverse events, routine laboratory analyses, and the presence of antibodies to golimumab. The incidence of malignancies was determined based on 100 patient-years of followup, with corresponding 95% confidence intervals.
- Similar baseline characteristics.
- All patients included in safety analysis.
- Serious infections in placebo, combined GOL groups: 4% and <1%; serious adverse events: 6% and <1%; injection site reactions: 3% and 3%. Thus there was no signal of increased serious infection rate with GLM compared to placebo.
- Three malignancies were reported, all in the golimumab 100 mg group (2 cases of basal cell carcinoma and 1 case of prostate cancer), representing an incidence of 2.32 (95% CI 0.48 to 6.78) per 100 patient-years versus 0.00 (95% CI 0.00 to 7.13) per 100 patient-years for placebo, with the 95% CI for golimumab fully contained within that for placebo.
- Eight golimumab-treated patients (3%) and 5 placebo treated patients (4%) discontinued the study agent due to adverse events occurring prior to week 24.

KRUEGER_LEONARDI_PAPP UST

AUTHOR YR: Leonardi 08, Papp 08, Krueger 07

Citations

Leonardi CL, Kimball AB, Papp KA, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double blind, placebo-controlled trial (PHOENIX 1). *Lancet*. 2008;371: 1665–1674. 43. PMID: 18486739

Papp KA, Langley RG, Lebwohl M, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double blind, placebo -controlled trial (PHOENIX 2). *Lancet*. 2008;371: 1675–1684. PMID: 18486740

Krueger GG, Langley RG, Leonardi C, et al. A human interleukin-12/23 monoclonal antibody for the treatment of psoriasis. N Engl J Med 2007; 356:580-92. DOI 10.1056/NEJMoa062382. PMID: 17287478

Study Type: RCTs

Agents of Interest: UST

Manufacture Involvement:
Leonardi 08: Centocor employees involved in desigh and conduct of study.
Papp 08: Centocor employees involved in design and conduct of study.
Krugeger 07: Authors recipients of grants from Centocor

Reviewer Comments

- Trials obtained from bibliographies and PubMed search to 11/15/10.
- All trials likely to be underpowered to find statistically significant safety differences in groups if they existed and therefore safety results are inconclusive.
- Similar serious infection, cancer, cardiovascular, adverse event rates leading to withdrawal.
- Centocor funded and was involved in analysis and writing of manuscripts (all trials).
- Reviews (Krulig 10, Scanlon 09), reported similar frequencies of adverse events in ustekinumab and placebo groups; common adverse events reported included nasopharyngitis, upper respiratory tract infection, headache, arthralgia, cough, and injection site reactions.
- The only head to head trial comparing ETN to UST (Griffiths 10) reported higher rate of injection site reactions: 24.8% ETN versus 4.3% of UST 45 mg group and 3.7% of UST 90 mg.
- Inconsistent signals of increased serious infection and withdrawal due to adverse events in the trials.

Results

Reference	Population/N	Intervention	Safety Findings	Reviewer Comments
Leonardi 08 PHOENIX 1	Moderate to severe psoriasis N=766	76 week safety study Placebo UST 45 mg UST 90 mg	• Infection rates ~20% all groups. • Serious infections in placebo group, 45mg UST group, 90mg UST group were 0.5%, 0% and 0.2% respectively. • Cutaneous, non-cutaneous cancer, cardiovascular event rates were similar. • Injection site reactions were 1% or less in all groups. • Similar withdrawal rates in the groups due to adverse events • No cases lymphoma or demyelinating disease.	• Generation Sequence: No details, except used minimization • Concealment Alloc: interactive voice technology • Baseline characteristics similar • Blinding: Yes for Subjects/Investigators; study sponsor was unblinded at week 52 for analysis purposes • All patients included in safety analysis at week 12 • 623 /766 included in safety analysis weeks 12-40 • Centocor funded and was involved in analysis and writing of manuscript
Papp 08 PHOENIX 2	N=1230 Psoriasis	40 week safety study Placebo UST 45 mg UST 90 mg	• Serious infections <2% all groups. • Similar malignancy rates in all groups (8 cutaneous and 2 non-cutaneous) • Injection site reactions were 1% or less in all groups. • No cases TB, lymphoma,	• Generation Sequence: No details, except used minimiation • Concealment Alloc: interactive voice technology • Baseline characteristics similar. • Blinding: Yes for Subjects/Invest/Assessors; study

Reference	Population/N	Intervention	Safety Findings	Reviewer Comments
			demyelinating disease.	sponsor was unblinded at week 52 for analysis purposes • All patients included in safety analysis at week 12 • 623 /766 included in safety analysis weeks 12-40 • Centocor funded and was involved in analysis and writing of manuscript
Krueger 07	Moderate to severe psoriasis N=320	Mean duration of safety f/u: 18-19 weeks Placebo UST 45 mg UST 90 mg	Significant differences were not observed in the rates of patients who had at least one adverse event (P= 0.19), adverse events leading to withdrawal of the study agent (P = 1.00), serious adverse events (P = 0.69), infections (P= .51), or malignant conditions (P=1.00), although the study was not designed or powered to detect small differences in rates of adverse events. • Adverse events leading to discontinuation were 4% of active treatment group, 3% in placebo group (P = 1.00). • Infections occurred in combined UST groups in 43% of patients versus 39% of patients in the placebo group. Serious adverse events, all of which were classified as serious because the patients required hospitalization, were observed in 4% of patients treated with the UST (9 of 252) and 1% of patients in the placebo group (1 of 67, P = 0.69). In the groups that received UST, two patients were hospitalized for infection (one for cellulitis and one for pneumonia). • No obvious association between a higher dose and an increased rate of adverse events or infections. • Serious adverse events (defined as requiring hospitalization) were 4% in treatment group and 1% in placebo group (P = 0.69). • Injection site reactions 2% UST and placebo groups.	• Generation sequence: adapative process • Concealment: no details • Baseline Characteristics: statistically significant differences in groups for sex; otherwise similar • Blinding: no details • 319/320 included in safety analysis • Centocor analyzed the data, and the steering committee and Centocor jointly interpreted the data and contributed to the manuscript

LISTING RABBIT SERIOUS ADV INF IFX ETN REGISTRY 05 FINAL

AUTHOR YR: Listing 05

Citation: Listing J, Strangfeld A, Kary S, Rau R, von Hinueber U, Stoyanova-Scholz M, Gromnica-Ihle E, Antoni C, Herzer P, Kekow J, Schneider M, Zink A. Infections in patients with rheumatoid arthritis treated with biologic agents. Arthritis Rheum2005 Nov;52(11):3403-12. PMID: 16255017

Study Type: Registry Cohort RABBIT, (Rheumatoid Arthritis–Observation of BiologicTherapy), German Biologics Registry

Manufacture Involvement: The study protocol stipulates that treatment decisions are not to be influenced by the principal investigators, the scientific advisory board, or the pharmaceutical companies sponsoring the register. The contract specifies that full responsibility for the conduct of the study, data ownership, and publication rights are in the hands of the principal investigators.

Abstract

Objective. To estimate the incidence rates of serious and nonserious infections in patients with rheumatoid arthritis (RA) who start treatment with a biologic agent, and to compare these rates with those in patients with RA who receive conventional treatment.

Methods. Patients enrolled in the German biologics register between May 2001 and September 2003 were included. Treating rheumatologists assessed adverse events and serious adverse events. All adverse events and serious adverse events experienced within 12 months after study entry were analyzed. Propensity score methods were applied to estimate which part of a rate increase was likely to be attributable to differences in patient characteristics.

Results. Data were available for 512 patients receiving etanercept, 346 patients receiving infliximab, 70 patients receiving anakinra, and 601 control patients treated with disease-modifying antirheumatic drugs. The total number of adverse events per 100 patient years was 22.6 (95% CI 18.7 to 27.2) among patients receiving etanercept, 28.3 (95% CI 23.1 to 34.7) among patients receiving infliximab, and 6.8 (95% CI 5.0 to 9.4) among controls ($P < 0.0001$). Significant differences in the rate of serious adverse events were also observed. For patients receiving etanercept, those receiving infliximab, and controls, the total numbers of serious adverse events per 100 patient-years were 6.4 (95% CI 4.5 to 9.1), 6.2 (95% CI 4.0 to 9.5), and 2.3 (95% CI 1.3 to 3.9), respectively (P =0.0016).

After adjusting for differences in the case patient mix, the relative risks of serious adverse events were 2.2 (95% CI 0.9–5.4) for patients receiving etanercept and 2.1 (95% CI 0.8 to 5.5) for patients receiving infliximab, compared with controls.

Conclusion. Patients treated with biologic agents have a higher a priori risk of infection. However, our data suggest that this risk is increased by treatment with tumor necrosis factor inhibitors.

Reviewer Comments

- In 2001, the German Society of Rheumatology invited all rheumatologists to contribute to a national register in order to investigate the long-term safety, effectiveness, and costs of biologic therapies in RA. The Epidemiology Unit at the German Rheumatism Research Center was charged with maintaining the register, and an advisory board was established by the German Society of Rheumatology.
- The authors presented the first results from the prospective cohort study known as RABBIT, which is the German acronym for rheumatoid arthritis–observation of biologic therapy. Authors investigated the incidence of serious and nonserious infections within the first year of treatment with biologic agents.
- Physicians assessed adverse events and serious adverse events according to accepted guidelines. For reasons of quality assurance, the rheumatologists were provided with the definitions of adverse events and serious adverse events according to International Conference on Harmonisation guideline E2A.
- Between May 1, 2001 and September 1, 2003, a total of 1,529 patients from 109 centers were entered into the RABBIT database. In this population, 601 patients had a change in their conventional DMARD therapy (control group), and 512 patients started treatment with etanercept, 346 started with infliximab, and 70 started with anakinra. Seventy-four percent of these patients completed the 12 months of followup in September 2004. The dropout rate was low: 6.9% for the first 6 months and 11.1% in total. In 15% of the patients, the followup was not yet completed.
- RR of serious infections compared to non-biologic DMARDs was similar for ETN and IFX

Serious Adverse Events Compared to Non-biologic DMARDs	ETN Relative Risk	IFX Relative Risk
Lower respiratory tract infection, total	2.66 (95% CI 0.7 to 11.8)	4.82 (95% CI 1.4 to 20.8)
Bone and joint infections	5.91 (95% CI 0.7 to 50.7)	1.75 (95% CI 0.1 to 28.0)
Bacterial skin and subcutaneous tissue infections	4.14 (95% CI 0.9 to 19.9)	3.51 (95% CI 0.6 to 19.2)
Skin and subcutaneous tissue infection, total	2.95 (95% CI 0.9 to 9.4)	2.63 (95% CI 0.7 to 9.3)
Bacterial skin and subcutaneous tissue infections	4.14 (95% CI 0.9 to 19.9)	3.51 (95% CI 0.6 to 19.2)
Total	2.82 (95% CI 1.4 to 5.9)	2.70 (95% CI 1.3 to 5.9)

LUNT REGISTRY MORTALITY RA 10 FINAL

AUTHOR YR: Lunt 10

Citation: Lunt M, Watson KD, Dixon WG, Symmons DP, Hyrich KL. No evidence of association between anti-TNF treatment and mortality in patients with rheumatoid arthritis: Results from the British Society for Rheumatology Biologics Register. Arthritis Rheum2010 Jul 26. PMID: 20662063

Study Type: Registry

Agents of Interest: TNFIs (etanercept, infliximab and adalimumab) and Mortality in RA

Safety Outcomes: Mortality

Manufacture Involvement: No.

ABSTRACT WITH RELEVANT SAFETY DATA

Objective: To study the association between anti-TNF therapy and mortality in a national cohort of RA patients.
Methods: We prospectively followed 12672 patients starting anti-TNF therapy and 3522 biologic-naive patients receiving DMARDs until 31/07/08 or death, whichever was sooner. Notification and cause of death were received from the UK national death register. Mortality was compared using Cox Proportional Hazards. Inverse Probability of Treatment Weighting (IPTW) was used to adjust for confounding effect of baseline differences between groups, including age, gender, disease severity, disability and comorbidity. Missing baseline data were accounted for using multiple imputation.
Results: Compared to the DMARD cohort, the anti-TNF patients were younger (median 57 vs 61 yrs), had higher disease activity (median DAS28 6.6 vs 5.1) and higher disability (median HAQ 2.1 v 1.6). Patients in the DMARD cohort were more likely to have a history of myocardial infarction (4.8 v 3.0%) and chronic obstructive pulmonary disease (8.1 v 4.8%) but less likely to have had depression (16.5 vs 18.9%). There were 9445 and 50803 person-years of follow-up in the DMARD and anti-TNF cohorts respectively, during which time 204 DMARD and 856 anti-TNF patients died. The weighted mortality hazard ratios in the anti-TNF cohort were: All cause 0.86 (95% CI 0.64, 1.16), Circulatory Disease (HR 0.73 (95% CI 0.44, 1.23), Neoplasm (HR 0.65 (95% CI 0.39, 1.09)) and Respiratory Disease (weighted HR 0.81 (95% CI 0.36, 1.83).

- To 31 July 2008, 12,672 patients with RA were recruited to the anti-TNF cohort (4,420 Etanercept, 4,161 Infliximab, 4,091 Adalimumab). The median age was 57 years and 76% were female.
- Over 50% of patients also had another comorbid condition at baseline, with the most common being hypertension, depression, asthma/COPD and peptic ulcer disease.
- On average, the 3522 patients recruited to the non-biologic DMARD cohort were slightly older and had a higher proportion of males compared to the anti-TNF cohort.
- The underlying causes of death, classified by ICD 10 chapter, were available for 98.4% of the cohort. The leading causes of death were circulatory disease, neoplasm, respiratory disease and musculoskeletal disease, primarily severe RA. Proportionately more people in the DMARD comparison group died of a neoplasm than in the anti-TNF group (32% versus 20%). There was a higher proportion of deaths in the anti-TNF group from diseases of the musculoskeletal system (15% versus 5%), primarily RA. Of note, RA was listed anywhere on the death certificate in only 31% of patients. Other causes of death were equally distributed between the 2 groups.
- After imputing data on missing covariates and adjusting for baseline differences investigators found no overall difference in mortality rates between the anti-TNF and the non-biologic DMARD cohort (weighted HR 0.86 (95% CI 0.64, 1.16).
- A similar pattern of mortality risk was found for each of the three leading causes of death within the cohort: circulatory disease (weighted HR 0.73 (95% CI 0.44, 1.23), neoplasm (weighted HR 0.65 (95% CI 0.39, 1.09)) and respiratory disease (weighted HR 0.81 (95% CI 0.36, 1.83).

Conclusions: Compared to patients treated with standard DMARDs, the addition of anti-TNF therapy was not associated with an increase in mortality.

Note: The findings in this study are in contrast to 2 previous publications on mortality and anti-TNF, one from the BIOBADASER in Spain (Carmona 07) and the second (Jacobsson)from the South Swedish Arthritis Treatment Group (SSATG), both of which found a substantial reduction in mortality in anti-TNF treated patients compared to those receiving standard DMARD therapy. The size of these studies (only 51 deaths in the Swedish study and 20 in the Spanish study), prevented a detailed breakdown of underlying causes of death.

Reviewer Comments

- Patients were participants in the British Society for Rheumatology Biologics Register (BSRBR). The primary aim of the BSRBR is to assess the long-term safety of these agents in patients with RA, with a goal recruitment of at least 4000 patients starting each of the three therapies. It reached this target for etanercept in May 2005, for infliximab in 2007 and for adalimumab at the end of 2008.
- The primary outcome in this study was death. Mortality rates between the anti-TNF treated and comparison cohorts were compared using Cox proportional hazards models and are presented as hazard ratios (HR) with 95% confidence intervals (CI).
- Underlying cause of death was death certificate.
- Models using logistic regression were employed for baseline adjustment in this observational study.

- Based on this observational registry data, the evidence is insufficient to conclude that there is a mortality difference between these three TNFIs and non-biologic DMARDs in the treatment of RA.

Key Points

- No overall difference in mortality rates between IFX, ADA and ETN and the non-biologic DMARD cohort (weighted HR 0.86 (95% CI 0.64 to 1.16)). 12,672 patients with RA were recruited to the anti-TNF cohort (4,420 ETN, 4,161 IFX, 4, 091 ADA).

MARCHESONI 09_Registry_Lombardy Italy withdraw_infections FINAL

AUTHOR YR: Marchesoni 09

Citation: Marchesoni A, Zaccara E, Gorla R, Bazzani C, Sarzi-Puttini P, Atzeni F, Caporali R, Bobbio-Pallavicini F, Favalli EG. TNF-alpha antagonist survival rate in a cohort of rheumatoid arthritis patients observed under conditions of standard clinical practice. Ann N Y Acad Sci. 2009 Sep;1173:837-46. PubMed PMID: 19758236.

Study Type: Registry Cohort

Manufacture Involvement: Only disclosure is that authors have received consultancy fees or Congress invitations from Schering-Plough, Wyeth and Abbott.

Abstract

A cohort of rheumatoid arthritis (RA) patients in the Lombardy Rheumatology Network (LOHREN) registry and receiving anti-TNF therapy was evaluated after 6, 12, 24, and 36 months. Of the 1114 patients in the registry 1064 met the clinical criteria for inclusion with 519 receiving infliximab, 303 adalimumab, and 242 etanercept.

Results

The therapeutic survival curve of these patients showed that the likelihood of continuing anti-TNF therapy was 78.8% after 12 months, 65.2% after 24 months, and 52.9% after 36 months, with a risk of dropout similar for inefficacy and adverse events. There were 405 anti-TNF therapy discontinuations (38.1%): 180 (16.9%) due to inefficacy, 194 (18.2%) adverse events, and 31 (2.9%) other reasons. Four deaths (2 septicemia, 1 postinfective cerebritis, 1 heart failure) were considered to be related to anti-TNF therapy. Of the discontinuations, 219 (54.1%) occurred within the first 12 months: 110 due to adverse events, 89 inefficacy, and 20 due to other reasons.

After 36 months, the likelihood of survival on etanercept (62.5%) was significantly greater than the likelihood of survival on infliximab (49.1%) or adalimumab (53.6%). The risk of ETN discontinuation started to be less than that of the other two agents between month 6 and 12, and was about 37.5% by month 36, when the risk of discontinuing adalimumab was 46.4% and the risk of discontinuing infliximab was 50.9% (*P* = 0.027). A higher risk of therapy discontinuations due to adverse events was associated with increasing age, a corticosteroid > 5 mg/day, a high erythrocyte sedimentation rate (ESR), a higher risk of therapy discontinuations due to inefficacy was associated with the previous use of > or = 4 disease-modifying antirheumatic drugs (DMARDs) and a high ESR. Comorbidities, increasing DAS28 values and co-therapy with methotrexate were associated with a lower risk of discontinuation.

Authors' Comments

In a setting of clinical practice, 1064 patients with RA refractory toDMARD therapy attending four different rheumatology centers had a likelihood of anti-TNF-α treatment retention rate of 78.8% after 12 months, 65.2% after 24 months, and 52.9% after 36 months. Adverse events were more likely than a lack of efficacy to cause drug discontinuations during the first 12 months of therapy, but not after 3 years. Serious infections were the most frequent adverse events responsible for drug discontinuation. Concomitant MTX greatly reduced the likelihood of drug discontinuation due to inefficacy, whereas a daily corticosteroid dose of >5 mg was associated with a higher risk of serious infections. Our data show that the long-term survival of etanercept (62.5% at month 36) was better than that of both infliximab (49.1%) and adalimumab (53.6%).

Reviewer Comments

- Agents of Interest: Adalimumab, etanercept, infliximab in RA
- Authors emphasize that this study was not designed to compare the three agents.
- Authors point out that the drugs became available at different times.
- The three groups were poorly matched with regard to disease duration, activity, and disability because the infliximab group had significantly higher DAS28 and DI-HAQ mean values, and a significantly larger number of patients who were RF positive, in functional class III, and on MTX. Therefore, patients treated with infliximab had a significantly higher level of disease activity and disability at the start of therapy.
- The number of patients receiving infliximab was much higher.
- Description from Favalli 08: Registry described as regional population-based registry in Italy. Described as including a cohort of all RA patients treated with anti-TNF agents in 4 major rheumatology units in Lombardy, Italy since 1999. Registry is described by authors as having an observational, everyday-practice design. In consequence, non-serious infections are often missing or incomplete—which raises questions about completeness of serious infections. Only infectious events recorded in medical charges or during outpatient visits were available for study. [Authors agree that infections may have been underreported.]
- The database includes all of the demographic features, clinical parameters and therapeutic data usually required to follow RA patients in clinical practice.
- Study is retrospective.
- The registry records only data collected baseline, after 6 months, 12 months and annually thereafter.
- Only data relating to the first 36 had been validated; however, there is no description of validation methods.
- No independent data validation efforts were described.
- All of the patients were treated in accordance with the Italian Society of Rheumatology guidelines for the use of anti-TNF-α agents: a diagnosis of RA (ACR criteria); failure to respond to at least one course of combination therapy with full-dose traditional disease modifying antirheumatic drugs (DMARDs), one of which should always be methotrexate (MTX) unless contraindicated; and active

disease as defined by a 28-joint Disease Activity Score (DAS28) of >3.5. Active infection, a history of malignancy, pre-malignant conditions, class III/IV congestive heart failure, and demyelinating disorders were absolute exclusion criteria. There was initially no specific indication concerning tubercular infection but, as soon as the role of anti-TNF-α agents in reactivating latent tuberculosis (TB) became clear, the patients had to be screened for the presence of previous or latent TB (history, Mantoux test, chest radiography). TB-positive patients could be treated with anti-TNF-α agents only after at least 3 weeks of anti-TB therapy, which had to be continued for at least 9 months.

- Patients' data were reported for first agent regardless of switching.
- There was no comparison population of non-treated patients.
- Authors report that only patients with at least 6 months data were included. However, they also state that they analyzed data for patients who had discontinued therapy within the first 6 months. Of 1114 patients recorded in the registry, 104 (9%) had been followed fewer than 6 months, but 54 of these patients had discontinued within the first 6 months and so were included in the analysis. 1064 (95.5%) of patients were, therefore, included in the analysis.
- The patients contributed to the survival models until the time of first discontinuation or the last time of observation on treatment during the first 36 months of treatment. The patients who discontinued therapy due to clinical remission were included in the analyses and censored at the time of drug discontinuation.
- Of the 194 discontinuations due to adverse events, 73 were serious infections (42 infliximab, 20 adalimumab, and 11 etanercept), 18 malignancies (6 infliximab, 8 adalimumab, and 4 etanercept), 58 local skin reactions or infusion intolerances (48 infliximab, 8 adalimumab, and 2 etanercept), 13 deaths (3 infliximab, 5 adalimumab, and 5 etanercept), and 32 other adverse events (6 infliximab, 19 adalimumab, and 7 etanercept).
- Various factors lead to death. Vascular disease was responsible for eight deaths; a relationship to therapy was considered likely or certain in four patients (three infections and one heart failure). At the time of data analysis, another three patients had died (one of myocardial infarction, one of heart failure, and one because of a road accident). As all of them had discontinued anti-TNF-α therapy at least one year before the event, any relationship to therapy was considered very unlikely.
- During the first year, infliximab and adalimumab were stopped more frequently because of adverse events (54.5% and 48.4% of the total number of discontinuations for each respectively) than because of inefficacy (38.4% and 43.8%); the number of discontinuations of etanercept for each reason was the same (41.9%).
- The survival curves of the three anti-TNF-α agents show the performance of etanercept was significantly better than the other agents, with a risk of discontinuation that started to be less than that of the other two agents between month 6 and 12, and was about 37.5% by month 36, when the risk of discontinuing adalimumab was 46.4% and the risk of discontinuing infliximab was 50.9% (P = 0.027). Significant differences in the risk of therapy discontinuation by each of the individual clinical features recorded at the start of anti-TNF-α treatment were noted. The risk of discontinuing etanercept was significantly higher than the risk of discontinuing either adalimumab or infliximab. Previous DMARD therapy with ≥3 agents (vs. ≤2), the use of corticosteroids at a dose of >5 mg/day (vs. no corticosteroid use), more tender joints, and higher ESR values were all associated with a significantly higher risk of therapy discontinuation. A significantly lower risk of anti-TNF-α discontinuation was associated with MTX cotherapy and high DAS28 values. Analysis of the risk of discontinuation due to inefficacy or adverse events showed that age was significantly associated with adverse events, adalimumab therapy with adverse events, infliximab therapy with a lack/loss of efficacy, four or more DMARDs before anti-TNF-α therapy with inefficacy, a steroid dose of >5 mg/day with adverse events, and high ESR values with both inefficacy and adverse events. MTX was significantly associated with a lower risk of discontinuations due to inefficacy and, strangely enough, co-morbidity was associated with a lower risk of discontinuations due to adverse events.

Risk of Withdrawal by Biologic DMARD Agent
Registry Studies (Marchesoni 09)

Agents	Outcomes
36 Months Study	Likelihood of Continuing Agent ("Survival")
ETN	62.5%*
ADA	53.6%
IFX	49.1%

*P<0.05 for difference between ETN and other agents

- Authors state that their data show that the long-term survival of etanercept (62.5% at month 36) was better than that of both infliximab (49.1%) and adalimumab (53.6%), and the previously mentioned observational studies found that the etanercept retention rate was similar to, or higher than that of the other drugs. The available data therefore seem to indicate that the likelihood of continuing therapy with etanercept is greater than that of the other two anti-TNF-α agents. They found that the risk of discontinuing infliximab was mainly due to primary or secondary loss of efficacy, whereas the risk of discontinuing adalimumab was mainly due to adverse events. However, this was not true in the first 12 months of therapy, during which both were more likely to be discontinued because of unwanted effects. The discontinuations of etanercept were equally likely to be due to adverse events or inefficacy throughout the study period. The difference in the reason for infliximab discontinuations in the first 12 months was probably attributable to infusion reactions, which were responsible for 31 drug discontinuations in the first year and 17 in the following 2 years.

Results

After 36 months, the likelihood of continuing on the drug (referred to as "survival") on ETN was 62.5% which was significantly higher than the likelihood of survival on IFX (49.1%) or ADA (53.6%). The risk of ETN discontinuation was lower than for the other two agents beginning at 6 months and was 37.5% by month 36, when the risk of discontinuing ADA was 46.4% and the risk of discontinuing IFX was 50.9% (P = 0.027).

MARIETTE _Registry_FRANCE_LYMPHOMA_10_ FINAL

AUTHOR YR: Mariette 10

Citation: Mariette X, Tubach F, Bagheri H, Bardet M, Berthelot JM, Gaudin P, Heresbach D, Martin A, Schaeverbeke T, Salmon D, Lemann M, Hermine O, Raphael M, Ravaud P. Lymphoma in patients treated with anti-TNF: results of the 3-year prospective French RATIO registry. Ann Rheum Dis. 2010 Feb;69(2):400-8. Epub 2009 Oct 14. PubMed PMID: 19828563; PubMed Central PMCID: PMC2925048.

Study Type: Registry Cohort French RATIO

Manufacture Involvement: Authors have received consultancy fees from relevant manufacturers which had no role in the study. The RATIO Registry support includes unrestricted industry grant funding from mixed sources.

Abstract

OBJECTIVE
To describe cases of lymphoma associated with anti-TNF therapy, identify risk factors, estimate the incidence and compare the risks for different anti-TNF agents.

METHODS
A national prospective registry was designed (Research Axed on Tolerance of bIOtherapies; RATIO) to collect all cases of lymphoma in French patients receiving anti-TNF therapy from 2004 to [through] 2006, whatever the indication. A case-control analysis was conducted including two controls treated with anti-TNF per case and an incidence study of lymphoma with the French population was used as the reference.

RESULTS
38 cases of lymphoma, 31 non-Hodgkin's lymphoma (NHL) (26 B cell and five T cell), five Hodgkin's lymphoma (HL) and two Hodgkin's-like lymphoma were collected. Epstein-Barr virus was detected in both of two Hodgkin's-like lymphoma, three of five HL and one NHL. Patients receiving adalimumab or infliximab had a higher risk than those treated with etanercept: standardised incidence ratio (SIR) 4.1 (2.3-7.1) and 3.6 (2.3-5.6) versus 0.9 (0.4-1.8). The exposure to adalimumab or infliximab versus etanercept was an independent risk factor for lymphoma in the case-control study: odds ratio 4.7 (1.3-17.7) and 4.1 (1.4-12.5), respectively. The sex and age-adjusted incidence rate of lymphoma was 42.1 per 100 000 patient-years. The SIR was 2.4 (95% CI 1.7 to 3.2).

CONCLUSION
The two to threefold increased risk of lymphoma in patients receiving anti-TNF therapy is similar to that expected for such patients with severe inflammatory diseases. Some lymphomas associated with immunosuppression may occur, and the risk of lymphoma is higher with monoclonal-antibody therapy than with soluble-receptor therapy.

COMPARISON OF INDIVIDUAL DRUGS

- Patients were those receiving anti-TNF agents without restriction for underlying disease
- Standardized incidence ratios (French population was used for comparison) in patients receiving ADA or IFX were higher than for those treated with ETN: standardized incidence ratio (SIR) 4.1 (2.3-7.1) and 3.6 (2.3-5.6) versus 0.9 (0.4-1.8).
- Investigators collected data on 41 cases of lymphomas, and 38 cases were validated. Among them, 31 were NHL (26 B-cell and 5 T-cell), 5 HL and 2 Hodgkin's-like lymphoma.
- The exposure to adalimumab or infliximab versus etanercept was an independent risk factor for lymphoma in an included case-control study: odds ratio 4.7 (1.3-17.7) and 4.1 (1.4-12.5), respectively.
- The sex and age-adjusted incidence rate of lymphoma was 42.1 per 100 000 patient-years. The authors concluded that the risk of lymphoma is higher with monoclonal-antibody therapy than with soluble-receptor therapy.
- The authors contrast their results with three previous observational cohort studies (Wolfe 07, Asking 08 and Wolfe 04) and state that previous studies failed to demonstrate a difference between the treatments in risk of lymphoma due to insufficient power and that although the design of the RATIO study has limitations, it is probably the only way (or at least the most powerful way) to investigate difference in risk with use of anti-TNF agents.

AUTHORS SUMMARY / CONCLUSION
Even though the overall risk of lymphoma in RA patients treated with anti-TNF therapy does not appear to differ greatly from what is expected in a population of patients with inflammatory diseases, the risk differs depending on the anti-TNF drug used (higher risk with monoclonal anti-TNF therapy, adalimumab and infliximab). This difference in risk depending on agent was found in the case-control study and confirmed in the comparison of incidence with the general population, which supports the robustness of this finding.

Reviewer Comments

- Agents of Interest: Adalimumab, etanercept, , infliximab in any indication
- Registry described as prospective and mandatory for the purpose of collecting all cases of lymphoma in French patients receiving anti-TNF therapy, regardless of indication from February 2004 through 2006. Multiple mailings and reminders encouraged physicians to report cases.
- Cases were all validated cases of lymphoma in the RATIO registry with a labeling indication for use of anti-TNF treatment (i.e. RA,

spondylarthropathy, Ulcerative Colitis or Crohn's disease or psoriasis). Controls were lymphoma-free patients receiving anti-TNF treatment in a labeling indication were included from centers participating in the RATIO registry (thus from the same population source) in a global pool of controls. From that pool, investigators randomly selected patients for a database of controls reflecting the proportion of patients receiving each of the three anti-TNF drug in France. Two controls per case were randomly matched by sex, age (within 5 years) and underlying inflammatory disease from this database of controls. They also used a second sample of controls randomly selected from the same database of controls, with the same matching criteria (second matching).

- Authors estimated the annual incidence rate of lymphoma in patients treated with anti- TNF therapy, adjusted for age and sex, with the French population as a reference.
- The underlying disease was RA in 27 cases, AS in 4 cases and psoriatic arthritis in 3 cases, Crohn's disease in 3 cases and primary Sjögren's syndrome in one case. Secondary Sjögren's syndrome was present in 3 of 27 patients with RA and lymphoma.
- Population for comparison was selected randomly and matched by sex, age within 5 years and underlying inflammatory disease.
- Cases of lymphoma were validated by consensus of 3 experts using detailed standardized case report form and additional documents. Biopsies were validated by single hematopathologist, including presence of Epstein-Barr virus (EBV).
- Sensitivity analyses were undertaken.
- The main analysis relied on a total number of 57,711 patient-years of use of anti-TNF therapy during the 2004–2006period, as the denominator of the incidence rate. The annual incidence rate of lymphoma adjusted for age and sex among patients receiving anti-TNF therapy, with the French population as a reference, was 42.1 (95% CI 6.9 to 77.2 per 100,000 person-years).
- The incidence rates for patients receiving etanercept, adalimumab, and infliximab were 15.3 (95% CI 0.0 to 45.6) per 100,000 person-years, 65.1 (95% CI 0.0 to 160.0) per 100,000 perso- years and 69.1 (95% CI 0.0 to 150.4) per 100,000 person-years, respectively. The SIRs were 0.9 (0.4 to 1.8; p=0.72), 4.1 (2.3 to 7.1; p<0.0001), and 3.6 (2.3 to 5.6; p<0.0001), respectively. Authors found a difference between etanercept and monoclonal-antibody therapy in the main analysis and in the sensitivity analyses, even when they separately used the different estimates from independent sources, which gave very consistent adjusted incidence rates and SIRs.
- In the multivariate analysis, 2 factors were independently associated with occurrence of lymphoma in patients receiving anti-TNF therapy: anti-TNF treatment duration less than 2 years (OR=3.30 [1.17 to 9.30]) and treatment with infliximab or adalimumab versus etanercept (OR=4.12 [1.36 to 12.49] and OR=4.73 [1.27 to 17.65], respectively). In the case-control study restricted to RA cases, only one factor was associated with occurrence of lymphoma: treatment with infliximab or adalimumab versus etanercept (OR=6.68 [1.90 to 23.54]).
- Authors state a limitation of the study was that the denominator was estimated. Per Tubach 09, anti-TNF manufacturers obtained estimation of patient-years based on number of doses sold and mean dosage used for each indication. The mean of these different estimates was used to estimate number of patients receiving each anti-TNF agent. Authors report that sensitivity analyses using independent sources gave consistent adjusted incidents rates and standardized incidence ratios (SIRs).
- Difference in risk depending on agents was consistent in the case-control study and also in the comparison with incidence with the general population.

Reviewer Comments

- Authors attempts to minimize bias:
  - Regarding possible reporting differences: reporting of adverse events could be lower in patients treated sub-cutaneously (SC; i.e. etanercept and adalimumab) outside the hospital. But, in France, the SC-treated patients are mandatorily seen by hospital physicians initially and yearly for renewal. Moreover, the lack of AE reporting is a main issue for minor side effects, but not for life-threatening side effects, particularly lymphomas that are a major concern for physicians and patients regarding anti-TNF agents. Furthermore, the patients treated with anti TNF agents that have lymphomas could be notified to RATIO by the anti-TNF agent prescriber (rheumatologist, gastro-enterologist, internist or others), by the oncohaematologist, or by the pharmacovigilance regional center. Finally, the authors found that the risk of lymphoma was similar for adalimumab and infliximab, that share the same mechanism of action (different from the one of etanercep), but adalimumab is a subcutaneous anti-TNF agent and infliximab I.V. anti-TNF agent.
  - Possible severity of disease differences: indirect markers of disease activity (median duration of the inflammatory underlying disease, percentage of patients treated with steroids, frequency of positive rheumatoid factor and anti-CCP in RA patients) were not greater in patients treated with infliximab or adalimumab than in those treated with etanercept. Also patients starting DMARDs before 2002 were at higher risk and so the comparison between the type of drug used and risk was adjusted for the time from onset of anti-TNF treatment.

- **Note**: Previous observational studies in RA patients have not reported an increased risk with anti-TNF agents compared to RA patients not taking TNFIs, e.g.:
  - OR 1.0 (95% CI 0.6 to 1.8) was reported by Wolfe 07a;
  - RR 1.0 (95% CI 0.6 to 1.8) was reported by Wolfe 07b;
  - RR 1.35 (95% CI 0.82 to 2.11) was reported by Askling 08;
  - RR 1.11 (95% CI 0.51 to 2.37) was reported by Wolfe 04.
- It is likely that these studies were underpowered to demonstrate a statistically significant difference between groups.

Summary Risk of Lymphoma by Biologic DMARD Agent French RATIO Registry Study*
Standardized Incidence Ratios (SIR) of IFX, ADA and Odds Ratio of IFX and ADA Versus ETN
(Mariette 10)

Agent	SIR with French Population as Reference	Odds Ratio of Agent Compared to ETN
IFX	3.6 (95% CI 2.3 to 5.6)	4.1 (95% CI 1.4 to 12.5)
ADA	4.1 (95% CI 2.3 to 7.1)	4.7 (95% CI 1.3 to 17.7)

ETN	0.9 (95% CI 0.4 to 1.8)	Reference agent
All Anti-TNF	12.2 (95% CI 9.7 to 15.5)	Not reported

*Population French subjects without restriction for underlying disease

MENTER PSORIASIS IFX RCT MALIG 06 FINAL

AUTHOR YR: Menter 06

Citation: Menter A, Feldman SR, Weinstein GD, Papp K, Evans R, Guzzo C, Li S, Dooley LT, Arnold C, Gottlieb AB. A randomized comparison of continuous vs. intermittent infliximab maintenance regimens over 1 year in the treatment of moderate-to-severe plaque psoriasis. J Am Acad Dermatol. 2007 Jan;56(1):31.e1-15. Epub 2006 Sep 6. PubMed PMID: 17097378.

Study Type: RCT

Agents of Interest: IFX in psoriasis

Safety Outcomes: Reported adverse events

Manufacture Involvement: One author employed by Centocor. Supported by Centocor, Inc, Malvern, Penn, and Schering-Plough, Kenilworth, NJ.

RELEVANT INFORMATION FROM PUBLISHED ABSTRACT AND TEXT
Background: Previous studies of infliximab in psoriasis have demonstrated rapid improvement with induction therapy and sustained response with regularly administered maintenance therapy. Objective: The efficacy and safety of continuous (everye8-week) and intermittent (as-needed) maintenance regimens were compared. Methods: Patients with moderate-to-severe psoriasis (n = 835) were randomized to induction therapy (weeks 0, 2, and 6) with infliximab 3 mg/kg or 5 mg/kg or placebo. Infliximab-treated patients were randomized again at week 14 to continuous or intermittent maintenance regimens at their induction dose. Results: At week 10, 75.5% and 70.3% of patients in the infliximab 5 mg/kg and 3 mg/kg groups, respectively, achieved PASI 75; 45.2% and 37.1% achieved PASI 90 (vs 1.9% [PASI 75] and 0.5% [PASI 90] for placebo; P\.001). Through week 50, PASI responses were better maintained with continuous compared with intermittent therapy within each dose, and with 5 mg/kg compared with 3 mg/kg continuous therapy. Limitations: Longer term ([1 year) maintenance therapy and further study of infliximab serum concentrations over this period, in both PASI 75 responders and non-responders, would be preferable. Conclusions: Through week 50, response was best maintained with continuous infliximab therapy. Infliximab was generally well-tolerated in most patients. (J Am Acad Dermatol 2007;56:31.e1-31.e15.)
Reviewer Comments N= 627 patients: a 1.9% malignancy rate in patients receiving IFX compared to no malignancies in the placebo group.

.

MOHAN TB ETA ALL CONDITIONS 04 FINAL

AUTHOR YR: Mohan 04

Citation: Mohan AK, Cote TR, Block JA, et al. Tuberculosis following the use of etanercept, a tumor necrosis factor inhibitor. Clin Infect Dis. 2004 Aug 1;39(3):295-9. PMID: 15306993

Study Design: Retrospective observational

Manufacture Involvement: No

Abstract

Infliximab, a tumor necrosis factor (TNF) antagonist, is associated with tuberculosis (TB), but it is unknown whether this phenomenon is true of all TNF antagonists. We reviewed 25 cases of TB due to another TNF antagonist, etanercept, that were reported to the US Food and Drug Administration (FDA) between November 1998 and March 2002. Such cases are sometimes incomplete and are subject to underreporting. Fifteen patients received other immunosuppressive medications. The median interval between the receipt of the first dose of etanercept and the diagnosis of TB was 11.5 months. Thirteen patients had extrapulmonary TB at the time of diagnosis. Diagnosis was made on the basis of culture results for 12 patients, biopsy findings for 9, and sputum staining for 4. There were 2 deaths, 1 of which was directly attributed to TB. The estimated number of TB cases reported to the FDA for each person-year of treatment with etanercept (i.e., the "reporting rate") among patients with rheumatoid arthritis (RA) was ~10 cases/100,000 patient-years of exposure. Clinicians considering etanercept for patients with RA should be alert to the possibility of the occurrence of TB, sometimes with an unusual extrapulmonary presentation. It is unclear whether etanercept therapy increases the risk of TB beyond the elevated TB rates already documented for patients with RA.

Reviewer Comments

- Agents of Interest: ETA in all conditions
- Results based on combination of selected RCT data and observational data resulting in high risk of selection, performance, attrition, reporting and assessment biases.

Summary

- As of April 2002, a total of 25 reports of TB associated with etanercept therapy had been reported to the FDA from November 1998 through March 2002. The authors contacted all 25 diagnosing physicians. Seventeen cases (68%) were reported from the United States, 7 (28%) were reported from Europe, and 1 (4%) was reported from India. Nine (36%) of the 25 cases were diagnosed in 2000, 15 (60%) were diagnosed during 2001, and 1 (4%) was diagnosed during the first 3 months of 2002. The median age at the time of TB diagnosis was 59 years (range, 9–84 years); 18 (72%) of the 25 patients were female. Indications for etanercept therapy were as follows: RA, 20 cases (80%); juvenile RA, 2 (8%); and psoriatic arthritis, panniculitis (not indicated in product package insert), and chronic heart failure (not indicated in product package insert), 1 case (4%) each. Concomitant with etanercept therapy, 21 patients (84%) received corticosteroids (3 patients), methotrexate (6), or both (12). The median interval between the initiation of etanercept treatment and the diagnosis of TB was 11.5 months (range, 1 to 20 months). Eleven (46%) of the 24 patients with a reported clinical manifestation had pulmonary TB exclusively, but 13 (54%) received the following diagnoses of extrapulmonary disease: disseminated disease (3 patients), tuberculous lymphadenitis (5 patients, including 2 with scrofula), and pleural, articular (in the same joint affected by rheumatoid arthritis), spinal, meningeal, and peritoneal disease (1 patient each). Diagnosis of TB was made on the basis of positive Mycobacterium tuberculosis cultures in 12 cases (48%), acid-fast bacilli (AFB)–positive biopsy specimens in 9 cases (36%), and AFB-positive sputum smears in 4 cases (16%). Two deaths occurred among the 25 patients, 1 of which resulted from disseminated TB leading to tuberculous meningitis.

- Small, retrospective observational study of TB following the use of ETN based on data reported to the Adverse Event Reporting System (AERS) of the US Food and Drug Administration (FDA) through March 2002, the estimated number of TB cases reported to the FDA for each person-year of treatment with ETN (i.e., the "reporting rate") in patients with RA was approximately 10 cases/100,000 patient-years of exposure

Risk of TB by Biologic DMARD (Mohan 04, Wolfe 04)		
Agent	**Reference**	**Incidence of TB / 100,000 PY**
ETN	Mohan 04, FDA reports ADEs to FDA between Nov 1998 and March 2002	10 cases (95% CI not provided) [compare to Wolfe 04)
IFX	Wolfe 04, Prospective cohort study 2 Yrs N=6,460	52.5 cases (95% CI 14.3 to 134.4)

NAM CRITIQUE SR adal inflix etan 10_final

AUTHOR YR: Nam 10

Citation: Nam JL, Winthrop KL, van Vollenhoven RF, Pavelka K, Valesini G, Hensor EM, Worthy G, Landewe R, Smolen JS, Emery P, Buch MH. Current evidence for the management of rheumatoid arthritis with biological disease-modifying antirheumatic drugs: a systematic literature review informing the EULAR recommendations for the management of RA. Ann Rheum Dis2010 Jun;69(6):976-86.PMID: 20447957

Supplementary material obtained from http://ard.bmj.com/content/suppl/2010/05/17/ard.2009.126573.DC1.html

Study Type: SR

Agents of Interest: Adalimumab, certolizumab etanercept, golimumbab, infliximab, in RA

Safety Outcomes: Serious infections, cancer, tuberculosis, lymphoma, demyelinating disease

Manufacture Involvement: No.

PUBLISHED ABSTRACT OR STUDY SAFETY DATA
OBJECTIVES: To review the evidence for the efficacy and safety of biological agents in patients with rheumatoid arthritis (RA) to provide data to develop treatment recommendations by the European League Against Rheumatism (EULAR) Task Force. METHODS: Medline, Embase and Cochrane databases were searched for relevant articles on infliximab (IFX), etanercept (ETN), adalimumab (ADA), certolizumab-pegol (CZP), golimumab (GLM), anakinra (ANA), abatacept (ABT), rituximab (RTX) and tocilizumab (TCZ) published between 1962 and February 2009; published abstracts from the 2007-2008 American College of Rheumatology (ACR) and EULAR conference were obtained. RESULTS: 87 articles and 40 abstracts were identified
Search: A systematic literature search was performed from 1962 to February 2009 using Medline, Embase and Cochrane databases. Studies evaluating nine biological agents: infliximab (IFX), etanercept(ETN), adalimumab (ADA), certolizumab-pegol(CZP), golimumab (GLM), anakinra (ANA), abatacept(ABT), rituximab (RTX) and tocilizumab (TCZ) were included. Abstracts were also obtained from the 2007–8 American College of Rheumatology(ACR) and EULAR conferences. Where full papers of these abstracts were published online during this period, the latter were obtained and used for data extraction. 1962-2009. Methods: For toxicity data, standardized incidence rates (with general population figures or those available for RA patients not on biologicalagents as the control) were extracted and risk ratios, odds ratios or hazards ratios documented. Results: TNFi are generally associated with an increased risk of serious bacterial infection, particularly within the first 6 months of treatment initiation; increased tuberculosis (TB) rates with TNFi are highest with the monoclonal antibodies. Authors' Conclusions: Safety data confirm an increased risk of bacterial infection and TB with TNFi compared with conventional DMARDs. The safety review shows no increased malignancy risk compared with conventional DMARDs. TNFi are generally associated with an increased risk of serious bacterial infection, particularly within the first 6 months of treatment initiation; increased tuberculosis (TB) rates with TNFi are highest with the monoclonal antibodies.
Reviewer Comments • Evidence current through January 2009 (date of search) • Most or all of the included clinical trials are likely to have been underpowered to reliably detect safety differences between groups if they existed. • Safety outcomes of interest were frequently not prespecified. • Registry data is observational. • CZP, GLM and IFX demonstrated signals of possibly higher incidence of severe infections but results are inconclusive. • Observational studies report higher mortality rates in RA patients and in RA patients taking biological agents compared to the general population. • Observational study reported reduced risk for overall mortality in patients taking TNF inhibitors.

Primary Studies Included in Delfini Review

1.	Bathon JM, Martin RW, Fleischmann RM, Tesser JR, Schiff MH, Keystone EC, Genovese MC, Wasko MC, Moreland LW, Weaver AL, Markenson J, Finck BK. A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. N Engl J Med2000 Nov 30;343(22):1586-93.
2.	Bejarano V, Quinn M, Conaghan PG, Reece R, Keenan AM, Walker D, Gough A, Green M, McGonagle D, Adebajo A, Jarrett S, Doherty S, Hordon L, Melsom R, Unnebrink K, Kupper H, Emery P. Effect of the early use of the anti-tumor necrosis factor adalimumab on the prevention of job loss in patients with early rheumatoid arthritis. Arthritis Rheum2008 Oct 15;59(10):1467-74.
3.	Breedveld FC, Weisman MH, Kavanaugh AF, Cohen SB, Pavelka K, van Vollenhoven R, Sharp J, Perez JL, Spencer-Green GT. The

	PREMIER study: A multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. Arthritis Rheum2006 Jan;54(1):26-37.
4.	Combe B, Codreanu C, Fiocco U, Gaubitz M, Geusens PP, Kvien TK, Pavelka K, Sambrook PN, Smolen JS, Khandker R, Singh A, Wajdula J, Fatenejad S. Efficacy, safety and patient-reported outcomes of combination etanercept and sulfasalazine versus etanercept alone in patients with rheumatoid arthritis: a double-blind randomised 2-year study. Ann Rheum Dis2009 Jul;68(7):1146-52.
5.	Combe B, Codreanu C, Fiocco U, Gaubitz M, Geusens PP, Kvien TK, Pavelka K, Sambrook PN, Smolen JS, Wajdula J, Fatenejad S. Etanercept and sulfasalazine, alone and combined, in patients with active rheumatoid arthritis despite receiving sulfasalazine: a double-blind comparison. Ann Rheum Dis2006 Oct;65(10):1357-62.
6.	Dixon WG, Hyrich KL, Watson KD, et al. Drug-Specific Risk of Tuberculosis in Patients with Rheumatoid Arthritis Treated with Anti-TNF Therapy: Results from the BSRBR *ACR abstract 1263*. 2008.
7.	Dixon WG, Hyrich KL, Watson KD, Lunt M, Galloway J, Ustianowski A, Symmons DP. Drug-specific risk of tuberculosis in patients with rheumatoid arthritis treated with anti-TNF therapy: results from the British Society for Rheumatology Biologics Register (BSRBR). Ann Rheum Dis2010 Mar;69(3):522-8. [Update of 2007 abstract].
8.	Emery P, Breedveld FC, Hall S, Durez P, Chang DJ, Robertson D, Singh A, Pedersen RD, Koenig AS, Freundlich B. Comparison of methotrexate monotherapy with a combination of methotrexate and etanercept in active, early, moderate to severe rheumatoid arthritis (COMET): a randomised, double-blind, parallel treatment trial. Lancet2008 Aug 2;372(9636):375-82.
9.	Emery P, Breedveld FC, Hall S, Durez P, Chang DJ, Robertson D, Singh A, Pedersen RD, Koenig AS, Freundlich B. Comparison of methotrexate monotherapy with a combination of methotrexate and etanercept in active, early, moderate to severe rheumatoid arthritis (COMET): a randomised, double-blind, parallel treatment trial. Lancet2008 Aug 2;372(9636):375-82.
10.	Emery P, Fleischmann RM, Moreland LW, Hsia EC, Strusberg I, Durez P, Nash P, Amante EJ, Churchill M, Park W, Pons-Estel BA, Doyle MK, Visvanathan S, Xu W, Rahman MU. Golimumab, a human anti-tumor necrosis factor alpha monoclonal antibody, injected subcutaneously every four weeks in methotrexate-naive patients with active rheumatoid arthritis: twenty-four-week results of a phase III, multicenter, randomized, double-blind, placebo-controlled study of golimumab before methotrexate as first-line therapy for early-onset rheumatoid arthritis. Arthritis Rheum2009 Aug;60(8):2272-83.
11.	Fleischmann R, Vencovsky J, van Vollenhoven RF, Borenstein D, Box J, Coteur G, Goel N, Brezinschek HP, Innes A, Strand V. Efficacy and safety of certolizumab pegol monotherapy every 4 weeks in patients with rheumatoid arthritis failing previous disease-modifying antirheumatic therapy: the FAST4WARD study. Ann Rheum Dis2009 Jun;68(6):805-11.
12.	Furst DE, Schiff MH, Fleischmann RM, et al. Adalimumab, a fully human anti tumor necrosis factor-alpha monoclonal antibody, and concomitant standard antirheumatic therapy for the treatment of rheumatoid arthritis: results of STAR (Safety Trial of Adalimumab in Rheumatoid Arthritis).[see comment]. Journal of Rheumatology. 2003;30:2563-2571.
13.	Gomez-Reino JJ, Carmona L, Angel Descalzo M. Risk of tuberculosis in patients treated with tumor necrosis factor antagonists due to incomplete prevention of reactivation of latent infection. Arthritis Rheum 2007 Jun 15;57(5):756-61.
14.	Keystone E, Heijde D, Mason D, Jr., Landewe R, Vollenhoven RV, Combe B, Emery P, Strand V, Mease P, Desai C, Pavelka K. Certolizumab pegol plus methotrexate is significantly more effective than placebo plus methotrexate in active rheumatoid arthritis: findings of a fifty-two-week, phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Arthritis Rheum2008 Nov;58(11):3319-29.
15.	Keystone EC, Kavanaugh AF, Sharp JT, Tannenbaum H, Hua Y, Teoh LS, Fischkoff SA, Chartash EK. Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti-tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: a randomized, placebo-controlled, 52-week trial. Arthritis Rheum2004 May;50(5):1400-11.
16.	Kim H, Lee S, Song Y, Yoo D, Koh EM, Yoo B, et al. A randomized, doubleblind, placebo controlled, phase III study of the human anti-tumor necrosis factor antibody adalimumab administered as subcutaneous injections in Korean rheumatoid arthritis patients treated with methotrexate. APLAR Journal of Rheumatology. 2007;10: 9-16.
17.	Klareskog L, van der Heijde D, de Jager JP, Gough A, Kalden J, Malaise M, Martin Mola E, Pavelka K, Sany J, Settas L, Wajdula J, Pedersen R, Fatenejad S, Sanda M. Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. Lancet2004 Feb 28;363(9410):675-81
18.	Maini R, St Clair EW, Breedveld F, Furst D, Kalden J, Weisman M, Smolen J, Emery P, Harriman G, Feldmann M, Lipsky P. Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. Lancet1999 Dec 4;354(9194):1932-9.
19.	Moreland LW, Schiff MH, Baumgartner SW, Tindall EA, Fleischmann RM, Bulpitt KJ, Weaver AL, Keystone EC, Furst DE, Mease PJ, Ruderman EM, Horwitz DA, Arkfeld DG, Garrison L, Burge DJ, Blosch CM, Lange ML, McDonnell ND, Weinblatt ME. Etanercept therapy in rheumatoid arthritis. A randomized, controlled trial. Ann Intern Med1999 Mar 16;130(6):478-86.
20.	Smolen J, Landewe RB, Mease P, Brzezicki J, Mason D, Luijtens K, van Vollenhoven RF, Kavanaugh A, Schiff M, Burmester GR, Strand V, Vencovsky J, van der Heijde D. Efficacy and safety of certolizumab pegol plus methotrexate in active rheumatoid arthritis: the RAPID 2 study. A randomised controlled trial. Ann Rheum Dis2009 Jun;68(6):797-804.
21.	St Clair EW, van der Heijde DM, Smolen JS, Maini RN, Bathon JM, Emery P, Keystone E, Schiff M, Kalden JR, Wang B, Dewoody K, Weiss R, Baker D. Combination of infliximab and methotrexate therapy for early rheumatoid arthritis: a randomized, controlled trial. Arthritis Rheum 2004 Nov;50(11):3432-43.
22.	van de Putte LB, Atkins C, Malaise M, Sany J, Russell AS, van Riel PL, Settas L, Bijlsma JW, Todesco S, Dougados M, Nash P,

	Emery P, Walter N, Kaul M, Fischkoff S, Kupper H. Efficacy and safety of adalimumab as monotherapy in patients with rheumatoid arthritis for whom previous disease modifying antirheumatic drug treatment has failed. Ann Rheum Dis2004 May;63(5):508-16.
23.	Watson KD, Dixon WG, King YE, et al. Cause Specific Mortality in Patients Receiving Anti-TNF Therapy for Rheumatoid Arthritis: Results from the British Society for Rheumatology Biologics Register (BSRBR) *ACR abstract 976*. 2007.
24.	Weinblatt ME, Keystone EC, Furst DE, Moreland LW, Weisman MH, Birbara CA, Teoh LA, Fischkoff SA, Chartash EK. Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. Arthritis Rheum2003 Jan;48(1):35-45.
25.	Weinblatt ME, Kremer JM, Bankhurst AD, Bulpitt KJ, Fleischmann RM, Fox RI, Jackson CG, Lange M, Burge DJ. A trial of etanercept, a recombinant tumor necrosis factor receptor:Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. N Engl J Med1999 Jan 28;340(4):253-9.
26.	Westhovens R, Yocum D, Han J, Berman A, Strusberg I, Geusens P, Rahman MU. The safety of infliximab, combined with background treatments, among patients with rheumatoid arthritis and various comorbidities: a large, randomized, placebo-controlled trial. Arthritis Rheum2006 Apr;54(4):1075-86.

RESULTS SUMMARY CLINICAL TRIALS AND OBSERVATIONAL STUDIES

Outcome	Findings Clinical Trials	Findings Observational Studies and Registries
SERIOUS INFECTIONS • Weak signals of possible increased infection with TNF inhibitors. Evidence suggests differential serious infection outcomes with monoclonal antibodies IFX and ADA being associated with serious infection.	Several but not all trials reported increased rates of serious infections with TNFIs; however, no P-values were reported; most trials reported similar serious infection rates in the study and comparison groups. Serious infections are relatively infrequent events and and trials were almost certainly underpowered to detect statistically significant differences. • CZP + MTX 6.3% vs placebo +MTX 2.2% (Keystone 08a) • CZP 2.2% vs placebo +MTX 0 (Smolen 07) • ADA 4% + MTX vs placebo +MTX 2.7% (Bejarano 08) • ADA 2.3% vs placebo 0 (van de Putte 04) • IFX + MTX 5.6% vs MTX 2.1%, P=0.04 (St Clair 04) • IFX 3.2% vs placebo +MTX 1.7% (Westhovens 06) • GLM 3% vs placebo +MTX 0.7% (Keystone 09) • ETN 10% vs placebo +SSZ 0 (Combe 09)	• IFX +ADA compared to MTX was associated with increased rate serious infection in first 6 mos. IRR was 2.4 (95% CI 1.4 to 5.2) (Curtis 07). • ETN was not associated with increased infection in first six months. IRR was 1.2 (95% CI 0.5 to 2.5) (Curtis 07).

TUBERCULOSIS
• Suggestive of increased risk with IFX and ADA.
	• Higher rates TB in IFX+MTX group, 6% vs 0 in MTX group; no P-values (St. Clair 04)	• IFX: RR was approximately 3.4 times higher than for RA patients not taking TNF inhibitors.
		  ○ IFX: Incidence 17/1578 (Gomez-Reino 03)
		  ○ ETN 0/1540 (Gomez-Reino 03)
		• IFX: IRR compared with ETN-treated patients was 3.1 (95% CI 1.0 to 9.5) (Dixon 10).
		  ○ IFX: 5/1303 (1.2 to 8.7 mos) (Gomez-Reino 07)
		  ○ ETN: 1/1740 (<2.5 mos) (Gomez-Reino 07)
		• IFX: RR 30.1 (95% CI 7.40 to 122.3) compared to general population (Seong 07)
		• ETN: no increased risk compared to general population (Seong 07)
		• ADA: IRR 4.2 (95% CI 1.4 to 12.4) compared to ETN (Dixon 10)
		• ADA: 1/565 (14 mos) (Gomez-Reino 07)
		• The median time to event was lowest for INF (5.5 months) compared with ETA (13.4 months) and ADA (18.5 months). Patients of non-white ethnicity had a sixfold increased risk of TB compared with white patients treated with anti-TNF therapy (Dixon 10 update of Dixon 08 abstract).

Outcome	Findings Clinical Trials	Findings Observational Studies and Registries
REACTION AT INJECTION SITE • Suggestive of increased risk with ETN compared to MTX.	• ETN vs MTX: 4% vs 7% (Weinblatt 99) • ETN vs MTX: 0 vs 5.7% (Weinblatt 03) • ETN vs MTX: 46.5% vs 13% (Moreland 99) • ETN vs MTX: 16% vs 2% (Klareskog 04) • ETN vs SSZ: 24% vs 2% (Combe 06) • ETN vs SSZ: 27% vs 4% (Combe 09) • ADA vs placebo: 10.6% vs 0.9% (van de Putte 04)	Not reported
LYMPHOMA TRIALS • Weak signals from registry data that the incidence of lymphoma is increased with IFX or ADA.	• Most trials did not report lymphoma rates • No trial reported more than 2 cases	• Increase risk in RA patients overall and for RA patients when studies of different biologics are combined (Wolfe, 2004; Mariette 2008) • Inconclusive results for individual agents. o IFX: SIR confidence intervals ranged from 0.6 to 4.9. o ADA: SIR confidence levels 0.90 to 23.1. o IFX or ADA: SIR confidence intervals ranged from 2.4 to 16. 48. o ETN: SIR confidence intervals ranged from 0.3 to 51.
MALIGNANCY • Inconclusive evidence regarding comparative risks of ADA, IFX, ETN	• Increased malignancy rate with CZP; no P-value (Keystone 08a).	• ETN, IFX, ADA: no statistically significant risk compared to general population (Burmester 2008, Wolfe 2007, Klareskog 2008)
INTERSTITIAL LUNG DISEASE • Inconclusive for increased risk for RA patients taking ETN and IFX.		• ETN, IFX: no statistically significant risk (comparison unclear) (Wolfe 2007).
DEMYELINATING DISEASE • LOE: inconclusive for agents of interest.	• Not reported in most studies. Several studies reported no cases of demyelinating disease. Westhovens 06 reported 2 cases in placebo group at 22 weeks and 28 cases in IFX at 54 weeks.	• Not reported
DEATH • Inconclusive regarding comparative safety of IFX, ADA, ETN	• Few reports; lack statistically significant differences between groups.	• ADA, ETN, IFX: increased risk for overall mortality compared to general population. o Standardized mortality rate (SMR) Male=2 (95% CI 1.7 to 2.3); SMR Female =1.7 (95% CI 1.5 to 1.9) (Watson 2007). o SMR 1.57 (95% CI 1.42 to 1.73) (Watson 2007). ▪ Neoplasms: NS ▪ Cardiovascular: Male=1.77 (95% CI 1.32-2.32); Female =1.26 (95% CI 1.01-1.54). • ADA, ETN, IFX: reduced risk for overall mortality in patients taking TNF inhibitors compared to TNF inhibitor-naïve patients. o RR 0.85 (95% CI 0.77 to 0.95) (Jacobsson 08).

REGISTRY DATA AND OBSERVATIONAL STUDIES

LOE: Inconclusive—increased SIRs for ADA, ETN, IFX

Wolfe 2004	**Populations**	**N**	**Standardized Incident Rates (SIR)**	**Reviewer Comments**
	All RA	18572	1.9 (95% CI 1.3 to 2.7)	Increased rates in RA patients taking IFX or ETN.
	RA-MTX	5501	1.7 (95% CI 0.9 to 3.2)	
	RA biologics	8614	2.9 (95% CI 1.7 to 4.9)	
	IFX	5233	2.2 (95% CI 1.0 to 4.9))	
	ETN	2149	3.5 (95% CI 2.5 to 8.4)	
	ADA	58	0	
Wolfe 2007	**Populations**	**N**	**Odds Ratios**	Rates not statistically increased in RA patients taking MTX, IFX, ETN or ADA compared to all patients taking any TNFi. This could be due to a type II error.
	RA patients	19591		
	RA TNF	10815	1.0** (95% CI 0.6 to 1.8)	
	RA MTX		1.3*** (95% CI 0.7 to 2.4)	
	RA IFX		1.2*** (95% CI 0.6 to 2.2)	
	RA ETN		0.7*** (95% CI 0.3 to 1.6)	
	RA ADA		4.5*** (95% CI 0.9 to 23.1) *(only 56 cases; 2 lymphoma*	
Burmester EULAR 2008	**Populations**	**N**	Standardized Incident Rates (SIR)	Increased rates with ADA compared with general population.
	RA ADA	3421	3.81 (95% CI 1.90 to 6.81)	
Klareskog EULAR 2008	**Populations**	**N**	Standardized Incident Rates (SIR)	Rates increased with ETN compared to general population.
	RA ETN	2054	3.53 (95% CI 1.82 to 6.16)	
Mariette ACR 2008 (French register)	**Populations**	**N**	**Standardized Incident Rates (SIR)**	• Increased rates in aggregate of all patients taking TNFi. • Increased rates in patients receiving IFX or ADA. • Rates not statistically increased in patients taking ETN.
	Total TNF		2.11 (95% CI 1.48 to 3.00)# 4.87 (95% CI 2.33 to 10.24)##	
	RA IFX or ADA		3.43 (95% CI 2.4 to 5.04)# 6.86 (95% CI 2.86 to 16.48)##	
	ETN		0.69 (95% CI 0.28 to 1.65)# 2.78 (95% CI 0.7 to 11.13)##	
Weinblatt ACR 2008	**Populations**	**N**	**Standardized Incident Rates (SIR)**	
	RA ETN		4.2 (95% CI 1.7 to 51)	Increased rates with ETN compared to general population (SEER data)

- * Compared to general population
- ** compared to RA nonbiologic treated group
- *** compared to all other malignancies
- ^compared to methotrexate
- $ patients with prior malignancies
- # non-Hodgkin's lymphoma
- ##Hodgkin's lymphoma)

Included RCTs Biological Agents in RA Patients Who are MTX Naïve, Incomplete Responders to MTX or Incomplete Responders to Other DMARDs

#	Ref and Study Details	Interventions	Outcomes (% or incidence rate per 100 patient-years or events per patient year)	Validity	Reviewer Comments
1	St Clair 2004(ASPIRE) Months: 12 N: 1004 Age: ~50 Duration: ~0.9 yrs % DMARD Naive: ~67 % on steroids: ~38 % on NSAIDs: ~84 HAQ score: 1.5	Placebo+ MTX IFX 3 mg/Kg weekly + MTX IFX 6 mg/Kg weekly + MTX	PNEUMONIA: 0 TB: 0 INFUSION RXN: 0 LYMPHOMA: 0 MALIGNANCY: 0 DEMYELINATING: NR DEATH: 2 WITHDRAWAL ADVERSE: (3.2) SERIOUS INFECTIONS (2.1%) PNEUMONIA: 8 (2) TB: 3 (0.8) INFUSION RXN: 2 (0.5) LYMPHOMA: 0 MALIGNANCY:0 DEMYELINAGING: NR DEATH: 1 WITHDRAWAL ADVERSE: (9.5) SERIOUS INFECTIONS:21 (5.6) P=0.02 PNEUMONIA: 11 (3) TB: 1 (0.3) INFUSION RXN: 2 (0.5) LYMPHOMA: 0 MALIGNANCY: 4 (1) DEMYELINAGING: NR DEATH: 1 WITHDRAWAL ADVERSE: (9.6) SERIOUS INFECTIONS:19 (5) P=0.04	Generation Sequence: Yes Concealment Alloc: Yes Blinding: Yes: Subjects/Invest/Assessors N Safety MTX: 291/298 N Safety IFX: 749/751	Placebo+ MTX vs IFX + MTX. Higher withdrawal due to adverse event in IFX +MTX group 9.6% .vs 3.2%; higher rates TB in IFX+MTX group, 6% vs 0; no P-value; higher rate serious infections in IFX + MTX group, 5% vs 2.1%, P = 0.04.
2.	Genovese 2002 Months: 24 N: 632 Age: ~50 Duration: 1 yrs % DMARD Naive: ~56 % on steroids: ~40 % on NSAIDs: ~83 HAQ score: 1.45	MTX ETN 10mg / 25mg sc. twice/week + placebo	PNEUMONIA: 3 (1) TB: NR INFUSION RXN: NR LYMPHOMA: NR MALIGNANCY: NR DEMYELINAGING: NR DEATH: 0 WITHDRAWAL ADVERSE: 24 (11) SERIOUS INFECTIONS:NR PNEUMONIA: 0 TB: NR INFUSION RXN: NR LYMPHOMA: NR MALIGNANCY: NR DEMYELINAGING: NR DEATH: 0 WITHDRAWAL ADVERSE: 11 (5); P< 0.04 for difference comparing 25mg ETN and MTX SERIOUS INFECTIONS:NR	Generation Sequence: Yes Concealment Alloc: Yes Blinding: Yes: Subjects/Invest/Assessors N Safety MTX: 217/217 N Safety ETN: 415/415 ITT: Yes	MTX vs ETN 10mg / 25mg sc. twice/week + placebo: Statistically significantly higher withdrawal due to adverse events in MTX group compared to ETN group; 11% vs 5%; P< 0.04 for 25mg ETN and MTX.
3	Emery 2008 (COMET) Months: 12 N: 542 Age: ~52 Duration: .75 yrs % DMARD Naive: ~79 % on steroids: ~50 % on NSAIDs: ~74	Placebo +MTX; N=268	PNEUMONIA: 1 TB: 0 INFUSION RXN: NR LYMPHOMA: NR MALIGNANCY: 4 DEMYELINAGING: 0 DEATH: ?1 WITHDRAWAL ADVERSE: 28 (10.2)	Generation Sequence: Yes Concealment Alloc: Yes Blinding: Yes: Subjects/Invest/Assessors N Safety MTX:	Placebo +MTX vs ETN 50mg weekly + MTX: similar adverse event rates; may be underpowered to show differences.

#	Ref and Study Details	Interventions	Outcomes (% or incidence rate per 100 patient-years or events per patient year)	Validity	Reviewer Comments
	HAQ score: ~1.65	ETN 50mg weekly + MTX; N=274	SERIOUS INFECTION: 8 PNEUMONIA: 1 TB: 0 INFUSION RXN: NR LYMPHOMA: NR MALIGNANCY:4 DEMYELINAGING: 0 DEATH: ?1 WITHDRAWAL ADVERSE: 34 (12.7) SERIOUS INFECTION:5	268/268 N Safety ETN: 274/274 ITT: Yes (LOCF)	
4.	Breedveld 2006 (PREMIER) Months: 24 N:799 Age: ~52 Duration:~ 1 yr % DMARD Naive: ~68 % on steroids: ~36 % on NSAIDs: NR HAQ score: ~1.55	MTX ADA 40mg sc. 2 weekly ADA 40mg sc. 2 weekly +MTX	PNEUMONIA: 2 TB: 0 INFUSION RXN: NR LYMPHOMA: [0.2] MALIGNANCY:[0.9] DEMYELINAGING: 0 DEATH: 1 WITHDRAWAL ADVERSE: 19 (7.4); P=0.21 SERIOUS INFECTION:[1.6] PNEUMONIA: 0 TB: 0 INFUSION RXN: NR LYMPHOMA: 0 MALIGNANCY:[0.9] DEMYELINAGING: 0 DEATH: 4 WITHDRAWAL ADVERSE: 26 (9.5); P=0.21 OTHER: SERIOUS INFECTION:[0.7] PNEUMONIA: 0 TB: [0.2] INFUSION RXN: NR LYMPHOMA: 0 MALIGNANCY:[0.4] DEMYELINAGING: 0 DEATH: 1 WITHDRAWAL ADVERSE: 32 (11.9); P=0.21 SERIOUS INFECTION:[2.9];P<0.05	Generation Sequence: No details Concealment Alloc: No details Blinding: Yes: Subjects/Invest/Assessors N Safety MTX: 257/257 N Safety ADA:274/274 N Safety ADA + MTX: 268/268 ITT: Yes (extreme case analysis)	3 arms; MTX vs ADA 40mg sc. 2 weekly vs ADA 40mg sc. 2 weekly +MTX; higher withdrawal due to adverse events in ADA group compared to MTX group 10.7% % vs 7.4%; P=0.21.
5.	Bejarano 2008 (PROWD) Months: 12 N:148 Age: ~47 Duration:~ .73 yrs % DMARD Naive: ~NR % on steroids: NR % on NSAIDs: NR HAQ score: 1.3 Other: Work Impairment	Placebo +MTX ADA 40mg sc. 2 weekly +MTX	PNEUMONIA: NR TB: 0 INFUSION RXN: NR LYMPHOMA: 0 MALIGNANCY:0 DEMYELINAGING: 0 DEATH: 0 WITHDRAWAL ADVERSE: NR SERIOUS INFECTION:(2.7)* PNEUMONIA: 0 TB: 0 INFUSION RXN: NR LYMPHOMA: 0 MALIGNANCY: 0 DEMYELINAGING: 0 DEATH: 0 WITHDRAWAL ADVERSE: NR	Generation Sequence: Yes Concealment Alloc: Yes Blinding: Yes: Subjects/Invest/Assessors N Safety Placebo +MTX: 73/73 N Safety ADA + MTX:75/75 ITT: Yes (extreme case analysis)	Placebo +MTX vs ADA 40mg sc. 2 weekly +MTX; similar adverse event rates; possible signal of serious infections with ADA; may be underpowered to show differences.

#	Ref and Study Details	Interventions	Outcomes (% or incidence rate per 100 patient-years or events per patient year)	Validity	Reviewer Comments
			SERIOUS INFECTION:(4)* * NS for difference		
6.	Emery EULAR 2008 Months: 12 N:542 Age: ~51 Duration:~ .75 yrs % DMARD Naive: ~79% % on steroids: ~50% % on NSAIDs: ~74% HAQ score: NR Other: DAS 28 (disease activity score based on 28 joints): 6.5	MTX 20mg MTX 20mg + ETN 50 mg sc. weekly	PNEUMONIA: 1 TB: 0 INFUSION RXN: NR LYMPHOMA: NR MALIGNANCY:4 (1) DEMYELINAGING: 0 DEATH: ?1 WITHDRAWAL ADVERSE: 34 (12.7) SERIOUS INFECTION: 8 PNEUMONIA: 1 TB: 0 INFUSION RXN: NR LYMPHOMA: NR MALIGNANCY:4 (1) DEMYELINAGING: 0 DEATH: ?1 WITHDRAWAL ADVERSE: 28 (10.2) SERIOUS INFECTION: 5	Generation Sequence: Yes Concealment Alloc: Yes Blinding: Yes: Subjects/Invest/Assessors N Safety MTX: 268/268 N Safety MTX +ETN:274/274 ITT: Yes (LOCF)	MTX 20mg vs MTX 20mg + ETN 50 mg sc. weekly; similar adverse event rates; may be underpowered to show differences.
7.	Emery EULAR 2009 Months: 6 N:637 Age: ~50 Duration:~ 1 yr % DMARD Naive: ~48% % on steroids: ~66% % on NSAIDs: ~97% HAQ score: ~1.5	Placebo +MTX 20mg/week GLM* 100mg + Placebo GLM* 50mg-100MG + MTX *GLM administered every 4 weeks	PNEUMONIA: 1 TB: 0 INJECTION SITE RXN: 3 (1.9) LYMPHOMA: 0 MALIGNANCY: 2 DEMYELINAGING: NR DEATH: 0 WITHDRAWAL ADVERSE: 2 (1.3) SERIOUS INFECTION: 3 (1.9) PNEUMONIA: 1 TB: 0 INJECTION SITE RXN: 17 (10.8) LYMPHOMA: 1 MALIGNANCY:2 DEMYELINAGING: NR DEATH: 0 WITHDRAWAL ADVERSE: 14 (3) SERIOUS INFECTION: 2 (1.3) PNEUMONIA: 2 TB: 1 INJECTION SITE RXN: 17 (5.4) LYMPHOMA: 1 MALIGNANCY:2 = DEMYELINATING: NR DEATH: 2 WITHDRAWAL ADVERSE: 13 (4.1) SERIOUS INFECTION: 9(2.85)	Generation Sequence: No details Concealment Alloc: No details Blinding: Yes: Subjects/ ?Invest/ Assessors N Safety Placebo + MTX: 160/160; N Safety GLM + Placebo: 157/157; N Safety GLM + MTX: 317/317	3 arms; Placebo +MTX 20mg/week; GLM + Placebo vs GLM + MTX; similar adverse event rates; may be underpowered to show differences.
8.	Maini 1999 Months:~7 N:428 Age: ~54 Duration: ~10 yrs Incomplete responders	Placebo + MTX	PNEUMONIA: NR TB: 0 INFUSION RXN: 0 LYMPHOMA: 0 MALIGNANCY: 0 DEMYELINAGING: NR	Generation Sequence: No details Concealment Alloc: No details Blinding: Yes:	Similar adverse event rates; may be underpowered to show differences.

#	Ref and Study Details	Interventions	Outcomes (% or incidence rate per 100 patient-years or events per patient year)	Validity	Reviewer Comments
	to MTX % on steroids: ~60 % on NSAIDs: ~73 HAQ score:~1.7	IFX 3mg/kg to 10mg/kg + MTX	DEATH: 3 (3) WITHDRAWAL ADVERSE: 7(8) SERIOUS INFECTION: 5 (6) PNEUMONIA: NR TB: 1 INFUSION RXN: 2 LYMPHOMA:1 MALIGNANCY:4 DEMYELINAGING: NR DEATH: 2 (0.6) WITHDRAWAL ADVERSE: 6(7) SERIOUS INFECTION: 14 (4)	Subjects/Invest/Assessors N Safety Placebo + MTX: 86/88 N Safety IFX + MTX: 340/342	
9.	Westhovens 2006 (START) Months:6 for placebo + MTX vs IFX N:1084 Age: ~52 Duration: ~7.5 yrs Incomplete responders to MTX % on steroids: 59 % on NSAIDs: ~40 HAQ score:~1.5	Placebo + MTX IFX 3mg/kg-10mg/kg q 8 weeks + MTX	PNEUMONIA: Week 22: 0; Week 54 (IFX Only): TB: 0 INFUSION RXN: NR LYMPHOMA: 0 MALIGNANCY: 2 DEMYELINAGING: NR DEATH: 1 WITHDRAWAL ADVERSE: 8 (2.2) SERIOUS INFECTION: 6 (1.7) PNEUMONIA: 6 (0.8); 12 (1.2) TB: 3 (0.4); 4 (0.4) INFUSION RXN: NR; 195 (2.6) LYMPHOMA: 1; 1 MALIGNANCY: NR; 28((2.8) DEMYELINATING: NR; NR DEATH: NR; 4 WITHDRAWAL ADVERSE: 31 (4.3); 49(4.9) SERIOUS INFECTION: 24(3.3); 31(3)	Generation Sequence: No details Concealment Alloc: No details Blinding: Yes: Subjects/Invest/Assessors N Safety Placebo + MTX: 361/361 (22 wks) N Safety IFX + MTX: 721/721 (22wks) No placebo group at week 54 N Safety IFX + MTX: 1001/1082	Increased serious infection in IFX group; may be underpowered to show differences.
10.	Weinblatt 1999 Months:6 N:89 Age: ~50 Duration: ~13 Incomplete responders to MTX % on steroids: 53 to 70 % on NSAIDs: ~77 HAQ score:~1.4	Placebo +MTX ETN 25mg sc. twice weekly + MTX	PNEUMONIA: NR TB:NR INFUSION RXN:NR LYMPHOMA:NR MALIGNANCY:NR DEMYELINATING:NR DEATH: 0 WITHDRAWAL ADVERSE: 0 SERIOUS INFECTION:NR REACTIONS AT INJECTION SITE: (7) PNEUMONIA: NR TB:NR INFUSION RXN:NR LYMPHOMA:NR MALIGNANCY:NR DEMYELINATING:NR DEATH: 0 WITHDRAWAL ADVERSE: 0 SERIOUS INFECTION:NR REACTIONS AT INJECTION SITE: (4)	Generation Sequence: No details Concealment Alloc: No details Blinding: Yes: No details N Safety Placebo + MTX: 30/30 N Safety ETN + MTX: 59/59	Similar adverse event rates; may be underpowered to show differences.
11.	Weinblatt 2003 (ARMADA) Months:6 N:271 Age: ~56 Duration: ~12 years Incomplete responders to MTX % on steroids: NR	Placebo + MTX	PNEUMONIA: 0 TB:0 INFUSION RXN:NR LYMPHOMA:NR MALIGNANCY:0 DEMYELINATING:NR DEATH: 0 WITHDRAWAL ADVERSE: 2 SERIOUS INFECTION:0	Generation Sequence: No details Concealment Alloc: No details Blinding: Yes: No details N Safety Placebo + MTX: 62/62	Similar adverse event rates; may be underpowered to show differences.

#	Ref and Study Details	Interventions	Outcomes (% or incidence rate per 100 patient-years or events per patient year)	Validity	Reviewer Comments
	% on NSAIDs: ~NR HAQ score:~1.6	ADA 40mg sc. 2 weekly+MTX ADA80mg sc. 2 weekly+MTX	REACTIONS AT INJECTION SITE: 0 PNEUMONIA: 2 TB:0 INFUSION RXN:NR LYMPHOMA:NR MALIGNANCY:1 DEMYELINATING:NR DEATH: 0 WITHDRAWAL ADVERSE: 5 SERIOUS INFECTION:2 (Pneumonia) REACTIONS AT INJECTION SITE: 12(5.7)	N Safety ADA + MTX: 209/209	
12.	Keystone 2008(RAPID1) Months:12 N:982 Age: ~52 Duration: ~6 years Incomplete responders to MTX % on steroids: NR % on NSAIDs: NR HAQ score:~1.7	Placebo + MTX; N=199 CZP 200mg to 400mg 2 weekly sc. +MTX; N=783	PNEUMONIA: NR TB:0 INFUSION RXN:NR LYMPHOMA:0 MALIGNANCY:1 DEMYELINATING:NR DEATH: 1 WITHDRAWAL ADVERSE: (3.3) SERIOUS INFECTION: (2.2) REACTIONS AT INJECTION SITE: 0 PNEUMONIA: NR TB (:0.85) INFUSION RXN:NR LYMPHOMA:1 MALIGNANCY:11 DEMYELINATING:NR DEATH: 7 WITHDRAWAL ADVERSE: (6.3) SERIOUS INFECTION:(6.3) REACTIONS AT INJECTION SITE:(1.6)	Generation Sequence: No details Concealment Alloc: No details Blinding: Yes for assessor; No other details N Safety Placebo + MTX: 190/199 N Safety CZP + MTX: 781/783	Increased serious infection, malignancy and withdrawal due to adverse events in CZP group. P-values not reported
13.	Smolen EULAR 2007(RAPID2) Months:6 N:619 Age: ~52 Duration: ~6 years Incomplete responders to MTX % on steroids: 59 % on NSAIDs: NR HAQ score:1.6	Placebo + MTX; N=127 CZP 200mg 2 weekly sc. + placebo; N=246 CZP 400mg 2 weekly sc. + placebo; N=246	PNEUMONIA: NR TB:0 INFUSION RXN:NR LYMPHOMA:0 MALIGNANCY:1 DEMYELINATING:NR DEATH: 1 WITHDRAWAL ADVERSE: 2 (1.6) SERIOUS INFECTION: 0 REACTIONS AT INJECTION SITE: 0 PNEUMONIA: NR TB:5 INFUSION RXN:NR LYMPHOMA:1 MALIGNANCY:11 DEMYELINATING:NR DEATH: 2 WITHDRAWAL ADVERSE: 15(3.45) SERIOUS INFECTION:14 (2.2) REACTIONS AT INJECTION SITE:8 (1.6)	Generation Sequence: No details Concealment Alloc: No details Blinding: No details N Safety Placebo + MTX: 125/127 N Safety CZP + MTX: 492/492	Increased rate of serious infections in CZP group; may be underpowered to show differences.

#	Ref and Study Details	Interventions	Outcomes (% or incidence rate per 100 patient-years or events per patient year)	Validity	Reviewer Comments
14.	Keystone EULAR 2009 (GO-FORWARD) Months:6 N:444 Age: ~52 Duration: ~6.2 years Incomplete responders to MTX % on steroids: 65/68/73 % on NSAIDs: NR HAQ score:1.4	Placebo + MTX; N=133 GLM 100mg 2 weekly sc. + placebo; N=133 GLM 50-100mg. + MTX; N=178	PNEUMONIA: NR TB:0 INFUSION RXN:NR LYMPHOMA:0 MALIGNANCY: 1 basal cell skin; 1 squamous cell skin DEMYELINATING:NR DEATH: 0 WITHDRAWAL ADVERSE: 6 SERIOUS INFECTION: 1 (0.7%): UTI REACTIONS AT INJECTION SITE: 0 PNEUMONIA: NR TB:(0.85) INFUSION RXN:NR LYMPHOMA:1 MALIGNANCY:1 squamous cell skin DEMYELINATING:NR DEATH: 1 WITHDRAWAL ADVERSE: 7 SERIOUS INFECTION: 4 (3%): 2 sepsis, 1 colitis, infective arthritis REACTIONS AT INJECTION SITE (1.05) PNEUMONIA, LOWER RTI: 1 TB:0 INFUSION RXN:NR LYMPHOMA:1 MALIGNANCY:1 breast cancer DEMYELINATING:NR DEATH: 0 WITHDRAWAL ADVERSE: 7 SERIOUS INFECTION: 7 (3.9%): cellulitis ,2 sepsis, UTI, bacterial arthritis, lower RTI, SC abscess REACTIONS AT INJECTION SITE 1) (1.1%)	Generation Sequence: No details Concealment Alloc: No details Blinding: Assessors N Safety Placebo + MTX: 133/133 N Safety GLM + Placebo: 133/133 N Safety GLM + MTX: 178/178	Increased rate serious infections with GLM; may be underpowered to show significant differences.
15.	Moreland 1999 Months:6 N:234 Age: ~52 Duration: ~11.5 years Incomplete responders to DMARDs % on steroids: 58 vs 81 % on NSAIDs: 84 vs 67 HAQ score:1.7	Placebo; N=80 ETN 10 or 25mg sc. twice weekly + placebo; N=154	PNEUMONIA: NR TB:NR INFUSION RXN:NR LYMPHOMA:NR MALIGNANCY:NR DEMYELINATING:NR DEATH: NR WITHDRAWAL ADVERSE: 3 SERIOUS INFECTION: NR REACTIONS AT INJECTION SITE: (13%) PNEUMONIA: NR TB:(0.85) INFUSION RXN:NR LYMPHOMA:1 MALIGNANCY:NR DEMYELINATING:NR DEATH: 7 WITHDRAWAL ADVERSE: 7 SERIOUS INFECTION: NR REACTIONS AT INJECTION SITE: (46.5%)	Generation Sequence: No details Concealment Alloc: No details Blinding: No details except similar appearance and constitution of placebo injection from placebo powder. Assessors N Safety Placebo: 80/80 N Safety ETN:154 /154	Increased reactions at injection site 46.5% vs 13%, no P-value.

#	Ref and Study Details	Interventions	Outcomes (% or incidence rate per 100 patient-years or events per patient year)	Validity	Reviewer Comments
16.	Klareskog 2004 (TEMPO) Months:24 N:682 Age: ~53 Duration: ~7 years Incomplete responders to DMARDs % on steroids: ~60 % on NSAIDs:~ 87 HAQ score:1.8	MTX; N=228 ETN 25mg sc. twice weekly; N=223 ETN 25mg sc. twice weekly + MTX; N=231	PNEUMONIA: NR TB:0 INFUSION RXN:NR LYMPHOMA:NR MALIGNANCY:1 DEMYELINATING:0 DEATH: 1 WITHDRAWAL ADVERSE: 32 SERIOUS INFECTION: 10 (4%) REACTIONS AT INJECTION SITE: 4 (2%) PNEUMONIA: 0 TB:0 INFUSION RXN:NR LYMPHOMA:1 MALIGNANCY:4 DEMYELINATING:0 DEATH: 1 WITHDRAWAL ADVERSE: 25 SERIOUS INFECTION: 10 (4%) REACTIONS AT INJECTION SITE:46 (21%) PNEUMONIA: 1 TB:0 INFUSION RXN:NR LYMPHOMA:1 MALIGNANCY:1 DEMYELINATING:0 DEATH:1 WITHDRAWAL ADVERSE: 24 SERIOUS INFECTION: 10 (4%) REACTIONS AT INJECTION SITE: 23 (10%)	Generation Sequence: No details Concealment Alloc: Centralized telephone Blinding: Stated double-blind; no details N Safety MTX: 228/228 N Safety ETN:223/223 N Safety ETN +MTX: 231/231	MTX vs ETN 25mg sc. twice weekly; increased reaction at injection site, no P-value provided
17.	Combe 2006 Months:6 N:260 Age: ~52 Duration: ~7 years Incomplete responders to DMARDs % on steroids: 40/59/49 % on NSAIDs:NR HAQ score:1.6	Placebo + SSZ; N=50 ETN 25mg sc. twice weekly +placebo; N=103 ETN 25mg sc. twice weekly + SSZ; N=101	PNEUMONIA: NR TB:0 INFUSION RXN:NR LYMPHOMA:NR MALIGNANCY:0 DEMYELINATING:NR DEATH: 0 WITHDRAWAL ADVERSE: (6%) SERIOUS INFECTION: 0 REACTIONS AT INJECTION SITE: 1 (2%) PNEUMONIA: NR TB:0 INFUSION RXN:NR LYMPHOMA:2 MALIGNANCY:2 DEMYELINATING:NR DEATH: 0 WITHDRAWAL ADVERSE: (6%) SERIOUS INFECTION: 3 REACTIONS AT INJECTION SITE:33 (32%) PNEUMONIA: NR TB:0 INFUSION RXN:NR LYMPHOMA:NR MALIGNANCY:0 DEMYELINATING:NR	Generation Sequence: Centraized telephone Concealment Alloc: No details Blinding: Stated double-blind; no details N Safety Placebo + SSZ: 50/50 N Safety ETN+ Placebo:103/103 N Safety ETN +SSZ: 101/101	3 arms: Placebo + SSZ vs ETN 25mg sc. twice weekly +placebo vs ETN 25mg sc. twice weekly + SSZ; Increased reactions at injection site in ETN groups, 15.8% (ETN +SSZ) vs 32% (ETN + placebo) vs 2% (placebo). No P-values provided.

#	Ref and Study Details	Interventions	Outcomes (% or incidence rate per 100 patient-years or events per patient year)	Validity	Reviewer Comments
			DEATH:0 WITHDRAWAL ADVERSE: (1%) SERIOUS INFECTION: 0 REACTIONS AT INJECTION SITE: 16 (15.8%)		
18.	Combe 2009 Months:2 years N:154 Age: ~52 Duration: ~7 years Incomplete responders to DMARDs % on steroids: 40/59/49 % on NSAIDs:NR HAQ score:1.6	Placebo + SSZ; N=50 ETN 25mg sc. twice weekly +placebo; N=103 ETN 25mg sc. twice weekly + SSZ; N=101	PNEUMONIA: NR TB:0 INFUSION RXN:NR LYMPHOMA:NR MALIGNANCY:0 DEMYELINATING:NR DEATH: 0 WITHDRAWAL ADVERSE: (8%) SERIOUS INFECTION: 0 REACTIONS AT INJECTION SITE: 2 (4%) PNEUMONIA: 1 TB:0 INFUSION RXN:NR LYMPHOMA:NR MALIGNANCY:2 DEMYELINATING:NR DEATH: 1 WITHDRAWAL ADVERSE: (19%) SERIOUS INFECTION: 11 (10.7%) REACTIONS AT INJECTION SITE:34 (33%) PNEUMONIA: 1 TB:0 INFUSION RXN:NR LYMPHOMA:NR MALIGNANCY:0 DEMYELINATING:NR DEATH:0 WITHDRAWAL ADVERSE: (10%) SERIOUS INFECTION: 5 (5%) REACTIONS AT INJECTION SITE: 21 (20.8%)	Generation Sequence: Centraized telephone Concealment Alloc: No details Blinding: Stated double-blind; no details N Safety Placebo + SSZ: 50/50 N Safety ETN+ Placebo:103/103 N Safety ETN +SSZ: 101/101	Increased serious infections, 10% (ETN + placebo), 5% (ETN + SSZ), 0 with placebo and reactions at injection site with ETN, 33% and ETN plus sulfasalazine, 20.8% vs 4% placebo group; increased rate of withdrawal due to adverse events in ETN group, 19% vs 10% and 8%; no P-values provided.

#	Ref and Study Details	Interventions	Outcomes (% or incidence rate per 100 patient-years or events per patient year)	Validity	Reviewer Comments
19.	van de Putte 2004 Months:6 N:544 Age: ~53 Duration: ~11.5 years Incomplete responders to DMARDs % on steroids: 67/68/82 % on NSAIDs:84/82/77 HAQ score:1.9	Placebo; N=110 ADA 20-40mg sc. 2 weekly or weekly; N=434	PNEUMONIA: NR TB:0 INFUSION RXN:NR LYMPHOMA:NR MALIGNANCY:1 (0.9%) DEMYELINATING:NR DEATH: 1 WITHDRAWAL ADVERSE: 4 SERIOUS INFECTION: 0 REACTIONS AT INJECTION SITE:1 (0.9%) PNEUMONIA: NR TB:0 INFUSION RXN:NR LYMPHOMA:NR MALIGNANCY:4 (0.9%) DEMYELINATING:NR DEATH: 3 WITHDRAWAL ADVERSE: 16 SERIOUS INFECTION: 10/434 (2.3%) REACTIONS AT INJECTION SITE:46 (10.6%)	Generation Sequence: Computer generated Concealment Alloc: No details Blinding: Stated double-blind; identical packaging N Safety Placebo: 106/110 N Safety ADA: 434/434	Placebo vs ADA 20-40mg sc. 2 weekly or weekly; increased reactions at injection site with ADA, 10.6% vs 0.9%; increased rate of withdrawal due to adverse events in the ADA group, 16 vs 4 subjects; no P-values provided.
20.	Fleischmann 09 Months:6 N:220 Age: ~54 Duration: ~9.5 years Incomplete responders to DMARDs % on steroids: 59/56 % on NSAIDs:NR HAQ score:1.6/1.4	Placebo + MTX; N=109 CZP 400mg 4 weekly;N-111	PNEUMONIA: 1 TB:0 LYMPHOMA:0 MALIGNANCY:0 INATING:0 DEATH: 0 WITHDRAWAL ADVERSE: 2 (1.8%) SERIOUS INFECTION: 0 OPPORTUNISTIC INFECTION:0 REACTIONS AT INJECTION SITE: NR PNEUMONIA: 1 TB:0 LYMPHOMA:0 MALIGNANCY:0 DEMYELINATING:0 DEATH: 0 WITHDRAWAL ADVERSE: 5 (4.5%) SERIOUS INFECTION: 2 (4 cases per 100 pt years) OPPORTUNISTIC INFECTION:0 REACTIONS AT INJECTION SITE:4.5%	Generation Sequence: Interactive voice Concealment Alloc: Unblinded pharmacists;blinded study personnel; Blinding: Stated double-blind; no details about patients or assessors N Safety Placebo + MTX; N=109/109 N Safety CZP;N-111/111	Increased reactions at injection site with CZP, 4.5% vs 0; increased rate of withdrawal due to adverse events in CZP group, 4.5% vs 1.8%; no P-values provided.

SAFETY DATA FROM OBSERVATIONAL STUDIES

Nam Table 9. Standardized mortality rates and relative risks of all cause mortality in patients on Biological DMARDs

Author	Biological DMARD	Patient Nos	Comparison	All Cause SMR/RR	Reviewer Comments
Watson ACR 2007 UK registry:	TNF inhibitors (Adalimumab, Etanercept, Infliximab)	9849	General population	SMR Male=2 (95% CI 1.7 to 2.3) SMR Female =1.7 (95% CI 1.5 to 1.9)	Abstract; no document filed in NLM
Jacobsson EULAR 2008 (ARTIS registry)	TNF inhibitors	6403	General population TNF naive RA patients	SMR 1.57 (95% CI 1.42 to 1.73) (RR =0.85 [95% CI 0.77 to 0.95] compared to TNF naïve)	Not filed in NLM; RR not significantly increased compared to TNF naive RA patients

Nam Table 10. Standardized mortality rates and relative risks of mortality related to specific organ systems in patients on Biological DMARDs

Author	Biological DMARD	Patient Nos	Comparison	Neoplasms SMR	Cardiovascular SMR	Respiratory SMR	Musculo-skeletal SMR	Reviewer Comments
Watson ACR 2007 UK registry	TNF inhibitors (Adalimumab, Etanercept, Infliximab)	9849	General popula-tion	Male=0.96 (95% CI 0.62 to 1.41) Female =0.79 (95% CI 0.59 to 1.04)	Male=1.77 (95% CI 1.32 to 2.32) Female =1.26 (95% CI 1.01 to 1.54)	Male=3.33 (95% CI 2.18 to 4.88) Female =2.15 (95% CI 1.55 to 2.9)	Male=66.8 (95% CI 42.8 to 99.4) Female =30.6 (95% CI 22.7 to 40.4)	Abstract; not compared to TNF naïve RA patients

SERIOUS INFECTIONS

Nam Table 11. Standardized incidence rates and relative risks of infections in patients on Biological DMARDs

Author	Biological DMARD (n=number of patients)	Comparator group	Serious infections IRR	Reviewer Comments
Curtis EULAR 2007 (US Health Care)	IFX+ADA (n=937) ETN (n=1201)	Methotrexate (n=2933)	2.4(95% CI 1.4 to 5.2)$$ 0.7(95% CI 0.3 to 1.7)** 1.2(95% CI 0.5 to 2.5)$$ 0.8(95% CI 0.5 to 1.5)**	IFX +ADA compared to MTX assoc. with increased rate serious infection only in first 6 mos; ETN not assoc. with increased infection

$$ Within 6 month of treatment start

** After 6 months of treatment start

TUBERCULOSIS

Nam Table 12. Standardised incidence rates and relative risks of tuberculosis in patients on Biological DMARDs

Author	Comparator groups	Incidence per 100 000/yr)	RR	Reviewer Comments
Gomez-Reino 2003 Spanish Registry	General population RA non biologic RA IFX	21 (in 2000) 95 1893 (in 2000) 1113 (in 2001)	1 4.13 (95% CI 2.59 to 6.83)* 53 (95% CI 35.4 to 89) (in 2001)* 11.7 (95% CI 9.5 to 14.6) (in 2001)**	IFX in RA patients associated with increased risk TB 17/1578 compared with subjects treated with ETA 0/1540
Seong 2007 (Korean registry)	General population RA non TNF RA IFX RA ETN	67.2 257 2558 0	1 8.9 (95% CI 4.60 to 17.2) 30.1 (95% CI 7.40 to 122.3)	IFX in RA patients associated with approximately 3.4 times higher risk of TB than RA patients not taking TNF; no increased risk found with ETN.
Gomez-Reino 2007 (Spanish registry)	RA IFX 5 RA ETN RA ADA	383 (95% CI 159 to 921) 114 (95% CI 28 to 459) 176 (95% CI 24 to 1245)		Cases/subjects (time to develop) IFX: 5/1303 (1.2-8.7 mos) ETN: 2/1740 (<2.5 mos) ADA: 1/565 (14 mos) Evaluated \ new cases of active tuberculosis (ATB) after

Author	Comparator groups	Incidence per 100 000/yr)	RR	Reviewer Comments
				March 2002 in patients treated with tumor necrosis factor (TNF) antagonists included in the national registry BIOBADASER (Base de Datos de Productos Biolo´gicos de la SociedadEspan˜ ola de Reumatologi´a) after the dissemination of recommendations to prevent reactivation of latent tuberculosisinfection (LTBI).
Dixon ACR 2008, 2010 (UK registry)	RA DMARD RA TNF RA IFX RA ETN RA ADA	0 111 (95% CI 77 to 154)* 131 (95% CI 68 to 228) 50 (95% CI 20 to 103) 196 (95% CI 112 to 319)	IRR 2.8 (95% CI 1.2 to 7.1) Referent 2.8 (95% CI 1.6 to 9.1)	Drug-specific data indicate risk of TB is 2.8 times higher with IFX and ADA as compared to ETN: data from abstract. Updated in 2010. Dixon 2010 update: in the anti-TNF cohort. The rate of TB was higher for the monoclonal antibodies INF (136/100 000 person-years; N=11/3718) ETN (39/100 000 person-years; N=5/5521) ADA 144 (72 to 258); N=11/7634. After adjustment, the incidence rate ratio compared with ETN-treated patients was 3.1 (95% CI 1.0 to 9.5) for INF and 4.2 (1.4 to 12.4) for ADA. The median time to event was lowest for INF (5.5 months) compared with ETA (13.4 months) and ADA (18.5 months). Patients of non-white ethnicity had a sixfold increased risk of TB compared with white patients treated with anti-TNF therapy.
Tubach EULAR 2009	General population TNF (RA; PsA; Crohn's, TA, Behcet's) IFX/ADA ETN	8.7** 39.2 71.5 6.00	OR from case control study Infliximab 13.29 (95% CI 2.56 to 69.04) Adalimumab 17.08 (95% CI 3.62 to 80.59) Etanercept 1 The standardized incidence ratio (SIR) was higher for therapy with infliximab and adalimumab than for therapy with etanercept (SIR 18.6 [95% CI 13.4 to 25.8] and SIR 29.3 [95% CI 20.3 to 42.4] versus SIR 1.8 [95% CI 0.7 to 4.3], respectively).	ORs from case control study over 3 years: TB risk in 68 TB patients and 136 control subjects receiving anti-TNF therapy, by multivariate analysis TB risk is 11.8 times higher with IFX or ADA compared to ETA.

*per 100 000 pt years; 88 per 100 000pt/yr; **March 2002 to Jan 2006

MALIGNANCY

Nam Table 13. Standardised incidence rates and relative risks of malignancy in patients on biological DMARDs

Author	Comparison	Patient Nos	All Ca SIR/*HR/OR/RR*	Haem Ca SIR/*HR*	Solid Ca SIR/*HR*	Reviewer Comments
Geborek 2005 (SSATG registry)	RA non-TNF RA-TNF	800 757	1.4 (95% CI 1.1 to 1.8) 1.1 (95% CI 0.6 to 1.8)	1.1 95% CI (0 to 1.4) 0 (95% CI 0 to 9.2)		Suggestive of no increased risk with TNFi agents
Askling 2005 (Swedish Register)	In-patient RA ERA non-TNF RA-TNF	53067 3703 4160		1.7 (95% CI 1.5 to 1.8) 1.6 (95% CI 0.9 to 2.6) 2.1 (95% CI 1.1 to 3.8)		
Askling 2005 (Swedish Register)	In-patient RA ERA non-TNF RA-TNF	53067 3703 4160			1.05 (95% CI 1.01 to 1.08) 1.1 (95% CI 0.9 to 1.3) 0.9 95% CI (0.7 to 1.2)	
Wolfe 2007	All RA RA biologics IFX ETN ADA ANA	12916 6282	*OR:* *1 (*95% CI *0.8 to 1.2)* *1 (*95% CI *0.8 to 1.3)* *1 (*95% CI *0.8 to 1.3)* *0.7 (*95% CI *0.3 to 1.6)* *0.8 (*95% CI *0.3 to 1.8)*			Incident cases 1998-2005 compared to SEER adjusted data: - Combined biologics: No increased risk with biologics for solid tumors or lymphoproliferative disorders; Increased risk for skin cancer; (OR 1.5, 95% CI 1.2 to 1.8) for combined biologics; melanoma (OR 2.3, 95% CI0.9 to 5.4); -Individual agents compared to SEER -IFX 161/4,430 OR 1.7 (1.3 to 2.2); - ETN 126/3,163 OR 1.2 (1.0 to 1.5); ADA 10/812 OR 0.9 (0.5 to 1.8). Non-significant findings may be due to type II error.
Askling EULAR 2007 (Swedish register)	General Pop RA non TNF RA TNF	470311 67094 5401	*RR of TNF compared to non-biologics 1.07 (95% CI 0.74 to 1.29)** *1.09 (95% CI 1.06,1.24)***			TNF compared to non-biologics: increased risk.
Askling EULAR 2008 (Swedish register)	RA no TNF RA TNF	66995 6403	*RR:* *0.94 (95% CI 0.8 to 1.12)*			TNF population compared to RA patients without TNF: No increased

Author	Comparison	Patient Nos	All Ca SIR/*HR/OR/RR*	Haem Ca SIR/*HR*	Solid Ca SIR/*HR*	Reviewer Comments
						risk. Type II error possible.
Burmester EULAR 2008	NCI SEER RA ADA	3421	0.89 (*95% CI* 0.68 to 1.13)			No increased risk with ADA compared to SEER data. Type II error possible.
Klareskog EULAR 2008	SEER RA ETN	2054	0.98 (*95% CI* 0.8 to 1.12)			No increased risk with ETN compared to SEER data. Type II error possible.
Abasolo ACR 2008 (Spanish register)	RA no TNF RA TNF	789 4529	*IRR (adjusted): 0.92 (95% CI 0.41 to 2.04)***			TNFi population compared to RA patients with non-biologics: No increased risk. Type II error possible.
Dixon ACR 2008 (UK register)	RA DMARDs RA TNF	118$ 177$	*RR (adjusted): 0.53 (95% CI 0.22 to 1.26)*			TNFi population compared to RA patients with non-biologics: No increased risk. Type II error possible.
Strangfeld ACR 2008 (German register)	RA conventional DMARDs RA Biologics	1836 3445			incidence rate: 5.8/1000	

- * compared to general population
- ** compared to RA non-biologic treated group
- $ patients with prior malignancies
- #excludes non-melanoma skin)

SUMMARY MALIGNANCY IFX, ADA, ETN–REGISTRY STUDIES RA

Reference	Agents and Population (N)	Outcomes^
Burmester 08	ADA in RA versus general population [SEER data used to estimate risk in general population] (3421)	ADA: SIR 0.89 (95% CI 0.69 to 1.13)
Klareskog 08	ETN versus general population (SEER data) (2054)	ETN: SIR 0.98 (95% CI 0.69 to 1.12)
Wolfe 07	IFX, ADA, ETN versus general population (SEER data) (13,001)	IFX: OR 1.0 (95% CI 0.8 to 1.3) ADA: OR 0.7 (95% CI 0.3 to 1.6) ETN: OR 1.0 (95% CI 0.8 to 1.3)

^SIR: standardized incidence rate with US population used as comparator; OR: odds ratio

LYMPHOMA

Nam Table 14 Standardised incidence rates (SIR), relative risks (RR), hazard ratios (HR) and odds ratios (OR) of lymphoma in patients receiving biological DMARDs

Author	Comparison	Patient Nos	SIR (95% CI)	RR/HR/OR (95% CI)	Reviewer Comments
Wolfe 2004	All RA RA-MTX RA biologics IFX ETN ANA	18572 5501 8614 5233 2149 58	1.9 (1.3 to 2.7) 1.7 (0.9 to 3.2) 2.9 (1.7 to 4.9) 2.2 (1.0 to 4.9)) 3.5 (2.5 to 8.4) 0		Increased rates with RA; some registry data show increased rates with TNFi; some show no increased rates with TNFi compared to nonbiological DMARDs.
Geborek 2005 (SSATG registry)	RA non-TNF RA-TNF	800 757	1.3 (0.2 to 4.5) 11.5 (3.7 to 26.9)		
Askling 2005 (Swedish Register)	In-patient RA ERA non-TNF RA-TNF	53067 3703 4160	1.9 (1.7 to 2.1) 2.0 (1.0 to 3.5) 2.9 (1.3 to 5.5)	**RR 1.1 (0.6 to 2.1)	TNFi population compared to RA patients with non-biologics: No increased risk. Type II error possible.
Setoguchi 2006	All RA RA-MTX RA-Biological DMARD	7830 7306 1152		HR^1.11 (0.51 to 2.37)	TNFi population compared to RA patients with non-biologics: No increased risk. Type II error possible.
Wolfe 2007	RA patients RA TNF RA MTX RA IFX RA ETN RA ADA	19591 10815		OR 1.0** (0.6 to 1.8) 1.3*** (0.7 to 2.4) 1.2*** (0.6 to 2.2) 0.7*** (0.3 to 1.6) 4.5*** (0.9 to 23.1) *(only 56 cases; 2 lymphoma*	Increased rates not statistically significant for any agent. Type II error posible.
Askling EULAR 2007 (Swedish register)	General population RA non TNF RA TNF	6304		*RR* *2.08(1.6 to 3.43)** *0.95 (0.5 to 1.67)***	Increased rates not statistically significant for TNFi compared to RA patients not taking TNFi. Type II error posible.
Callegari EULAR 2007 (US register)	General population (SEER) RA nonTNF RA TNF		1.76 (0.57 to 4.11) 2.08 (0.76 to 4.53)		Increased rates not statistically significant compared to SEER data for general population. Type II error posible.
Burmester EULAR 2008	NCI SEER RA ADA	3421	3.81 (1.90 to 6.81)		Increased rate compared to SEER data.
Klareskog EULAR 2008	General population (SEER)RA ETN	2054	3.53 (1.82 to 6.16)		Increased rate compared to SEER data.
Mariette ACR 2008 (French register)	General Population Total TNF RA IFX or ADA RA ETN		2.11 (1.48 to 3.00)# 4.87 (2.33 to 10.24)## 3.43 (2.4 to 5.04)# 6.86 (2.86 to 16.48)## 0.69 (0.28 to 1.65)# 2.78 (0.7 to 11.13)##		Not in NLM; suggestive of differential effect-higher risk with IFX or ADA compared to general population and non-biological DMARD group.
Smitten ACR 2008	General population (SEER) RA non Biological DMARDs RA ABAT	 41529 4150	 1.61* 0.43 to 0.88**		
Weinblatt ACR 2008	General population (SEER) RA ETN		 4.2 (1.7 to 51)		Suggests increased risk with ETN compared to general population.

- * compared to general population
- ** compared to RA nonbiologic treated group
- *** compared to all other malignancies
- ^compared to methotrexate
- $ patients with prior malignancie
- # non-Hodgkin's lymphoma
- ##Hodgkin's lymphoma

4.4 INTERSTITIAL LUNG DISEASE

Nam Table 15 Risks and standardized mortality rates of interstitial lung disease in patients on Biological DMARDs

Author	Comparitor groups	Hazards ratio	Reviewer Comments
Wolfe 2007[106]	Prednisolone Methotrexate IFX ETN	2.5 (95% CI 1.5 to 4.1) 1.2 (95% CI 0.7 to 1.9) 0.7 (95% CI 0.4 to 1.3) 0.9 (95% CI 0.4 to 1.7)	Neither IFX nor ETN reported to have statistically significantly increased risk of interstitial lung disease; referent unclear. Type II error possible.

POULIN 09 FINAL

AUTHOR YR: Poulin 09

Citation: Poulin Y, Langley RG, Teixeira HD, Martel MJ, Cheung S. Biologics in the treatment of psoriasis: clinical and economic overview. J Cutan Med Surg. 2009 Sep-Oct;13 Suppl 2:S49-57. Review. PubMed PMID: 19799827.

Study Design: Review Psoriasis

Manufacture Involvement: No

Abstract: Not included

Psoriasis

<table>
<tr><th>Reference</th><th>Reviewer Comments</th><th colspan="5">Relevant Safety Findings</th></tr>
<tr><td rowspan="6">Poulin 09
REVIEW
USED ONLY
AS SOURCE
FOR RCTS</td><td rowspan="6">• Heterogeneity in study designs, populations, duration, agents studied

Summary of ranges in 4 trials (exclude Chaudhari 01)
• SEVERE INFECTIONS IFX:0.5%
• SERIOUS AEs IFX:1.9% to 8.9%</td><td>Study</td><td>Severe Infection</td><td>Serious AE (%)</td><td>Serious Infusion Reactions or Adverse events associated with Infusion</td><td>Other</td></tr>
<tr><td>Chaudhari 01, RCT, N=31 (exclude)</td><td>NR</td><td>NR</td><td>0</td><td></td></tr>
<tr><td>Gottlieb 04 RCT reported safety outcomes through week 30; N=51 placebo, 197 combined IFX group</td><td>placebo: 0
IFX: 0.5%</td><td>placebo: 0
IFX: 6.1%</td><td>6.6% IFX,
0.3% rated as serious</td><td></td></tr>
<tr><td>Reich 05, N=378, cross-over week 24, safety outcomes through week 24</td><td>NR</td><td>placebo: 3%
IFX: 6%</td><td>placebo: 2%
IFX:3%</td><td>Malignancies
placebo: 0
IFX: 1%</td></tr>
<tr><td>Menter 06, N=835, 50 wk safety data 627 IFX patients</td><td>NR</td><td>placebo: 5 (2.4%)
IFX: 5 (1.9%)</td><td>placebo: 12 (5.8%)
IFX: 81 (4.35%)</td><td>Malignancy:
placebo: 0
induction phase
IFX: 12 (1.9%)

TB:
placebo: 0
IFX: 2 (0.32%)</td></tr>
<tr><td>Antoni 08, N=78</td><td></td><td>7/78, 8.9%
Reported in IFX group only</td><td>4/78, 5.1% IFX
Reported in IFX group only</td><td></td></tr>
</table>

REICH 05_SCHMITT 08_UHLENHAKE 10

AUTHORS YR: Reich 05, Uhlenhake 10, Schmitt 08

Citations:
Reich K, Nestle FO, Papp K, Ortonne JP, Evans R, Guzzo C, Li S, Dooley LT, Griffiths CE; EXPRESS study investigators. Infliximab induction and maintenance therapy for moderate-to-severe psoriasis: a phase III, multicentre, double-blind trial. Lancet. 2005 Oct 15-21;366(9494):1367-74. PubMed PMID: 16226614.

Schmitt J, Zhang Z, Wozel G, Meurer M, Kirch W. Efficacy and tolerability of biologic and nonbiologic systemic treatments for moderate-to-severe psoriasis: meta-analysis of randomized controlled trials. Br J Dermatol. 2008 Sep;159(3):513-26. Epub 2008 Jul 9. Review. PubMed PMID: 18627372.

Uhlenhake EE, Feldman SR. Efficacy and safety of ustekinumab and etanercept for the treatment of psoriasis. Expert Opin Biol Ther. 2010 Jul;10(7):1105-12. Review. PubMed PMID: 20446825.

Study Designs:
Reich 05: RCT
Uhlenhake 10: Systematic Review
Schmitt 08: Meta-analysis

Manufacture Involvement:
Reich 05: Centocor staff participated in study design, data analysis and manuscript writing.
Uhlenhake 10: Appears to be funded by grant from Galderma Laboratories
Schmitt 08: none

Abstract: Not included

<table>
<tr><th>Reference</th><th>Reviewer Comments</th><th>Serious AE (%)</th><th>Serious Infusion Reactions or Adverse events associated with Infusion</th><th>Other</th></tr>
<tr><td>Reich 05</td><td>• Small, 24 week crossover study</td><td>placebo: 3%
IFX: 6%</td><td>placebo: 2%
IFX:3%</td><td>Malignancies
placebo: 0
IFX: 1%</td></tr>
<tr><td>Uhlenhake 10</td><td>• Systematic review with focus on UST and ETN</td><td colspan="3">Reviewer Comments
• Narrative review
• N not provided
• Reviewed RCTs and observational studies published in past 20 years.
• No evidence of increased serious infections with ETN or UST compared to placebo.</td></tr>
<tr><td>Schmitt 08</td><td>• Meta-analysis
• ADA, IFX and ETN trials
• Assessed withdrawals
• Newer meta-analysis of 5 trials, observational studies and case reports(Schmitt 09) reported serious AEs in ADA studies: range 0.5% to 1.9%.</td><td colspan="3">Withdrawals for any reason
<table>
<tr><th>Biologic</th><th># Trials</th><th># Pts</th><th>Weighted By Number Participants Mean Average Incidence Rate (Range) Monthly Withdrawal Rate Due To Any Reason (%)</th><th>Monthly Withdrawals Due To Any Adverse Events (%)</th></tr>
<tr><td>ADA</td><td>1</td><td>814</td><td>2.9%</td><td>16.6%</td></tr>
<tr><td>ETN 2 X 25 mg weekly</td><td>2
3</td><td>253
415</td><td>1.3% (95% CI 1.0 to 2.5)</td><td></td></tr>
<tr><td>ETN 2 X 50 mg weekly</td><td>2
1</td><td>505
311</td><td>0.6% (0.6 to 0.8)</td><td>
17.6%</td></tr>
<tr><td>IFX 5mg / kg</td><td>3</td><td>711</td><td>2.5% (1.8 to 3.0)</td><td>17.8% (95 CI 12.1 to 22.5)</td></tr>
</table></td></tr>
</table>

SAAD 08_ MEASE 09_ STERRY 10_ GOTTLIEB 09

Citations:

Saad AA, Ashcroft DM, Watson KD, Hyrich KL, Noyce PR, Symmons DP; British Society for Rheumatology Biologics Register. Persistence with anti-tumour necrosis factor therapies in patients with psoriatic arthritis: observational study from the British Society of Rheumatology Biologics Register. Arthritis Res Ther. 2009;11(2):R52. Epub 2009 Apr 8. PubMed PMID: 19356232.

Mease PJ, Ory P, Sharp JT, Ritchlin CT, Van den Bosch F, Wellborne F, Birbara C, Thomson GT, Perdok RJ, Medich J, Wong RL, Gladman DD. Adalimumab for long-term treatment of psoriatic arthritis: 2-year data from the Adalimumab Effectiveness in Psoriatic Arthritis Trial (ADEPT). Ann Rheum Dis. 2009 May;68(5):702-9. Epub 2008 Aug 6. PubMed PMID: 18684743; PubMed Central PMCID: PMC2663711.

Sterry W, Ortonne JP, Kirkham B, Brocq O, Robertson D, Pedersen RD, Estojak J, Molta CT, Freundlich B. Comparison of two etanercept regimens for treatment of psoriasis and psoriatic arthritis: PRESTA randomised double blind multicentre trial. BMJ. 2010 Feb 2;340:c147. doi: 10.1136/bmj.c147. PubMed PMID: 20124563.

Gottlieb A, Menter A, Mendelsohn A, Shen YK, Li S, Guzzo C, Fretzin S, Kunynetz R, Kavanaugh A. Ustekinumab, a human interleukin 12/23 monoclonal antibody, for psoriatic arthritis: randomised, double-blind, placebo-controlled, crossover trial. Lancet. 2009 Feb 21;373(9664):633-40. Epub 2009 Feb 11. Erratum in: Lancet. 2009 Apr 18;373(9672):1340. PubMed PMID: 19217154.

Study Designs:
Saad 08: Registry
Mease 09: Follow-up data from RCT
Sterry 08: RCT
Gottlieb 09: RCT

Manufacture Involvement:
Reich 05: Centocor staff participated in study design, data analysis and manuscript writing.
Uhlenhake 10: Appears to be funded by grant from Galderma Laboratories
Schmitt 08: none
Gottlieb 09: Centocor staff participated in study design, data analysis and manuscript writing. 4 authors were employed by Centocor

Abstracts: not included

PsA

Reference	Reviewer Comments	Results	

Saad 08	• Meta-analysis; included 6 RCTs, N=982, ADA, ETN, IFX
	• Similar withdrawal rates to placebo
	• Underpowered to detect differences
		Relative Risks Compared To Placebo
		• Withdrawal for any reason: 5 trials; compared to placebo
		  ○ RR compared to placebo: ADA: 0.83 (95% CI 0.39 to 1.74)
		  ○ RR ETN: 0.24 (0.12 to 0.49)
		  ○ RR IFX: 1.50 (0.26 to 8.61)
		• Withdrawal due to AE: 5 trials
		  ○ RR compared to placebo: ADA: 1.98 (0.35 to 11.28)
		  ○ RR ETN: 1.03 (0.07 to 16.24)
		  ○ RR IFX: 2.90 (0.60 to 13.96)
		• Serious AE: 5 TRIALS
		  ○ RR ADA: 0.70 (0.25 to 1.94)
		  ○ RR ETN: 0.86 (0.25 to 3.01)
		  ○ RR IFX: 1.35 (0.56 to 3.27)
		• Injection site reactions: 4 trials
		  ○ RR ADA 1.44 (0.65 to 3.17)
		  ○ RR ETN 4.27 (2.25 to 8.13)
		• Infusion reactions: IFX
		  ○ RR 1.03 (0.48 to 2.20)	

Mease 09	• RCT (24 wk) open label extension (2 year), N=298 • Patients with PsA who completed a 24-week, double-	N/162 (%) Placebo group 24 Weeks • Severe AE: 11 (6.8) • AE leading to discontinuation: 5 (3.1) • Serious infections: 1(0.6) • Lymphoma: 0 • Non-melanoma skin cancers: 0 • Other malignancies: 0 • Injection site reactions: 5 (3.1)	N/151 (%) ADA group 24 Weeks • Severe AE: 5 (5.3) • AE leading to discontinuation: 6(4.0) • Serious infections: 1 (0.7) • Lymphoma: 0 • Non-melanoma skin cancers: 0 • Other malignancies: 0 • Injection site reactions: 10 (6.6)

<table>
<tr><td rowspan="3"></td><td rowspan="3">blind study of ADA versus placebo were eligible to enroll in an open-label extension study and receive adalimumab 40 mg subcutaneously every other week for up to an additional 120 weeks
• Supersedes reports at 24 and 48 weeks by same authors</td><td></td><td>• Non-TB opportunistic infections: 0
• TB: 0</td></tr>
<tr><td colspan="2">• N/298 (%) ADA group Up To 2 Years
○ Severe AE: 54 (18.1)
○ AE leading to discontinuation: 20 (6.7)
○ Serious infections: 15 (5.0)
○ Lymphoma: 1 (0.3)
○ Non-melanoma skin cancers: 2 (0.7)
○ Other malignancies: 1 (0.3)
○ Injection site reactions: 43 (14.4)
○ Non-TB opportunistic infections: 4 (1.3)
○ TB: 1 (0.3)
○ Heart failure: 0
○ Death: 3 (1.0)</td></tr>
<tr><td colspan="2">• Throughout 2 years of adalimumab exposure, one patient had peritoneal tuberculosis and four patients experienced opportunistic infections (oral candidiasis). One patient had nonHodgkin's B-cell lymphoma, two patients had basal cell carcinoma and one patient had neuroendocrine carcinoma of the skin.
• There were no reports of central nervous system demyelinating disease, lupus-like syndrome, congestive heart failure, or adalimumab-related allergic reactions
• Three deaths occurred among the 298 patients. One patient experienced cardiopulmonary arrest and myocardial infarction. Another patient experienced sudden death that was attributed to acute pulmonary edema. The third death was caused by myocardial infarction 104 days after the last dose of adalimumab.</td></tr>
<tr><td>Gottlieb 09</td><td>• Crossover RCT; N=146 UST
• Carryover effect likely
• All patients received UST</td><td colspan="2">• At 36 weeks serious infections were less than 1%
• Serious AEs 4.8%, 7/146
• Discontinued because of AEs 11/146, 7.5%
• Injection site reactions 8/146, 5.5%</td></tr>
<tr><td>Sterry 10</td><td>• RCT Patients with psoriasis and PsA
• ETN 50mg once (N=373)versus twice weekly (N=379)
• 12 week double blind then 12 week open label
• 98 settings Europe, Asia Pacific, SA</td><td colspan="2">Safety Summary (percentages)
<table>
<tr><th>AE</th><th>50mg BIW Weely</th><th>50 mg QW (weekly)</th><th>Total</th><th>P-Value</th></tr>
<tr><td>Any adverse event</td><td>213 (56.2)</td><td>190 (50.9)</td><td>403 (53.6)</td><td>0.16</td></tr>
<tr><td>Serious adverse events</td><td>15 (4.0)</td><td>11 (2.9)</td><td>26 (3.5)</td><td>0.55</td></tr>
<tr><td>Death</td><td>0</td><td>0</td><td>0</td><td></td></tr>
<tr><td>Malignancy</td><td>3 (0.8)</td><td>1 (0.3)</td><td>4 (0.5)</td><td>-</td></tr>
<tr><td>Serious infections</td><td>2 (0.5)</td><td>3 (0.8)</td><td>5 (0.7)</td><td>0.68</td></tr>
</table></td></tr>
</table>

SALMON-CERON OPPORTUNISTIC FRENCH REGISTRY 10 FINAL

AUTHOR YR: Salmon-Ceron 10

Citation: Salmon-Ceron D, Tubach F, Lortholary O, Chosidow O, Bretagne S, Nicolas N, Cuillerier E, Fautrel B, Michelet C, Morel J, Puéchal X, Wendling D, Lemann M, Ravaud P, Mariette X; for the RATIO group. Drug-specific risk of non-tuberculosis opportunistic infections in patients receiving anti-TNF therapy reported to the 3-year prospective French RATIO registry. Ann Rheum Dis. 2010 Dec 21. [Epub ahead of print] PubMed PMID: 21177290.

RATIO: (Research Axed on Tolerance of bIOtherapies)

Study Type: Incidence and Case-Control Study French RATIO Registry

Manufacture Involvement: Authors have received consultancy fees from relevant manufacturers which had no role in the study. RATIO was supported by a research grant from INSERM (Réseau derecherche clinique 2003 and 2006) and by an unrestricted grant from Abbott, Schering Plough and Wyeth. The pharmaceutical companies Abbott, Schering Plough and Wyeth had no role in the study design, data collection, data analysis, data interpretation or writing of the report.

Abstract

Background
Anti-tumour necrosis factor (TNF) therapy may be associated with opportunistic infections (OIs). Objective To describe the spectrum of non-tuberculosis OIs associated with anti-TNF therapy and identify their risk factors.

Methods
A 3-year national French registry (RATIO) collected all cases of OI in patients receiving anti-TNF treatment for any indication in France. A case–control study was performed with three controls treated with anti-TNF agents per case, matched for gender and underlying inflammatory disease.

Results
45 cases were collected of non-TB OIs in 43 patients receiving infliximab (n=29), adalimumab (n=10) or etanercept (n=4) for rheumatoid arthritis (n=26), spondyloarthritides (n=3), inflammatory colitis (n=8), psoriasis (n=1) or other conditions (n=5). One-third (33%) of OIs were bacterial (4 listeriosis, 4 nocardiosis, 4 atypical mycobacteriosis, 3 non-typhoid salmonellosis), 40% were viral (8 severe herpes zoster, 3 varicella, 3 extensive herpes simplex, 4 disseminated cytomegalovirus infections), 22% were fungal (5 pneumocystosis, 3 invasive aspergillosis, 2 cryptococcosis) and 4% were parasitic (2 leishmaniasis). Ten patients (23%) required admission to the intensive care unit, and four patients (9%) died. Risk factors for OIs were treatment with
infliximab (OR=17.6 (95% CI 4.3 - 72.9); p<0.0001) or adalimumab (OR=10.0 (2.3 to 44.4); p=0.002) versus etanercept, and oral steroid use >10 mg/day or intravenous boluses during the previous year (OR=6.3 (2.0 to 20.0); p=0.002).

Conclusion
Various and severe OIs, especially those with intracellular micro-organisms, may develop in patients receiving anti-TNF treatment. Monoclonal anti-TNF antibody rather than soluble TNF receptor therapy and steroid use >10 mg/day are independently associated with OI.

Reviewer Comments

- Agents of Interest: Adalimumab, etanercept, , infliximab in any indication
- Registry described as prospective.
- The French RATIO registry was designed by a multidisciplinary expert group to prospectively collect all cases of OI occurring from 1 February 2004 to 1 February 2007, in patients who were receiving or had received anti-TNF treatment before the occurrence of the OI. This registry involved cases from clinicians of all concerned medical specialties and the French drug agency (Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSAPS)) and its network of 31 regional pharmacovigilance centres.
- Authors conducted an incidence study and performed a case–control analysis to investigate the risk factors for newly diagnosed non-TB OIs in patients receiving anti-TNF agents.
- Exclusions: TB because it represented most of the collected cases of OI, as well as legionellosis, which were the subject of specific analyses.
- Cases were validated by panel of three infectious disease experts.
- For patients who had received more than one anti-TNF agent, authors considered three ways of examining the exposure: first anti-TNF agent, last anti-TNF agent, and any use of the anti-TNF agent.
- Annual incidence rate of OIs in patients receiving anti-TNF treatment was determined, adjusted for age and sex, with the French population used as reference.
- Numerator was validated OI cases.
- Denominator was based on the number of patient-years of receipt of anti-TNF agents in France during the 3-year period of the study (2004, 2005 and 2006) from different sources: the national French agency of drugs (AFSSAPS), the three pharmaceutical firms (Abbott,

Schering- Plough and Wyeth) and the Régime Social des Indépendants (RSI) (the French health insurance fund for self-employed workers).

- A case–control study was performed with cases from the RATIO registry. Patients were included in the case–control analysis if they were being treated with an anti-TNF agent at the time of first symptoms of OI or if the anti-TNF treatment had been stopped <24 months before the first symptoms.
- Controls were patients treated with anti-TNF agents (current treatment or stopped for <24 months), for a labeled indication, in whom no OI had ever developed. Three controls for each case were randomly selected from that database, matched to cases by sex and underlying inflammatory disease.
- The diagnosis of the 45 validated infections was as follows: 15 bacterial infections (four listeriosis, four nocardiosis, four atypical mycobacteriosis, three non-typhoid bacteraemic salmonellosis), 18 severe viral infections (8 severe herpes zoster, 3 varicella with visceral involvement, 3 extensive herpes simplex infection, 4 disseminated cytomegalovirus (CMV) infection), 10 fungal infections (5 pneumocystosis, 3 invasive aspergillosis, 2 cryptococcosis), and 2 parasitic infections (2 leishmaniasis).
- For the 34 patients who had received only one anti-TNF agent, 25 had received infliximab, 7 adalimumab and 2 etanercept. For the 2 patients with two OIs, 1 received infliximab for RA and presented aspergillosis, then infliximab was resumed and the patient secondarily developed listeriosis. The second received infliximab for inflammatory colitis and presented concomitantly a disseminated CMV infection and a pneumocystosis (HIV-positive patient). Six patients had another cause of immunosupression than anti-TNF (1 diabetes mellitus, 1 history of cancer, 1 AIDS, 3 chronic obstructive pulmonary disease).
- The main analysis relied on a total number of 57,711 patient-years of use of anti-TNF therapy in France during the 2004–6 study period, with 18% receiving adalimumab, 51% etanercept and 31% infl iximab as the denominator of the incidence rate. The annual incidence rate of OI adjusted for age and sex for patients receiving anti-TNF treatment, with the French population as a reference, was 151.6 (95% CI 0.0 to 468.3) per 100,000 patient-years. The incidence of OI for patients receiving anti-TNF treatment differed depending on the agent used without reaching statistical signifi cance. The annual adjusted incidence rate of OI was 7.1 (95% CI 0.0 to 24.2) per 100,000 patient-years with etanercept, 290.9 (0.0 to 835.8) with infliximab and 61.8 (0.0 to 162.5) with adalimumab.
- The case–control study involved 38 cases (only cases treated for approved indication) and 114 controls. Among them, only two had stopped anti-TNF for more than 4 months (4.33 and 11 months). In the final model of the multivariate analysis, the following factors were predictive of OI: treatment with infl ximab versus etanercept (OR=17.6 (95% CI 4.3 to 72.9), p<0.0001); treatment with adalimumab versus etanercept (OR=10.28 (95% CI 2.35 to 44.94), p=0.002), and treatment with steroids >10 mg/day or intravenous boluses during the previous year (OR=10.0 (95% CI 2.3 to 44.4), p=0.002). Multiple sensitivity analyses gave similar results.
- In almost all cases, infections were due to intracellular multiplying micro-organisms, with a severe course: 26% of patients required hospitalization in an intensive care unit and 9% died from the OI.
- Authors conclude study provides clear evidence of the high risk of occurrence of non-TB OIs with monoclonal anti-TNF antibody rather than soluble TNF receptor therapy.

Reviewer Comments

- Although the number of cases is small, the authors state the methodology of including cases when OI occurs provides the most power to detect differences and that many more cases were collected than by all other registries.
- This study demonstrated a higher risk of OI for patients receiving monoclonal antibody treatment (infliximab or adalimumab) than for those receiving soluble TNF receptor treatment (etanercept), with a 10- to 17-fold difference in risk in the case–control analysis, similar to findings in the RATIO TB study (Mariette 10). However, the 95% CIs of the OR and incidence rates are wide.
- There is a risk of missed cases. Authors make the assumption that reporting was equal between agents. However, differences in care experiences between agents could confound results.

Key Points

Agent	Annual Rate OI/100,000 Patient-years
IFX	290.9 (95% CI 0.0 to 835.8)
ADA	61.8 (95% CI 0.0 to 162.5)
ETN	7.1 (95% CI 0.0 to 24.2)
Odds Ratio (Comparator was patients receiving TNFIs without previous OI)	
Treatment with IFX versus treatment with ETN	17.6 (95% CI 4.3 to 72.9)
Treatment with ADA versus treatment with ETN	10.28 (95% CI 2.35 to 44.94)
Treatment with steroids >10 mg/day or intravenous boluses during the previous year	10.0 (95% CI 2.3 to 44.4)

SCANLON CRITIQUE SR ustekinunab psoriasis 09 FINAL

AUTHOR YR: Scanlon 09

Citation: Scanlon JV, Exter BP, Steinberg M, Jarvis CI. Ustekinumab: treatment of adult moderate-to-severe chronic plaque psoriasis. Ann Pharmacother2009 Sep;43(9):1456-65. PMID: 19671802

Study Type: SR

Agents of Interest: Ustekinumab in Psoriasis

Safety Outcomes: as reported in trials

Manufacture Involvement: Not stated.

ABSTRACT WITH RELEVANT SAFETY DATA

OBJECTIVE: To systematically review the pharmacology, pharmacokinetics, clinical efficacy, and safety profile of ustekinumab to inform pharmacists and other healthcare professionals of this new biologic therapy for psoriasis.

DATA SOURCES: A search of PubMed/MEDLINE, EMBASE, and *International Pharmaceutical Abstracts* was performed through **July 2009,** limited to publications in English, using the search terms CNTO-1275, ustekinumab, interleukin-12, interleukin-23, and/or psoriasis to identify literature sources. References from the retrieved articles were also evaluated to identify relevant literature. An abstract from a Congress of the European Academy of Dermatology and Venereology and unpublished Phase 3 clinical trials in progress (using www. clinicaltrials.gov) were also reviewed. The Food and Drug Administration, European Medicines Agency, and Health Canada Web sites were used to retrieve product monographs, regulatory guidances, and advisory committee briefing packets.

STUDY SELECTION AND DATA EXTRACTION: All available studies relevant to the pharmacology, pharmacokinetics, and clinical safety/efficacy of ustekinumab for the treatment of psoriasis were included, with preference for human data.

DATA SYNTHESIS: Ustekinumab is an anti-interleukin-12/23 monoclonal antibody.The frequency of adverse events was similar between ustekinumab and placebo; common adverse events reported included nasopharyngitis, upper respiratory tract infection, headache, arthralgia, cough, and injection site reactions. Phase 3 studies indicate that the optimal dosing appears to be 45 mg for patients weighing less than 100 kg or 90 mg for patients weighing more than 100 kg, with both doses administered subcutaneously. In these studies, the second dose was given 4 weeks after the first and then every 8–12 weeks thereafter, based upon response.

CONCLUSIONS: Ustekinumab was well tolerated in clinical trials. Ongoing clinical trials will allow clinicians to further assess the efficacy/safety profile of this novel biologic. KEY WORDS: CNTO-1275, interleukin-12, interleukin-23, psoriasis, ustekinumab. *Ann Pharmacother* 2009;43:1456-65.

Reviewer Comments

- Study details provided but formal quality assessment of trials not done.
- 3 trials included in safety review, N not stated.
- Search quality: high
- Search dates: 1966 through July 2009
- Heterogeneity: not provided.
- Power: high likelihood of being underpowered to detect differences between groups if they exist.
- Studies were relatively small

Primary Studies Included in Safety Review

Krueger GG, Langley RG, Leonardi C, et al. A human interleukin-12/23 monoclonal antibody for the treatment of psoriasis. N Engl J Med 2007; 356:580-92. DOI 10.1056/NEJMoa062382

Leonardi CL, Kimball AB, Papp KA, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo- controlled trial (PHOENIX 1). Lancet 2008;371:1665-74. DOI 10.1016/S0140-6736(08)60725-4

Papp KA, Langley RG, Lebwohl M, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo- controlled trial (PHOENIX 2). Lancet 2008;371:1675-84. DOI 10.1016/S0140-6736(08)60726-6

Primary Studies Included in Safety Review (Weighted Mean Of The Group For Each Trial)

Category	Papp 08	Leonardi 08	Krueger 07
Sample size (N)	1230	766	320
Age (y)	46	45	45
Sex (% male)	68.3	69.3	69.2
Weight (kg)	91	93.9	92.9
Duration of psoriasis (y)	20.1	19.9	18.2
BSA involved (%)	26.4	26.7	27.2
PGA (% marked or severe)	39.70	43.70	NR
PASI score	19.6	20.2	19.1
DLQI score	12.4	11.5	12.08
Pts. with latent tuberculosis (%)	3.5	3.2	0

BSA = body surface area; DLQI = Dermatology Life Quality Index; NR = not reported; PASI = Psoriasis Area and Severity Index; PGA = Physician's Global Assessment.

Adverse Events

Authors reviewed the 3 large-scale clinical trials with published safety data conducted in patients with moderate-to severe psoriasis and concluded ustekinumab can be classified as generally well tolerated, as demonstrated by its comparable safety profile to placebo. The most common adverse events (>5%) reported in the large-scale PHOENIX trials were nasopharyngitis and upper respiratory tract infection; headache, arthralgia, cough, and injection site reactions were also commonly reported.

Authors concluded that ustekinumab may have the potential for causing several serious adverse events, such as malignancy, infections, and immunogenicity, due to its selective immunomodulator activity. Despite this potential, based on the placebo-controlled data available, there does not appear to be a significant risk of malignancy with ustekinumab use.

In the PHOENIX trials, most of the reported cancers in any of the study arms were cutaneous malignancies. Any assessment of causality is inherently confounded by the high rate of baseline phototherapy (>50%) in these patients. In the placebo-controlled trials conducted in patients with psoriasis, the incidence of malignancies, excluding nonmelanoma skin cancers, was 0.36 per 100 patient-years of follow-up for ustekinumab-treated patients (8 patients in 2249 patientyears of follow-up), similar to the rate in the general population.

12-week data from the ACCEPT trial revealed 3 patients in the ustekinumab arms with non- melanoma skin cancers; however, given the short trial duration, the clinical relevance is unknown.

Despite the fact that infections occurred in more than 20% of patients, rates were similar when compared with placebo; both serious and nonserious infections occurred at similar rates to placebo in the PHOENIX trials

The **combined rate of infection** exhibited in these trials was 1.39 per patient-year of follow-up in ustekinumab treated patients and 1.21 per patient-year of follow-up in placebo-treated patients. In the pivotal trials (Leonardi 08, Papp 08) rates for serious infections were:

Study	Leonardi 08			Papp 08		
Category	Placebo N=255	UST 45 mg N=255	UST 90 mg N=255	Placebo N=405	UST 45 mg N=409	UST 90 mg N=411
Serious Infections	2 (0.5)	0	1 (0.2)	1 (0.4)	0	2 (0.8)
Cutaneous Cancers	1 (0.2)	0	1 (0.2)	0	0	0
Noncutaneous Cancers	1 (0.2)	0	0	0	0	0
CV Events	0	0	1 (0.2)	0	1 (0.4)	0

Twenty-four serious infections were reported, including pneumonias, urinary tract infections, viral infections, osteomyelitis, diverticulitis, and cellulitis, in all of the placebo-controlled trials, including 2251 patients treated with ustekinumab.

Anti-ustekinumab antibody formation was rarely observed in psoriasis clinical trials (approximately 5% of all ustekinumab-treated patients). Although a correlation between antibody formation and efficacy has not been proven, there was a trend toward lower ustekinumab serum concentrations and less of a clinical response seen in patients who were seropositive for anti-ustekinumab antibodies.

Key point: Three of these RCTs, totaling 2,316 patients reported a serious infection rate of less than 1% for placebo, UST 45mg and UST 90 mg groups up to 12 weeks.

SCHIFF TUBERCULOSIS RA IFX 06 FINAL

AUTHOR YR: Schiff 06

Citation: Schiff MH, Burmester GR, Kent JD, Pangan AL, Kupper H, Fitzpatrick SB, Donovan C. Safety analyses of adalimumab (HUMIRA) in global clinical trials and US postmarketing surveillance of patients with rheumatoid arthritis. Ann Rheum Dis. 2006 Jul;65(7):889-94. Epub 2006 Jan 26. PubMed PMID: 16439435.

Manufacture Involvement: 3/5 authors employed by Abbott Laboratories. In addition Michael Nissen, ELS, of Abbott Laboratories; and Discovery International of Chicago participated in the writing of the manuscript. Joseph Beason of Abbott Laboratories participated in data acquisition.

Abstract

Objective: To assess the safety of adalimumab in global clinical trials and postmarketing surveillance among patients with rheumatoid arthritis (RA).

Methods: Safety data for adalimumab treated patients from randomised controlled trials, open label extensions, and two phase IIIb open label trials were analysed. In addition, postmarketing spontaneous reports of adverse events in the United States were collected following Food and Drug Administration approval of adalimumab on 31 December 2002.

Results: As of 15 April 2005, the RA clinical trial safety database analysed covered 10 050 patients, representing 12 506 patient-years (PYs) of adalimumab exposure. The rate of serious infections, 5.1/ 100 PYs, was comparable to that reported on 31 August 2002 (4.9/100 PYs), and to published reports of RA populations naive to anti-tumour necrosis factor (TNF) therapy. Following implementation of tuberculosis (TB) screening in clinical trials, the rate of TB decreased. There were 34 cases of TB as of this analysis (0.27/100 PYs). The standardised incidence ratio for lymphoma was 3.19 (95% CI 1.78 to 5.26), consistent with the observed increased incidence in the general RA population. As of 30 June 2005, there were an estimated 78 522 PYs of exposure to adalimumab in the US postmarketing period. Seventeen TB cases were spontaneously reported (0.02/100 PYs) from the US. Rates of other postmarketing events of interest, such as congestive heart failure, systemic lupus erythematosus, opportunistic infections, blood dyscrasias, lymphomas, and demyelinating disease, support observations from clinical trials.

Conclusion: Analyses of these data demonstrate that long term adalimumab treatment is generally safe and well tolerated in patients with RA.

Reviewer Comments

- Agents of Interest: ADA
- Useful post-marketing data

Summary

Relative Risk Of Demyelinating Disease In Controlled And Open Label Clinical Trials of RA Patients Receiving ADA

Reference	Population	Experimental Incidence/100,000	Control Incidence/100,000 (from Incidence of Multiple Sclerosis and Optic Neuritis in US population)	RR^
Schiff 06	Adalimumab in RA	80 (10 of 12,506)	8.0	1.3

^95% CI not reported

Relative Risk Of Demyelinating Disease In Post-Marketing Surveillance Studies Of RA Patients Receivng ADA

Reference	Population	Experimental Incidence/100,000	Control Incidence/100,000 8.0(from Incidence of MS and ON in US population)	RR^
Schiff 06	Adalimumab in RA	~7.0 (of 78,522)	8.0	1.3

Abbreviations: 0N= optic neuritis, MS=multiple sclerosis
*Assumed 1 year of exposure
^95% CI not reported

Risk of Tuberculosis

The incidence of tuberculosis prior to routine TB screening in patients receiving adalimumab was 7 cases of TB in 534 patient-years (PY) of adalimumab exposure (1.3/100 PY), but the incidence was only 23 cases in 7,058 PY (0.27/100 PY) beginning in 1999 when trial protocols called for tuberculosis screening. Following the initiation of TB screening 5/866 patients receiving tuberculosis prophylaxis (0.6%) developed active tuberculosis.

SEONG KOREAN REGISTRY 07 FINAL

AUTHOR YR: Seong 07

Citation: Seong SS, Choi CB, Woo JH, Bae KW, Joung CL, Uhm WS, Kim TH, Jun JB, Yoo DH, Lee JT, Bae SC. Incidence of tuberculosis in Korean patients with rheumatoid arthritis (RA): effects of RA itself and of tumor necrosis factor blockers. J Rheumatol. 2007 Apr;34(4):706-11. Epub 2007 Feb 15. PubMed PMID: 17309133.

Study Type: Registry Korean

Manufacture Involvement: No mention.

Abstract

OBJECTIVE: To elucidate the incidence rate and relative risk of tuberculosis (TB) in patients with rheumatoid arthritis (RA) and in patients with RA treated with tumor-necrosis-factor (TNF) blockers in Korea.

METHODS: Using data from the Korean National Tuberculosis Association (KNTA) as a control and data from a single-center cohort of patients with RA, we conducted an evaluation of 1285 patients with RA not exposed to TNF blockers and reviewed medical records of 90 and 103 patients with RA treated with infliximab and etanercept, respectively, between 2001 and 2005. RESULTS: The mean incidence rate of TB, reported by the KNTA, was 67.2 per 100,000 person years (PY) from 2001 to 2004. In the TNF-blocker-naïve RA cohort, 9 cases of TB developed during 3497 PY of followup (257 per 100,000). In the infliximab-treated RA group, 2 cases of TB developed during 78.17 PY of followup (2558 per 100,000 PY), and there was no case of TB during 73.67 PY of followup in the etanercept-treated RA group. The risk of TB was higher in RA patients not treated with TNF blockers (sex- and age-adjusted risk ratio 8.9; 95% confidence interval 4.6-17.2), and in those treated with infliximab (sex- and age-adjusted risk ratio, 30.1; 95% confidence interval, 7.4-122.3) compared with the general Korean population.

CONCLUSION: The risk of TB infection is 8.9-fold higher in Korean patients with RA and 30.1-fold higher in RA patients treated with infliximab, compared with the general Korean population.

Reviewer Comments

Risk of TB by Biologic DMARD (Seong 07)

Agent	Cases/Subjects (Time-to-Develop)	Sex- And Age-adjusted Risk Ratio (Compared to Korean Population)
IFX	2/90	30.1 (95% CI 7.4 to 122.3)
ETN	0/103	1

- Korean Tuberculosis Surveillance System (KTBS) is an Internet-based reporting system serving 254 public health centers and 3 TB-specialized hospitals in the public sector, as well as 282 general hospitals, 636 hospitals, and 18,869 clinics in the private sectors, to report new TB patients to the Korean Center for Disease Control and Prevention (CDC) and the KNTA. It is mandatory for physicians to report active TB to the KTBS in Korea.
- Followup period of this study was short (8.6 ± 6.4 months).

Systematic Review of Safety of Biologic Agents in Rheumatoid Arthritis, Psoriasis and Psoriatic Arthritis: Six Agents

SINGH 09 COCHRANE BIOLOGICS RA 09 FINAL

AUTHOR YR: Singh 09

Citation: Singh JA, Christensen R, Wells GA, Suarez-Almazor ME, Buchbinder R, Lopez-Olivo MA, Tanjong Ghogomu E, Tugwell P. Biologics for rheumatoid arthritis: an overview of Cochrane reviews. *Cochrane Database of Systematic Reviews* 2009, Issue 4. Art. No.: CD007848. DOI: 10.1002/14651858.CD007848.pub2.

Study Type: SR and Meta-analysis

Agents of Interest: Adalimumab, etanercept, infliximab, in RA

Safety Outcomes: Withdrawal due to serious adverse events

Manufacture Involvement: No.

PUBLISHED ABSTRACT SAFETY INFORMATION

Background

The biologic disease-modifying anti-rheumatic drugs (DMARDs) are very effective in treating rheumatoid arthritis (RA), however there is a lack of head-to-head comparison studies. Objectives To compare the efficacy and safety of abatacept, adalimumab, anakinra, etanercept, infliximab, and rituximab in patients with RA.

Methods

This 'Overview of Reviews' was done by including all Cochrane Reviews on Biologics for RA available in The Cochrane Library. We included only data on standard dosing regimens for these biologic DMARDs from placebo-controlled trials. The primary efficacy and safety outcomes were ACR50 and withdrawals due to adverse events. We calculated Odds Ratios (OR) for efficacy and safety outcomes and combined estimates of events across the placebo groups as the expected Control Event Rate (CER). Indirect comparisons of biologics were performed for efficacy and safety using a hierarchical generalized linear mixed model (GLMM) incorporating the most important study-level characteristic (i.e. type of biologic) as a fixed factor and study and study*drug interaction as random factors.

Main results

From the six available Cochrane reviews, we obtained data from seven studies on abatacept, eight on adalimumab, five on anakinra, four on etanercept, four on infliximab, and three on rituximab. In terms of safety, adalimumab was more likely to lead to withdrawals compared to etanercept, with a ratio of ORs of 1.89 (1.18 to 3.04; P = 0.009); anakinra more likely than etanercept, 2.05 (1.27 to 3.29; P = 0.003); and likewise etanercept less likely than infliximab, 0.37 (0.19 to 0.70; P = 0.002).

Authors' conclusions

Etanercept seemed to cause fewer withdrawals due to adverse events than adalimumab, anakinra and infliximab. Significant heterogeneity in characteristics of trial populations imply that these finding must be interpreted with caution. These findings can inform physicians and patients regarding their choice of biologic for treatment of RA.

Reviewer Comments

- Six Cochrane reviews with 8 studies on adalimumab in adults (2944 subjects with safety evaluations), 4 on etanercept (1248 subjects with safety evaluations) and 4 on infliximab (835 subjects with safety evaluations).
- Search quality: high
- Inclusion criteria: Completed/updated/available Cochrane systematic reviews of biologic DMARDs for RA. A review was included if it contained at least one RCT, had clinically relevant outcomes, and included clear inclusion and exclusion criteria for studies. They only included studies using the standard dosing regimens of biologic DMARDs.
- Interventions: Biologic DMARDs (including abatacept, adalimumab, anakinra, etanercept, infliximab, rituximab and other biologic DMARDs) alone used in standard, approved-doses or in combination with other biologic/traditional DMARD compared to placebo alone or to placebo plus biologic/traditional DMARD.
- For infliximab, the review included randomized controlled trials comparing infliximab 1, 3, 5 or 10 mg/kg with methotrexate (MTX) to MTX alone, or without MTX to placebo, with a minimum duration of 6 months and at least 2 infusions.
- For adalumimab, the review included randomized controlled trials (RCTs) or controlled clinical trials (CCTs) comparing adalimumab alone or in combination with DMARDs to placebo or other DMARDs.
- For etanercept, the review included randomized controlled (RCTs) or controlled clinical trials (CCTs) comparing etanercept to placebo, etanercept to methotrexate, or etanercept plus methotrexate to methotrexate alone that were of at least six months duration.
- Using GRADE* ratings the quality of evidence was rated as low for adalumimab, moderate for etanercept and high for infliximab. Randomization and blinding were not described and allocation concealment was not clear in 7 of the adalimumab studies: Breedveld 2007; Furst 2003; Keystone 2004; Kim 2007; Miyasaka 2008; van de Putte 2004; Weinblatt 2003.
- Non-standard doses were used in some trials.
- The etanercept trials included a study without a description of randomization (TEMPO 2004); in another etanercept trial allocation concealment and blinding were not described (COMET 2008).
- Withdrawals due to adverse events were significantly higher in patients allocated to adalimumab, NNH 39 (19 to 162) and infliximab, NNH 18 (8 to 72) than in those allocated to placebo.

- Withdrawals due to etanercept did not differ significantly from placebo.
- Indirect comparisons for withdrawals due to adverse events showed that adalimumab and infliximab each were significantly more likely to lead to withdrawals compared to etanercept.
- The authors reviewed a previous systematic review (Lee YH, Woo JH, Rho YH, Choi SJ, Ji JD, Song GG. Metaanalysis of the combination of TNF inhibitors plus MTX compared to MTX monotherapy, and the adjusted indirect comparison of TNF inhibitors in patients suffering from active rheumatoid arthritis. *Rheumatology International* 2008;**28**(6):553–9.) and concluded that the the authors of the earlier review failed to reduce the between-study variation and did not interpret their data in absolute terms. Withdrawals due to adverse events among the 3 TNF inhibitors in the earlier meta-analysis were as follows: etanercept versus infliximab, 1.01 (95% CI 0.30 to 3.42, P = 0.98); etanercept versus adalimumab, 0.38 (0.17 to 0.86, P= 0.02); and infliximab versus adalimumab, 0.37 (0.11 to 1.36, P=0.14).
- The Cochrane comparisons suggest that increased adherence to treatment is likely with etanercept compared to adalimumab and infliximab.
- Suggestive of decreased incidence of withdrawals due to adverse events with etanercept compared infliximab OR 0.37 (0.19 to 0.70; P = 0.002).
- Suggestive of increased incidence of withdrawals due to adalimumab compared to etanercept OR 1.89 (1.18 to 3.04; P = 0.009).

*GRADE: The GRADE approach to evaluating quality of studies specifies four levels of quality:

- High quality for randomized trials; or double-upgraded observational studies;
- Moderate quality for downgraded randomized trials; or upgraded observational studies;
- Low quality for double-downgraded randomized trials; or observational studies; and,
- Very low quality for triple-downgraded randomized trials or downgraded observational studies or case series/case reports.

  Authors could downgrade randomized trial evidence by one or two levels depending on the presence of five factors:
  - Serious (-1) or very serious (-2) limitation to study quality
  - Important inconsistency (-1)
  - Some (-1) or major (-2) uncertainty about directness
  - Imprecise or sparse data (-1)
  - High probability of reporting bias (-1).

Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, et al.Grading quality of evidence and strength of recommendations. BMJ 2004;328(7454):1490.

Primary Studies Included in Cochrane Review

Bejarano V, Quinn M, Conaghan PG, Reece R, Keenan AM, Walker D, Gough A, Green M, McGonagle D, Adebajo A, Jarrett S, Doherty S, Hordon L, Melsom R, Unnebrink K, Kupper H, Emery P. Effect of the early use of the anti-tumor necrosis factor adalimumab on the prevention of job loss in patients with early rheumatoid arthritis. Arthritis Rheum2008 Oct 15;59(10):1467-74.
Breedveld FC, Weisman MH, Kavanaugh AF, Cohen SB, Pavelka K, van Vollenhoven R, Sharp J, Perez JL, Spencer-Green GT. The PREMIER study: A multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. Arthritis Rheum2006 Jan;54(1):26-37.
Emery P, Breedveld FC, Hall S, Durez P, Chang DJ, Robertson D, Singh A, Pedersen RD, Koenig AS, Freundlich B. Comparison of methotrexate monotherapy with a combination of methotrexate and etanercept in active, early, moderate to severe rheumatoid arthritis (COMET): a randomised, double-blind, parallel treatment trial. Lancet2008 Aug 2;372(9636):375-82.
Furst DE, Schiff MH, Fleischmann RM, et al. Adalimumab, a fully human anti tumor necrosis factor-alpha monoclonal antibody, and concomitant standard antirheumatic therapy for the treatment of rheumatoid arthritis: results of STAR (Safety Trial of Adalimumab in Rheumatoid Arthritis).[see comment]. Journal of Rheumatology. 2003;30:2563-2571.
Keystone E, Heijde D, Mason D, Jr., Landewe R, Vollenhoven RV, Combe B, Emery P, Strand V, Mease P, Desai C, Pavelka K. Certolizumab pegol plus methotrexate is significantly more effective than placebo plus methotrexate in active rheumatoid arthritis: findings of a fifty-two-week, phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Arthritis Rheum2008 Nov;58(11):3319-29.
Kim H, Lee S, Song Y, Yoo D, Koh EM, Yoo B, et al. A randomized, doubleblind, placebo controlled, phase III study of the human anti-tumor necrosis factor antibody adalimumab administered as subcutaneous injections in Korean rheumatoid arthritis patients treated with methotrexate. APLAR Journal of Rheumatology. 2007;10: 9-16.
Klareskog L, van der Heijde D, de Jager JP, Gough A, Kalden J, Malaise M, Martin Mola E, Pavelka K, Sany J, Settas L, Wajdula J, Pedersen R, Fatenejad S, Sanda M. Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. Lancet2004 Feb 28;363(9410):675-81
Lipsky PE, van der Heijde DM, St Clair EW, Furst DE, Breedveld FC, Kalden JR, et al. Infliximab and methotrexate in the treatment of rheumatoid arthritis. Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. New England Journal of Medicine. 2000 Nov 30;343(22):1594-602.

Maini R, St Clair EW, Breedveld F, Furst D, Kalden J, Weisman M, Smolen J, Emery P, Harriman G, Feldmann M, Lipsky P. Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. Lancet1999 Dec 4;354(9194):1932-9.
Miyasaka N. Clinical investigation in highly disease-affected rheumatoid arthritis patients in Japan with adalimumab applying standard and general evaluation: the CHANGE study. Modern Rheumatology. 2008;18(3): 252-62.
Moreland LW, Schiff MH, Baumgartner SW, Tindall EA, Fleischmann RM, Bulpitt KJ, Weaver AL, Keystone EC, Furst DE, Mease PJ, Ruderman EM, Horwitz DA, Arkfeld DG, Garrison L, Burge DJ, Blosch CM, Lange ML, McDonnell ND, Weinblatt ME. Etanercept therapy in rheumatoid arthritis. A randomized, controlled trial. Ann Intern Med1999 Mar 16;130(6):478-86.
Quinn MA, Conaghan PG, O'Connor PJ, KarimZ,Greenstein A, Brown A, et al. Very early treatment with infliximab in addition to methotrexate in early, poor-prognosis rheumatoid arthritis reduces magnetic resonance imaging evidence of synovitis and damage, with sustained benefit after infliximab withdrawal: results from a twelvemonth randomized, doubleblind, placebocontrolled trial. Arthritis and Rheumatism. 2005 Jan;52(1): 27-35.
St Clair EW, van der Heijde DM, Smolen JS, Maini RN, Bathon JM, Emery P, Keystone E, Schiff M, Kalden JR, Wang B, Dewoody K, Weiss R, Baker D. Combination of infliximab and methotrexate therapy for early rheumatoid arthritis: a randomized, controlled trial. Arthritis Rheum 2004 Nov;50(11):3432-43.
van de Putte LB, Atkins C, Malaise M, Sany J, Russell AS, van Riel PL, Settas L, Bijlsma JW, Todesco S, Dougados M, Nash P, Emery P, Walter N, Kaul M, Fischkoff S, Kupper H. Efficacy and safety of adalimumab as monotherapy in patients with rheumatoid arthritis for whom previous disease modifying antirheumatic drug treatment has failed. Ann Rheum Dis2004 May;63(5):508-16.
Weinblatt ME, Keystone EC, Furst DE, Moreland LW, Weisman MH, Birbara CA, Teoh LA, Fischkoff SA, Chartash EK. Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. Arthritis Rheum2003 Jan;48(1):35-45.
Weinblatt ME, Kremer JM, Bankhurst AD, Bulpitt KJ, Fleischmann RM, Fox RI, Jackson CG, Lange M, Burge DJ. A trial of etanercept, a recombinant tumor necrosis factor receptor:Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. N Engl J Med1999 Jan 28;340(4):253-9.

Comparison of Biologics to Placebo for Safety (Withdrawals Because of Adverse Events)

BIOLOGIC	WITHDRAWALS BIOLOGIC	WITHDRAWALS PLACEBO	ODDS RATIO
ADA: 8 Trials	123/1822	54/1122	1.57 (95% CI 1.11 to 2.21)
ETN: 4 Trials	56/642	70/606	0.75 (95% CI 0.52 to 1.09)
IFX: 4 Trials	40/455	16/380	1.79 (95% CI 0.56 to 5.73)

Indirect Comparison of Biologics for Safety (Withdrawals Because of Adverse Events)

Drug 1	Drug 2	Odds Ratio	Favors
ADA	ETN	1.89 (95% CI 1.18 to 3.04)	ETN
ADA	IFX	0.70 (95% CI 0.38 to 1.28)	ADA
ETN	IFX	0.37 (95% CI 0.19 to 0.7)	ETN

Key Points:

This review included 8 ADA trials (2944 subjects with safety evaluations), 4 ETN trials (1248 subjects with safety evaluations) and 4 IFX trials (835 subjects with safety evaluations). ADA was more likely to lead to withdrawals compared to ETN, with a ratio of ORs of 1.89 (95% CI 1.18 to 3.04), P = 0.009. ETN was less likely than IFX to result in withdrawals than placebo with a ratio of ORs of 0.37 (95% CI 0.19 to 0.70), P = 0.002 compared to controls. The Cochrane investigators estimated the NNH (withdrawal due to adverse event) and 95% confidence interval (CI) compared to placebo as follows (studies were of 6 to 12 months duration): 39 (95% CI 19 to 162) for ADA and 18 (95% CI 8 to 72) for infliximab. Based on this data, an additional 5 to 6 patients out of 100 treated with IFX and an additional 2 to 3 patients treated with ADA will withdraw compared to ETN.

SINGH SR GOLIMUMAB RA cochrane 10 FINAL UPDATED DELFINI

AUTHOR YR: Singh 10

Citation: Singh JA, Noorbaloochi S, Singh G. Golimumab for rheumatoid arthritis: a systematic review. J Rheumatol. 2010 Jun;37(6):1096-104. Epub 2010 May 1. Review. PubMed PMID: 20436075.

Study Type: SR and Meta-analysis

Agents of Interest: Golimumbab (GLM) Simponi in RA

Safety Outcomes: serious adverse events, infections, serious infections, lung infections, tuberculosis, cancer, withdrawals due to adverse events and deaths.

Manufacture Involvement: No.

PUBLISHED ABSTRACT WITH RELEVANT SAFETY DATA COCHRANE

Background
Golimumab is a humanized inhibitor of tumor necrosis factor-alpha, recently approved by the Food and Drug Administration (FDA) for the treatment of Rheumatoid arthritis (RA).

Objectives The objective of this systematic review was to compare the efficacy and safety of golimumab (alone or in combination with DMARDs or biologics) to placebo (alone or in combination with DMARDs or biologics) in randomized or quasi-randomized clinical trials in adults with RA.

Search strategy
An expert librarian searched six databases for any clinical trials of golimumab in RA, including the Cochrane Central Register of Controlled Trials (CENTRAL), OVID MEDLINE, CINAHL, EMBASE, Science Citation Index (Web of Science) and Current Controlled Trials databases.

Selection criteria
Studies were included if they used golimumab in adults with RA, were randomized or quasi-randomized and provided clinical outcomes. Data collection and analysis Two review authors (JS, SN) independently reviewed all titles and abstracts, selected appropriate studies for full review and reviewed the full-text articles for the final selection of included studies. For each study, they independently abstracted study characteristics, safety and efficacy data and performed risk of bias assessment. Disagreements were resolved by consensus. For continuous measures, we calculated mean differences or standardized mean differences and for categorical measures, relative risks. 95% confidence intervals were calculated.

Main results
Four RCTs with 1,231 patients treated with golimumab and 483 patients treated with placebo were included. Of these, 436 were treated with the FDA-approved dose of golimumab 50 mg every four weeks. No significant differences were noted between golimumab and placebo regarding serious adverse events, infections, serious infections, lung infections, tuberculosis, cancer, withdrawals due to adverse events and deaths.

Reviewer Comments

- Authors state that randomized controlled trials included in the review are limited in their ability to assess safety. They searched U.S. Food and Drug Administration (FDA) web site for labels and warnings and other similar regulatory agency's web sites to summarize warnings related to golimumab.
- 148 relevant studies, 4 included in review
- Cochrane N=1231
- Search quality: high
- Search dates: 1966 to June Week 3, 2009
- Additional safety searches: FDA web site for warnings and adverse events related to golimumab use on 09/01/2009.
- Inclusion criteria: Studies were included if they used golimumab in adults with RA, were randomized or quasi-randomized and provided clinical outcomes.
- Intervention: golimumab 50 mg and 100 mg every four weeks plus methotrexate verus placebo plus methotrexate.
- Quality assessment
    - The following were assessed: blinding of participant, care provider and outcome assessor in the studies, allocation concealment, random sequence generation, incomplete outcome data, and selective outcome reporting. Each trial was assessed as being at high, low or unclear risk of bias. All studies reported adequate methods of randomization, allocation concealment and blinding.
    - The overall possibility of bias rated as low.
- Heterogeneity: moderately high and statistically significant heterogeneity in the golimumab 50 mg and 100 mg every four weeks plus

methotrexate verus placebo plus methotrexate groups with I^2 values of 76% and 77%(P-values of 0.005 for each).
- Studies were relatively small and of relatively short duration.
- Golimumab (50mg every 4-weeks) was not associated with statistically significant higher risk of infections, serious infections, tuberculosis, lung infections, cancer or death in Cochrane review.
- Withdrawals due to adverse events not statistically significantly different in groups.
- None of the RCTs had safety as the primary outcome.
- High likelihood of being underpowered to detect differences between groups if they exist.

Additional Information From Delfini Updated Search and Review of Additional Studies
- Keystone 10: Patients who received the 100 mg dose of golimumab with or without methotrexate appeared to have greater rates of serious adverse events and serious infections compared with patients who received 50 mg with methotrexate.
- Kremer 10 reported increased serious adverse events and serious infections with GLM compared to placebo.

Conclusions
- Based on safety data from 2723 patients, there are weak signals of increased serious adverse events and serious infections with GLM compared to placebo and a suggestion of higher rates with 100mg doses. Long-term surveillance studies and RCTs with safety as primary outcome are needed to provide reliable safety data.

Primary Studies Included in Cochrane Review

Emery P, Fleischmann RM, Moreland LW, Hsia EC, Strusberg I, Durez P, et al. Golimumab, a human anti-tumor necrosis factor alpha monoclonal antibody, injected subcutaneously every four weeks in methotrexate-naive patients with active rheumatoid arthritis: Twenty-four-week results of a phase III, multicenter, randomized, double-blind, placebo-controlled study of golimumab before methotrexate as first-line therapy for early-onset rheumatoid arthritis. *Arthritis Rheum* 2009;60(8):2272–83.

Kay J, Matteson EL, Dasgupta B, Nash P, Durez P, Hall S, et al. Golimumab in patients with active rheumatoid arthritis despite treatment with methotrexate: a randomized, double-blind, placebocontrolled, dose-ranging study. *Arthritis Rheum* 2008;58:964–75.

Keystone EC, Genovese MC, Klareskog L, Hsia EC, Hall ST, Miranda PC, et al. Golimumab, a human antibody to tumour necrosis factor {alpha} given by monthly subcutaneous injections, in active rheumatoid arthritis despite methotrexate therapy: the GO-FORWARD Study. *Ann Rheum Dis* 2009;68:789–96.

Smolen JS, Kay J, Doyle MK, Landewe R, Matteson EL, Wollenhaupt J, et al. Golimumab in patients with active rheumatoid arthritis after treatment with tumour necrosis factor alpha inhibitors (GO-AFTER study): a multicentre, randomised, double-blind, placebo-controlled, phase III trial. *Lancet* 2009;374(9685):210–21.

UPDATED SEARCH 11/15/10

Kavanaugh A, McInnes I, Mease P, Krueger GG, Gladman D, Gomez-Reino J, Papp K, Zrubek J, Mudivarthy S, Mack M, Visvanathan S, Beutler A. Golimumab, a new human tumor necrosis factor alpha antibody, administered every four weeks as a subcutaneous injection in psoriatic arthritis: Twenty-four-week efficacy and safety results of a randomized, placebo-controlled study. Arthritis Rheum2009 Apr;60(4):976-86.PMID: 19333944

Keystone E, Genovese MC, Klareskog L, Hsia EC, Hall S, Miranda PC, Pazdur J, Bae SC, Palmer W, Xu S, Rahman MU. Golimumab in patients with active rheumatoid arthritis despite methotrexate therapy: 52-week results of the GO-FORWARD study. Ann Rheum Dis2010 Jun;69(6):1129-35.

Kremer J, Ritchlin C, Mendelsohn A, Baker D, Kim L, Xu Z, Han J, Taylor P. Golimumab, a new human anti-tumor necrosis factor alpha antibody, administered intravenously in patients with active rheumatoid arthritis: Forty-eight-week efficacy and safety results of a phase III randomized, double-blind, placebo-controlled study. Arthritis Rheum2010 Apr;62(4):917-28.

From Cochrane

Golimumbab with MTX to Placebo for Withdrawals Due to Adverse Events
- All four studies provided data from 1231 patients (Emery 2009, Kay 2008, Keystone 2009, Smolen 2009).
- The odds ratio (95% CI) for withdrawals due to adverse events in golimumab-treated RA patients was 0.80 (95% CI 0.26, 2.42), compared to placebo.
- Authors comment: The safety profile of golimumab was similar to that of methotrexate with regards to number of adverse events, serious adverse events, infections, serious infections and cancer. Withdrawals rates overall and due to adverse events were similar.

Golimumab 100 mg every four weeks + methotrexate versus placebo + methotrexate
- Number and type of adverse effects (AEs) and serious adverse events (SAEs): There was no significant difference between the number of adverse events and serious adverse events occurring for golimumab treated patients compared to placebo treated patients with (P= 0.14) and (P=0.9) respectively.

Golimumab 50 mg every two weeks + methotrexate versus placebo + methotrexate
- Number and type of adverse effects (AEs) and serious adverse events (SAEs): There was no significant difference between the number of adverse events and serious adverse events occurring for golimumab treated patients compared to placebo treated patients with (P=0.3) and (P=0.6) respectively.

Delfini Update 11/15/10:

Keystone 2010

52 week study: 444 patients. Patients were randomly assigned to receive placebo plus methotrexate (group 1), golimumab 100 mg plus placebo (group 2), golimumab 50 mg plus methotrexate (group 3) and golimumab 100 mg plus methotrexate (group 4). At week 16, patients in groups 1, 2 and 3 who had less than 20% improvement in tender and swollen joints entered early escape (removed from group due to lack of efficacy). At week 24, patients in group 1 who had not entered early escape crossed over to 50 mg golimumab plus methotrexate. See Keystone 10 above for results.

Kremer 2010

- Phase III, multicenter, randomized, double-blind, placebo-controlled, 48-week study of 643 patients to assess the efficacy and safety of intravenous administration of golimumab (with and without MTX) in patients in whom RA remained active despite treatment with MTX.
- Eligible patients were randomly assigned (1:1:1:1:1), using an interactive voice-response system, to receive blinded intravenous infusions of placebo plus MTX, 2 mg/kg golimumab with or without MTX, or 4 mg/kg golimumab with or without MTX.
- Golimumab and placebo were supplied as sterile liquid (aqueous medium of histidine, sorbitol, polysorbate 80, pH 5.5, with or without golimumab) ready for intravenous infusion. Active and placebo MTX were supplied as matching opaque capsules (microcrystalline cellulose filled with or without MTX; those with MTX were overencapsulated and provided the stable prescreening dose).
- Safety evaluations through week 48 included assessment for adverse events, including infusion site reactions, routine laboratory analyses, and determination of antibodies to golimumab.
- Higher proportions of golimumab-treated patients than placebo plus MTX–treated patients had serious adverse events (63 [10%] of 626 patients and 7 [5%] of 129 patients, respectively)
- Serious infections (23 [4%] of 626 GLM-treated patients and 2 [2%] of 129 placebo patients,) through week 48.
- Two cases of TB occurred between week 24 and week 48 in patients who initially tested negative for TB at the time of screening (1 patient each from Argentina and Mexico, and 1 each receiving 4 mg/kg golimumab plus placebo and 4 mg/kg golimumab plus MTX).

Kavanaugh 2009

- 24 week placebo-controlled, double blind trial: 405 patients were randomized in a blinded manner (1:1.3:1.3) by a centralized interactive voice response system (113, 146, 146 patients to placebo, golimumab 50mg + stable dose of MTX, corticosteroids and NSAIDs and golimumab 100mg + stable doses as above.
- Safety evaluations included adverse events, routine laboratory analyses, and the presence of antibodies to golimumab. The incidence of malignancies was determined based on 100 patient-years of followup, with corresponding 95% confidence intervals (95% CIs).
- Similar baseline characteristics.
- All patients included in safety analysis.
- Serious infections in placebo, combined GOL groups: 4% and <1%; serious adverse events: 6% and <1%; injection site reactions: 3% and 3%. Thus there was no signal of increased serious infection rate with GLM compared to placebo.
- Three malignancies were reported, all in the golimumab 100 mg group (2 cases of basal cell carcinoma and 1 case of prostate cancer), representing an incidence of 2.32 (95% CI 0.48 to 6.78) per 100 patient-years versus 0.00 (95% CI 0.00 to 7.13) per 100 patient-years for placebo, with the 95% CI for golimumab fully contained within that for placebo.
- Eight golimumab-treated patients (3%) and 5 placebo treated patients (4%) discontinued the study agent due to adverse events occurring prior to week 24.

SINGH 11 COCHRANE SAFETY ADA_CZP_ETN_GLN_IFX_
AUTHOR YR: Singh 11

Citation: Singh JA, Wells GA, Christensen R, Tanjong Ghogomu E, Maxwell L, MacDonald JK, Filippini G, Skoetz N, Francis D, Lopes LC, Guyatt GH, Schmitt J, La Mantia L, Weberschock T, Roos JF, Siebert H, Hershan S, Lunn MPT, Tugwell P, Buchbinder R. Adverse effects of biologics: a network meta-analysis and Cochrane overview. *Cochrane Database of Systematic Reviews* 2011, Issue 2. Art. No.: CD008794. DOI: 10.1002/14651858.CD008794.pub2.. PubMed PMID:

Study Type: SR and Meta-analysis

Agents of Interest: ADA, CZP, ETN ,GLN, IFX

Safety Outcomes: serious adverse events, infections, serious infections, , tuberculosis, withdrawals due to adverse events in patients with any disease condition except human immunodeficiency disease (HIV/AIDS).

Manufacture Involvement: No.

PUBLISHED ABSTRACT WITH RELEVANT SAFETY DATA COCHRANE

Background
Biologics are used for the treatment of rheumatoid arthritis and many other conditions. While the efficacy of biologics has been established, there is uncertainty regarding the adverse effects of this treatment. Since serious risks such as tuberculosis (TB) reactivation, serious infections, and lymphomas may be common to the biologics but occur in small numbers across the various indications, we planned to combine the results from biologics used in many conditions to obtain the much needed risk estimates.

Objectives
To compare the adverse effects of tumor necrosis factor blocker (etanercept, adalimumab, infliximab, golimumab, certolizumab), interleukin (IL)-1 antagonist (anakinra), IL-6 antagonist (tocilizumab), anti-CD28 (abatacept), and anti-B cell (rituximab) therapy in patients with any disease condition except human immunodeficiency disease (HIV/AIDS).

Methods
Randomized controlled trials (RCTs), controlled clinical trials (CCTs) and open-label extension (OLE) studies that studied one of the nine biologics for use in any indication (with the exception of HIV/AIDS) and that reported our pre-specified adverse outcomes were considered for inclusion. We searched The Cochrane Library, MEDLINE, and EMBASE (to January 2010). Identifying search results and data extraction were performed independently and in duplicate. For the network meta-analysis, we performed mixed-effects logistic regression using an arm-based, random-effects model within an empirical Bayes framework.

Main results
We included 163 RCTs with 50,010 participants and 46 extension studies with 11,954 participants. The median duration of RCTs was six months and 13 months for OLEs. Data were limited for tuberculosis (TB) reactivation, lymphoma, and congestive heart failure. Adjusted for dose, biologics as a group were associated with a statistically significant higher rate of total adverse events (odds ratio (OR) 1.19, 95% CI 1.09 to 1.30; number needed to treat to harm (NNTH) = 30, 95% CI 21 to 60) and withdrawals due to adverse events (OR 1.32, 95% CI 1.06 to 1.64; NNTH = 37, 95% CI 19 to 190) and an increased risk of TB reactivation (OR 4.68, 95% CI 1.18 to 18.60; NNTH = 681, 95% CI 143 to 14706) compared to control.

The rate of serious adverse events, serious infections, lymphoma, and congestive heart failure were not statistically significantly different between biologics and control treatment.

Certolizumab pegol was associated with significantly higher risk of serious infections compared to control treatment (OR 3.51, 95% CI 1.59 to 7.79; NNTH = 17, 95% CI 7 to 68).

Infliximab was associated with significantly higher risk of withdrawals due to adverse events compared to control (OR 2.04, 95% CI 1.43 to 2.91; NNTH = 12, 95% CI 8 to 28).

Indirect comparisons revealed that abatacept and anakinra were associated with a significantly lower risk of serious adverse events compared to most other biologics. Although the overall numbers are relatively small, certolizumab pegol was associated with significantly higher odds of serious infections compared to etanercept, adalimumab, abatacept, anakinra, golimumab, infliximab, and rituximab; abatacept was significantly less likely than infliximab and tocilizumab to be associated with serious infections. Abatacept, adalimumab, etanercept and golimumab were significantly less likely than infliximab to result in withdrawals due to adverse events.

Authors' conclusions
Overall, in the short term biologics were associated with significantly higher rates of total adverse events, withdrawals due to adverse

events and TB reactivation. Some biologics had a statistically higher association with certain adverse outcomes compared to control, but there was no consistency across the outcomes so caution is needed in interpreting these results. There is an urgent need for more research regarding the long-term safety of biologics and the comparative safety of different biologics. National and international registries and other types of large databases are relevant sources for providing complementary evidence regarding the short- and longer-term safety of biologics.

Reviewer Comments

- Search quality: high
- Search dates: 1966 to January 2010
- RCTs and open label extensions both Likely to be underpowered to detect relative differences in most outcomes between agents.
- Quality of evidence synthesis was rated as moderate for agents and outcomes of interest.
- Due mainly to lack of data, authors' confidence in the results for TB reactivation, lymphoma, and congestive heart failure was graded as 'low'.
- Quality assessment: levels of evidence were assessed as moderate for all outcomes of interest presented in table below.
    - Allocation concealment, random sequence generation, presence of blinding in the studies (patients, assessors and physicians), incomplete outcome data, selective outcome reporting, and evidence of major baseline imbalance. In addition, the following criteria, specific to the assessment of adverse effects, were assessed. Adverse event definition: did the study provide a definition for 'severe adverse events'? Method of adverse event assessment: did the researchers actively monitor for AEs (low risk of bias) or did they simply provide spontaneous reporting of AEs that arose (high risk of bias)? The risk of bias of each study was explicitly judged on each criterion using the following: Yes (low risk of bias), No (high risk of bias), or Unclear (either lack of information or uncertainty over the potential for bias).
    - Reported an overall grading of the evidence related to each of the main outcomes, using the GRADE approach. The control event rates used in the calculation of absolute risks were: 118 per 1000 for serious adverse events; 26 per 1000 for serious infections; 724 per 1000 for total adverse events; 98 per 1000 for withdrawals due to adverse events; 8 per 1000 for congestive heart failure; 9 per 10,000 for lymphoma; and 4 per 10,000 for tuberculosis reactivation. These control event rates were calculated based on the number of events in the included studies.
    - A total of 163 RCTs with 50,010 participants and 46 open label extenstion with 11,954 participants were included in this review. Four CCTs were found and analyzed with the RCT data. The median duration of the RCTs was six months and the majority of the RCTs assessed etanercept or infliximab in people with RA or cancer.

SUMMARY OF FINDINGS AGENTS COMPARED TO CONTROLS FROM CLINICAL TRIAL DATA

Note: Except when results were statistically different the 95% confidence interval around the pooled effect includes both no effect and appreciable benefit or harm.

- The rate of serious adverse events, serious infections, lymphoma, and congestive heart failure were not statistically significantly different between biologics and control treatment.
- Certolizumab pegol was associated with significantly higher risk of serious infections compared to control treatment (OR 3.51, 95% CI 1.59 to 7.79; NNTH = 17, 95% CI 7 to 68).

SERIOUS INFECTIONS CZP COMPARED TO CONTROLS

Intervention	Comparison	Risk Comparator	Risk With Agent (95% CI)	Relative Effect	N	Quality Rating (GRADE)	NNH (95% CI)
CZP	Control	26 per 1000	86 per 1000 (41 to 172)	OR 3.51 (95% CI 1.59 to 7.79)	1929 (4 studies)	Moderate	17 (7 to 68)

- Certolizumab pegol was associated with significantly higher odds of serious infections compared to ADA, ETN, GLM and IFX: etanercept (OR 3.32, 95% CI 1.43 to 7.75), adalimumab (OR 3.15, 95%CI 1.31 to 7.52), infliximab (OR 2.42, 95% CI 1.05 to 5.60)

SUMMARY OF INDIRECT COMPARISONS OF AGENTS OF INTEREST

Agent	Comparator	Odds Ratio (95% CI)
ADA*	**CZP**	0.32 (95% CI 0.13 to 0.76)
CZP*	**ETN**	3.32 (95% CI 0.1.43 to 7.75)
CZP*	**GLM**	2.73 (95% CI 1.04 to 7.13)
CZP*	**IFX**	2.42 (95% CI 1.05 to 5.60)
CZP*	**Placebo**	3.51 (95% CI 1.59 to 7.79)

*Statistically significant

- Infliximab was associated with significantly higher risk of withdrawals due to adverse events compared to control (OR 2.04, 95% CI 1.43 to 2.91; NNTH = 12, 95% CI 8 to 28).

RISK OF WITHDRAWAL DUE TO ADVERSE EVENTS: IFX COMPARED TO CONTROLS

Intervention	Comparison	Risk Comparator	Risk With Agent (95% CI)	Relative Effect (95% CI)	N	Quality Rating (GRADE)	NNH (95% CI)
IFX	Control	98 per 1000	181 per 1000 (134 to 240)	OR 2.04 (1.43 to 2.91)	7559 (33 studies)	Moderate	12 (8 to 28)

- ADA, ETN and GLM were significantly less likely than IFX to result in withdrawals due to adverse events. Compared to infliximab, adalimumab (OR 0.50, 95% CI 0.32 to 0.78), etanercept (OR 0.63, 95% CI 0.41 to 0.95), and golimumab (OR 0.55, 95% CI 0.30 to 0.99) were associated with significantly fewer withdrawals due to adverse events.

INDIRECT COMPARISONS: WITHDRAWALS DUE TO ADVERSE EVENTS				
Agent	Comparator	Odds Ratio	Lower Confidence Interval	Higher Confidence Interval
adalimumab*	Infliximab	0.50	0.32	0.78
Etanercept*	Infliximab	0.63	0.41	0.95
Golimumab*	Infliximab	0.55	0.30	0.99
Infliximab*	Placebo	2.04	1.43	2.91
*Statistically significant				

ST CLAIR 04_MAINI 99_WESTHOVENS 06_KLARESKOG 2004_BREEDVELD 06

Citations:

St Clair EW, van der Heijde DM, Smolen JS, Maini RN, Bathon JM, Emery P, Keystone E, Schiff M, Kalden JR, Wang B, Dewoody K, Weiss R, Baker D; Active-Controlled Study of Patients Receiving Infliximab for the Treatment of Rheumatoid Arthritis of Early Onset Study Group. Combination of infliximab and methotrexate therapy for early rheumatoid arthritis: a randomized, controlled trial. Arthritis Rheum. 2004 Nov;50(11):3432-43. PubMed PMID: 15529377.

Maini R, St Clair EW, Breedveld F, Furst D, Kalden J, Weisman M, Smolen J, Emery P, Harriman G, Feldmann M, Lipsky P. Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. Lancet. 1999 Dec 4;354(9194):1932-9. PubMed PMID: 10622295.

Westhovens R, Yocum D, Han J, Berman A, Strusberg I, Geusens P, Rahman MU; START Study Group. The safety of infliximab, combined with background treatments, among patients with rheumatoid arthritis and various comorbidities: a large, randomized, placebo-controlled trial. Arthritis Rheum. 2006 Apr;54(4):1075-86. Erratum in: Arthritis Rheum. 2007 May;56(5):1675. Dosage error in article text. PubMed PMID: 16572442.

Klareskog L, van der Heijde D, de Jager JP, Gough A, Kalden J, Malaise M, Martín Mola E, Pavelka K, Sany J, Settas L, Wajdula J, Pedersen R, Fatenejad S, Sanda M; TEMPO (Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes) study investigators. Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. Lancet. 2004 Feb 28;363(9410):675-81. PubMed PMID: 15001324.

Breedveld FC, Emery P, Keystone E, Patel K, Furst DE, Kalden JR, St Clair EW, Weisman M, Smolen J, Lipsky PE, Maini RN. Infliximab in active early rheumatoid arthritis. Ann Rheum Dis. 2004 Feb;63(2):149-55. PubMed PMID: 14722203; PubMed Central PMCID: PMC1754899.

Study Designs: RCTs

Manufacturer Involvement:
St Claire 04: Statistical design and data analysis
Maini 99: funded by Centocor, one author employed by Centocor
Westhovens 06:
Kareskog 04: Wyeth Research sponsored this trial as a postapproval commitment to the European Agency for the Evaluation of Medicinal Products. The sponsor was responsible for the collection and analysis of data.
Breedveld 06: Funded by Abbott Laboratories.

Abstracts: Not included

Reviewer Comments

#	Ref and Study Details	Interventions	Outcomes (% or incidence rate per 100 patient-years or events per PTYR)	Validity	Reviewer Comments
1	St Clair 2004(ASPIRE) Months: 12 N: 1004 Age: ~50 Duration: ~0.9 yrs % DMARD Naive: ~67 % on steroids: ~38 % on NSAIDs: ~84 HAQ score: 1.5	Placebo+ MTX	PNEUMONIA: 0 TB: 0 INFUSION RXN: 0 LYMPHOMA: 0 MALIGNANCY: 0 DEMYELINATING: NR DEATH: 2 WITHDRAWAL ADVERSE: (3.2) SERIOUS INFECTIONS (2.1%)	Generation Sequence: Yes Concealment Alloc: Yes Blinding: Yes: Subjects/Invest/ Assessors N Safety MTX: 291/298 N Safety IFX: 749/751	Placebo+ MTX vs IFX + MTX. Higher withdrawal due to adverse event in IFX +MTX group 9.6% .vs 3.2%; higher rates TB in IFX+MTX group, 6% vs 0; no P-value; higher rate serious infections in IFX + MTX group, 5% vs 2.1%, P = 0.04.
		IFX 3 mg/Kg 8 weekly + MTX	PNEUMONIA: 8 (2) TB: 3 (0.8) INFUSION RXN: 2 (0.5) LYMPHOMA: 0 MALIGNANCY:0 DEMYELINAGING: NR DEATH: 1 WITHDRAWAL ADVERSE: (9.5) SERIOUS INFECTIONS:21 (5.6) P=0.02		
		IFX 6 mg/Kg 8 weekly + MTX	PNEUMONIA: 11 (3) TB: 1 (0.3) INFUSION RXN: 2 (0.5) LYMPHOMA: 0 MALIGNANCY: 4 (1) DEMYELINAGING: NR		

#	Ref and Study Details	Interventions	Outcomes (% or incidence rate per 100 patient-years or events per PTYR)	Validity	Reviewer Comments
			DEATH: 1 WITHDRAWAL ADVERSE: (9.6) SERIOUS INFECTIONS:19 (5) P=0.04		
2.	Maini 1999 Months:~7 N:428 Age: ~54 Duration: ~10 yrs Incomplete responders to MTX % on steroids: ~60 % on NSAIDs: ~73 HAQ score:~1.7	Placebo + MTX IFX 3mg/kg to 10mg/kg + MTX	PNEUMONIA: NR TB: 0 INFUSION RXN: 0 LYMPHOMA: 0 MALIGNANCY: 0 DEMYELINAGING: NR DEATH: 3 (3) WITHDRAWAL ADVERSE: 7(8) SERIOUS INFECTION: 5 (6) PNEUMONIA: NR TB: 1 INFUSION RXN: 2 LYMPHOMA:1 MALIGNANCY:4 DEMYELINAGING: NR DEATH: 2 (0.6) WITHDRAWAL ADVERSE: 6(7) SERIOUS INFECTION: 14 (4)	Generation Sequence: No details Concealment Alloc: No details Blinding: Yes: Subjects/Invest/ Assessors N Safety Placebo + MTX: 86/88 N Safety IFX + MTX: 340/342	Similar adverse event rates; may be underpowered to show differences.
3.	Westhovens 2006 (START) Months:6 for placebo + MTX vs IFX N:1084 Age: ~52 Duration: ~7.5 yrs Incomplete responders to MTX % on steroids: 59 % on NSAIDs: ~40 HAQ score:~1.5	Placebo + MTX IFX 3mg/kg-10mg/kg q 8 weeks + MTX	Week 22 PNEUMONIA 0 TB 0 INFUSION RXN: NR LYMPHOMA 0 MALIGNANCY 2 DEMYELINATING NR DEATH 1 WITHDRAWAL ADVERSE 8 (2.2) SERIOUS INFECTION 6 (1.7) PNEUMONIA 6 (0.8) TB 3 (0.4) INFUSION RXN NR LYMPHOMA 1 MALIGNANCY NR DEMYELINATING NR DEATH NR WITHDRAWAL ADVERSE 31 (4.3) SERIOUS INFECTION 24 (3.3)	Week 54 (IFX Only) 12 (1.2) 4 (0.4) 195 (2.6) 1 28((2.8) NR 4 49(4.9) 31(3)	Generation Sequence: No details Concealment Alloc: No details Blinding: Yes: Subjects/Invest/Assessors N Safety Placebo + MTX: 361/361 (22 wks) N Safety IFX + MTX: 721/721 (22wks) No placebo group at week 54 N Safety IFX + MTX: 1001/1082	Increased serious infection in IFX group; may be underpowered to show differences.
4.	Klareskog 2004 (TEMPO) Months:24 N:682 Age: ~53 Duration: ~7 years Incomplete responders to DMARDs % on steroids: ~60 % on NSAIDs:~ 87 HAQ score:1.8	MTX; N=228 ETN 25mg sc. twice weekly; N=223 ETN 25mg sc. twice weekly + MTX; N=231	PNEUMONIA: NR TB:0 INFUSION RXN:NR LYMPHOMA:NR MALIGNANCY:1 DEMYELINATING:0 DEATH: 1 WITHDRAWAL ADVERSE: 32 SERIOUS INFECTION: 10 (4%) REACTIONS AT INJECTION SITE: 4 (2%) PNEUMONIA: 0 TB:0 INFUSION RXN:NR LYMPHOMA:1 MALIGNANCY:4 DEMYELINATING:0 DEATH: 1 WITHDRAWAL ADVERSE: 25 SERIOUS INFECTION: 10 (4%) REACTIONS AT INJECTION SITE:46 (21%) PNEUMONIA: 1 TB:0 INFUSION RXN:NR LYMPHOMA:1	Generation Sequence: No details Concealment Alloc: Centralized telephone Blinding: Stated double-blind; no details N Safety MTX: 228/228 N Safety ETN:223/223 N Safety ETN +MTX: 231/231	MTX vs ETN 25mg sc. twice weekly; increased reaction at injection site, no P-value provided

#	Ref and Study Details	Interventions	Outcomes (% or incidence rate per 100 patient-years or events per PTYR)	Validity	Reviewer Comments
			MALIGNANCY:1 DEMYELINATING:0 DEATH:1 WITHDRAWAL ADVERSE: 24 SERIOUS INFECTION: 10 (4%) REACTIONS AT INJECTION SITE: 23 (10%)		
5.	Breedveld 2006 (PREMIER) Months: 24 N:799 Age: ~52 Duration:~ 1 yr % DMARD Naive: ~68 % on steroids: ~36 % on NSAIDs: NR HAQ score: ~1.55	MTX ADA 40mg sc. 2 weekly ADA 40mg sc. 2 weekly +MTX	PNEUMONIA: 2 TB: 0 INFUSION RXN: NR LYMPHOMA: [0.2] MALIGNANCY:[0.9] DEMYELINAGING: 0 DEATH: 1 WITHDRAWAL ADVERSE: 19 (7.4); P=0.21 SERIOUS INFECTION:[1.6] PNEUMONIA: 0 TB: 0 INFUSION RXN: NR LYMPHOMA: 0 MALIGNANCY:[0.9] DEMYELINAGING: 0 DEATH: 4 WITHDRAWAL ADVERSE: 26 (9.5); P=0.21 OTHER: SERIOUS INFECTION:[0.7] PNEUMONIA: 0 TB: [0.2] INFUSION RXN: NR LYMPHOMA: 0 MALIGNANCY:[0.4] DEMYELINAGING: 0 DEATH: 1 WITHDRAWAL ADVERSE: 32 (11.9); P=0.21 SERIOUS INFECTION:[2.9];P<0.05	Generation Sequence: No details Concealment Alloc: No details Blinding: Yes: Subjects/Invest/Assessors N Safety MTX: 257/257 N Safety ADA:274/274 N Safety ADA + MTX: 268/268 ITT: Yes (extreme case analysis)	3 arms; MTX vs ADA 40mg sc. 2 weekly vs ADA 40mg sc. 2 weekly +MTX; higher withdrawal due to adverse events in ADA group compared to MTX group 10.7% vs 7.4%; P=0.21.

Reviewer Comments

- Underpowered to reliably demonstrate safety differences in groups if one existed.

TAN META UST 10

Citation: Tan JY, Li S, Yang K, Ma B, Chen W, Zha C, Zhang J. Ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: a meta-analysis. J Dermatolog Treat. 2010 Oct 5. [Epub ahead of print] PubMed PMID: 20923370.

Study Design: Meta-analysis

Manufacturer Involvement: None repdorted

Abstract: Not included

Reference	Population and N	Intervention	Safety Results	Reviewer Comments
Tan 10	Psoriasis N=2316	UST 45mg and 90mg versus placebo	• There was no statistically significant difference in rates of serious AEs including infection compared to placebo in the UST 45mg group and 90 mg group with respective relative risks of 1.17 (95% CI 0.98 to 1.38) and 1.06 (95% CI 0.89 to 1.27). • Injection site reactions not reported	High likelihood of being underpowered to detect difference

THALER SR INJECTION RXN ETN ADA 09 FINAL

AUTHOR YR: Thaler 09

Citation: Thaler K, Chandiramani DV, Hansen RA, Gartlehner G. Efficacy and safety of anakinra for the treatment of rheumatoid arthritis: an update of the Oregon Drug Effectiveness Review Project. Biologics. 2009;3:485-98. Epub 2009 Dec 29. PubMed PMID: 20054439.

Study Type: SR and Meta-analysis

Manufacture Involvement: None

Abstract: not included
Reviewer Comments
• For safety, both experimental and observational studies were eligible. Two persons independently reviewed abstracts and full text articles and extracted relevant data. • Searched Medline to April 2009. • Authors calculated crude incidence of injection site reactions (7 ADA studies, 4 ETN studies: adalimumab (17.5%, 95%CI 7.1 to 27.9) and etanercept (22.4%, 95% CI 8.5 to 36.3).

TSIODRAS fungal 3 drugs 08 FINAL

AUTHOR YR: Tsiodras 08

Citation: Tsiodras S, Samonis G, Boumpas DT, Kontoyiannis DP. Fungal infections complicating tumor necrosis factor alpha blockade therapy. Mayo Clin Proc2008 Feb;83(2):181-94. PMID: 18241628

Study Type: Review of reports of invasive fungal infections (IFIs) associated with IFX, ADA, ETN

Manufacture Involvement: No mention.

Abstract

Tumor necrosis factor α (TNF-α) blockade has emerged as a useful therapy for collagen vascular diseases or graft-vs-host disease. Fungal infections complicating such therapy have been reported sporadically. MEDLINE and PubMed databases (from January 1, 1966, to June 1, 2007) were searched for reports of invasive fungal infections (IFIs) associated with the 3 available anti–TNF-α agents, ie, infliximab, etanercept, and adalimumab.

Of the 281 cases of IFI associated with TNF-α inhibition, 226 (80%) were associated with infliximab, 44 (16%) with etanercept, and 11 (4%) with adalimumab. Fungal infections associated with infliximab occurred a median of 55 days (interquartile range [IQR], 15-140 days) after initiation of therapy and 3 infusions of the medication (IQR, 2-5), whereas those associated with etanercept occurred a median of 144 days (IQR, 46-240 days) after initiation of therapy. The median age of patients was 58 years (IQR, 44-68 years), and 62% were male. Use of at least 1 other immunosuppressant medication, typically a systemic corticosteroid, was reported during the course of the fungal infection in 102 (98%) of the 104 patients for whom data were available. The most prevalent IFIs were histoplasmosis (n=84 [30%]), candidiasis (n=64 [23%]), and aspergillosis (n=64 [23%]). Pneumonia was the most common pattern of infection. Of the 90 (32%) of 281 cases for which outcome information was available, 29 fatalities (32%) were recorded.

Tumor necrosis factor α blockade is associated with IFI across a range of host groups. A high index of suspicion in patients treated with TNF-α antagonists is recommended because the course of such infections can be serious or fulminant, and rapid access to health care should be provided. Surveillance of IFIs complicating TNF-α blockade and other biologic therapies is warranted through well-organized prospective patient registries.

Reviewer Comments

- Included case series, letters, postmarketing data.
- Populations were heterogeneous and included patients not treated for RA, PsA or psoriasis.
- Subject to selection, performance, reporting biases.
- Aspergillosis: Authors found 64 reported cases of aspergillosis associated with the use of TNF-[alpha] antagonists. 48 (75%) were associated with infliximab, 14 (22%) with etanercept, and 2 (3%) with adalimumab. Of the 24 cases for which data were available, 18 patients (75%) had received a TNF-[alpha] antagonist for graft versus host disease (GVHD) following allogeneic bone marrow transplant for hematologic malignancy, 2 (8%) for inflammatory bowel disease, and 4 (17%) for rheumatoid arthritis. One of the patients had evidence of coinfection with PCP and*Candida* species. All but 1 of the patients were exposed to other immunosuppressant medications, such as corticosteroids or methotrexate.
- Candida Infections: Of 64 identified cases of *Candida* infection associated with TNF-[alpha] antagonist therapy, 54 (84%) were associated with infliximab, 9 (14%) with etanercept, and 1 (2%) with adalimumab. The pattern of underlying disease was GVHD in 11 of 18 cases (5, *Candida glabrata;* 5, other species; all but 1 received infliximab), inflammatory bowel disease in 5 cases, and rheumatoid arthritis in 2 cases.
- Cryptococcus: Twenty-eight cases of *Cryptococcus* infection associated with TNF-[alpha] blockade were identified: 17 (61%) associated with infliximab, 10 (36%) with etanercept, and 1 (3%) with adalimumab. Of 8 patients with data available for review, 6 with rheumatoid arthritis had received infliximab after a median of 3 infusions (IQR, 3-10).
- Tinea and Pityriasis: Three tinea corporis and 3 pityriasis versicolor cases of patients receiving anti-TNF-[alpha] inhibitors, in which 13 of the 35 had new onset of cutaneous infections. Three patients had received infliximab (range of infusions, 2-7; all for ankylosing spondylitis), 1 etanercept (for rheumatoid arthritis), and 2 adalimumab (range of infusions, 26-36; both for rheumatoid arthritis).
- Coccidioidomycosis: Authors found 29 cases of coccidioidomycosis: 27 (93%) were associated with infliximab and 2 (7%) with etanercept. All patients were concomitantly taking either corticosteroids or methotrexate. All had pneumonia, and 4 had evidence of disseminated infection.
- Histoplasmosis: Authors identified 84 cases of histoplasmosis: 72 (86%) were associated with infliximab, 8 (10%) with etanercept, and 4 (5%) with adalimumab. Most cases for which data were available occurred in areas endemic for the fungus, and all patients received concomitant immunosuppressant medication.
- Of the entire group of 281 patients who developed fungal infection in association with TNF-[alpha] blockade, 226 (80%) had received infliximab; 44 (16%), etanercept; and 11 (4%), adalimumab.
- Histoplasmosis (n = 84), candidiasis (n = 64), and aspergillosis (n = 64) were the most frequently observed fungal infections.
- One hundred two of the 104 (98%) patients for whom data were available received at least 1 other immunomodulating

medication (eg, corticosteroids, methotrexate) during the course of the fungal infection.
- Potentially weak signal of increased fungal infection rates with IFX

Key points

- Of 281 cases of IFX obtained in a search of PubMed and MEDLINE databases (based on National Library of Medicine filing dates from January 1, 1966, to June 1, 2007), 226 cases (80%) were associated with IFX, 44 (16%) with ETN, and 11 (4%) with ADA. Histoplasmosis (n = 84), candidiasis (n = 64), and aspergillosis (n = 64) were the most frequently observed fungal infections in the study.
- The authors identified 84 cases of histoplasmosis: 72 (86%) were associated with IFX, 8 (10%) with ETN, and 4 (5%) with ADA. Most cases for which data were available occurred in areas endemic for the fungus, and all patients received concomitant immunosuppressant medication.
- Candida Infections: 64 of cases of Candida infection were identified in patients receiving TNFI therapy. 54 (84%) were associated with IFX, 9 (14%) with ETN, and 1 (2%) with ADA.
- Aspergillosis: 64 cases of aspergillosis associated with the use of TNFIs were identified. 48 (75%) were associated with IFX, 14 (22%) with ETN, and 2 (3%) with ADA. All but one of the patients were exposed to other immunosuppressant medications, such as corticosteroids or methotrexate.
- Cryptococcus Infections: 28 cases of Cryptococcus infection associated with TNFIs were identified. 17 (61%) were associated with IFX, 10 (36%) with ETN, and 1 (3%) with ADA. Of 8 patients with data available for review, 6 with rheumatoid arthritis had received IFX after a median of 3 infusions (interquartile range (IQR) 3-10).
- There were 3 tinea corporis and 3 pityriasis versicolor cases of patients receiving anti-TNF-[alpha] inhibitors, in which 13 of the 35 had new onset of cutaneous infections. Three patients had received IFX (range of infusions, 2-7; all for ankylosing spondylitis), 1 ETN (for rheumatoid arthritis), and 2 ADA (range of infusions, 26-36; both for rheumatoid arthritis).
- Coccidioidomycosis: 29 cases were identified. 27 (93%) were associated with IFX and 2 (7%) were associated with ETN. All patients were concomitantly taking either corticosteroids or MTX. All had pneumonia, and 4 had evidence of disseminated infection.
- Of the entire group of 281 patients who developed fungal infection in association with TNF-[alpha] blockade, 226 (80%) had received IFX; 44 (16%), ETN; and 11 (4%), ADA.
- One hundred and two of the 104 (98%) patients for whom data were available received at least 1 other immunomodulating medication (e.g., corticosteroids, MTX) during the course of the fungal infection.

TUBACH 09_Registry_French_TB_3Agents_FINAL

AUTHOR YR: Tubach 09

Citation: Tubach F, Salmon D, Ravaud P, Allanore Y, Goupille P, Bréban M, Pallot-Prades B, Pouplin S, Sacchi A, Chichemanian RM, Bretagne S, Emilie D, Lemann M, Lortholary O, Mariette X; Research Axed on Tolerance of Biotherapies Group. Risk of tuberculosis is higher with anti-tumor necrosis factor monoclonal antibody therapy than with soluble tumor necrosis factor receptor therapy: The three-year prospective French Research Axed on Tolerance of Biotherapies registry. Arthritis Rheum. 2009 Jul;60(7):1884-94. Erratum in: Arthritis Rheum. 2009 Aug;60(8):2540. Lorthololary, O [corrected to Lortholary, O]. PubMed PMID: 19565495.

Study Type: Registry Cohort

Manufacture Involvement: Authors have received consultancy fees from relevant manufacturers which had no role in the study. The RATIO Registry support includes unrestricted industry grant funding from mixed sources.

Abstract

OBJECTIVE

Tuberculosis (TB) is associated with anti-tumor necrosis factor (anti-TNF) monoclonal antibody (mAb) therapy, but whether this association is drug-specific remains a concern. Our objective was to describe cases of TB associated with anti-TNF mAb therapy, identify risk factors, and estimate the incidence.

METHODS

We conducted an incidence study and a case-control analysis to investigate the risk of newly diagnosed TB associated with the use of anti-TNF agents. As part of the French Research Axed on Tolerance of Biotherapies (RATIO) registry, for 3 years we collected cases of TB among French patients receiving anti-TNF mAb therapy for **any indication**; for each case, 2 patients treated with anti-TNF agents served as control subjects.

RESULTS

We collected 69 cases of TB in patients treated for rheumatoid arthritis (n = 40), spondylarthritides (n = 18), inflammatory colitis (n = 9), psoriasis (n = 1) and Behçet's disease (n = 1) with infliximab (n = 36), adalimumab (n = 28), and etanercept (n = 5). None of the patients had received correct chemoprophylactic treatment. The sex- and age-adjusted incidence rate of TB was 116.7 per 100,000 patient-years. The standardized incidence ratio (SIR) was 12.2 (95% confidence interval [95% CI] 9.7-15.5) and was higher for therapy with infliximab and adalimumab than for therapy with etanercept (SIR 18.6 [95% CI 13.4-25.8] and SIR 29.3 [95% CI 20.3-42.4] versus SIR 1.8 [95% CI 0.7-4.3], respectively). In the case-control analysis, exposure to infliximab or adalimumab versus etanercept was an independent risk factor for TB (odds ratio [OR] 13.3 [95% CI 2.6-69.0] and OR 17.1 [95% CI 3.6-80.6], respectively). Other risk factors were age, the first year of anti-TNF mAb treatment, and being born in an endemic area.

CONCLUSION

The risk of TB is higher for patients receiving anti-TNF mAb therapy than for those receiving soluble TNF receptor therapy. The increased risk with early anti-TNF treatment and the absence of correct chemoprophylactic treatment favor the reactivation of latent TB.

Notes on the Setting

French guidelines, in 2002, recommended anti-TB chemoprophylaxis before all anti-TNF mAb therapy for patients presenting with at least 1 of the following: diameter of tuberculin skin test reaction 10 mm (revised to 5 mm in July 2005), abnormal chest radiography results with calcifications >1 cm, previous untreated exposure to TB, or episode of TB. Correct chemoprophylaxis was defined as a 9-month course of treatment with isoniazide or a 3-month course of treatment with 2 anti-TB drugs, including rifampin.

Reviewer Comments

- Agents of Interest: Adalimumab, etanercept, , infliximab in any indication
- Registry described as prospective and mandatory for the purpose of collecting all cases of TB in French patients receiving anti-TNF therapy, regardless of indication from February 2004 through 2006. Multiple mailings and reminders encouraged physicians to report cases.
- There is a risk of missed cases in the registry. In Tubach 09, authors state they make the assumption that reporting was equal between agents. Differences in care experiences between agents could confound results.
- Cases were also obtained from the French national public surveillance system that monitors TB via mandatory reporting.
- An expert committee comprising 3 experts on TB (DS, SB, and OL) validated cases by consensus on the basis of the detailed standardized case report form and additional documents.
- For patients who received >1 anti-TNF agent, authors addressed exposure as follows: first anti-TNF agent, last anti-TNF agent, and any use of the anti-TNF agent in sensitivity analyses.
- French population was used as reference.
- Anti-TNF manufacturers obtained estimation of patient years based on number of doses sold and mean dosage used for each indication. The mean of these different estimates was used to estimate number of patients receiving each anti-TNF agent.
- Authors conducted sensitivity analyses using independent data from the French health insurance fund for self-employed workers (5%

of population) for information on use of etanercept and adalimumab.
- Surveys were also used for information on patients receiving etanercept and adalimumab.
- Information was missing for infliximab.
- Population for comparison was selected from TB-free registry patients receiving anti-TNF treatment. 2 controls per case were randomly and matched by sex and underlying inflammatory disease (age was not listed as a matching criterion). Another control per case was chosen, adding time from onset of anti-TNF treatment as another matching criterion.

TB In 68 Patients Receiving Biologic Agents Compared To 136 Control Subjects Without TB Receiving Anti-TNF Therapy RATIO French Registry (Tubach 09)

Last anti-TNF Agent Received	Odds Ratio	P-Value
ETN	1	n/a
ADA	17.08 (95% CI 3.62 to 80.59)	<0.001
IFX	13.29 (95% CI 2.56 to 69.04)	0.002

Risk of TB by Biologic Agent
Standardized Incidence Ratios (SIR) of IFX, ADA and Odds Ratio of IFX and ADA Versus ETN (Tubach 09)

Agent	N	SIR with French Population as Reference	Odds Ratio of Agent Compared to ETN
Only IFX	34	18.6 (95% CI 13.4 to 25.8)	13.3 (95% CI 2.6 to 69.0)
Only ADA	23	29.3 (95% CI 20.3 to 42.4)	17.1 (95% CI 3.6 to 80.6)
Only ETN	1	1.8 (95% CI 0.7 to 4.3)	Reference agent
All Anti-TNF	69	12.2 (95% CI 9.7 to 15.5)	Not reported

- Authors state a limitation of the study was that the denominator was estimated. Per Tubach 09, anti-TNF manufacturers obtained estimation of patient years based on number of doses sold and mean dosage used for each indication. The mean of these different estimates was used to estimate number of patients receiving each anti-TNF agent. Authors report that sensitivity analyses using independent sources gave consistent adjusted incidents rates and standardized incidence ratios (SIRs). Also, they used different estimates from different sources in sensitivity analyses and received consistent results.

In the French registry study (Tubach 09), investigators conducted an incidence study and case-control analysis to determine the risk of newly diagnosed TB associated with the use of monoclonal anti-TNF agents received for any indication. Data from the French Research Axed on Tolerance of Biotherapies (RATIO) registry was used. For the incidence study the investigators estimated the annual incidence rate of TB in patients treated with anti-TNF mAb therapy, adjusted for age and sex, with the French population used as the reference. Data was prospectively collected for all cases of TB occurring from February 1, 2004 to January 1, 2007 in patients who were receiving anti-TNF monoclonal antibody therapy. In the case-control study for each case of TB occurring in patients receiving IFX or ADA, 2 patients treated with anti-TNF agents served as control subjects. 75 cases of TB were identified, and 69 cases were validated. Investigators identified 69 cases of TB in patients treated for rheumatoid arthritis (n = 40), spondylarthritides (n =18), inflammatory colitis (n =9), psoriasis (n =1) and Behcet's disease (n =1) with infliximab (n =36), adalimumab (n =28), and etanercept (n =5). Among the 58 patients receiving only 1 anti-TNF agent, 34 (58.6%) had received infliximab, 23 (39.7%) had received adalimumab, and 1 (1.7%) had received etanercept. The standardized incidence ratios (SIR) and odds ratios were reported. The authors conclude that the risk of TB is higher for patients receiving anti-TNF monoclonal antibody therapy than for those receiving soluble TNF receptor therapy. They also state that the numerous registries set up in numerous countries to investigate the safety of anti-TNF agents set up after the FDA alert regarding the risk of TB associated with the use of infliximab with the exception of the French registry are cohort studies involving only a part of the population of focus and thus are not powered enough to demonstrate very rare events or investigate a difference in risk depending on the anti-TNF agent used, nor are the randomized controlled trials. The authors point out that in the earlier registry reports extremely small numbers are used for the calculations. For example, in an early British registry report report the incidence of TB was 1.5 per 1,000 patient-years with infliximab and 0.5 per 1,000 patient-years with etanercept, but the numbers of cases were only 7 and 2, respectively (Dixon 06). In the Swedish registry, the incidence rates were 1.5 per 1,000 patient-years with infliximab and 0.8 per 1,000 patient-years with etanercept; 9 cases were treated with infliximab alone, and 4 cases were treated with etanercept alone (Asking 05). And in the Korean report, 2 cases of TB were observed among 90 patients receiving infliximab, and no case was observed among 103 patients receiving etanercept (Seong 07). The investigators conclude that difference in risk between the types of anti-TNF agents was only suggested in these earlier registry studies, but was clearly demonstrated in the RATIO registry.

WEINBLATT OPPORTUNIISTIC SAFETY ETN 10 FINAL

AUTHOR YR: Weinblatt 10

Citation: Weinblatt ME, Bathon JM, Kremer JM, Fleischmann RM, Schiff MH, Martin RW, Baumgartner SW, Park GS, Mancini EL, Genovese MC. Safety and efficacy of etanercept beyond 10 years of therapy in North American patients with early and long-standing rheumatoid arthritis. Arthritis Care Res (Hoboken). 2010 Oct 18. [Epub ahead of print] PubMed PMID: 20957659.

Study Type: Review of reports obtained from searches of MEDLINE and PubMed (from January 1, 1966, to June 1, 2007) focusing on invasive fungal infections (IFIs) associated with the 3 available anti-TNF-[alpha] agents, ie, infliximab, etanercept, and adalimumab.

Manufacture Involvement: No information

Abstract

Objective. To evaluate long-term safety and efficacy of etanercept therapy in rheumatoid arthritis (RA) patients.

Methods. Adult patients with early RA (ERA) or long-standing RA (LRA) received etanercept in open-label extension studies following initial double-blind trials of etanercept.

Results. Of 558 ERA and 714 LRA patients who received at least 1 dose of etanercept, a total of 194 ERA and 217 LRA patients were treated with 25 mg etanercept twice weekly through 10 years. Five opportunistic infections were reported: in ERA, 1 Candida septicemia; in LRA, 1 herpes zoster, 1 atypical mycobacterium infection, 1 meningoencephalitis (unspecified), and 1 fungal sepsis (unspecified). Twenty-nine cases of sepsis occurred (10, ERA; 19, LRA). Occurrence of all malignancies was similar to that expected in the general population, but the occurrence of lymphomas was higher than expected in the general population. Fourteen lymphomas (7, ERA; 7, LRA) and 2 cases of demyelinating disease (1, ERA; 1, LRA) were reported. Deaths occurred in 18 ERA patients and 43 LRA patients. Both patient groups showed sustained improvement in American College of Rheumatology responses, swollen joint counts, Health Assessment Questionnaire scores, and C-reactive protein levels.

Conclusion. Etanercept maintained therapeutic benefits beyond 10 years of therapy in both ERA and LRA patients, suggesting that etanercept is well tolerated and effective as a long-term, continuous therapy for the treatment of RA with a favorable risk-benefit ratio.

Reviewer Comments

- The primary objective of the extension studies was to evaluate the long-term safety of etanercept in patients with early RA (ERA) or moderate to severe longstanding RA (LRA).
- The definition of OI was based on that provided for patients with human immunodeficiency virus by the Centers for Disease Control and Prevention Wonder online database (1992).
- ERA and LRA patients were required to receive 25 mg BIW in the extension study. A total of 632 patients were enrolled in the ERA parent study (415 etanercept patients and 217 MTX patients). Of these, 468 patients continued in the extension study and received etanercept 25 mg BIW. 581 LRA patients entered the extension study. A total of 558 ERA patients (415 original etanercept patients plus 143 of the 217 original MTX patients) and 714 LRA patients received at least 1 dose of etanercept in either the parent or long-term extension study and were included in the safety analysis.
- The exposure adjusted rate of SIEs per 100 patient-years was 2.6 for ERA patients (0.026 events/patient year) and 4.4 for LRA patients (0.044 events/patient year).
- No cases of tuberculosis were observed. An opportunistic infection (OI) of *Candida* septicemia was reported in 1 ERA patient who was hospitalized with pneumococcal pneumonia, sepsis, and respiratory failure. 1 month later, bronchial lavage showed *Candida*.
- Four infections considered OIs were reported in LRA patients: 1 herpes zoster, 1 atypical mycobacterium infection, 1 meningoencephalitis (unspecified) > 30 days past last dose date), and 1 fungal sepsis (unspecified) > 30 days past last dose date.
- The exposure-adjusted rates of SIEs (0.03 events/patient year for ERA patients and 0.04 events/patient year for LRA patients) are similar to the rates observed in the Olmsted County, MN RA cohort (0.10 events/patient year) and to the control and etanercept groups of controlled phases of the studies.
- Authors state that this is the longest prospective study of anti-TNF therapy to date with some patients receiving over 10 years of treatment.
- Open-label extension studies following initial double-blind trials of ETN the authors reported finding 5 opportunistic infections in 1,272 patients with RA.
- The authors found 1,272 patients (558 ERA and 714 LRA patients) who had received at least one dose of ETN.
- A total of 194 ERA and 217 LRA patients were treated with 25 mg ETN twice weekly through 10 years.
- Five opportunistic infections were reported: 1 Candida septicemia, 1 herpes zoster, 1 atypical mycobacterium infection, 1 meningoencephalitis (unspecified) and 1 fungal sepsis (unspecified).

Systematic Review of Safety of Biologic Agents in Rheumatoid Arthritis, Psoriasis and Psoriatic Arthritis: Six Agents

WIENS CRITIQUE SR adal inflix etan 10_FINAL

AUTHOR YR: Wiens 10

Citation: Wiens A, Venson R, Correr CJ, Otuki MF, Pontarolo R. Meta-analysis of the efficacy and safety of adalimumab, etanercept, and infliximab for the treatment of rheumatoid arthritis. Pharmacotherapy2010 Apr;30(4):339-53. PMID: 20334454

Study Type: SR and Meta-analysis

Manufacture Involvement: None

Abstract

Study Objective. To evaluate the efficacy and safety of using the anti–tumor necrosis factor drugs adalimumab, etanercept, and infliximab for the treatment of rheumatoid arthritis. **Design.** Systematic review and meta-analysis of 21 randomized, placebo controlled trials (eight adalimumab, seven infliximab, six etanercept). **Patients.** Adults with rheumatoid arthritis who received adalimumab (1524 patients), infliximab (1116 patients), etanercept (1029 patients), or placebo (2834 patients) with or without concomitant methotrexate in all groups. **Measurements and Main Results.** A literature search of several databases from **January 1995–December 2008** was performed. There were no restrictions based on language or date of publication, and low-quality studies (based on Jadad score) were excluded. Safety was compared based on frequency of **serious adverse events, serious infections, malignancy, and death.** Withdrawals due to adverse events and lack of efficacy were also evaluated.

Safety Results. No statistically significant differences were noted in the safety of any of the three drugs compared with placebo. Infliximab had the highest RRs for withdrawing from the study due to adverse events (2.05, 95% CI 1.33–3.16).

Conclusion. Clinicians should be aware that each of the three drugs has different rates of efficacy and different safety considerations that must be taken into account when selecting the best treatment for an individual with rheumatoid arthritis.

(Pharmacotherapy 2010;30(4):339–353)

Reviewer Comments

- Agents of Interest: Adalimumab, etanercept, , infliximab, in RA
- Compared agents to placebo with or without MTX.
- Prespecified Safety Outcomes: Serious adverse events (those adverse events that required prolonged hospitalization, led to the risk of death, resulted in death, or were classified as serious by the investigator), serious infections (infections that required treatment with parenteral antibiotics or led to hospitalization or the risk of death), cancer, lymphoma, death. Withdrawals due to adverse events and lack of efficacy were also evaluated.
- Search dates: January 1995–December 2008
- Included randomized, placebo controlled trials where usual dosages were used.
- Methodological quality by applying Jadad Scale: included trials with scores of 3-5 (Jadad 96). Jadad Scale ratings of 3 or higher do not assure that study quality is medium or high. The Jadad scale consists of three items for which points are awarded: randomization, double blinding, and reporting of withdrawals or dropouts. However, the scale does not address these items adequately. For instance, in the domain of randomization, the scale addresses the sequence generation, but not concealment of allocation of the sequence. Other methodological flaws are also not assessed when using the Jadad scale. For example,a low quality study found to have numerous flaws such as no concealment of allocation, a large number of dropouts that are well-described, a per-protocol analysis, and myriad other biases such as multiple differences in care delivered to the study groups could receive five points and be judged to be a study of the highest quality. The Jadad scale has therefore been criticized by several authors as being inadequate for assessing bias in RCTs (Juni 99, Lundh 08). Meta-analyses that employ the Jadad scale as the sole instrument for assessing quality may, therefore, include trials that are distorted by bias and confounding.
- After exclusions and appraisal yield was 21 trials— 8 ADA trials, 7 IFX trials, 6 ETN trials.
- Adequate search strategy— yielded 727 RCTs.
- Many trials with adequate randomization, blinding, retention of subjects.
- Conclusion: This meta-analysis of RCTs did not demonstrate statistically significant safety differences in serious adverse events, death, serious infections or malignancy with ADA, ETN or IFX compared to placebo with or without MTX. Most or all of the included clinical trials are likely to have been underpowered to reliably detect differences in safety outcomes of interest between groups if they existed. Even though this meta-analysis included included over 12,000 patients, the study was likely to have been underpowered to detect differences in the prespecified safety outcomes.

Note: A previous meta-analysis (Alonso-Ruiz 08) reported that patients treated with anti–TNF drugs demonstrated a significantly higher frequency of adverse events compared to placebo (RR 1.02 [95% CI 1.00 to 1.04]), which was not found in this study. In keeping with the Alonso-Ruiz metaanalysis, ADA and IFX, but not ETN, demonstrated statistically significant higher relative risk for withdrawal due to adverse events compared with the placebo group, but the group treated with etanercept had the RR favoring the placebo group (i.e., people in the placebo group dropped out of the studies due to adverse events in a higher frequency). For ADA the RR was 1.56 (95% CI 1.04 to 2.35). For IFX, the RR was 2.05 (95% CI 1.33 to 3.16). For ETN, the RR was 0.86 (95% CI 0.63 to 1.16) which is statistically insignificant. The Wien 10 meta-analysis, like the Alonso-Ruiz 08 meta-analysis, reported similar data regarding serious adverse events, malignancy, and deaths for the three biologic drugs compared with the placebo group, i.e., no statistically significant differences. Data

about serious infections were statistically significant, reporting a higher rate with IFX in the Alonso-Ruiz 08 meta-analysis. This finding differs from the Wien 10 meta-analysis which reported non-significant results for all the safety parameters when compared with the placebo group.

Primary Studies Included in Wien Review

<table>
<tr><th>Wien Ref No.</th><th>Citation</th></tr>
<tr><td>3</td><td>Klareskog L, van der Heijde D, de Jager JP, Gough A, Kalden J, Malaise M, Martin Mola E, Pavelka K, Sany J, Settas L, Wajdula J, Pedersen R, Fatenejad S, Sanda M. Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. Lancet2004 Feb 28;363(9410):675-81.</td></tr>
<tr><td>15</td><td>Emery P, Breedveld FC, Hall S, et al. Comparison of methotrexate monotherapy with a combination of methotrexate and etanercept in active, early, moderate to severe rheumatoid arthritis (COMET): a randomised, double-blind, parallel treatment trial. Lancet 2008;372:375–82.</td></tr>
<tr><td>18</td><td>Keystone EC, Kavanaugh AF, Sharp JT, et al. Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti-tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: a randomized, placebocontrolled, 52-week trial. Arthritis Rheum 2004;50:1400–11.</td></tr>
<tr><td>20</td><td>Weinblatt ME, Keystone EC, Furst DE, et al. Adalimumab, a fully human anti–tumor necrosis factor-_ monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. Arthritis Rheum 2003;48:35–45.</td></tr>
<tr><td>19</td><td>Kim HY, Lee SK, Song YW, Koh EM, Yoo B, Luo A. A randomized, double-blind, placebo-controlled, phase III study of the human anti–tumor necrosis factor antibody adalimumab administered as subcutaneous injections in Korean rheumatoid arthritis patients treated with methotrexate. APLAR J Rheumatol 2007;10:9–16.</td></tr>
<tr><td>21 (audit)</td><td>Lipsky PE, van der Heijde DM, St Clair EW, et al, for the Anti–Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. Infliximab and methotrexate in the treatment of rheumatoid arthritis. N Engl J Med 2000;343:1594–602.

No details generation or concealment
Blinding: assessors, clinicians and patients blinded x 1 yr. Details of IV fluid blinding adequate. 1 year f/u
Randomized: 428
Included in safety analysis: 428
Serious infections: 8.5%
TB: 1 case
Pneumonia: 3 cases
Demyelinating: NR
Deaths 1.2%

<table>
<tr><th>Category</th><th>MTX + placebo; N=86/88</th><th>IFX 3mg to 10mg every 4 or 8 wks +MTX; N=342/340</th></tr>
<tr><td>Serious Events</td><td>21%</td><td>16.8%</td></tr>
<tr><td>Serious Infections</td><td>8%</td><td>6%</td></tr>
</table></td></tr>
<tr><td>23</td><td>Maini R, St Clair EW, Breedveld F, et al, for the ATTRACT Study Group. Infliximab (chimeric anti–tumour necrosis factor-_ monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. Lancet 1999;354:1932–9.</td></tr>
<tr><td>25</td><td>Miyasaka N. Clinical investigation in highly disease-affected rheumatoid arthritis patients in Japan with adalimumabMaini R, St Clair EW, Breedveld F, et al, for the ATTRACT Study Group. Infliximab (chimeric anti–tumour necrosis factor-_ monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: applying standard and general evaluation: the CHANGE study. Mod Rheumatol 2008;18:252–62.</td></tr>
<tr><td>27</td><td>Furst DE, Schiff MH, Fleishmann RM, et al. Adalimumab, a fully human anti–tumor necrosis factor-_ monoclonal antibody, and concomitant standard antirheumatic therapy for the treatment of rheumatoid arthritis: results of STAR (safety trial of adalimumab in rheumatoid arthritis). J Rheumatol 2003;30: 2563–71.</td></tr>
<tr><td>28</td><td>St Clair EW, van der Heijde DM, Smolen JS, et al. Combination of infliximab and methotrexate therapy for early rheumatoid arthritis: a randomized, controlled trial. Arthritis Rheum 2004;50:3432–43.</td></tr>
<tr><td>29</td><td>van de Putte LB, Atkins C, Malaise M, et al. Efficacy and safety of adalimumab as monotherapy in patients with rheumatoid arthritis for whom previous disease modifying antirheumatic drug treatment has failed. Ann Rheum Dis 2004;63:508–16.</td></tr>
<tr><td>30 (audit)</td><td>van de Putte LB, Rau R, Breedveld FC, et al. Efficacy and safety of the fully human anti–tumour necrosis factor-_ monoclonal antibody adalimumab (D2E7) in DMARD refractory patients with rheumatoid arthritis: a 12 week, phase II study. Ann Rheum Dis 2003;62:1168–77.

No details regarding randomization, concealment of allocation or blinding.
Safety analysis included

70/70 placebo; 72/72 80 mg; 70/70 40 mg; 71/72 20 mg.

</td></tr>
<tr><td>31</td><td>van der Heijde D, Klareskog L, Landewe R, et al. Disease remission and sustained halting of radiographic progression</td></tr>
</table>

	with combination etanercept and methotrexate in patients with rheumatoid arthritis. Arthritis Rheum 2007;56:3928–39.
35	Zhang F-C, Hou Y, Huang F, et al. Infliximab versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a preliminary study from China. APLAR J Rheumatol 2006;9:127–30.
38	Breedveld FC, Weisman MH, Kavanaugh AF, et al. The PREMIER study: a multicenter, randomized, double-blind clinical trial of van der Heijde D combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. Arthritis Rheum 2006;54:26–37.
41	Westhovens R, Yocum D, Han J, et al. The safety of infliximab, combined with background treatments, among patients with rheumatoid arthritis and various comorbidities: a large, randomized, placebo-controlled trial. Arthritis Rheum 2006; 54:1075–86.
43 (audit)	Schiff M, Keiserman M, Codding C, et al. Efficacy and safety of abatacept or infliximab vs placebo in ATTEST: a phase III, multi-centre, randomised, double-blind, placebo-controlled study in patients with rheumatoid arthritis and an inadequate response to methotrexate. Ann Rheum Dis 2008;67:1096–103. • Randomized: Placebo + MTX 110, Placebo + MTX165; all included in safety analysis. • Randomization: no details of generation of sequence or concealment of allocation. • Blinding: patients, clinicians, assessors x1 year. • Analysis: Signal—increased serious infections with infliximab. Days 1–197 / Days 1–365 Placebo + MTX | Infliximab + MTXn=165 | Infliximab +MTX n =165) Serious infections 3 (2.7) 7 (4.2) 14 (8.5)
44	Weinblatt ME, Kremer JM, Bankhurst AD, et al. A trial of etanercept, a recombinant tumor necrosis factor receptor:Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. N Engl J Med 1999;340:253–9.
46	Lan JL, Chou SJ, Chen DY, Chen YH, Hsieh TY, Young MJ. A comparative study of etanercept plus methotrexate and methotrexate alone in Taiwanese patients with active rheumatoid arthritis: a 12-week, double-blind, randomized, placebo–controlled study. J Formos Med Assoc 2004;103: 618–23.
47	van der Heijde D, Klareskog L, Rodriguez-Valverde V, et al. Comparison of etanercept and methotrexate, alone and combined, in the treatment of rheumatoid arthritis: two-year clinical and radiographic results from the TEMPO study, a double-blind, randomized trial. Arthritis Rheum 2006;54: 1063–74.

SAFETY RESULTS FOR ADALIMUMAB, ETANERCEPT AND INFLIXIMAB COMPARED TO PLACEBO

Drug	Outcome	Number of Patients	Relative Risk	P Value
Adalimumab				
Kim 07, Miyasaka 07, Furst 03, van de Putte 04, Breedveld 06	Serious adverse events	1529	0.98 (95% CI 0.67 to 1.43)	0.90
Keystone 04, Kim 07, Miyasaka 07, Furst 03, van de Putte 03, Breedveld 06	Serious infections	2300	2.22 (95% CI 0.83 to 5.99)	0.11
Kim 07, Miyasaka 07, Furst 03, Breedveld 06	Malignancy	1467	0.55 (95% CI 0.14 to 2.11)	0.38
Keystone 04, Kim 07, Miyasaka 07, Furst 03, van de Putte 03, Breedveld 06	Deaths	2428	2.52 (95% CI 0.72 to 8.86)	0.15
Furst 2003, van de Putte 2003, Breedveld 2006, Kim 2007, Miyasaka 2008	Withdrawal due to adverse events	1609	1.56 (95% CI 1.04 to 2.35)	
Etanercept				
Klareskog 04, Emery 08, Lan 04	Serious adverse events	1045	0.70 (95% CI 0.41 to 1.22)	0.36
Klareskog 04, Emery 08, Lan 04	Serious infections	1302	0.89 (95% CI 0.54 to 1.48)	0.66
Klareskog 04, Emery 08, Lan 04	Malignancy	1302	0.98 (95% CI 0.32 to 3.02)	0.97
Van der Heijde 07, Weinblatt 99, Lan 04	Deaths	1178	1.54 (95% CI 0.19 to 12.48)	0.68
Emery 08, Klareskog 04, Lan 04, Moreland 99, van der Heijde 06, Weinblatt 99	Withdrawal due to adverse events	1549	0.86 (95% CI 0.63 to 1.16)	
Infliximab				
Lipsky 00, Maini 99, St Clair 04, Westhovens 06, Abe 06, Schiff 08	Serious adverse events	2610	1.12 (95% CI 0.90 to 1.41)	0.32

Lipsky 00, Maini 99, St Clair 04, Westhovens 06, Schiff 08	Serious infections	2017	0.96 (95% CI 0.39 to 2.38)	0.93
Maini 99, St Clair 04, Zhang F-C, Schiff 08	Malignancy	2016	1.64 (95% CI 0.30 to 8.89)	0.57
St Clair 04, Abe 06, Schiff 08	Death	1042	0.71 (95% CI 0.11 to 4.85)	0.73
Abe 2006,Lipsky 2000, Quinn 2005, Schiff 2008, St Clair 2004, Westhovens 2006, Zhang 2006	Withdrawal due to adverse events	2132	2.05 (95% CI 1.33 to 3.16)	

Risk of Malignancy in RA, Psoriasis and PsA With IFX, ADA, ETN

Wiens 10	IFX, ADA, ETN in RA versus Placebo with or without MTX (2,145)	IFX: RR 1.64 (95% CI 0.30 to 8.89) ADA: RR 0.55 (95% CI 0.14 to 2.11) ETN: RR 0.98 (95% CI 0.32 to 3.02)

WOLFE 07a_Registry_Cancer_3Agents_FINAL

AUTHOR YR: Wolfe 07a

Citation: Wolfe F, Michaud K. Biologic treatment of rheumatoid arthritis and the risk of malignancy: analyses from a large US observational study. Arthritis Rheum2007 Sep;56(9):2886-95.. PubMed PMID: 17729297
Study Type: Registry Cohort

Manufacture Involvement: During the period of data collection, the National Data Bank for Rheumatic Diseases received research support from Abbott, Amgen, Bristol-Myers Squibb, Centocor, Merck, Pfizer, and Wyeth-Australia.

Abstract

Objective. Induction of malignancy is a major concern when rheumatoid arthritis (RA) is treated with biologic therapy. A meta-analysis of RA biologic clinical trials found a general increased risk of malignancy, but this risk was not found in a large observational study. We undertook this study to assess the risk of malignancy among biologic-treated patients in a large US observational database.

Methods. We studied incident cases of cancer among 13,001 patients during approximately 49,000 patient-years of observation in the years 1998–2005. Cancer rates were compared with population rates using the US National Cancer Institute SEER (Surveillance, Epidemiology, and End-Results) database. Assessment of the risk of biologic therapy utilized conditional logistic regression to calculate odds ratios (ORs) as estimates of the relative risk, further adjusted for 6 confounders: age, sex, education level, smoking history, RA severity, and prednisone use.

Results. Biologic exposure was 49%. There were 623 incident cases of nonmelanotic skin cancer and 537 other cancers. The standardized incidence ratios and 95% confidence intervals (95% CIs) compared with SEER data were as follows: all cancers 1.0 (1.0–1.1), breast 0.8 (0.6–0.9), colon 0.5 (0.4–0.6), lung 1.2 (1.0– 1.4), lymphoma 1.7 (1.3–2.2). Biologics were associated with an increased risk of nonmelanotic skin cancer (OR 1.5, 95% CI 1.2–1.8) and melanoma (OR 2.3, 95% CI 0.9–5.4). No other malignancy was associated with biologic use; the OR (overall risk) of any cancer was 1.0 (95% CI 0.8–1.2).

Conclusion. Biologic therapy is associated with increased risk for skin cancers, but not for solid tumors or lymphoproliferative malignancies. These associations were consistent across different biologic therapies.

Reviewer Comments

- Agents of Interest: **Adalimumab, etanercept, , infliximab, in RA**
- Participants were members of the US National Data Bank for Rheumatic Diseases (NDB) longitudinal study of RA outcomes who completed semiannual questionnaires in the period 1998 through 2005. NDB participants are recruited on an ongoing basis from the practices of US rheumatologists and are followed up prospectively with semiannual, detailed, 28-page questionnaires.
- To determine expected rates of specific cancers, investigators used the US SEER (Surveillance, Epidemiology, and End- Results) database as a comparison population. The SEER Program of the National Cancer Institute is an authoritative source of information on cancer incidence and survival in the US. The SEER Program currently collects and publishes cancer incidence and survival data from population-based cancer registries covering approximately 26% of the US population. Investigators used age and sex categories from the SEER database to determine the standardized incidence ratio (SIR) for each cancer studied in the RA sample compared with the US population.
- Assessment of the risk of biologic therapy utilized conditional logistic regression to calculate odds ratios (ORs) as estimates of the relative risk, further adjusted for 6 confounders: age, sex, education level, smoking history, RA severity, and prednisone use.
- Odds ratios for individual agents compared to US population cancer rates (excluding non-melanoma skin cancer) were: infliximab OR 1.0 (95% CI 0.8 to 1.3), P= 0.820; adalimumab OR 0.7 (95% CI 0.3 to 1.6), P= 0.393; etanercept OR 1.0 (95% CI 0.8 to 1.3), P= 0.962.
- Odds ratios for individual agents compared to US population melanoma rates were: infliximab OR 2.6 (95% CI 1.0 to 6.7), P = 0.056 and etanercept OR 2.4 (95% CI 1.0 to 5.8), P = 0.054.
- Infliximab (OR 1.7 [95% CI 1.3 to 2.2], P = 0.001) and etanercept (OR 1.2 [95% CI 1.0 to 1.5], P =0.081) were associated with non-melanotic skin cancer.
- Findings of no statistically significant difference raise questions of sufficient power.

WOLFE 07b_lymphoma _3Agents_FINAL

AUTHOR YR: Wolfe 07b

Citation: Wolfe F, Michaud K. The effect of methotrexate and anti-tumor necrosis factor therapy on the risk of lymphoma in rheumatoid arthritis in 19,562 patients during 89,710 person-years of observation. Arthritis Rheum 2007;56(5):1433–9. PMID: 17469100

Study Type: Registry Cohort

Manufacture Involvement: The National Data Bank for Rheumatic Diseases has conducted safety registries for Centocor, Sanofi-Aventis, and Bristol-Meyers Squibb and has received grant support from Abbott, Amgen, Wyeth-Australia, Merck, and Pfizer. Completed manuscript was reviewed by Centocor. No changes in the manuscript were made after their review.

Abstract

Objective. To ascertain the relationship between anti–tumor necrosis factor (anti-TNF) therapy, methotrexate (MTX), and the risk of lymphoma in patients with rheumatoid arthritis (RA). This report updates our previous report during 29,314 person-years of followup.

Methods. Participants in the National Data Bank for Rheumatic Diseases (NDB) longitudinal study of long-term outcomes of RA completed semiannual questionnaires from 1998 through 2005, during 89,710 person-years of followup. Lymphoma reports were validated by medical records. The association between lymphoma and treatment was investigated using conditional logistic regression, adjusted for severity and demographic covariates.

Results. Of the 19,591 participants, 55.3% received biologic agents and 68.0% received MTX while enrolled in the NDB. The lymphoma incidence rate was 105.9 (95% confidence interval [95% CI] 86.6–129.5) per 100,000 person-years of exposure. Compared with the SEER (Surveillance, Epidemiology, and End-Results) lymphoma database, the standardized incidence ratio was 1.8(95% CI 1.5 to 2.2). The odds ratio (OR) for lymphoma in patients who received anti-TNF therapy compared with patients who did not receive anti-TNF therapy was 1.0 (95% CI 0.6–1.8 [P = 0.875]). The OR for lymphoma in patients who received anti-TNF plus MTX therapy compared with patients who received MTX treatment alone was 1.1 (95% CI 0.6–2.0 [P = 0.710]). Infliximab and etanercept considered individually also were not associated with a risk of lymphoma.

Conclusion. In a study of lymphoma in 19,591 RA patients over 89,710 person-years of followup, which included exposure to anti-TNF therapy in 10,815 patients, we did not observe evidence for an increase in the incidence of lymphoma among patients who received anti-TNF therapy.

Reviewer Comments

- Agents of Interest: Adalimumab, etanercept, , infliximab, in RA
- Participants were members of the US National Data Bank for Rheumatic Diseases (NDB) longitudinal study of RA outcomes who completed semiannual questionnaires in the period 1998 through 2005. NDB participants are recruited on an ongoing basis from the practices of US rheumatologists and are followed up prospectively with semiannual, detailed, 28-page questionnaires.
- To determine expected rates of specific cancers, investigators used the US SEER (Surveillance, Epidemiology, and End- Results) database as a comparison population. The SEER Program of the National Cancer Institute is an authoritative source of information on cancer incidence and survival in the US. The SEER Program currently collects and publishes cancer incidence and survival data from population-based cancer registries covering approximately 26% of the US population. Investigators used age and sex categories from the SEER database to determine the standardized incidence ratio (SIR) for each cancer studied in the RA sample compared with the US population.
- Assessment of the risk of biologic therapy utilized conditional logistic regression to calculate odds ratios (ORs) as estimates of the relative risk, further adjusted for 6 confounders: age, sex, education level, smoking history, RA severity, and prednisone use.

Individual Agents

- Some modesl for infliximab and etanercept, respectively, showed no association of these treatments with lymphoma. The OR for the association of any Infliximab treatment with lymphoma was 1.2 (95% CI 0.6 to 2.2), P=0.646.
- Any etanercept treatment was 0.7 (95% CI 0.3 to 1.6), P =0.422.
- One model showed a statistically significant association between adalimumab treatment and lymphoma based on 56 cases and 2 lymphomas in the adalimumab-treated group. The limited number of cases reflects the study requirement that patients receiving specific anti-TNF therapies not have been treated with other anti-TNF therapies first. When this requirement was relaxed for adalimumab, the number of cases expanded to 1,482 and the OR for adalimumab versus all other therapies was 1.2 (95% CI 0.3 to 5.10), P =0.812.
- Findings of no statistically significant difference raise questions of sufficient power.

Wolfe TB IFX 04 FINAL

AUTHOR YR: Wolfe 04

Citation: Wolfe F, Michaud K, Anderson J, Urbansky K. Tuberculosis infection in patients with rheumatoid arthritis and the effect of infliximab therapy. Arthritis Rheum2004 Feb;50(2):372-9. PMID: 14872478

Study Type: Prospective cohort study with historical controls

Manufacture Involvement: Funding Centocor

Abstract

Objective. According to the Centers for Disease Control and Prevention, the 1999 and 2000 incidence rates for tuberculosis (TB) in the US population were 6.4 and 5.8, respectively, per 100,000 persons. Recently, reports of TB following infliximab administration have raised questions regarding the rate of TB in patients with rheumatoid arthritis (RA) generally and in those treated with infliximab in clinical practice. We undertook this study to determine the baseline rate of TB in RA prior to the introduction of infliximab and to determine the rate of TB among those currently receiving infliximab.

Methods. We surveyed patients with questionnaires, followed by detailed validation from medical records and physician reports. In study 1, we evaluated 10,782 RA patients in 1998–1999 prior to the widespread use of infliximab. In study 2, we evaluated 6,460 infliximab-treated patients in 2000–2002. *Results.* In study 1, the lifetime rate of TB was 696 per 100,000 patients (95% confidence interval [95% CI] 547–872). Of these cases, 76.8% occurred prior to the onset of RA. During the period of prospective followup, 1 case of TB developed during 16,173 patient-years of followup, yielding a rate of 6.2 cases (95% CI 1.6–34.4) per 100,000 patients. In study 2, the TB incidence rate among infliximab-treated patients was 52.5 cases (95% CI 14.3–134.4) per 100,000 patient-years of exposure. Three of the 4 cases occurred in patients with a history of TB exposure, and no cases occurred in persons with recent TB skin tests or prophylaxis.

Conclusion. The rate of TB is not increased in RA patients generally. Among infliximab-treated patients, the rate is 52.5 cases (95% CI 14.3–134.4) per 100,000 patient-years of exposure. A thorough medical history regarding TB, as well as tuberculin testing and radiographic examination (if indicated), should be an essential component of anti–tumor necrosis factor therapy.

Reviewer Comments

- Prospective cohort study with historical controls
- Results based on combination of observational data resulting in high risk of selection, performance, attrition, reporting and assessment biases.
- Using data from the National Data Bank of Rheumatic Diseases (NBI), reported an eightfold higher rate of tuberculosis in patients treated with infliximab than in patients in a historic control group who had been treated with synthetic DMARDs. The analysis yielded rates of 6.2 cases per 100,000 patient-years in the control group and 52.5 cases per 100,000 patient-years in patients on infliximab.

ZIDI GOLimumab malignancy and lymphoma 10_FINAL

AUTHOR YR: Zidi 10

Citation: Zidi I, Bouaziz A, Mnif W, Bartegi A, Ben Amor N. Golimumab and malignancies: true or false association? Med Oncol2010 Apr 7.PMID: 20373059

Study Type: Narrative Review

Manufacture Involvement: No information

Abstract

Malignancy is one of the comorbidities linked to golimumab, a biological TNF-alpha blocker. In this systematic review and meta-analysis, we searched different databases and analyzed original publications to elucidate the remaining open question about the real association of malignancies with golimumab therapy. The most frequent cancer in patients treated with golimumab, in association or not with methotrexate, is the lung adenocarcinoma. However, lymphoma is not very commonly represented in these patients. We show that there is no major and evident risk of malignancies associated with golimumab in current scientific literature. An increased risk of malignancies may be associated with golimumab, but this warrants further clinical confirmation. Also, this risk mentioned in different studies must be taken with caution because of number of limits and biases.

Reviewer Comments

- Search: PubMed, Highwire, EBESCO, Cochrane, FDA database to January 2010.
- Search Terms: golimumab, Simponi, CNTO 148 limited to French and English.
- Authors provide estimates of various malignancies with GLN reported in 6 RCTs (Emery 09, Kavanaugh 09, Kay 08, Keystone 09, Kremer 10, Smolen 08). The incidence of malignancy in the trials was not statistically different from control groups. Likely to have been underpowered to demonstrate differences if they existed.

Category	GLN	Control	Controls (Placebo + /- MTX): No statistical difference for any cancer
Lung adenocarcinoma	3.1%		**LABEL INFORMATION FROM FDA MEDICAL REVIEW** **Lymphoma**: FDA statement: During the controlled portions of the Phase 2 trials in RA, and the Phase 3 trials in RA, PsA and AS, the incidence of lymphoma per 100 patient-years of follow-up was 0.21 (95% CI 0.03 to 0.77) in the combined SIMPONI group compared with an incidence of 0 (95% CI 0 to 0.96) in the placebo group. **TB**: In the controlled and uncontrolled portions of the Phase 2 RA and Phase 3 RA, PsA, and AS trials, the incidence of active TB was 0.23 and 0 per 100 patient-years in 2347 SIMPONI-treated patients and 674 placebo-treated patients, respectively. Cases of TB included pulmonary and extra pulmonary TB. The overwhelming majority of the TB cases occurred in countries with a high incidence rate of TB. Ref. http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/125289s006lbl.pdf
Basal cell carcinoma	1%	0.8%	
Squamous cell carcinoma	1%	0.6%	
Breast carcinoma	0.8%	0.6%	
Bladder cancer	0.8%		
Ovarian cancer	0.8%		
Colon cancer	0.7%		
Prostate cancer	0.7%		
Lung cancer	0.7%		
Lymphoma	0.6%		

V. SEARCH DOCUMENTATION

Safety of Biologic Agents: Search Documentation

SEARCH 1_etanercept RA meta 3 condit

Category	Description
Clinical question or focus	BIOLOGICAL AGENTS FINAL
Source	PubMed
Terms	etanercept AND (rheumatoid arthritis OR psoriatic arthritis OR psoriasis)
Limits	Meta-Analysis
▪ Date limits	
▪ Other limits	
Query Translation (eg, "Details" in PubMed)	("TNFR-Fc fusion protein"[Substance Name] OR "TNFR-Fc fusion protein"[All Fields] OR "etanercept"[All Fields]) AND (("arthritis, rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "rheumatoid"[All Fields]) OR "rheumatoid arthritis"[All Fields] OR ("rheumatoid"[All Fields] AND "arthritis"[All Fields])) OR ("arthritis, psoriatic"[MeSH Terms] OR ("arthritis"[All Fields] AND "psoriatic"[All Fields]) OR "psoriatic arthritis"[All Fields] OR ("psoriatic"[All Fields] AND "arthritis"[All Fields])) OR ("psoriasis"[MeSH Terms] OR "psoriasis"[All Fields])) AND Meta-Analysis[ptyp]
Date of Search	8/15/10
Total Yield	37
Total marked for retrieval	12 Wiens 10, Singh Cochrane 09, Bongatz 09, Poulin 09, Alonso-Ruiz 08, Brimhall 08, Saad 08, Schmitt 08, Gartlehner 06, Woolacott 06, Gottlieb 06, Fleischmann 06
Exclusions after title +/- abstract review	• Not focus of review: population, intervention, comparison, outcome • Superseded by more recent larger study • Lacking safety data • Duplicates

Secondary Studies

1: Wiens A, Venson R, Correr CJ, Otuki MF, Pontarolo R. Meta-analysis of the efficacy and safety of adalimumab, etanercept, and infliximab for the treatment of rheumatoid arthritis. Pharmacotherapy. 2010 Apr;30(4):339-53. Review. PubMed PMID: 20334454.

2: Petitpain N, Gambier N, Wahl D, Chary-Valckenaere I, Loeuille D, Gillet P; French Network of Pharmacovigilance Centers. Arterial and venous thromboembolic events during anti-TNF therapy: a study of 85 spontaneous reports in the period 2000-2006. Biomed Mater Eng. 2009;19(4-5):355-64. PubMed PMID: 20042802.

3: Blasco AJ, Lázaro P, Ferrándiz C, García-Díez A, Liso J. [Efficiency of biologic agents in the treatment of moderate to severe psoriasis]. Actas Dermosifiliogr. 2009 Nov;100(9):792-803. Spanish. PubMed PMID: 19889301.

4: Singh JA, Christensen R, Wells GA, Suarez-Almazor ME, Buchbinder R, Lopez-Olivo MA, Ghogomu ET, Tugwell P. A network meta-analysis of randomized controlled trials of biologics for rheumatoid arthritis: a Cochrane overview. CMAJ. 2009 Nov 24;181(11):787-96. Epub 2009 Nov 2. PubMed PMID: 19884297; PubMed Central PMCID: PMC2780484.

5: Singh JA, Christensen R, Wells GA, Suarez-Almazor ME, Buchbinder R, Lopez-Olivo MA, Tanjong Ghogomu E, Tugwell P. Biologics for rheumatoid arthritis: an overview of Cochrane reviews. Cochrane Database Syst Rev. 2009 Oct 7;(4):CD007848. Review. PubMed PMID: 19821440.

6: Frankel AJ, Van Voorhees AS, Hsu S, Korman NJ, Lebwohl MG, Bebo BF Jr, Gottlieb AB; National Psoriasis Foundation. Treatment of psoriasis in patients

with hepatitis C: from the Medical Board of the National Psoriasis Foundation. J Am Acad Dermatol. 2009 Dec;61(6):1044-55. Epub 2009 Oct 7. Review. PubMed PMID: 19811848.

7: Poulin Y, Langley RG, Teixeira HD, Martel MJ, Cheung S. Biologics in the treatment of psoriasis: clinical and economic overview. J Cutan Med Surg. 2009 Sep-Oct;13 Suppl 2:S49-57. Review. PubMed PMID: 19799827.

8: Wiens A, Correr CJ, Pontarolo R, Venson R, Quinalha JV, Otuki MF. A systematic review and meta-analysis of the efficacy and safety of etanercept for treating rheumatoid arthritis. Scand J Immunol. 2009 Oct;70(4):337-44. Review. PubMed PMID: 19751268.

9: Christensen R, Kristensen LE, Geborek P, Danneskiold-Samsøe B, Saxne T, Bliddal H. [The efficacy of the three available anti-tumour necrosis factor therapies in patients with rheumatoid arthritis. A meta-analytic literature review--secondary publication]. Ugeskr Laeger. 2009 Jun 22;171(26):2192-4. Review. Danish. PubMed PMID: 19678436.

10: Bansback N, Sizto S, Sun H, Feldman S, Willian MK, Anis A. Efficacy of systemic treatments for moderate to severe plaque psoriasis: systematic review and meta-analysis. Dermatology. 2009;219(3):209-18. Epub 2009 Aug 5. Review. PubMed PMID: 19657180.

11: Brown BC, Warren RB, Grindlay DJ, Griffiths CE. What's new in psoriasis? Analysis of the clinical significance of systematic reviews on psoriasis published in 2007 and 2008. Clin Exp Dermatol. 2009 Aug;34(6):664-7. Epub 2009 Jun 30. Review. PubMed PMID: 19572945.

12: Zhang Z, Schmitt J, Wozel G, Kirch W. [Treatment of plaque psoriasis with biologics. A meta-analysis of randomized controlled trials]. Med Klin (Munich). 2009 Feb 15;104(2):125-36. Epub 2009 Feb 26. German. PubMed PMID: 19242664.

13: Bongartz T, Warren FC, Mines D, Matteson EL, Abrams KR, Sutton AJ. Etanercept therapy in rheumatoid arthritis and the risk of malignancies: a systematic review and individual patient data meta-analysis of randomised controlled trials. Ann Rheum Dis. 2009 Jul;68(7):1177-83. Epub 2008 Nov 19. Review. PubMed PMID: 19019889.

14: Venkateshan SP, Sidhu S, Malhotra S, Pandhi P. Efficacy of biologicals in the treatment of rheumatoid arthritis. a meta-analysis. Pharmacology. 2009;83(1):1-9. Epub 2008 Oct 28. Review. PubMed PMID: 18957873.

15: Schmitt J, Zhang Z, Wozel G, Meurer M, Kirch W. Efficacy and tolerability of biologic and nonbiologic systemic treatments for moderate-to-severe psoriasis: meta-analysis of randomized controlled trials. Br J Dermatol. 2008 Sep;159(3):513-26. Epub 2008 Jul 9. Review. PubMed PMID: 18627372.

16: Brimhall AK, King LN, Licciardone JC, Jacobe H, Menter A. Safety and efficacy of alefacept, efalizumab, etanercept and infliximab in treating moderate to severe plaque psoriasis: a meta-analysis of randomized controlled trials. Br J Dermatol. 2008 Aug;159(2):274-85. Epub 2008 Jun 10. Review. PubMed PMID: 18547300.

17: Alonso-Ruiz A, Pijoan JI, Ansuategui E, Urkaregi A, Calabozo M, Quintana A. Tumor necrosis factor alpha drugs in rheumatoid arthritis: systematic review and metaanalysis of efficacy and safety. BMC Musculoskelet Disord. 2008 Apr 17;9:52. Review. PubMed PMID: 18419803; PubMed Central PMCID: PMC2377247.

18: Saad AA, Symmons DP, Noyce PR, Ashcroft DM. Risks and benefits of tumor necrosis factor-alpha inhibitors in the management of psoriatic arthritis: systematic review and metaanalysis of randomized controlled trials. J Rheumatol.

2008 May;35(5):883-90. Epub 2008 Mar 15. Review. PubMed PMID: 18381787.

19: Nelson AA, Pearce DJ, Fleischer AB Jr, Balkrishnan R, Feldman SR. Cost-effectiveness of biologic treatments for psoriasis based on subjective and objective efficacy measures assessed over a 12-week treatment period. J Am Acad Dermatol. 2008 Jan;58(1):125-35. Epub 2007 Nov 8. Review. PubMed PMID: 17996329.

20: Bravo Vergel Y, Hawkins NS, Claxton K, Asseburg C, Palmer S, Woolacott N, Bruce IN, Sculpher MJ. The cost-effectiveness of etanercept and infliximab for the treatment of patients with psoriatic arthritis. Rheumatology (Oxford). 2007 Nov;46(11):1729-35. PubMed PMID: 17956918.

21: Lee YH, Woo JH, Rho YH, Choi SJ, Ji JD, Song GG. Meta-analysis of the combination of TNF inhibitors plus MTX compared to MTX monotherapy, and the adjusted indirect comparison of TNF inhibitors in patients suffering from active rheumatoid arthritis. Rheumatol Int. 2008 Apr;28(6):553-9. Epub 2007 Oct 18. PubMed PMID: 17943257.

22: Brodszky V, Czirják L, Géher P, Hodinka L, Kárpáti K, Péntek M, Poór G, Szekanecz Z, Gulácsi L. [Rituximab in patients with rheumatoid arthritis: systematic review]. Orv Hetil. 2007 Oct 7;148(40):1883-93. Review. Hungarian. PubMed PMID: 17905683.

23: Heiligenhaus A, Horneff G, Greiner K, Mackensen F, Zierhut M, Foeldvari I, Michels H. [Inhibitors of tumour necrosis factor-alpha for the treatment of arthritis and uveitis in childhood]. Klin Monbl Augenheilkd. 2007 Jun;224(6):526-31. Review. German. PubMed PMID: 17594625.

24: Nixon R, Bansback N, Brennan A. The efficacy of inhibiting tumour necrosis factor alpha and interleukin 1 in patients with rheumatoid arthritis: a meta-analysis and adjusted indirect comparisons. Rheumatology (Oxford). 2007 Jul;46(7):1140-7. Epub 2007 May 3. PubMed PMID: 17478472.

25: Katugampola RP, Lewis VJ, Finlay AY. The Dermatology Life Quality Index: assessing the efficacy of biological therapies for psoriasis. Br J Dermatol. 2007 May;156(5):945-50. Epub 2007 Mar 28. Review. PubMed PMID: 17388922.

26: Gartlehner G, Hansen RA, Jonas BL, Thieda P, Lohr KN. The comparative efficacy and safety of biologics for the treatment of rheumatoid arthritis: a systematic review and metaanalysis. J Rheumatol. 2006 Dec;33(12):2398-408. Review. PubMed PMID: 17225293.

27: Koó E, Brodszky V, Péntek M, Ujfalussy I, Nagy MB, Gulácsi L. [The role of biological agents in the treatment of psoriatic arthritis, literature review]. Orv Hetil. 2006 Oct 15;147(41):1963-70. Review. Hungarian. PubMed PMID: 17120686.

28: Chen YF, Jobanputra P, Barton P, Jowett S, Bryan S, Clark W, Fry-Smith A, Burls A. A systematic review of the effectiveness of adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis in adults and an economic evaluation of their cost-effectiveness. Health Technol Assess. 2006 Nov;10(42):iii-iv, xi-xiii, 1-229. Review. PubMed PMID: 17049139.

29: Woolacott N, Bravo Vergel Y, Hawkins N, Kainth A, Khadjesari Z, Misso K, Light K, Asseburg C, Palmer S, Claxton K, Bruce I, Sculpher M, Riemsma R. Etanercept and infliximab for the treatment of psoriatic arthritis: a systematic review and economic evaluation. Health Technol Assess. 2006 Sep;10(31):iii-iv, xiii-xvi, 1-239. Review. PubMed PMID: 16948890.

30: Kemény L, Brodszky V, Kárpáti K, Gulácsi L. [The role of biological drugs in the treatment of psoriasis, results from 9 randomized placebo-controlled trials]. Orv Hetil. 2006 May 28;147(21):981-90. Review. Hungarian. PubMed PMID: 16812973.

31: Fransen J, Antoni C, Mease PJ, Uter W, Kavanaugh A, Kalden JR, Van Riel PL. Performance of response criteria for assessing peripheral arthritis in patients with psoriatic arthritis: analysis of data from randomised controlled trials of two tumour necrosis factor inhibitors. Ann Rheum Dis. 2006 Oct;65(10):1373-8. Epub 2006 Apr 27. PubMed PMID: 16644783; PubMed Central PMCID: PMC1798317.

32: Chung CP, Thompson JL, Koch GG, Amara I, Strand V, Pincus T. Are American College of Rheumatology 50% response criteria superior to 20% criteria in distinguishing active aggressive treatment in rheumatoid arthritis clinical trials reported since 1997? A meta-analysis of discriminant capacities. Ann Rheum Dis. 2006 Dec;65(12):1602-7. Epub 2006 Feb 27. Review. PubMed PMID: 16504992; PubMed Central PMCID: PMC1798472.

33: Gottlieb AB, Leonardi CL, Goffe BS, Ortonne JP, van der Kerkhof PC, Zitnik R, Nakanishi A, Jahreis A. Etanercept monotherapy in patients with psoriasis: a summary of safety, based on an integrated multistudy database. J Am Acad Dermatol. 2006 Mar;54(3 Suppl 2):S92-100. PubMed PMID: 16488335.

34: Gordon K, Korman N, Frankel E, Wang H, Jahreis A, Zitnik R, Chang T. Efficacy of etanercept in an integrated multistudy database of patients with psoriasis. J Am Acad Dermatol. 2006 Mar;54(3 Suppl 2):S101-11. PubMed PMID: 16488320.

35: Fleischmann R, Baumgartner SW, Weisman MH, Liu T, White B, Peloso P. Long term safety of etanercept in elderly subjects with rheumatic diseases. Ann Rheum Dis. 2006 Mar;65(3):379-84. Epub 2005 Sep 8. PubMed PMID: 16150792; PubMed Central PMCID: PMC1798057.

36: Blumenauer B, Judd M, Cranney A, Burls A, Coyle D, Hochberg M, Tugwell P, Wells G. Etanercept for the treatment of rheumatoid arthritis. Cochrane Database Syst Rev. 2003;(4):CD004525. Review. PubMed PMID: 14584021.

37: Hochberg MC, Tracy JK, Hawkins-Holt M, Flores RH. Comparison of the efficacy of the tumour necrosis factor alpha blocking agents adalimumab, etanercept, and infliximab when added to methotrexate in patients with active rheumatoid arthritis. Ann Rheum Dis. 2003 Nov;62 Suppl 2:ii13-6. Review. PubMed PMID: 14532140; PubMed Central PMCID: PMC1766753.

SEARCH 2_infliximab_ RA meta 3 condit

Category	Description
Clinical question or focus	BIOLOGICAL AGENTS FINAL
Source	PubMed
Terms	infliximab AND (rheumatoid arthritis OR psoriatic arthritis OR psoriasis)
Limits	Meta-Analysis
▪ Date limits	
▪ Other limits	
Query Translation (eg, “Details” in PubMed)	("infliximab"[Substance Name] OR "infliximab"[All Fields]) AND (("arthritis, rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "rheumatoid"[All Fields]) OR "rheumatoid arthritis"[All Fields] OR ("rheumatoid"[All Fields] AND "arthritis"[All Fields])) OR ("arthritis, psoriatic"[MeSH Terms] OR ("arthritis"[All Fields] AND "psoriatic"[All Fields]) OR "psoriatic arthritis"[All Fields] OR ("psoriatic"[All Fields] AND "arthritis"[All Fields])) OR ("psoriasis"[MeSH Terms] OR "psoriasis"[All Fields])) AND Meta-Analysis[ptyp]
Date of Search	8/15/10
Total Yield	38
Total marked for retrieval	All are duplicates
Exclusions	• Not focus of review: population, intervention, comparison, outcome • Superseded by more recent larger study • Lacking safety data • Duplicates

Secondary Studies: Yield and Disposition

1: Wiens A, Venson R, Correr CJ, Otuki MF, Pontarolo R. Meta-analysis of the efficacy and safety of adalimumab, etanercept, and infliximab for the treatment of rheumatoid arthritis. Pharmacotherapy. 2010 Apr;30(4):339-53. Review. PubMed PMID: 20334454.

2: Lee YH, Ji JD, Bae SC, Song GG. Associations between tumor necrosis factor-alpha (TNF-alpha) -308 and -238 G/A polymorphisms and shared epitope status and responsiveness to TNF-alpha blockers in rheumatoid arthritis: a metaanalysis update. J Rheumatol. 2010 Apr;37(4):740-6. Epub 2010 Mar 1. PubMed PMID: 20194454.

3: Petitpain N, Gambier N, Wahl D, Chary-Valckenaere I, Loeuille D, Gillet P; French Network of Pharmacovigilance Centers. Arterial and venous thromboembolic events during anti-TNF therapy: a study of 85 spontaneous reports in the period 2000-2006. Biomed Mater Eng. 2009;19(4-5):355-64. PubMed PMID: 20042802.

4: Blasco AJ, Lázaro P, Ferrándiz C, García-Díez A, Liso J. [Efficiency of biologic agents in the treatment of moderate to severe psoriasis]. Actas Dermosifiliogr. 2009 Nov;100(9):792-803. Spanish. PubMed PMID: 19889301.

5: Singh JA, Christensen R, Wells GA, Suarez-Almazor ME, Buchbinder R, Lopez-Olivo MA, Ghogomu ET, Tugwell P. A network meta-analysis of randomized controlled trials of biologics for rheumatoid arthritis: a Cochrane overview. CMAJ. 2009 Nov 24;181(11):787-96. Epub 2009 Nov 2. PubMed PMID: 19884297; PubMed Central PMCID: PMC2780484.

6: Singh JA, Christensen R, Wells GA, Suarez-Almazor ME, Buchbinder R, Lopez-Olivo MA, Tanjong Ghogomu E, Tugwell P. Biologics for rheumatoid arthritis: an overview of Cochrane reviews. Cochrane Database Syst Rev. 2009 Oct 7;(4):CD007848. Review. PubMed PMID: 19821440.

7: Köller MD, Aletaha D, Funovits J, Pangan A, Baker D, Smolen JS. Response of elderly patients with rheumatoid arthritis to methotrexate or TNF inhibitors compared with younger patients. Rheumatology (Oxford). 2009 Dec;48(12):1575-80. Epub 2009 Oct 7. PubMed PMID: 19812228.

8: Poulin Y, Langley RG, Teixeira HD, Martel MJ, Cheung S. Biologics in the treatment of psoriasis: clinical and economic overview. J Cutan Med Surg. 2009 Sep-Oct;13 Suppl 2:S49-57. Review. PubMed PMID: 19799827.

9: Wiens A, Correr CJ, Venson R, Grochocki MC, Otuki MF, Pontarolo R. A meta-analysis of the efficacy and safety of using infliximab for the treatment of rheumatoid arthritis. Clin Rheumatol. 2009 Dec;28(12):1365-73. Epub 2009 Sep 22. Review. PubMed PMID: 19771491.

10: Christensen R, Kristensen LE, Geborek P, Danneskiold-Samsøe B, Saxne T, Bliddal H. [The efficacy of the three available anti-tumour necrosis factor therapies in patients with rheumatoid arthritis. A meta-analytic literature review--secondary publication]. Ugeskr Laeger. 2009 Jun 22;171(26):2192-4. Review. Danish. PubMed PMID: 19678436.

11: Bansback N, Sizto S, Sun H, Feldman S, Willian MK, Anis A. Efficacy of systemic treatments for moderate to severe plaque psoriasis: systematic review and meta-analysis. Dermatology. 2009;219(3):209-18. Epub 2009 Aug 5. Review. PubMed PMID: 19657180.

12: Brown BC, Warren RB, Grindlay DJ, Griffiths CE. What's new in psoriasis?

Analysis of the clinical significance of systematic reviews on psoriasis published in 2007 and 2008. Clin Exp Dermatol. 2009 Aug;34(6):664-7. Epub 2009 Jun 30. Review. PubMed PMID: 19572945.

13: Zhang Z, Schmitt J, Wozel G, Kirch W. [Treatment of plaque psoriasis with biologics. A meta-analysis of randomized controlled trials]. Med Klin (Munich). 2009 Feb 15;104(2):125-36. Epub 2009 Feb 26. German. PubMed PMID: 19242664.

14: Zintzaras E, Dahabreh IJ, Giannouli S, Voulgarelis M, Moutsopoulos HM. Infliximab and methotrexate in the treatment of rheumatoid arthritis: a systematic review and meta-analysis of dosage regimens. Clin Ther. 2008 Nov;30(11):1939-55. Review. PubMed PMID: 19108784.

15: Venkateshan SP, Sidhu S, Malhotra S, Pandhi P. Efficacy of biologicals in the treatment of rheumatoid arthritis. a meta-analysis. Pharmacology. 2009;83(1):1-9. Epub 2008 Oct 28. Review. PubMed PMID: 18957873.

16: Doyle MK, Rahman MU, Han C, Han J, Giles J, Bingham CO 3rd, Bathon J. Treatment with infliximab plus methotrexate improves anemia in patients with rheumatoid arthritis independent of improvement in other clinical outcome measures-a pooled analysis from three large, multicenter, double-blind, randomized clinical trials. Semin Arthritis Rheum. 2009 Oct;39(2):123-31. Epub 2008 Sep 27. Review. PubMed PMID: 18823645.

17: Schmitt J, Zhang Z, Wozel G, Meurer M, Kirch W. Efficacy and tolerability of biologic and nonbiologic systemic treatments for moderate-to-severe psoriasis: meta-analysis of randomized controlled trials. Br J Dermatol. 2008 Sep;159(3):513-26. Epub 2008 Jul 9. Review. PubMed PMID: 18627372.

18: Brimhall AK, King LN, Licciardone JC, Jacobe H, Menter A. Safety and efficacy of alefacept, efalizumab, etanercept and infliximab in treating moderate to severe plaque psoriasis: a meta-analysis of randomized controlled trials. Br J Dermatol. 2008 Aug;159(2):274-85. Epub 2008 Jun 10. Review. PubMed PMID: 18547300.

19: Alonso-Ruiz A, Pijoan JI, Ansuategui E, Urkaregi A, Calabozo M, Quintana A. Tumor necrosis factor alpha drugs in rheumatoid arthritis: systematic review and metaanalysis of efficacy and safety. BMC Musculoskelet Disord. 2008 Apr 17;9:52. Review. PubMed PMID: 18419803; PubMed Central PMCID: PMC2377247.

20: Saad AA, Symmons DP, Noyce PR, Ashcroft DM. Risks and benefits of tumor necrosis factor-alpha inhibitors in the management of psoriatic arthritis: systematic review and metaanalysis of randomized controlled trials. J Rheumatol. 2008 May;35(5):883-90. Epub 2008 Mar 15. Review. PubMed PMID: 18381787.

21: Nelson AA, Pearce DJ, Fleischer AB Jr, Balkrishnan R, Feldman SR. Cost-effectiveness of biologic treatments for psoriasis based on subjective and objective efficacy measures assessed over a 12-week treatment period. J Am Acad Dermatol. 2008 Jan;58(1):125-35. Epub 2007 Nov 8. Review. PubMed PMID: 17996329.

22: Bravo Vergel Y, Hawkins NS, Claxton K, Asseburg C, Palmer S, Woolacott N, Bruce IN, Sculpher MJ. The cost-effectiveness of etanercept and infliximab for the treatment of patients with psoriatic arthritis. Rheumatology (Oxford). 2007 Nov;46(11):1729-35. PubMed PMID: 17956918.

23: Lee YH, Woo JH, Rho YH, Choi SJ, Ji JD, Song GG. Meta-analysis of the combination of TNF inhibitors plus MTX compared to MTX monotherapy, and the adjusted indirect comparison of TNF inhibitors in patients suffering from active rheumatoid arthritis. Rheumatol Int. 2008 Apr;28(6):553-9. Epub 2007 Oct 18. PubMed PMID: 17943257.

24: Brodszky V, Czirják L, Géher P, Hodinka L, Kárpáti K, Péntek M, Poór G,

Szekanecz Z, Gulácsi L. [Rituximab in patients with rheumatoid arthritis: systematic review]. Orv Hetil. 2007 Oct 7;148(40):1883-93. Review. Hungarian. PubMed PMID: 17905683.

25: Heiligenhaus A, Horneff G, Greiner K, Mackensen F, Zierhut M, Foeldvari I, Michels H. [Inhibitors of tumour necrosis factor-alpha for the treatment of arthritis and uveitis in childhood]. Klin Monbl Augenheilkd. 2007 Jun;224(6):526-31. Review. German. PubMed PMID: 17594625.

26: Nixon R, Bansback N, Brennan A. The efficacy of inhibiting tumour necrosis factor alpha and interleukin 1 in patients with rheumatoid arthritis: a meta-analysis and adjusted indirect comparisons. Rheumatology (Oxford). 2007 Jul;46(7):1140-7. Epub 2007 May 3. PubMed PMID: 17478472.

27: Katugampola RP, Lewis VJ, Finlay AY. The Dermatology Life Quality Index: assessing the efficacy of biological therapies for psoriasis. Br J Dermatol. 2007 May;156(5):945-50. Epub 2007 Mar 28. Review. PubMed PMID: 17388922.

28: Gartlehner G, Hansen RA, Jonas BL, Thieda P, Lohr KN. The comparative efficacy and safety of biologics for the treatment of rheumatoid arthritis: a systematic review and metaanalysis. J Rheumatol. 2006 Dec;33(12):2398-408. Review. PubMed PMID: 17225293.

29: Koó E, Brodszky V, Péntek M, Ujfalussy I, Nagy MB, Gulácsi L. [The role of biological agents in the treatment of psoriatic arthritis, literature review]. Orv Hetil. 2006 Oct 15;147(41):1963-70. Review. Hungarian. PubMed PMID: 17120686.

30: Chen YF, Jobanputra P, Barton P, Jowett S, Bryan S, Clark W, Fry-Smith A, Burls A. A systematic review of the effectiveness of adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis in adults and an economic evaluation of their cost-effectiveness. Health Technol Assess. 2006 Nov;10(42):iii-iv, xi-xiii, 1-229. Review. PubMed PMID: 17049139.

31: Woolacott N, Bravo Vergel Y, Hawkins N, Kainth A, Khadjesari Z, Misso K, Light K, Asseburg C, Palmer S, Claxton K, Bruce I, Sculpher M, Riemsma R. Etanercept and infliximab for the treatment of psoriatic arthritis: a systematic review and economic evaluation. Health Technol Assess. 2006 Sep;10(31):iii-iv, xiii-xvi, 1-239. Review. PubMed PMID: 16948890.

32: Kemény L, Brodszky V, Kárpáti K, Gulácsi L. [The role of biological drugs in the treatment of psoriasis, results from 9 randomized placebo-controlled trials]. Orv Hetil. 2006 May 28;147(21):981-90. Review. Hungarian. PubMed PMID: 16812973.

33: Bongartz T, Sutton AJ, Sweeting MJ, Buchan I, Matteson EL, Montori V. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. JAMA. 2006 May 17;295(19):2275-85. Review. Erratum in: JAMA. 2006 Jun 7;295(21):2482. PubMed PMID: 16705109.

34: Fransen J, Antoni C, Mease PJ, Uter W, Kavanaugh A, Kalden JR, Van Riel PL. Performance of response criteria for assessing peripheral arthritis in patients with psoriatic arthritis: analysis of data from randomised controlled trials of two tumour necrosis factor inhibitors. Ann Rheum Dis. 2006 Oct;65(10):1373-8. Epub 2006 Apr 27. PubMed PMID: 16644783; PubMed Central PMCID: PMC1798317.

35: Chung CP, Thompson JL, Koch GG, Amara I, Strand V, Pincus T. Are American College of Rheumatology 50% response criteria superior to 20% criteria in distinguishing active aggressive treatment in rheumatoid arthritis clinical trials reported since 1997? A meta-analysis of discriminant capacities. Ann Rheum Dis. 2006 Dec;65(12):1602-7. Epub 2006 Feb 27. Review. PubMed PMID: 16504992; PubMed Central PMCID: PMC1798472.

36: Hochberg MC, Tracy JK, Hawkins-Holt M, Flores RH. Comparison of the efficacy of the tumour necrosis factor alpha blocking agents adalimumab, etanercept, and infliximab when added to methotrexate in patients with active rheumatoid arthritis. Ann Rheum Dis. 2003 Nov;62 Suppl 2:ii13-6. Review. PubMed PMID: 14532140; PubMed Central PMCID: PMC1766753.

37: Jones G, Halbert J, Crotty M, Shanahan EM, Batterham M, Ahern M. The effect of treatment on radiological progression in rheumatoid arthritis: a systematic review of randomized placebo-controlled trials. Rheumatology (Oxford). 2003 Jan;42(1):6-13. Review. PubMed PMID: 12509606.

38: Rodewald EJ, Housman TS, Mellen BG, Feldman SR. The efficacy of 308nm laser treatment of psoriasis compared to historical controls. Dermatol Online J. 2001 Dec;7(2):4. PubMed PMID: 12165220.

SEARCH 3_adalimumab_ meta 3 condit

Category	Description
Clinical question or focus	BIOLOGICAL AGENTS FINAL
Source	PubMed
Terms	**adalimumab** AND (rheumatoid arthritis OR psoriatic arthritis OR psoriasis)
Limits	Meta-Analysis
▪ Date limits	
▪ Other limits	
Query Translation (eg, “Details” in PubMed)	("adalimumab"[Substance Name] OR "adalimumab"[All Fields]) AND (("arthritis, rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "rheumatoid"[All Fields]) OR "rheumatoid arthritis"[All Fields] OR ("rheumatoid"[All Fields] AND "arthritis"[All Fields])) OR ("arthritis, psoriatic"[MeSH Terms] OR ("arthritis"[All Fields] AND "psoriatic"[All Fields]) OR "psoriatic arthritis"[All Fields] OR ("psoriatic"[All Fields] AND "arthritis"[All Fields])) OR ("psoriasis"[MeSH Terms] OR "psoriasis"[All Fields])) AND Meta-Analysis[ptyp]
Date of Search	8/16/10
Total Yield	30
Total marked for retrieval	0
Exclusions	• Not focus of review: population, intervention, comparison, outcome • Superseded by more recent larger study • Lacking safety data • Duplicates

Secondary Studies: Yield and Disposition

1: Wiens A, Venson R, Correr CJ, Otuki MF, Pontarolo R. Meta-analysis of the efficacy and safety of adalimumab, etanercept, and infliximab for the treatment of rheumatoid arthritis. Pharmacotherapy. 2010 Apr;30(4):339-53. Review. PubMed PMID: 20334454.

2: Petitpain N, Gambier N, Wahl D, Chary-Valckenaere I, Loeuille D, Gillet P; French Network of Pharmacovigilance Centers. Arterial and venous thromboembolic events during anti-TNF therapy: a study of 85 spontaneous reports in the period 2000-2006. Biomed Mater Eng. 2009;19(4-5):355-64. PubMed PMID: 20042802.

3: Blasco AJ, Lázaro P, Ferrándiz C, García-Díez A, Liso J. [Efficiency of biologic agents in the treatment of moderate to severe psoriasis]. Actas Dermosifiliogr. 2009 Nov;100(9):792-803. Spanish. PubMed PMID: 19889301.

4: Singh JA, Christensen R, Wells GA, Suarez-Almazor ME, Buchbinder R, Lopez-Olivo MA, Ghogomu ET, Tugwell P. A network meta-analysis of randomized controlled trials of biologics for rheumatoid arthritis: a Cochrane overview.

CMAJ. 2009 Nov 24;181(11):787-96. Epub 2009 Nov 2. PubMed PMID: 19884297; PubMed Central PMCID: PMC2780484.

5: Singh JA, Christensen R, Wells GA, Suarez-Almazor ME, Buchbinder R, Lopez-Olivo MA, Tanjong Ghogomu E, Tugwell P. Biologics for rheumatoid arthritis: an overview of Cochrane reviews. Cochrane Database Syst Rev. 2009 Oct 7;(4):CD007848. Review. PubMed PMID: 19821440.

6: Köller MD, Aletaha D, Funovits J, Pangan A, Baker D, Smolen JS. Response of elderly patients with rheumatoid arthritis to methotrexate or TNF inhibitors compared with younger patients. Rheumatology (Oxford). 2009 Dec;48(12):1575-80. Epub 2009 Oct 7. PubMed PMID: 19812228.

7: Poulin Y, Langley RG, Teixeira HD, Martel MJ, Cheung S. Biologics in the treatment of psoriasis: clinical and economic overview. J Cutan Med Surg. 2009 Sep-Oct;13 Suppl 2:S49-57. Review. PubMed PMID: 19799827.

8: Christensen R, Kristensen LE, Geborek P, Danneskiold-Samsøe B, Saxne T, Bliddal H. [The efficacy of the three available anti-tumour necrosis factor therapies in patients with rheumatoid arthritis. A meta-analytic literature review--secondary publication]. Ugeskr Laeger. 2009 Jun 22;171(26):2192-4. Review. Danish. PubMed PMID: 19678436.

9: Bansback N, Sizto S, Sun H, Feldman S, Willian MK, Anis A. Efficacy of systemic treatments for moderate to severe plaque psoriasis: systematic review and meta-analysis. Dermatology. 2009;219(3):209-18. Epub 2009 Aug 5. Review. PubMed PMID: 19657180.

10: Brown BC, Warren RB, Grindlay DJ, Griffiths CE. What's new in psoriasis? Analysis of the clinical significance of systematic reviews on psoriasis published in 2007 and 2008. Clin Exp Dermatol. 2009 Aug;34(6):664-7. Epub 2009 Jun 30. Review. PubMed PMID: 19572945.

11: Zhang Z, Schmitt J, Wozel G, Kirch W. [Treatment of plaque psoriasis with biologics. A meta-analysis of randomized controlled trials]. Med Klin (Munich). 2009 Feb 15;104(2):125-36. Epub 2009 Feb 26. German. PubMed PMID: 19242664.

12: Burmester GR, Mease P, Dijkmans BA, Gordon K, Lovell D, Panaccione R, Perez J, Pangan AL. Adalimumab safety and mortality rates from global clinical trials of six immune-mediated inflammatory diseases. Ann Rheum Dis. 2009 Dec;68(12):1863-9. Epub 2009 Jan 15. PubMed PMID: 19147611; PubMed Central PMCID: PMC2770105.

13: Venkateshan SP, Sidhu S, Malhotra S, Pandhi P. Efficacy of biologicals in the treatment of rheumatoid arthritis. a meta-analysis. Pharmacology. 2009;83(1):1-9. Epub 2008 Oct 28. Review. PubMed PMID: 18957873.

14: Schmitt J, Zhang Z, Wozel G, Meurer M, Kirch W. Efficacy and tolerability of biologic and nonbiologic systemic treatments for moderate-to-severe psoriasis: meta-analysis of randomized controlled trials. Br J Dermatol. 2008 Sep;159(3):513-26. Epub 2008 Jul 9. Review. PubMed PMID: 18627372.

15: Alonso-Ruiz A, Pijoan JI, Ansuategui E, Urkaregi A, Calabozo M, Quintana A. Tumor necrosis factor alpha drugs in rheumatoid arthritis: systematic review and metaanalysis of efficacy and safety. BMC Musculoskelet Disord. 2008 Apr 17;9:52. Review. PubMed PMID: 18419803; PubMed Central PMCID: PMC2377247.

16: Saad AA, Symmons DP, Noyce PR, Ashcroft DM. Risks and benefits of tumor necrosis factor-alpha inhibitors in the management of psoriatic arthritis: systematic review and metaanalysis of randomized controlled trials. J Rheumatol. 2008 May;35(5):883-90. Epub 2008 Mar 15. Review. PubMed PMID: 18381787.

17: Nelson AA, Pearce DJ, Fleischer AB Jr, Balkrishnan R, Feldman SR. Cost-effectiveness of biologic treatments for psoriasis based on subjective and objective efficacy measures assessed over a 12-week treatment period. J Am Acad Dermatol. 2008 Jan;58(1):125-35. Epub 2007 Nov 8. Review. PubMed PMID: 17996329.

18: Lee YH, Woo JH, Rho YH, Choi SJ, Ji JD, Song GG. Meta-analysis of the combination of TNF inhibitors plus MTX compared to MTX monotherapy, and the adjusted indirect comparison of TNF inhibitors in patients suffering from active rheumatoid arthritis. Rheumatol Int. 2008 Apr;28(6):553-9. Epub 2007 Oct 18. PubMed PMID: 17943257.

19: Brodszky V, Czirják L, Géher P, Hodinka L, Kárpáti K, Péntek M, Poór G, Szekanecz Z, Gulácsi L. [Rituximab in patients with rheumatoid arthritis: systematic review]. Orv Hetil. 2007 Oct 7;148(40):1883-93. Review. Hungarian. PubMed PMID: 17905683.

20: Heiligenhaus A, Horneff G, Greiner K, Mackensen F, Zierhut M, Foeldvari I, Michels H. [Inhibitors of tumour necrosis factor-alpha for the treatment of arthritis and uveitis in childhood]. Klin Monbl Augenheilkd. 2007 Jun;224(6):526-31. Review. German. PubMed PMID: 17594625.

21: Nixon R, Bansback N, Brennan A. The efficacy of inhibiting tumour necrosis factor alpha and interleukin 1 in patients with rheumatoid arthritis: a meta-analysis and adjusted indirect comparisons. Rheumatology (Oxford). 2007 Jul;46(7):1140-7. Epub 2007 May 3. PubMed PMID: 17478472.

22: Koó E, Brodszky V, Péntek M, Ujfalussy I, Nagy MB, Gulácsi L. [The role of biological agents in the treatment of psoriatic arthritis, literature review]. Orv Hetil. 2006 Oct 15;147(41):1963-70. Review. Hungarian. PubMed PMID: 17120686.

23: Chen YF, Jobanputra P, Barton P, Jowett S, Bryan S, Clark W, Fry-Smith A, Burls A. A systematic review of the effectiveness of adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis in adults and an economic evaluation of their cost-effectiveness. Health Technol Assess. 2006 Nov;10(42):iii-iv, xi-xiii, 1-229. Review. PubMed PMID: 17049139.

24: Bongartz T, Sutton AJ, Sweeting MJ, Buchan I, Matteson EL, Montori V. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. JAMA. 2006 May 17;295(19):2275-85. Review. Erratum in: JAMA. 2006 Jun 7;295(21):2482. PubMed PMID: 16705109.

25: Navarro-Sarabia F, Ariza-Ariza R, Hernández-Cruz B, Villanueva I. Adalimumab for treating rheumatoid arthritis. J Rheumatol. 2006 Jun;33(6):1075-81. Epub 2006 May 1. Review. PubMed PMID: 16652437.

26: Chung CP, Thompson JL, Koch GG, Amara I, Strand V, Pincus T. Are American College of Rheumatology 50% response criteria superior to 20% criteria in distinguishing active aggressive treatment in rheumatoid arthritis clinical trials reported since 1997? A meta-analysis of discriminant capacities. Ann Rheum Dis. 2006 Dec;65(12):1602-7. Epub 2006 Feb 27. Review. PubMed PMID: 16504992; PubMed Central PMCID: PMC1798472.

27: Navarro-Sarabia F, Ariza-Ariza R, Hernandez-Cruz B, Villanueva I. Adalimumab for treating rheumatoid arthritis. Cochrane Database Syst Rev. 2005 Jul 20;(3):CD005113. Review. PubMed PMID: 16034967.

28: Torrance GW, Tugwell P, Amorosi S, Chartash E, Sengupta N. Improvement in health utility among patients with rheumatoid arthritis treated with adalimumab (a human anti-TNF monoclonal antibody) plus methotrexate. Rheumatology (Oxford). 2004 Jun;43(6):712-8. Epub 2004 Mar 23. PubMed PMID: 15039494.

29: Hochberg MC, Tracy JK, Hawkins-Holt M, Flores RH. Comparison of the efficacy of the tumour necrosis factor alpha blocking agents adalimumab, etanercept, and infliximab when added to methotrexate in patients with active rheumatoid arthritis. Ann Rheum Dis. 2003 Nov;62 Suppl 2:ii13-6. Review. PubMed PMID: 14532140; PubMed Central PMCID: PMC1766753.

30: Rau R. Adalimumab (a fully human anti-tumour necrosis factor alpha monoclonal antibody) in the treatment of active rheumatoid arthritis: the initial results of five trials. Ann Rheum Dis. 2002 Nov;61 Suppl 2:ii70-3. Review. PubMed PMID: 12379628; PubMed Central PMCID: PMC1766697.

SEARCH 4_certolizumab_ clinical trial 3 condit

Category	Description
Clinical question or focus	BIOLOGICAL AGENTS FINAL
Source	PubMed
Terms	**certolizumab** AND (rheumatoid arthritis OR psoriatic arthritis OR psoriasis)
Limits	Clinical Trial
▪ Date limits	
▪ Other limits	
Query Translation (eg, "Details" in PubMed)	("CDP870"[Substance Name] OR "CDP870"[All Fields] OR "certolizumab"[All Fields]) AND (("arthritis, rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "rheumatoid"[All Fields]) OR "rheumatoid arthritis"[All Fields] OR ("rheumatoid"[All Fields] AND "arthritis"[All Fields])) OR ("arthritis, psoriatic"[MeSH Terms] OR ("arthritis"[All Fields] AND "psoriatic"[All Fields]) OR "psoriatic arthritis"[All Fields] OR ("psoriatic"[All Fields] AND "arthritis"[All Fields])) OR ("psoriasis"[MeSH Terms] OR "psoriasis"[All Fields])) AND Clinical Trial[ptyp
Date of Search	8/16/10
Total Yield	6
Marked for retrieval	Nam 10, Statkute 10, Smolen 09, Fleishman 09
Exclusions	• Not focus of review: population, intervention, comparison, outcome • Superseded by more recent larger study • Lacking safety data • Duplicates

Secondary Studies: No Meta-Analyses for certolizumab; following found with SR limit

1: Nam JL, Winthrop KL, van Vollenhoven RF, Pavelka K, Valesini G, Hensor EM, Worthy G, Landewé R, Smolen JS, Emery P, Buch MH. Current evidence for the management of rheumatoid arthritis with biological disease-modifying antirheumatic drugs: a systematic literature review informing the EULAR recommendations for the management of RA. Ann Rheum Dis. 2010 Jun;69(6):976-86. Epub 2010 May 6. PubMed PMID: 20447957.

2: Statkute L, Ruderman EM. Novel TNF antagonists for the treatment of rheumatoid arthritis. Expert Opin Investig Drugs. 2010 Jan;19(1):105-15. Review. PubMed PMID: 20001558.

1: Strand V, Mease P, Burmester GR, Nikaï E, Coteur G, van Vollenhoven R, Combe B, Keystone EC, Kavanaugh A. Rapid and sustained improvements in health-related quality of life, fatigue, and other patient-reported outcomes in rheumatoid arthritis patients treated with certolizumab pegol plus methotrexate over 1 year: results from the RAPID 1 randomized controlled trial. Arthritis Res Ther. 2009;11(6):R170. Epub 2009 Nov 12. PubMed PMID: 19909548.

2: Kavanaugh A, Smolen JS, Emery P, Purcaru O, Keystone E, Richard L, Strand V,

van Vollenhoven RF. Effect of certolizumab pegol with methotrexate on home and work place productivity and social activities in patients with active rheumatoid arthritis. Arthritis Rheum. 2009 Nov 15;61(11):1592-600. PubMed PMID: 19877104.

3: Smolen J, Landewé RB, Mease P, Brzezicki J, Mason D, Luijtens K, van Vollenhoven RF, Kavanaugh A, Schiff M, Burmester GR, Strand V, Vencovsky J, van der Heijde D. Efficacy and safety of certolizumab pegol plus methotrexate in active rheumatoid arthritis: the RAPID 2 study. A randomised controlled trial. Ann Rheum Dis. 2009 Jun;68(6):797-804. Epub 2008 Nov 17. PubMed PMID: 19015207; PubMed Central PMCID: PMC2674556.

4: Fleischmann R, Vencovsky J, van Vollenhoven RF, Borenstein D, Box J, Coteur G, Goel N, Brezinschek HP, Innes A, Strand V. Efficacy and safety of certolizumab pegol monotherapy every 4 weeks in patients with rheumatoid arthritis failing previous disease-modifying antirheumatic therapy: the FAST4WARD study. Ann Rheum Dis. 2009 Jun;68(6):805-11. Epub 2008 Nov 17. PubMed PMID: 19015206; PubMed Central PMCID: PMC2674555.

5: Keystone E, Heijde D, Mason D Jr, Landewé R, Vollenhoven RV, Combe B, Emery P, Strand V, Mease P, Desai C, Pavelka K. Certolizumab pegol plus methotrexate is significantly more effective than placebo plus methotrexate in active rheumatoid arthritis: findings of a fifty-two-week, phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Arthritis Rheum. 2008 Nov;58(11):3319-29. Erratum in: Arthritis Rheum. 2009 May;60(5):1249. PubMed PMID: 18975346.

6: Choy EH, Hazleman B, Smith M, Moss K, Lisi L, Scott DG, Patel J, Sopwith M, Isenberg DA. Efficacy of a novel PEGylated humanized anti-TNF fragment (CDP870) in patients with rheumatoid arthritis: a phase II double-blinded, randomized, dose-escalating trial. Rheumatology (Oxford). 2002 Oct;41(10):1133-7. PubMed PMID: 12364632.

UPDATED SEARCH 11/15/10

SEARCH 5_golimumab_ meta 3 condit

Category	Description
Clinical question or focus	BIOLOGICAL AGENTS FINAL
Source	PubMed
Terms	**golimumab** AND (rheumatoid arthritis OR psoriatic arthritis OR psoriasis)
Limits	Meta-Analysis
▪ Date limits	
▪ Other limits	
Query Translation (eg, “Details” in PubMed)	("golimumab"[Substance Name] OR "golimumab"[All Fields]) AND (("arthritis, rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "rheumatoid"[All Fields]) OR "rheumatoid arthritis"[All Fields] OR ("rheumatoid"[All Fields] AND "arthritis"[All Fields])) OR ("arthritis, psoriatic"[MeSH Terms] OR ("arthritis"[All Fields] AND "psoriatic"[All Fields]) OR "psoriatic arthritis"[All Fields] OR ("psoriatic"[All Fields] AND "arthritis"[All Fields])) OR ("psoriasis"[MeSH Terms] OR "psoriasis"[All Fields])) AND Meta-Analysis[ptyp]
Date of Search	8/16/10
Total Yield	1
Total marked for retrieval	Singh 10
Exclusions	• Not focus of review: population, intervention, comparison, outcome • Superseded by more recent larger study • Lacking safety data • Duplicates

Secondary Studies: Yield and Disposition

1. Singh JA, Noorbaloochi S, Singh G. Golimumab for rheumatoid arthritis. Cochrane Database Syst Rev. 2010 Jan 20;(1):CD008341. Review. PubMed PMID: 20091667.

SEARCH 6_ ustekinumab_ meta 3 condit

Category	Description
Clinical question or focus	BIOLOGICAL AGENTS FINAL
Source	PubMed
Terms	**ustekinumab** AND (rheumatoid arthritis OR psoriatic arthritis OR psoriasis)
Limits	Meta-Analysis
▪ Date limits	
▪ Other limits	
Query Translation (eg, "Details" in PubMed)	("monoclonal antibody CNTO 1275"[Substance Name] OR "monoclonal antibody CNTO 1275"[All Fields] OR "ustekinumab"[All Fields]) AND (("arthritis, rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "rheumatoid"[All Fields]) OR "rheumatoid arthritis"[All Fields] OR ("rheumatoid"[All Fields] AND "arthritis"[All Fields])) OR ("arthritis, psoriatic"[MeSH Terms] OR ("arthritis"[All Fields] AND "psoriatic"[All Fields]) OR "psoriatic arthritis"[All Fields] OR ("psoriatic"[All Fields] AND "arthritis"[All Fields])) OR ("psoriasis"[MeSH Terms] OR "psoriasis"[All Fields])) AND Meta-Analysis[ptyp]
Date of Search	8/16/10
Total Yield	1
Total marked for retrieval	0
Notes	Exclude: no safety data

Secondary Studies: Yield

1: Poulin Y, Langley RG, Teixeira HD, Martel MJ, Cheung S. Biologics in the treatment of psoriasis: clinical and economic overview. J Cutan Med Surg. 2009 Sep-Oct;13 Suppl 2:S49-57. Review. PubMed PMID: 19799827.

SEARCH 7_ ustekinumab_ SR 3 condit

Category	Description
Clinical question or focus	BIOLOGICAL AGENTS FINAL
Source	PubMed
Terms	**ustekinumab** AND (rheumatoid arthritis OR psoriatic arthritis OR psoriasis)
Limits	Systematic Review
▪ Date limits	
▪ Other limits	
Query Translation (eg, "Details" in PubMed)	("monoclonal antibody CNTO 1275"[Substance Name] OR "monoclonal antibody CNTO 1275"[All Fields] OR "ustekinumab"[All Fields]) AND (("arthritis, rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "rheumatoid"[All Fields]) OR "rheumatoid arthritis"[All Fields] OR ("rheumatoid"[All Fields] AND "arthritis"[All Fields])) OR ("arthritis, psoriatic"[MeSH Terms] OR ("arthritis"[All Fields] AND "psoriatic"[All Fields]) OR "psoriatic arthritis"[All Fields] OR ("psoriatic"[All Fields] AND "arthritis"[All Fields])) OR ("psoriasis"[MeSH Terms] OR "psoriasis"[All Fields])) AND systematic[sb]
Date of Search	9/7/10
Total Yield	7
Total marked for retrieval	Tan 10, Uhlenhake 10, Scanlon 09

Notes	• Excluded:
	  • Not focus of review: population, intervention, comparison, outcome
	  • Superseded by more recent larger study

	• Wrong study type • Lacking safety data • Duplicates

Secondary Studies: Yield and Disposition

1: Tan JY, Li S, Yang K, Ma B, Chen W, Zha C, Zhang J. Ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: a meta-analysis. J Dermatolog Treat. 2010 Oct 5. [Epub ahead of print] PubMed PMID: 20923370.

2: Papoutsaki M, Talamonti M, Giunta A, Costanzo A, Ruzzetti M, Teoli M, Chimenti S. The impact of methodological approaches for presenting long-term clinical data on estimates of efficacy in psoriasis illustrated by three-year treatment data on infliximab. Dermatology. 2010;221 Suppl 1:43-7. Epub 2010 Aug 9. PubMed PMID: 20733314.

3: Mercuri SR, Naldi L. Potential role of ustekinumab in the treatment of chronic plaque psoriasis. Biologics. 2010 May 25;4:119-29. PubMed PMID: 20531968; PubMed Central PMCID: PMC2880344.
Retrieved; not a SR

4: Gospodarevskaya E, Picot J, Cooper K, Loveman E, Takeda A. Ustekinumab for the treatment of moderate to severe psoriasis. Health Technol Assess. 2009 Oct;13 Suppl 3:61-6. Review. PubMed PMID: 19846031.
Manufacturer's info review

5: Uhlenhake EE, Feldman SR. Efficacy and safety of ustekinumab and etanercept for the treatment of psoriasis. Expert Opin Biol Ther. 2010 Jul;10(7):1105-12. Review. PubMed PMID: 20446825.

6: Poulin Y, Langley RG, Teixeira HD, Martel MJ, Cheung S. Biologics in the treatment of psoriasis: clinical and economic overview. J Cutan Med Surg. 2009 Sep-Oct;13 Suppl 2:S49-57. Review. PubMed PMID: 19799827.

7: Scanlon JV, Exter BP, Steinberg M, Jarvis CI. Ustekinumab: treatment of adult moderate-to-severe chronic plaque psoriasis. Ann Pharmacother. 2009 Sep;43(9):1456-65. Epub 2009 Aug 11. Review. PubMed PMID: 19671802.

SEARCH 8_ VONV HEDGE final

Category	Description
Clinical question or focus	BIOLOGICAL AGENTS FINAL
Source	PubMed
Terms	"meta-analysis as topic"[MeSH] OR Meta-Analysis[ptyp] OR "systematic literature"[tiab] OR "systematic review*"[tiab] OR meta-analys*[tiab] OR "cochrane database syst rev"[Journal] OR "cochrane database of systematic reviews online"[Journal] OR "research synthesis"[tiab] OR "research integration"[tiab] OR "medline"[tiab] OR "data synthesis"[tiab] AND (adalimumab OR certolizumab OR etanercept OR golimumab OR infliximab OR ustekinumab) AND (Rheumatoid arthritis OR psoriasis OR psoriatic arthritis)
Limits	Systematic Review VonVille HEDGE as above
▪ Date limits	None
▪ Other limits	None
Query Translation (eg, "Details" in PubMed)	"meta-analysis as topic"[MeSH] OR Meta-Analysis[ptyp] OR "systematic literature"[tiab] OR "systematic review*"[tiab] OR (meta analysable[tiab] OR meta analyse[tiab] OR meta analysed[tiab] OR meta analysers[tiab] OR meta analyses[tiab] OR meta analyses/reviews[tiab] OR meta analyses/systematic[tiab] OR meta analysia[tiab] OR meta analysic[tiab] OR meta analysing[tiab] OR meta analysis[tiab] OR meta analysis/further[tiab] OR meta analysis/metaregression[tiab] OR meta

	analysis/practiced[tiab] OR meta analysis/sr[tiab] OR meta analysis/systematic[tiab] OR meta analysis/systemic[tiab] OR meta analysis's[tiab] OR meta analysises[tiab] OR meta analysisevaluating[tiab] OR meta analyst[tiab] OR meta analysticians[tiab] OR meta analysts[tiab]) OR "cochrane database syst rev"[Journal] OR "cochrane database of systematic reviews online"[Journal] OR "research synthesis"[tiab] OR "research integration"[tiab] OR "medline"[tiab] OR "data synthesis"[tiab] AND (("adalimumab"[Substance Name] OR "adalimumab"[All Fields]) OR ("CDP870"[Substance Name] OR "CDP870"[All Fields] OR "certolizumab"[All Fields]) OR ("TNFR-Fc fusion protein"[Substance Name] OR "TNFR-Fc fusion protein"[All Fields] OR "etanercept"[All Fields]) OR ("golimumab"[Substance Name] OR "golimumab"[All Fields]) OR ("infliximab"[Substance Name] OR "infliximab"[All Fields]) OR ("monoclonal antibody CNTO 1275"[Substance Name] OR "monoclonal antibody CNTO 1275"[All Fields] OR "ustekinumab"[All Fields])) AND (("arthritis, rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "rheumatoid"[All Fields]) OR "rheumatoid arthritis"[All Fields] OR ("rheumatoid"[All Fields] AND "arthritis"[All Fields])) OR ("psoriasis"[MeSH Terms] OR "psoriasis"[All Fields]) OR ("arthritis, psoriatic"[MeSH Terms] OR ("arthritis"[All Fields] AND "psoriatic"[All Fields]) OR "psoriatic arthritis"[All Fields] OR ("psoriatic"[All Fields] AND "arthritis"[All Fields
Date of Search	8/18/10
Total Yield	148
Total marked for retrieval	Dharamsi 10, Krueger 04
Exclusions	• Not focus of review: population, intervention, comparison, outcome • Superseded by more recent larger study • Lacking safety data • Wrong study type • Duplicates
Notes	All relevant studies were duplicates

1: Collamer AN, Battafarano DF. Psoriatic Skin Lesions Induced by Tumor Necrosis Factor Antagonist Therapy: Clinical Features and Possible Immunopathogenesis. Semin Arthritis Rheum. 2010 Jun 25. [Epub ahead of print] PubMed PMID: 20580412.

2: Rozin AP, Hasin T, Toledano K, Guralnik L, Balbir-Gurman A. Seronegative polyarthritis as severe systemic disease. Neth J Med. 2010 Jun;68(6):236-41. PubMed PMID: 20558853.

3: Pedraz J, Daudén E. [Psoriatic arthritis and etanercept]. Actas Dermosifiliogr. 2010 May;101 Suppl 1:26-34. Spanish. PubMed PMID: 20492877.

4: Fleischmann R. The efficacy and safety of golimumab in the treatment of arthritis. Expert Opin Biol Ther. 2010 Jul;10(7):1131-43. PubMed PMID: 20504106.

5: Papp KA, Carey W. Psoriasis care: new and emerging pharmacologic trends. J Cutan Med Surg. 2010 May-Jun;14(3):119-29. PubMed PMID: 20487672.

6: Nam JL, Winthrop KL, van Vollenhoven RF, Pavelka K, Valesini G, Hensor EM, Worthy G, Landewé R, Smolen JS, Emery P, Buch MH. Current evidence for the management of rheumatoid arthritis with biological disease-modifying antirheumatic drugs: a systematic literature review informing the EULAR recommendations for the management of RA. Ann Rheum Dis. 2010 Jun;69(6):976-86. Epub 2010 May 6. PubMed PMID: 20447957.

7: Singh JA, Noorbaloochi S, Singh G. Golimumab for rheumatoid arthritis: a systematic review. J Rheumatol. 2010 Jun;37(6):1096-104. Epub 2010 May 1. Review. PubMed PMID: 20436075.

8: Kuriya B, Arkema EV, Bykerk VP, Keystone EC. Efficacy of initial methotrexate monotherapy versus combination therapy with a biological agent in early rheumatoid arthritis: a meta-analysis of clinical and radiographic remission. Ann Rheum Dis. 2010 Jul;69(7):1298-304. Epub 2010 Apr 26. PubMed PMID: 20421343.

9: Pollono EN, Lopez-Olivo MA, Lopez JA, Suarez-Almazor ME. A systematic review of the effect of TNF-alpha antagonists on lipid profiles in patients with

rheumatoid arthritis. Clin Rheumatol. 2010 Apr 10. [Epub ahead of print] PubMed PMID: 20383550.

10: Bojke L, Claxton K, Bravo-Vergel Y, Sculpher M, Palmer S, Abrams K. Eliciting Distributions to Populate Decision Analytic Models. Value Health. 2010 Mar 22. [Epub ahead of print] PubMed PMID: 20345548.

11: Wiens A, Venson R, Correr CJ, Otuki MF, Pontarolo R. Meta-analysis of the efficacy and safety of adalimumab, etanercept, and infliximab for the treatment of rheumatoid arthritis. Pharmacotherapy. 2010 Apr;30(4):339-53. Review. PubMed PMID: 20334454.

12: Fleischmann R. The clinical efficacy and safety of certolizumab pegol in rheumatoid arthritis. Expert Opin Biol Ther. 2010 May;10(5):773-86. Review. PubMed PMID: 20230188.

13: Bergman GJ, Hochberg MC, Boers M, Wintfeld N, Kielhorn A, Jansen JP. Indirect comparison of tocilizumab and other biologic agents in patients with rheumatoid arthritis and inadequate response to disease-modifying antirheumatic drugs. Semin Arthritis Rheum. 2010 Jun;39(6):425-41. Epub 2010 Mar 11. PubMed PMID: 20223500.

14: Storage SS, Agrawal H, Furst DE. Description of the efficacy and safety of three new biologics in the treatment of rheumatoid arthritis. Korean J Intern Med. 2010 Mar;25(1):1-17. Epub 2010 Feb 26. Review. PubMed PMID: 20195397; PubMed Central PMCID: PMC2829405.

15: Lee YH, Ji JD, Bae SC, Song GG. Associations between tumor necrosis factor-alpha (TNF-alpha) -308 and -238 G/A polymorphisms and shared epitope status and responsiveness to TNF-alpha blockers in rheumatoid arthritis: a metaanalysis update. J Rheumatol. 2010 Apr;37(4):740-6. Epub 2010 Mar 1. PubMed PMID: 20194454.

16: Tritar F, Zendah I, Ben M'rad S, Daghfous H. [Anti-TNF: beneficial or hamful for the lung?]. Tunis Med. 2009 Sep;87(9):607-9. Review. French. PubMed PMID: 20180383.

17: McCluggage LK, Scholtz JM. Golimumab: a tumor necrosis factor alpha inhibitor for the treatment of rheumatoid arthritis. Ann Pharmacother. 2010 Jan;44(1):135-44. Review. PubMed PMID: 20118145.

18: Singh JA, Noorbaloochi S, Singh G. Golimumab for rheumatoid arthritis. Cochrane Database Syst Rev. 2010 Jan 20;(1):CD008341. Review. PubMed PMID: 20091667.

19: Maxwell LJ, Singh JA. Abatacept for rheumatoid arthritis: a Cochrane systematic review. J Rheumatol. 2010 Feb;37(2):234-45. Epub 2010 Jan 15. Review. Erratum in: J Rheumatol. 2010 Mar;37(3):682. PubMed PMID: 20080922.

20: Thaler K, Chandiramani DV, Hansen RA, Gartlehner G. Efficacy and safety of anakinra for the treatment of rheumatoid arthritis: an update of the Oregon Drug Effectiveness Review Project. Biologics. 2009;3:485-98. Epub 2009 Dec 29. PubMed PMID: 20054439; PubMed Central PMCID: PMC2802074.

21: Petitpain N, Gambier N, Wahl D, Chary-Valckenaere I, Loeuille D, Gillet P; French Network of Pharmacovigilance Centers. Arterial and venous thromboembolic events during anti-TNF therapy: a study of 85 spontaneous reports in the period 2000-2006. Biomed Mater Eng. 2009;19(4-5):355-64. PubMed PMID: 20042802.

22: Turner D, Picot J, Cooper K, Loveman E. Adalimumab for the treatment of psoriasis. Health Technol Assess. 2009 Sep;13 Suppl 2:49-54. Review. PubMed PMID: 19804689.

23: Blasco AJ, Lázaro P, Ferrándiz C, García-Díez A, Liso J. [Efficiency of biologic agents in the treatment of moderate to severe psoriasis]. Actas Dermosifiliogr. 2009 Nov;100(9):792-803. Spanish. PubMed PMID: 19889301.

24: Leboime A, Berthelot JM, Allanore Y, Khalil-Kallouche L, Herman P, Orcel P, Lioté F. Sinus aspergilloma in rheumatoid arthritis before or during tumor necrosis factor-alpha antagonist therapy. Arthritis Res Ther. 2009;11(6):R164. Epub 2009 Nov 3. PubMed PMID: 19886992.

25: Alivernini S, Laria A, Gremese E, Zoli A, Ferraccioli G. ACR70-disease activity score remission achievement from switches between all the available biological agents in rheumatoid arthritis: a systematic review of the literature. Arthritis Res Ther. 2009;11(6):R163. Epub 2009 Nov 3. Review. PubMed PMID: 19886983.

26: Singh JA, Christensen R, Wells GA, Suarez-Almazor ME, Buchbinder R, Lopez-Olivo MA, Ghogomu ET, Tugwell P. A network meta-analysis of randomized controlled trials of biologics for rheumatoid arthritis: a Cochrane overview. CMAJ. 2009 Nov 24;181(11):787-96. Epub 2009 Nov 2. PubMed PMID: 19884297; PubMed Central PMCID: PMC2780484.

27: Borrás-Blasco J, Navarro-Ruiz A, Borrás C, Casterá E. Adverse cutaneous reactions induced by TNF-alpha antagonist therapy. South Med J. 2009 Nov;102(11):1133-40. Review. PubMed PMID: 19864977.

28: Dommasch E, Gelfand JM. Is there truly a risk of lymphoma from biologic therapies? Dermatol Ther. 2009 Sep-Oct;22(5):418-30. Review. PubMed PMID: 19845719; PubMed Central PMCID: PMC2768030.

29: Singh JA, Christensen R, Wells GA, Suarez-Almazor ME, Buchbinder R, Lopez-Olivo MA, Tanjong Ghogomu E, Tugwell P. Biologics for rheumatoid arthritis: an overview of Cochrane reviews. Cochrane Database Syst Rev. 2009 Oct 7;(4):CD007848. Review. PubMed PMID: 19821440.

30: Köller MD, Aletaha D, Funovits J, Pangan A, Baker D, Smolen JS. Response of elderly patients with rheumatoid arthritis to methotrexate or TNF inhibitors compared with younger patients. Rheumatology (Oxford). 2009 Dec;48(12):1575-80. Epub 2009 Oct 7. PubMed PMID: 19812228.

31: Frankel AJ, Van Voorhees AS, Hsu S, Korman NJ, Lebwohl MG, Bebo BF Jr, Gottlieb AB; National Psoriasis Foundation. Treatment of psoriasis in patients with hepatitis C: from the Medical Board of the National Psoriasis Foundation. J Am Acad Dermatol. 2009 Dec;61(6):1044-55. Epub 2009 Oct 7. Review. PubMed PMID: 19811848.

32: van Roon EN, van den Bemt PM, Jansen TL, Houtman NM, van de Laar MA, Brouwers JR. An evidence-based assessment of the clinical significance of drug-drug interactions between disease-modifying antirheumatic drugs and non-antirheumatic drugs according to rheumatologists and pharmacists. Clin Ther. 2009 Aug;31(8):1737-46. Review. PubMed PMID: 19808132.

33: Poulin Y, Langley RG, Teixeira HD, Martel MJ, Cheung S. Biologics in the treatment of psoriasis: clinical and economic overview. J Cutan Med Surg. 2009 Sep-Oct;13 Suppl 2:S49-57. Review. PubMed PMID: 19799827.

34: Wiens A, Correr CJ, Venson R, Grochocki MC, Otuki MF, Pontarolo R. A meta-analysis of the efficacy and safety of using infliximab for the treatment of rheumatoid arthritis. Clin Rheumatol. 2009 Dec;28(12):1365-73. Epub 2009 Sep 22. Review. PubMed PMID: 19771491.

35: Wiens A, Correr CJ, Pontarolo R, Venson R, Quinalha JV, Otuki MF. A systematic review and meta-analysis of the efficacy and safety of etanercept for

treating rheumatoid arthritis. Scand J Immunol. 2009 Oct;70(4):337-44. Review. PubMed PMID: 19751268.

36: Wiens A, Correr CJ, Venson R, Otuki MF, Pontarolo R. A systematic review and meta-analysis of the efficacy and safety of adalimumab for treating rheumatoid arthritis. Rheumatol Int. 2010 Jun;30(8):1063-70. Epub 2009 Aug 26. PubMed PMID: 19707765.

37: Schmitt J, Wozel G. Targeted treatment of psoriasis with adalimumab: a critical appraisal based on a systematic review of the literature. Biologics. 2009;3:303-18. Epub 2009 Jul 13. PubMed PMID: 19707417; PubMed Central PMCID: PMC2726069.

38: Christensen R, Kristensen LE, Geborek P, Danneskiold-Samsøe B, Saxne T, Bliddal H. [The efficacy of the three available anti-tumour necrosis factor therapies in patients with rheumatoid arthritis. A meta-analytic literature review--secondary publication]. Ugeskr Laeger. 2009 Jun 22;171(26):2192-4. Review. Danish. PubMed PMID: 19678436.

39: Scanlon JV, Exter BP, Steinberg M, Jarvis CI. Ustekinumab: treatment of adult moderate-to-severe chronic plaque psoriasis. Ann Pharmacother. 2009 Sep;43(9):1456-65. Epub 2009 Aug 11. Review. PubMed PMID: 19671802.

40: Bansback N, Sizto S, Sun H, Feldman S, Willian MK, Anis A. Efficacy of systemic treatments for moderate to severe plaque psoriasis: systematic review and meta-analysis. Dermatology. 2009;219(3):209-18. Epub 2009 Aug 5. Review. PubMed PMID: 19657180.

41: Brown BC, Warren RB, Grindlay DJ, Griffiths CE. What's new in psoriasis? Analysis of the clinical significance of systematic reviews on psoriasis published in 2007 and 2008. Clin Exp Dermatol. 2009 Aug;34(6):664-7. Epub 2009 Jun 30. Review. PubMed PMID: 19572945.

42: Emi Aikawa N, de Carvalho JF, Artur Almeida Silva C, Bonfá E. Immunogenicity of Anti-TNF-alpha agents in autoimmune diseases. Clin Rev Allergy Immunol. 2010 Apr;38(2-3):82-9. Review. PubMed PMID: 19565360.

43: Braun J, Baraliakos X. Treatment of ankylosing spondylitis and other spondyloarthritides. Curr Opin Rheumatol. 2009 Jul;21(4):324-34. Review. PubMed PMID: 19461519.

44: Naldi L, Rzany B. Psoriasis (chronic plaque). Clin Evid (Online). 2009 Jan 9;2009. pii: 1706. PubMed PMID: 19445765.

45: Dharamsi JW, Bhosle M, Balkrishnan R, Yentzer BA, Feldman SR. Using 'number needed to treat' to help conceptualize the magnitude of benefit and risk of tumour necrosis factor-alpha inhibitors for patients with severe psoriasis. Br J Dermatol. 2009 Sep;161(3):605-16. Epub 2009 Apr 24. Review. PubMed PMID: 19438475.

46: Noiles K, Vender R. Biologic survival. J Drugs Dermatol. 2009 Apr;8(4):329-33. Review. PubMed PMID: 19363851.

47: Levy-Roy A, Porcher R, de Fonclare AL, Morel P, Dupuy A. [Efficacy of TNF-alpha antagonists for plaque-type psoriasis: a systematic review and graphical presentation]. Ann Dermatol Venereol. 2009 Apr;136(4):315-22. Epub 2009 Jan 30. Review. French. PubMed PMID: 19361697.

48: Noiles K, Vender R. Nail psoriasis and biologics. J Cutan Med Surg. 2009 Jan-Feb;13(1):1-5. Review. PubMed PMID: 19298765.

49: Zhang Z, Schmitt J, Wozel G, Kirch W. [Treatment of plaque psoriasis with

biologics. A meta-analysis of randomized controlled trials]. Med Klin (Munich). 2009 Feb 15;104(2):125-36. Epub 2009 Feb 26. German. PubMed PMID: 19242664.

50: Fiorino G, Allez M, Malesci A, Danese S. Review article: anti TNF-alpha induced psoriasis in patients with inflammatory bowel disease. Aliment Pharmacol Ther. 2009 May 1;29(9):921-7. Epub 2009 Feb 10. Review. PubMed PMID: 19210297.

51: Burmester GR, Mease P, Dijkmans BA, Gordon K, Lovell D, Panaccione R, Perez J, Pangan AL. Adalimumab safety and mortality rates from global clinical trials of six immune-mediated inflammatory diseases. Ann Rheum Dis. 2009 Dec;68(12):1863-9. Epub 2009 Jan 15. PubMed PMID: 19147611; PubMed Central PMCID: PMC2770105.

52: Sizto S, Bansback N, Feldman SR, Willian MK, Anis AH. Economic evaluation of systemic therapies for moderate to severe psoriasis. Br J Dermatol. 2009 Jun;160(6):1264-72. Epub 2008 Dec 15. PubMed PMID: 19120346.

53: Zintzaras E, Dahabreh IJ, Giannouli S, Voulgarelis M, Moutsopoulos HM. Infliximab and methotrexate in the treatment of rheumatoid arthritis: a systematic review and meta-analysis of dosage regimens. Clin Ther. 2008 Nov;30(11):1939-55. Review. PubMed PMID: 19108784.

54: Bongartz T, Warren FC, Mines D, Matteson EL, Abrams KR, Sutton AJ. Etanercept therapy in rheumatoid arthritis and the risk of malignancies: a systematic review and individual patient data meta-analysis of randomised controlled trials. Ann Rheum Dis. 2009 Jul;68(7):1177-83. Epub 2008 Nov 19. Review. PubMed PMID: 19019889.

55: Roundtree AK, Kallen MA, Lopez-Olivo MA, Kimmel B, Skidmore B, Ortiz Z, Cox V, Suarez-Almazor ME. Poor reporting of search strategy and conflict of interest in over 250 narrative and systematic reviews of two biologic agents in arthritis: a systematic review. J Clin Epidemiol. 2009 Feb;62(2):128-37. Epub 2008 Nov 14. Review. PubMed PMID: 19013763.

56: Lopez-Olivo MA, Kallen MA, Ortiz Z, Skidmore B, Suarez-Almazor ME. Quality appraisal of clinical practice guidelines and consensus statements on the use of biologic agents in rheumatoid arthritis: a systematic review. Arthritis Rheum. 2008 Nov 15;59(11):1625-38. Review. PubMed PMID: 18975351.

57: Venkateshan SP, Sidhu S, Malhotra S, Pandhi P. Efficacy of biologicals in the treatment of rheumatoid arthritis. a meta-analysis. Pharmacology. 2009;83(1):1-9. Epub 2008 Oct 28. Review. PubMed PMID: 18957873.

58: Guignard S, Gossec L, Bandinelli F, Dougados M. Comparison of the clinical characteristics of vasculitis occurring during anti-tumor necrosis factor treatment or not in rheumatoid arthritis patients. A systematic review of 2707 patients, 18 vasculitis. Clin Exp Rheumatol. 2008 May-Jun;26(3 Suppl 49):S23-9. PubMed PMID: 18799049.

59: Ko JM, Gottlieb AB, Kerbleski JF. Induction and exacerbation of psoriasis with TNF-blockade therapy: a review and analysis of 127 cases. J Dermatolog Treat. 2009;20(2):100-8. Review. PubMed PMID: 18923992.

60: Doyle MK, Rahman MU, Han C, Han J, Giles J, Bingham CO 3rd, Bathon J. Treatment with infliximab plus methotrexate improves anemia in patients with rheumatoid arthritis independent of improvement in other clinical outcome measures-a pooled analysis from three large, multicenter, double-blind, randomized clinical trials. Semin Arthritis Rheum. 2009 Oct;39(2):123-31. Epub 2008 Sep 27. Review. PubMed PMID: 18823645.

61: Schmitt J, Zhang Z, Wozel G, Meurer M, Kirch W. Efficacy and tolerability of biologic and nonbiologic systemic treatments for moderate-to-severe psoriasis:

meta-analysis of randomized controlled trials. Br J Dermatol. 2008 Sep;159(3):513-26. Epub 2008 Jul 9. Review. PubMed PMID: 18627372.

62: Collamer AN, Guerrero KT, Henning JS, Battafarano DF. Psoriatic skin lesions induced by tumor necrosis factor antagonist therapy: a literature review and potential mechanisms of action. Arthritis Rheum. 2008 Jul 15;59(7):996-1001. Review. PubMed PMID: 18576309.

63: Brimhall AK, King LN, Licciardone JC, Jacobe H, Menter A. Safety and efficacy of alefacept, efalizumab, etanercept and infliximab in treating moderate to severe plaque psoriasis: a meta-analysis of randomized controlled trials. Br J Dermatol. 2008 Aug;159(2):274-85. Epub 2008 Jun 10. Review. PubMed PMID: 18547300.

64: Du Pan SM, Gabay C, Finckh A. A systematic review of infliximab in the treatment of early rheumatoid arthritis. Ther Clin Risk Manag. 2007 Oct;3(5):905-11. PubMed PMID: 18473014; PubMed Central PMCID: PMC2376089.

65: Alonso-Ruiz A, Pijoan JI, Ansuategui E, Urkaregi A, Calabozo M, Quintana A. Tumor necrosis factor alpha drugs in rheumatoid arthritis: systematic review and metaanalysis of efficacy and safety. BMC Musculoskelet Disord. 2008 Apr 17;9:52. Review. PubMed PMID: 18419803; PubMed Central PMCID: PMC2377247.

66: Huang W, Cordoro KM, Taylor SL, Feldman SR. To test or not to test? An evidence-based assessment of the value of screening and monitoring tests when using systemic biologic agents to treat psoriasis. J Am Acad Dermatol. 2008 Jun;58(6):970-7. Epub 2008 Apr 2. Review. PubMed PMID: 18384909.

67: Wailoo AJ, Bansback N, Brennan A, Michaud K, Nixon RM, Wolfe F. Biologic drugs for rheumatoid arthritis in the Medicare program: a cost-effectiveness analysis. Arthritis Rheum. 2008 Apr;58(4):939-46. PubMed PMID: 18383356.

68: Saad AA, Symmons DP, Noyce PR, Ashcroft DM. Risks and benefits of tumor necrosis factor-alpha inhibitors in the management of psoriatic arthritis: systematic review and metaanalysis of randomized controlled trials. J Rheumatol. 2008 May;35(5):883-90. Epub 2008 Mar 15. Review. PubMed PMID: 18381787.

69: Reich K, Sinclair R, Roberts G, Griffiths CE, Tabberer M, Barker J. Comparative effects of biological therapies on the severity of skin symptoms and health-related quality of life in patients with plaque-type psoriasis: a meta-analysis. Curr Med Res Opin. 2008 May;24(5):1237-54. Epub 2008 Mar 19. Review. PubMed PMID: 18355421.

70: Ducharme E, Weinberg JM. Etanercept. Expert Opin Biol Ther. 2008 Apr;8(4):491-502. Review. PubMed PMID: 18352852.

71: O'Donnell S, O'Morain C. Review article: use of antitumour necrosis factor therapy in inflammatory bowel disease during pregnancy and conception. Aliment Pharmacol Ther. 2008 May;27(10):885-94. Epub 2008 Feb 14. Review. PubMed PMID: 18284649.

72: Kristensen LE, Christensen R, Bliddal H, Geborek P, Danneskiold-Samsøe B, Saxne T. The number needed to treat for adalimumab, etanercept, and infliximab based on ACR50 response in three randomized controlled trials on established rheumatoid arthritis: a systematic literature review. Scand J Rheumatol. 2007 Nov-Dec;36(6):411-7. Review. PubMed PMID: 18092260.

73: Donahue KE, Gartlehner G, Jonas DE, Lux LJ, Thieda P, Jonas BL, Hansen RA, Morgan LC, Lohr KN. Systematic review: comparative effectiveness and harms of disease-modifying medications for rheumatoid arthritis. Ann Intern Med. 2008 Jan 15;148(2):124-34. Epub 2007 Nov 19. Review. PubMed PMID: 18025440.

74: Nelson AA, Pearce DJ, Fleischer AB Jr, Balkrishnan R, Feldman SR. Cost-effectiveness of biologic treatments for psoriasis based on subjective and objective efficacy measures assessed over a 12-week treatment period. J Am Acad Dermatol. 2008 Jan;58(1):125-35. Epub 2007 Nov 8. Review. PubMed PMID: 17996329.

75: Bravo Vergel Y, Hawkins NS, Claxton K, Asseburg C, Palmer S, Woolacott N, Bruce IN, Sculpher MJ. The cost-effectiveness of etanercept and infliximab for the treatment of patients with psoriatic arthritis. Rheumatology (Oxford). 2007 Nov;46(11):1729-35. PubMed PMID: 17956918.

76: Lee YH, Woo JH, Rho YH, Choi SJ, Ji JD, Song GG. Meta-analysis of the combination of TNF inhibitors plus MTX compared to MTX monotherapy, and the adjusted indirect comparison of TNF inhibitors in patients suffering from active rheumatoid arthritis. Rheumatol Int. 2008 Apr;28(6):553-9. Epub 2007 Oct 18. PubMed PMID: 17943257.

77: Salvana EM, Cooper GS, Salata RA. Mycobacterium other than tuberculosis (MOTT) infection: an emerging disease in infliximab-treated patients. J Infect. 2007 Dec;55(6):484-7. Epub 2007 Oct 17. Review. PubMed PMID: 17920687.

78: Brodszky V, Czirják L, Géher P, Hodinka L, Kárpáti K, Péntek M, Poór G, Szekanecz Z, Gulácsi L. [Rituximab in patients with rheumatoid arthritis: systematic review]. Orv Hetil. 2007 Oct 7;148(40):1883-93. Review. Hungarian. PubMed PMID: 17905683.

79: Bertele' V, Assisi A, Di Muzio V, Renzo D, Garattini S. New antirheumatic drugs: any real added value? A critical overview of regulatory criteria for their marketing approval. Eur J Clin Pharmacol. 2007 Sep;63(9):879-89. Epub 2007 Jul 24. PubMed PMID: 17646975.

80: Grinblat B, Scheinberg M. The enigmatic development of psoriasis and psoriasiform lesions during anti-TNF therapy: a review. Semin Arthritis Rheum. 2008 Feb;37(4):251-5. Epub 2007 Jul 20. Review. PubMed PMID: 17640718.

81: Ramos-Casals M, Brito-Zerón P, Muñoz S, Soria N, Galiana D, Bertolaccini L, Cuadrado MJ, Khamashta MA. Autoimmune diseases induced by TNF-targeted therapies: analysis of 233 cases. Medicine (Baltimore). 2007 Jul;86(4):242-51. PubMed PMID: 17632266.

82: Jones JL, Loftus EV Jr. Lymphoma risk in inflammatory bowel disease: is it the disease or its treatment? Inflamm Bowel Dis. 2007 Oct;13(10):1299-307. Review. PubMed PMID: 17600819.

83: Heiligenhaus A, Horneff G, Greiner K, Mackensen F, Zierhut M, Foeldvari I, Michels H. [Inhibitors of tumour necrosis factor-alpha for the treatment of arthritis and uveitis in childhood]. Klin Monbl Augenheilkd. 2007 Jun;224(6):526-31. Review. German. PubMed PMID: 17594625.

84: Carmona L, Ortiz A, Abad MA. How good is to switch between biologics? A systematic review of the literature. Acta Reumatol Port. 2007 Apr-Jun;32(2):113-28. Review. PubMed PMID: 17572650.

85: Gartlehner G, Hansen RA, Jonas BL, Thieda P, Lohr KN. Biologics for the treatment of juvenile idiopathic arthritis: a systematic review and critical analysis of the evidence. Clin Rheumatol. 2008 Jan;27(1):67-76. Epub 2007 Jun 15. Review. PubMed PMID: 17570009.

86: Langley RG, Gupta AK, Cherman AM, Inniss KA. Biologic therapeutics in the treatment of psoriasis. Part 1: review. J Cutan Med Surg. 2007 May-Jun;11(3):99-122. Review. PubMed PMID: 17511926.

87: Nixon R, Bansback N, Brennan A. The efficacy of inhibiting tumour necrosis

factor alpha and interleukin 1 in patients with rheumatoid arthritis: a meta-analysis and adjusted indirect comparisons. Rheumatology (Oxford). 2007 Jul;46(7):1140-7. Epub 2007 May 3. PubMed PMID: 17478472.

88: Kievit W, Fransen J, Oerlemans AJ, Kuper HH, van der Laar MA, de Rooij DJ, De Gendt CM, Ronday KH, Jansen TL, van Oijen PC, Brus HL, Adang EM, van Riel PL. The efficacy of anti-TNF in rheumatoid arthritis, a comparison between randomised controlled trials and clinical practice. Ann Rheum Dis. 2007 Nov;66(11):1473-8. Epub 2007 Apr 10. Review. PubMed PMID: 17426065.

89: Katugampola RP, Lewis VJ, Finlay AY. The Dermatology Life Quality Index: assessing the efficacy of biological therapies for psoriasis. Br J Dermatol. 2007 May;156(5):945-50. Epub 2007 Mar 28. Review. PubMed PMID: 17388922.

90: von Bültzingslöwen I, Sollecito TP, Fox PC, Daniels T, Jonsson R, Lockhart PB, Wray D, Brennan MT, Carrozzo M, Gandera B, Fujibayashi T, Navazesh M, Rhodus NL, Schiødt M. Salivary dysfunction associated with systemic diseases: systematic review and clinical management recommendations. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2007 Mar;103 Suppl:S57.e1-15. Review. PubMed PMID: 17379156.

91: Leon A, Nguyen A, Letsinger J, Koo J. An attempt to formulate an evidence-based strategy in the management of moderate-to-severe psoriasis: a review of the efficacy and safety of biologics and prebiologic options. Expert Opin Pharmacother. 2007 Apr;8(5):617-32. Review. PubMed PMID: 17376017.

92: Gartlehner G, Hansen RA, Jonas BL, Thieda P, Lohr KN. The comparative efficacy and safety of biologics for the treatment of rheumatoid arthritis: a systematic review and metaanalysis. J Rheumatol. 2006 Dec;33(12):2398-408. Review. PubMed PMID: 17225293.

93: Walker-Bone K, Farrow S. Rheumatoid arthritis. Clin Evid (Online). 2007 Aug 1;2007. pii: 1124. PubMed PMID: 19454108.

94: Woolacott NF, Khadjesari ZC, Bruce IN, Riemsma RP. Etanercept and infliximab for the treatment of psoriatic arthritis: a systematic review. Clin Exp Rheumatol. 2006 Sep-Oct;24(5):587-93. Review. PubMed PMID: 17181932.

95: Koó E, Brodszky V, Péntek M, Ujfalussy I, Nagy MB, Gulácsi L. [The role of biological agents in the treatment of psoriatic arthritis, literature review]. Orv Hetil. 2006 Oct 15;147(41):1963-70. Review. Hungarian. PubMed PMID: 17120686.

96: Woolacott N, Hawkins N, Mason A, Kainth A, Khadjesari Z, Vergel YB, Misso K, Light K, Chalmers R, Sculpher M, Riemsma R. Etanercept and efalizumab for the treatment of psoriasis: a systematic review. Health Technol Assess. 2006 Nov;10(46):1-233, i-iv. Review. PubMed PMID: 17083854.

97: Lassoued S, Zabraniecki L, Marin F, Billey T. Toxoplasmic chorioretinitis and antitumor necrosis factor treatment in rheumatoid arthritis. Semin Arthritis Rheum. 2007 Feb;36(4):262-3. Epub 2006 Oct 25. PubMed PMID: 17067660.

98: Chen YF, Jobanputra P, Barton P, Jowett S, Bryan S, Clark W, Fry-Smith A, Burls A. A systematic review of the effectiveness of adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis in adults and an economic evaluation of their cost-effectiveness. Health Technol Assess. 2006 Nov;10(42):iii-iv, xi-xiii, 1-229. Review. PubMed PMID: 17049139.

99: Ariza-Ariza R, Navarro-Sarabia F, Hernández-Cruz B, Rodríguez-Arboleya L, Navarro-Compán V, Toyos J. Dose escalation of the anti-TNF-alpha agents in patients with rheumatoid arthritis. A systematic review. Rheumatology (Oxford). 2007 Mar;46(3):529-32. Epub 2006 Sep 29. Review. PubMed PMID: 17012439.

100: Doan QV, Chiou CF, Dubois RW. Review of eight pharmacoeconomic studies of

the value of biologic DMARDs (adalimumab, etanercept, and infliximab) in the management of rheumatoid arthritis. J Manag Care Pharm. 2006 Sep;12(7):555-69. Review. PubMed PMID: 16981801.

101: Woolacott N, Bravo Vergel Y, Hawkins N, Kainth A, Khadjesari Z, Misso K, Light K, Asseburg C, Palmer S, Claxton K, Bruce I, Sculpher M, Riemsma R. Etanercept and infliximab for the treatment of psoriatic arthritis: a systematic review and economic evaluation. Health Technol Assess. 2006 Sep;10(31):iii-iv, xiii-xvi, 1-239. Review. PubMed PMID: 16948890.

102: Sari I, Akar S, Birlik M, Sis B, Onen F, Akkoc N. Anti-tumor necrosis factor-alpha-induced psoriasis. J Rheumatol. 2006 Jul;33(7):1411-4. PubMed PMID: 16821276.

103: Kemény L, Brodszky V, Kárpáti K, Gulácsi L. [The role of biological drugs in the treatment of psoriasis, results from 9 randomized placebo-controlled trials]. Orv Hetil. 2006 May 28;147(21):981-90. Review. Hungarian. PubMed PMID: 16812973.

104: Ting PT, Koo JY. Use of etanercept in human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS) patients. Int J Dermatol. 2006 Jun;45(6):689-92. Review. PubMed PMID: 16796629.

105: Soriano ER, McHugh NJ. Therapies for peripheral joint disease in psoriatic arthritis. A systematic review. J Rheumatol. 2006 Jul;33(7):1422-30. Epub 2006 May 15. Review. PubMed PMID: 16724372.

106: Helliwell PS. Therapies for dactylitis in psoriatic arthritis. A systematic review. J Rheumatol. 2006 Jul;33(7):1439-41. Epub 2006 May 15. Review. PubMed PMID: 16724369.

107: Boehncke WH, Prinz J, Gottlieb AB. Biologic therapies for psoriasis. A systematic review. J Rheumatol. 2006 Jul;33(7):1447-51. Epub 2006 May 15. Review. PubMed PMID: 16724367.

108: Bongartz T, Sutton AJ, Sweeting MJ, Buchan I, Matteson EL, Montori V. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. JAMA. 2006 May 17;295(19):2275-85. Review. Erratum in: JAMA. 2006 Jun 7;295(21):2482. PubMed PMID: 16705109.

109: Alexis AF, Strober BE. Off-label dermatologic uses of anti-TNF-a therapies. J Cutan Med Surg. 2005 Dec;9(6):296-302. Review. PubMed PMID: 16699906.

110: Navarro-Sarabia F, Ariza-Ariza R, Hernández-Cruz B, Villanueva I. Adalimumab for treating rheumatoid arthritis. J Rheumatol. 2006 Jun;33(6):1075-81. Epub 2006 May 1. Review. PubMed PMID: 16652437.

111: Fransen J, Antoni C, Mease PJ, Uter W, Kavanaugh A, Kalden JR, Van Riel PL. Performance of response criteria for assessing peripheral arthritis in patients with psoriatic arthritis: analysis of data from randomised controlled trials of two tumour necrosis factor inhibitors. Ann Rheum Dis. 2006 Oct;65(10):1373-8. Epub 2006 Apr 27. PubMed PMID: 16644783; PubMed Central PMCID: PMC1798317.

112: Chung CP, Thompson JL, Koch GG, Amara I, Strand V, Pincus T. Are American College of Rheumatology 50% response criteria superior to 20% criteria in distinguishing active aggressive treatment in rheumatoid arthritis clinical trials reported since 1997? A meta-analysis of discriminant capacities. Ann Rheum Dis. 2006 Dec;65(12):1602-7. Epub 2006 Feb 27. Review. PubMed PMID: 16504992; PubMed Central PMCID: PMC1798472.

113: Gottlieb AB, Leonardi CL, Goffe BS, Ortonne JP, van der Kerkhof PC, Zitnik R, Nakanishi A, Jahreis A. Etanercept monotherapy in patients with psoriasis: a

summary of safety, based on an integrated multistudy database. J Am Acad Dermatol. 2006 Mar;54(3 Suppl 2):S92-100. PubMed PMID: 16488335.

114: Gordon K, Korman N, Frankel E, Wang H, Jahreis A, Zitnik R, Chang T. Efficacy of etanercept in an integrated multistudy database of patients with psoriasis. J Am Acad Dermatol. 2006 Mar;54(3 Suppl 2):S101-11. PubMed PMID: 16488320.

115: Dundar Y, Dodd S, Dickson R, Walley T, Haycox A, Williamson PR. Comparison of conference abstracts and presentations with full-text articles in the health technology assessments of rapidly evolving technologies. Health Technol Assess. 2006 Feb;10(5):iii-iv, ix-145. Review. PubMed PMID: 16487455.

116: Sesin CA, Bingham CO 3rd. Remission in rheumatoid arthritis: wishful thinking or clinical reality? Semin Arthritis Rheum. 2005 Dec;35(3):185-96. PubMed PMID: 16325659.

117: Fleischmann R, Baumgartner SW, Weisman MH, Liu T, White B, Peloso P. Long term safety of etanercept in elderly subjects with rheumatic diseases. Ann Rheum Dis. 2006 Mar;65(3):379-84. Epub 2005 Sep 8. PubMed PMID: 16150792; PubMed Central PMCID: PMC1798057.

118: Sauder DN, Mamelak AJ. Understanding the new clinical landscape for psoriasis: a comparative review of biologics. J Cutan Med Surg. 2004 Jul-Aug;8(4):205-12. Review. PubMed PMID: 16091996.

119: Navarro-Sarabia F, Ariza-Ariza R, Hernandez-Cruz B, Villanueva I. Adalimumab for treating rheumatoid arthritis. Cochrane Database Syst Rev. 2005 Jul 20;(3):CD005113. Review. PubMed PMID: 16034967.

120: Bansback NJ, Regier DA, Ara R, Brennan A, Shojania K, Esdaile JM, Anis AH, Marra CA. An overview of economic evaluations for drugs used in rheumatoid arthritis : focus on tumour necrosis factor-alpha antagonists. Drugs. 2005;65(4):473-96. Review. PubMed PMID: 15733011.

121: Gupta AK, Skinner AR. A review of the use of infliximab to manage cutaneous dermatoses. J Cutan Med Surg. 2004 Mar-Apr;8(2):77-89. Epub 2004 May 4. Review. PubMed PMID: 15685387.

122: Fisher VS. Clinical monograph for drug formulary review: systemic agents for psoriasis/psoriatic arthritis. J Manag Care Pharm. 2005 Jan-Feb;11(1):33-55. Review. PubMed PMID: 15667232.

123: Saini R, Tutrone WD, Weinberg JM. Advances in therapy for psoriasis: an overview of infliximab, etanercept, efalizumab, alefacept, adalimumab, tazarotene, and pimecrolimus. Curr Pharm Des. 2005;11(2):273-80. Review. PubMed PMID: 15638763.

124: Scheinfeld N. A comprehensive review and evaluation of the side effects of the tumor necrosis factor alpha blockers etanercept, infliximab and adalimumab. J Dermatolog Treat. 2004 Sep;15(5):280-94. Review. PubMed PMID: 15370396.

125: Messori A, Santarlasci B, Vaiani M. New drugs for rheumatoid arthritis. N Engl J Med. 2004 Aug 26;351(9):937-8. PubMed PMID: 15329436.

126: Scheinfeld N. Off-label uses and side effects of infliximab. J Drugs Dermatol. 2004 May-Jun;3(3):273-84. Review. PubMed PMID: 15176162.

127: Clark W, Jobanputra P, Barton P, Burls A. The clinical and cost-effectiveness of anakinra for the treatment of rheumatoid arthritis in adults: a systematic review and economic analysis. Health Technol Assess. 2004 May;8(18):iii-iv, ix-x, 1-105. Review. PubMed PMID: 15130461.

128: Torrance GW, Tugwell P, Amorosi S, Chartash E, Sengupta N. Improvement in health utility among patients with rheumatoid arthritis treated with adalimumab (a human anti-TNF monoclonal antibody) plus methotrexate. Rheumatology (Oxford). 2004 Jun;43(6):712-8. Epub 2004 Mar 23. PubMed PMID: 15039494.

129: Barton P, Jobanputra P, Wilson J, Bryan S, Burls A. The use of modelling to evaluate new drugs for patients with a chronic condition: the case of antibodies against tumour necrosis factor in rheumatoid arthritis. Health Technol Assess. 2004 Mar;8(11):iii, 1-91. Review. PubMed PMID: 14982655.

130: Krueger G, Callis K. Potential of tumor necrosis factor inhibitors in psoriasis and psoriatic arthritis. Arch Dermatol. 2004 Feb;140(2):218-25. Review. PubMed PMID: 14967799.

131: Weinberg JM. An overview of infliximab, etanercept, efalizumab, and alefacept as biologic therapy for psoriasis. Clin Ther. 2003 Oct;25(10):2487-505. Review. PubMed PMID: 14667953.

132: Blumenauer B, Judd M, Cranney A, Burls A, Coyle D, Hochberg M, Tugwell P, Wells G. Etanercept for the treatment of rheumatoid arthritis. Cochrane Database Syst Rev. 2003;(4):CD004525. Review. PubMed PMID: 14584021.

133: Hochberg MC, Tracy JK, Hawkins-Holt M, Flores RH. Comparison of the efficacy of the tumour necrosis factor alpha blocking agents adalimumab, etanercept, and infliximab when added to methotrexate in patients with active rheumatoid arthritis. Ann Rheum Dis. 2003 Nov;62 Suppl 2:ii13-6. Review. PubMed PMID: 14532140; PubMed Central PMCID: PMC1766753.

134: Nahar IK, Shojania K, Marra CA, Alamgir AH, Anis AH. Infliximab treatment of rheumatoid arthritis and Crohn's disease. Ann Pharmacother. 2003 Sep;37(9):1256-65. Review. PubMed PMID: 12921510.

135: Maksymowych WP, Inman RD, Gladman D, Thomson G, Stone M, Karsh J, Russell AS; Spondyloarthritis Research Consortium of Canada (SPARCC). Canadian Rheumatology Association Consensus on the use of anti-tumor necrosis factor-alpha directed therapies in the treatment of spondyloarthritis. J Rheumatol. 2003 Jun;30(6):1356-63. Review. PubMed PMID: 12784417.

136: Jones G, Halbert J, Crotty M, Shanahan EM, Batterham M, Ahern M. The effect of treatment on radiological progression in rheumatoid arthritis: a systematic review of randomized placebo-controlled trials. Rheumatology (Oxford). 2003 Jan;42(1):6-13. Review. PubMed PMID: 12509606.

137: Brockbank J, Gladman D. Diagnosis and management of psoriatic arthritis. Drugs. 2002;62(17):2447-57. Review. PubMed PMID: 12421102.

138: Jobanputra P, Barton P, Bryan S, Burls A. The effectiveness of infliximab and etanercept for the treatment of rheumatoid arthritis: a systematic review and economic evaluation. Health Technol Assess. 2002;6(21):1-110. Review. PubMed PMID: 12387732.

139: Rau R. Adalimumab (a fully human anti-tumour necrosis factor alpha monoclonal antibody) in the treatment of active rheumatoid arthritis: the initial results of five trials. Ann Rheum Dis. 2002 Nov;61 Suppl 2:ii70-3. Review. PubMed PMID: 12379628; PubMed Central PMCID: PMC1766697.

140: Cummins C, Connock M, Fry-Smith A, Burls A. A systematic review of effectiveness and economic evaluation of new drug treatments for juvenile idiopathic arthritis: etanercept. Health Technol Assess. 2002;6(17):1-43. Review. PubMed PMID: 12234456.

141: Rodewald EJ, Housman TS, Mellen BG, Feldman SR. The efficacy of 308nm laser treatment of psoriasis compared to historical controls. Dermatol Online J. 2001 Dec;7(2):4. PubMed PMID: 12165220.

142: Blumenauer B, Judd M, Wells G, Burls A, Cranney A, Hochberg M, Tugwell P. Infliximab for the treatment of rheumatoid arthritis. Cochrane Database Syst Rev. 2002;(3):CD003785. Review. PubMed PMID: 12137712.

143: Paget SA. Efficacy of anakinra in bone: comparison to other biologics. Adv Ther. 2002 Jan-Feb;19(1):27-39. Review. PubMed PMID: 12008859.

144: Hochberg MC, Tracy JK, Flores RH. "Stepping-up" from methotrexate: a systematic review of randomised placebo controlled trials in patients with rheumatoid arthritis with an incomplete response to methotrexate. Ann Rheum Dis. 2001 Nov;60 Suppl 3:iii51-4. Review. PubMed PMID: 11890654; PubMed Central PMCID: PMC1766673.

145: Russell A, Haraoui B, Keystone E, Klinkhoff A. Current and emerging therapies for rheumatoid arthritis, with a focus on infliximab: clinical impact on joint damage and cost of care in canada. Clin Ther. 2001 Nov;23(11):1824-38; discussion 1791. Review. PubMed PMID: 11768835.

146: Johnson CJ, Reilly KM, Murray KM. Etanercept in juvenile rheumatoid arthritis. Ann Pharmacother. 2001 Apr;35(4):464-71. Review. PubMed PMID: 11302411.

147: Luong BT, Chong BS, Lowder DM. Treatment options for rheumatoid arthritis: celecoxib, leflunomide, etanercept, and infliximab. Ann Pharmacother. 2000 Jun;34(6):743-60. Review. PubMed PMID: 10860137.

148: Schuna AA. Update on treatment of rheumatoid arthritis. J Am Pharm Assoc (Wash). 1998 Nov-Dec;38(6):728-35; quiz 735-7. Review. PubMed PMID: 9861791.

SEARCH 9_cert OR gol OR ustek_ clinical trial 3 condit

Category	Description
Clinical question or focus	BIOLOGICAL AGENTS FINAL
Source	PubMed
Terms	(certolizumab OR golimumab OR ustekinumab) AND (Rheumatoid arthritis OR psoriasis OR psoriatic arthritis)
Limits	Clinical Trial
▪ Date limits	
▪ Other limits	
Query Translation (eg, “Details” in PubMed)	(("CDP870"[Substance Name] OR "CDP870"[All Fields] OR "certolizumab"[All Fields]) OR ("golimumab"[Substance Name] OR "golimumab"[All Fields]) OR ("monoclonal antibody CNTO 1275"[Substance Name] OR "monoclonal antibody CNTO 1275"[All Fields] OR "ustekinumab"[All Fields])) AND (("arthritis, rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "rheumatoid"[All Fields]) OR "rheumatoid arthritis"[All Fields] OR ("rheumatoid"[All Fields] AND "arthritis"[All Fields])) OR ("psoriasis"[MeSH Terms] OR "psoriasis"[All Fields]) OR ("arthritis, psoriatic"[MeSH Terms] OR ("arthritis"[All Fields] AND "psoriatic"[All Fields]) OR "psoriatic arthritis"[All Fields] OR ("psoriatic"[All Fields] AND "arthritis"[All Fields]))) AND Clinical Trial[ptyp]
Date of Search	8/18/10
Total Yield	22
Total marked for retrieval	Kremer 10, Keystone 10, Griffiths 10, Emery 09, Kavanaugh 09, Gottlieb 09, Keystone 08, Papp 08, Leonardi 08, Kay 08
Notes	Updated search of abstracts 10/18/10 Searched using Cntrl F and terms “frequent” and “difference” and “common” and “NNH” and “harm” and

	"adverse"
Exclusions	• Not focus of review: population, intervention, comparison, outcome • Superseded by more recent larger study • Lacking safety data • Wrong study type • Duplicates

1: Kremer J, Ritchlin C, Mendelsohn A, Baker D, Kim L, Xu Z, Han J, Taylor P. Golimumab, a new human anti-tumor necrosis factor alpha antibody, administered intravenously in patients with active rheumatoid arthritis: Forty-eight-week efficacy and safety results of a phase III randomized, double-blind, placebo-controlled study. Arthritis Rheum. 2010 Apr;62(4):917-28. PubMed PMID: 20131276.

2: Griffiths CE, Strober BE, van de Kerkhof P, Ho V, Fidelus-Gort R, Yeilding N, Guzzo C, Xia Y, Zhou B, Li S, Dooley LT, Goldstein NH, Menter A; ACCEPT Study Group. Comparison of ustekinumab and etanercept for moderate-to-severe psoriasis. N Engl J Med. 2010 Jan 14;362(2):118-28. PubMed PMID: 20071701.

3: Zhou H, Hu C, Zhu Y, Lu M, Liao S, Yeilding N, Davis HM. Population-based exposure-efficacy modeling of ustekinumab in patients with moderate to severe plaque psoriasis. J Clin Pharmacol. 2010 Mar;50(3):257-67. Epub 2009 Nov 23. PubMed PMID: 19934030.

4: Strand V, Mease P, Burmester GR, Nikaï E, Coteur G, van Vollenhoven R, Combe B, Keystone EC, Kavanaugh A. Rapid and sustained improvements in health-related quality of life, fatigue, and other patient-reported outcomes in rheumatoid arthritis patients treated with certolizumab pegol plus methotrexate over 1 year: results from the RAPID 1 randomized controlled trial. Arthritis Res Ther. 2009;11(6):R170. Epub 2009 Nov 12. PubMed PMID: 19909548.

5: Lebwohl M, Papp K, Han C, Schenkel B, Yeilding N, Wang Y, Krueger GG. Ustekinumab improves health-related quality of life in patients with moderate-to-severe psoriasis: results from the PHOENIX 1 trial. Br J Dermatol. 2010 Jan;162(1):137-46. Epub 2009 Nov 9. PubMed PMID: 19903183.

6: Kavanaugh A, Smolen JS, Emery P, Purcaru O, Keystone E, Richard L, Strand V, van Vollenhoven RF. Effect of certolizumab pegol with methotrexate on home and work place productivity and social activities in patients with active rheumatoid arthritis. Arthritis Rheum. 2009 Nov 15;61(11):1592-600. PubMed PMID: 19877104.

7: Emery P, Fleischmann RM, Moreland LW, Hsia EC, Strusberg I, Durez P, Nash P, Amante EJ, Churchill M, Park W, Pons-Estel BA, Doyle MK, Visvanathan S, Xu W, Rahman MU. Golimumab, a human anti-tumor necrosis factor alpha monoclonal antibody, injected subcutaneously every four weeks in methotrexate-naive patients with active rheumatoid arthritis: twenty-four-week results of a phase III, multicenter, randomized, double-blind, placebo-controlled study of golimumab before methotrexate as first-line therapy for early-onset rheumatoid arthritis. Arthritis Rheum. 2009 Aug;60(8):2272-83. PubMed PMID: 19644849.

8: Xu Z, Vu T, Lee H, Hu C, Ling J, Yan H, Baker D, Beutler A, Pendley C, Wagner C, Davis HM, Zhou H. Population pharmacokinetics of golimumab, an anti-tumor necrosis factor-alpha human monoclonal antibody, in patients with psoriatic arthritis. J Clin Pharmacol. 2009 Sep;49(9):1056-70. Epub 2009 Jul 17. PubMed PMID: 19617465.

9: Smolen JS, Kay J, Doyle MK, Landewé R, Matteson EL, Wollenhaupt J, Gaylis N, Murphy FT, Neal JS, Zhou Y, Visvanathan S, Hsia EC, Rahman MU; GO-AFTER study investigators. Golimumab in patients with active rheumatoid arthritis after treatment with tumour necrosis factor alpha inhibitors (GO-AFTER study): a

multicentre, randomised, double-blind, placebo-controlled, phase III trial. Lancet. 2009 Jul 18;374(9685):210-21. Epub 2009 Jun 26. Erratum in: Lancet. 2009 Oct 24;374(9699):1422. PubMed PMID: 19560810.

10: Visvanathan S, Wagner C, Rojas J, Kay J, Dasgupta B, Matteson EL, Mack M, Baker DG, Rahman MU. E-selectin, interleukin 18, serum amyloid a, and matrix metalloproteinase 9 are associated with clinical response to golimumab plus methotrexate in patients with active rheumatoid arthritis despite methotrexate therapy. J Rheumatol. 2009 Jul;36(7):1371-9. Epub 2009 Jun 1. PubMed PMID: 19487269.

11: Kavanaugh A, McInnes I, Mease P, Krueger GG, Gladman D, Gomez-Reino J, Papp K, Zrubek J, Mudivarthy S, Mack M, Visvanathan S, Beutler A. Golimumab, a new human tumor necrosis factor alpha antibody, administered every four weeks as a subcutaneous injection in psoriatic arthritis: Twenty-four-week efficacy and safety results of a randomized, placebo-controlled study. Arthritis Rheum. 2009 Apr;60(4):976-86. PubMed PMID: 19333944.

12: Gottlieb A, Menter A, Mendelsohn A, Shen YK, Li S, Guzzo C, Fretzin S, Kunynetz R, Kavanaugh A. Ustekinumab, a human interleukin 12/23 monoclonal antibody, for psoriatic arthritis: randomised, double-blind, placebo-controlled, crossover trial. Lancet. 2009 Feb 21;373(9664):633-40. Epub 2009 Feb 11. Erratum in: Lancet. 2009 Apr 18;373(9672):1340. PubMed PMID: 19217154.

13: Keystone EC, Genovese MC, Klareskog L, Hsia EC, Hall ST, Miranda PC, Pazdur J, Bae SC, Palmer W, Zrubek J, Wiekowski M, Visvanathan S, Wu Z, Rahman MU; GO-FORWARD Study. Golimumab, a human antibody to tumour necrosis factor {alpha} given by monthly subcutaneous injections, in active rheumatoid arthritis despite methotrexate therapy: the GO-FORWARD Study. Ann Rheum Dis. 2009 Jun;68(6):789-96. Epub 2008 Dec 9. PubMed PMID: 19066176; PubMed Central PMCID: PMC2674549.

14: Smolen J, Landewé RB, Mease P, Brzezicki J, Mason D, Luijtens K, van Vollenhoven RF, Kavanaugh A, Schiff M, Burmester GR, Strand V, Vencovsky J, van der Heijde D. Efficacy and safety of certolizumab pegol plus methotrexate in active rheumatoid arthritis: the RAPID 2 study. A randomised controlled trial. Ann Rheum Dis. 2009 Jun;68(6):797-804. Epub 2008 Nov 17. PubMed PMID: 19015207; PubMed Central PMCID: PMC2674556.

15: Fleischmann R, Vencovsky J, van Vollenhoven RF, Borenstein D, Box J, Coteur G, Goel N, Brezinschek HP, Innes A, Strand V. Efficacy and safety of certolizumab pegol monotherapy every 4 weeks in patients with rheumatoid arthritis failing previous disease-modifying antirheumatic therapy: the FAST4WARD study. Ann Rheum Dis. 2009 Jun;68(6):805-11. Epub 2008 Nov 17. PubMed PMID: 19015206; PubMed Central PMCID: PMC2674555.

16: Keystone E, Heijde D, Mason D Jr, Landewé R, Vollenhoven RV, Combe B, Emery P, Strand V, Mease P, Desai C, Pavelka K. Certolizumab pegol plus methotrexate is significantly more effective than placebo plus methotrexate in active rheumatoid arthritis: findings of a fifty-two-week, phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Arthritis Rheum. 2008 Nov;58(11):3319-29. Erratum in: Arthritis Rheum. 2009 May;60(5):1249. PubMed PMID: 18975346.

17: Papp KA, Langley RG, Lebwohl M, Krueger GG, Szapary P, Yeilding N, Guzzo C, Hsu MC, Wang Y, Li S, Dooley LT, Reich K; PHOENIX 2 study investigators. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2). Lancet. 2008 May 17;371(9625):1675-84. PubMed PMID: 18486740.

18: Leonardi CL, Kimball AB, Papp KA, Yeilding N, Guzzo C, Wang Y, Li S, Dooley LT, Gordon KB; PHOENIX 1 study investigators. Efficacy and safety of ustekinumab,

a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). Lancet. 2008 May 17;371(9625):1665-74. Erratum in: Lancet. 2008 May 31;371(9627):1838. PubMed PMID: 18486739.

19: Bartlett BL, Tyring SK. Ustekinumab for chronic plaque psoriasis. Lancet. 2008 May 17;371(9625):1639-40. PubMed PMID: 18486724.

20: Kay J, Matteson EL, Dasgupta B, Nash P, Durez P, Hall S, Hsia EC, Han J, Wagner C, Xu Z, Visvanathan S, Rahman MU. Golimumab in patients with active rheumatoid arthritis despite treatment with methotrexate: a randomized, double-blind, placebo-controlled, dose-ranging study. Arthritis Rheum. 2008 Apr;58(4):964-75. PubMed PMID: 18383539.

21: Zhou H, Jang H, Fleischmann RM, Bouman-Thio E, Xu Z, Marini JC, Pendley C, Jiao Q, Shankar G, Marciniak SJ, Cohen SB, Rahman MU, Baker D, Mascelli MA, Davis HM, Everitt DE. Pharmacokinetics and safety of golimumab, a fully human anti-TNF-alpha monoclonal antibody, in subjects with rheumatoid arthritis. J Clin Pharmacol. 2007 Mar;47(3):383-96. PubMed PMID: 17322150.

22: Choy EH, Hazleman B, Smith M, Moss K, Lisi L, Scott DG, Patel J, Sopwith M, Isenberg DA. Efficacy of a novel PEGylated humanized anti-TNF fragment (CDP870) in patients with rheumatoid arthritis: a phase II double-blinded, randomized, dose-escalating trial. Rheumatology (Oxford). 2002 Oct;41(10):1133-7. PubMed PMID: 12364632.

SEARCH 10_ tb lymph ms carcin all

Category	Description
Clinical question or focus	BIOLOGICAL AGENTS FINAL
Source	PubMed
Terms	(tuberculosis OR lymphoma OR multiple sclerosis OR carcinoma OR demyelinating) AND (adalimumab OR certolizumab OR etanercept OR golimumab OR infliximab OR ustekinumab) AND (Rheumatoid arthritis OR psoriasis OR psoriatic arthritis)
Limits	Clinical trial
▪ Date limits	
▪ Other limits	
Query Translation (eg, “Details” in PubMed)	("tuberculosis"[MeSH Terms] OR "tuberculosis"[All Fields]) OR ("lymphoma"[MeSH Terms] OR "lymphoma"[All Fields]) OR ("multiple sclerosis"[MeSH Terms] OR ("multiple"[All Fields] AND "sclerosis"[All Fields]) OR "multiple sclerosis"[All Fields]) OR ("carcinoma"[MeSH Terms] OR "carcinoma"[All Fields]) OR demyelinating[All Fields]) AND (("adalimumab"[Substance Name] OR "adalimumab"[All Fields]) OR ("CDP870"[Substance Name] OR "CDP870"[All Fields] OR "certolizumab"[All Fields]) OR ("TNFR-Fc fusion protein"[Substance Name] OR "TNFR-Fc fusion protein"[All Fields] OR "etanercept"[All Fields]) OR ("golimumab"[Substance Name] OR "golimumab"[All Fields]) OR ("infliximab"[Substance Name] OR "infliximab"[All Fields]) OR ("monoclonal antibody CNTO 1275"[Substance Name] OR "monoclonal antibody CNTO 1275"[All Fields] OR "ustekinumab"[All Fields])) AND (("arthritis, rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "rheumatoid"[All Fields]) OR "rheumatoid arthritis"[All Fields] OR ("rheumatoid"[All Fields] AND "arthritis"[All Fields])) OR ("psoriasis"[MeSH Terms] OR "psoriasis"[All Fields]) OR ("arthritis, psoriatic"[MeSH Terms] OR ("arthritis"[All Fields] AND "psoriatic"[All Fields]) OR "psoriatic arthritis"[All Fields] OR ("psoriatic"[All Fields] AND "arthritis"[All Fields]))) AND Clinical Trial[ptyp]
Date of Search	8/18/10
Total Yield	23
Total marked for retrieval	Favalli 08, van de Kerkhof 08, Gómez-Reino 07, Burmester 07, Geborek 05, Gómez-Reino 03

Exclusions	• Not focus of review: population, intervention, comparison, outcome • Superseded by more recent larger study • Lacking safety data • Wrong study type • Duplicates

1: Laffitte E, Janssens JP, Roux-Lombard P, Thielen AM, Barde C, Marazza G, Panizzon RG, Saurat JH. Tuberculosis screening in patients with psoriasis before antitumour necrosis factor therapy: comparison of an interferon-gamma release assay vs. tuberculin skin test. Br J Dermatol. 2009 Oct;161(4):797-800. Epub 2009 Jun 5. PubMed PMID: 19659473.

2: Luzi G, Laganà B, Salemi S, Di Rosa R. Are glucocorticoids a consistent risk factor for infections in rheumatoid arthritis patients under treatment with methotrexate and etanercept? Clin Ter. 2009 Mar-Apr;160(2):121-3. PubMed PMID: 19452100.

3: Kavanaugh A, McInnes I, Mease P, Krueger GG, Gladman D, Gomez-Reino J, Papp K, Zrubek J, Mudivarthy S, Mack M, Visvanathan S, Beutler A. Golimumab, a new human tumor necrosis factor alpha antibody, administered every four weeks as a subcutaneous injection in psoriatic arthritis: Twenty-four-week efficacy and safety results of a randomized, placebo-controlled study. Arthritis Rheum. 2009 Apr;60(4):976-86. PubMed PMID: 19333944.

4: Favalli EG, Desiati F, Atzeni F, Sarzi-Puttini P, Caporali R, Pallavicini FB, Gorla R, Filippini M, Marchesoni A. Serious infections during anti-TNFalpha treatment in rheumatoid arthritis patients. Autoimmun Rev. 2009 Jan;8(3):266-73. Epub 2008 Nov 18. PubMed PMID: 19022409.

5: Smolen J, Landewé RB, Mease P, Brzezicki J, Mason D, Luijtens K, van Vollenhoven RF, Kavanaugh A, Schiff M, Burmester GR, Strand V, Vencovsky J, van der Heijde D. Efficacy and safety of certolizumab pegol plus methotrexate in active rheumatoid arthritis: the RAPID 2 study. A randomised controlled trial. Ann Rheum Dis. 2009 Jun;68(6):797-804. Epub 2008 Nov 17. PubMed PMID: 19015207; PubMed Central PMCID: PMC2674556.

6: Fleischmann R, Vencovsky J, van Vollenhoven RF, Borenstein D, Box J, Coteur G, Goel N, Brezinschek HP, Innes A, Strand V. Efficacy and safety of certolizumab pegol monotherapy every 4 weeks in patients with rheumatoid arthritis failing previous disease-modifying antirheumatic therapy: the FAST4WARD study. Ann Rheum Dis. 2009 Jun;68(6):805-11. Epub 2008 Nov 17. PubMed PMID: 19015206; PubMed Central PMCID: PMC2674555.

7: Zachariae C, Mørk NJ, Reunala T, Lorentzen H, Falk E, Karvonen SL, Johannesson A, Claréus B, Skov L, Mørk G, Walker S, Qvitzau S. The combination of etanercept and methotrexate increases the effectiveness of treatment in active psoriasis despite inadequate effect of methotrexate therapy. Acta Derm Venereol. 2008;88(5):495-501. PubMed PMID: 18779890.

8: van de Kerkhof PC, Segaert S, Lahfa M, Luger TA, Karolyi Z, Kaszuba A, Leigheb G, Camacho FM, Forsea D, Zang C, Boussuge MP, Paolozzi L, Wajdula J. Once weekly administration of etanercept 50 mg is efficacious and well tolerated in patients with moderate-to-severe plaque psoriasis: a randomized controlled trial with open-label extension. Br J Dermatol. 2008 Nov;159(5):1177-85. Epub 2008 Jul 31. PubMed PMID: 18673365.

9: Lovell DJ, Reiff A, Ilowite NT, Wallace CA, Chon Y, Lin SL, Baumgartner SW, Giannini EH; Pediatric Rheumatology Collaborative Study Group. Safety and efficacy of up to eight years of continuous etanercept therapy in patients with juvenile rheumatoid arthritis. Arthritis Rheum. 2008 May;58(5):1496-504. PubMed PMID: 18438876.

10: Cavazzana I, Bobbio-Pallavicini F, Franceschini F, Bazzani C, Ceribelli A, Bravi E, Zingarelli S, Caporali R, Cattaneo R, Montecucco CM. Anti-TNF-alpha treatment in rheumatoid arthritis with anti-Ro/SSA antibodies. Analysis of 17 cases among a cohort of 322 treated patients. Clin Exp Rheumatol. 2007 Sep-Oct;25(5):676-83. PubMed PMID: 18078613.

11: Gómez-Reino JJ, Carmona L, Angel Descalzo M; Biobadaser Group. Risk of tuberculosis in patients treated with tumor necrosis factor antagonists due to incomplete prevention of reactivation of latent infection. Arthritis Rheum. 2007 Jun 15;57(5):756-61. PubMed PMID: 17530674.

12: Botsios C, Sfriso P, Furlan A, Ostuni P, Biscaro M, Fiocco U, Todesco S, Punzi L. [Anakinra, a recombinant human IL-1 receptor antagonist, in clinical practice. Outcome in 60 patients with severe rheumatoid arthritis]. Reumatismo. 2007 Jan-Mar;59(1):32-7. Italian. PubMed PMID: 17435840.

13: Burmester GR, Mariette X, Montecucco C, Monteagudo-Sáez I, Malaise M, Tzioufas AG, Bijlsma JW, Unnebrink K, Kary S, Kupper H. Adalimumab alone and in combination with disease-modifying antirheumatic drugs for the treatment of rheumatoid arthritis in clinical practice: the Research in Active Rheumatoid Arthritis (ReAct) trial. Ann Rheum Dis. 2007 Jun;66(6):732-9. Epub 2007 Feb 28. PubMed PMID: 17329305; PubMed Central PMCID: PMC1954645.

14: Hatemi G, Melikoglu M, Fresko I, Masatlioglu S, Tascilar K, Yazici H. Infliximab does not suppress the tuberculin skin test (purified protein derivative). J Rheumatol. 2007 Mar;34(3):474-80. Epub 2007 Feb 1. PubMed PMID: 17299840.

15: Kavanaugh A, Krueger GG, Beutler A, Guzzo C, Zhou B, Dooley LT, Mease PJ, Gladman DD, de Vlam K, Geusens PP, Birbara C, Halter DG, Antoni C; IMPACT 2 Study Group. Infliximab maintains a high degree of clinical response in patients with active psoriatic arthritis through 1 year of treatment: results from the IMPACT 2 trial. Ann Rheum Dis. 2007 Apr;66(4):498-505. Epub 2006 Nov 17. PubMed PMID: 17114188; PubMed Central PMCID: PMC1856065.

16: Menter A, Feldman SR, Weinstein GD, Papp K, Evans R, Guzzo C, Li S, Dooley LT, Arnold C, Gottlieb AB. A randomized comparison of continuous vs. intermittent infliximab maintenance regimens over 1 year in the treatment of moderate-to-severe plaque psoriasis. J Am Acad Dermatol. 2007 Jan;56(1):31.e1-15. Epub 2006 Sep 6. PubMed PMID: 17097378.

17: Smith CH, Jackson K, Bashir SJ, Perez A, Chew AL, Powell AM, Wain M, Barker JN. Infliximab for severe, treatment-resistant psoriasis: a prospective, open-label study. Br J Dermatol. 2006 Jul;155(1):160-9. PubMed PMID: 16792769.

18: Pontikaki I, Gerloni V, Gattinara M, Luriati A, Salmaso A, De Marco G, Teruzzi B, Valcamonica E, Fantini F. [Side effects of anti-TNFalpha therapy in juvenile idiopathic arthritis]. Reumatismo. 2006 Jan-Mar;58(1):31-8. Italian. PubMed PMID: 16639486.

19: Westhovens R, Yocum D, Han J, Berman A, Strusberg I, Geusens P, Rahman MU; START Study Group. The safety of infliximab, combined with background treatments, among patients with rheumatoid arthritis and various comorbidities: a large, randomized, placebo-controlled trial. Arthritis Rheum. 2006 Apr;54(4):1075-86. Erratum in: Arthritis Rheum. 2007 May;56(5):1675. Dosage error in article text. PubMed PMID: 16572442.

20: Klareskog L, Gaubitz M, Rodriguez-Valverde V, Malaise M, Dougados M, Wajdula J; Etanercept Study 301 Investigators. A long-term, open-label trial of the safety and efficacy of etanercept (Enbrel) in patients with rheumatoid arthritis not treated with other disease-modifying antirheumatic drugs. Ann Rheum Dis. 2006

Dec;65(12):1578-84. Epub 2006 Mar 15. PubMed PMID: 16540554; PubMed Central PMCID: PMC1798461.

21: Geborek P, Bladström A, Turesson C, Gulfe A, Petersson IF, Saxne T, Olsson H, Jacobsson LT. Tumour necrosis factor blockers do not increase overall tumour risk in patients with rheumatoid arthritis, but may be associated with an increased risk of lymphomas. Ann Rheum Dis. 2005 May;64(5):699-703. Epub 2005 Feb 4. PubMed PMID: 15695534; PubMed Central PMCID: PMC1755491.

22: Gómez-Reino JJ, Carmona L, Valverde VR, Mola EM, Montero MD; BIOBADASER Group. Treatment of rheumatoid arthritis with tumor necrosis factor inhibitors may predispose to significant increase in tuberculosis risk: a multicenter active-surveillance report. Arthritis Rheum. 2003 Aug;48(8):2122-7. PubMed PMID: 12905464.

23: Temekonidis TI, Georgiadis AN, Alamanos Y, Bougias DV, Voulgari PV, Drosos AA. Infliximab treatment in combination with cyclosporin A in patients with severe refractory rheumatoid arthritis. Ann Rheum Dis. 2002 Sep;61(9):822-5. PubMed PMID: 12176808; PubMed Central PMCID: PMC1754214.

SEARCH 11_all agents with hedge

Category	Description
Clinical question or focus	BIOLOGICAL AGENTS FINAL
Source	PubMed
Terms	health technology assessment* [tiab] OR "Technology Assessment, Biomedical" [mh] OR HTA [tiab] OR HTAs [tiab] AND (adalimumab OR certolizumab OR etanercept OR golimumab OR infliximab OR ustekinumab) AND (Rheumatoid arthritis OR psoriasis OR psoriatic arthritis) OR health technology appraisal*[tiab]
Limits	none
▪ Date limits	none
▪ Other limits	
Query Translation (eg, “Details” in PubMed)	essment/assessment[tiab] OR health technology assessments[tiab]) OR "Technology Assessment, Biomedical"[mh] OR HTA[tiab] OR HTAs[tiab] AND (("adalimumab"[Substance Name] OR "adalimumab"[All Fields]) OR ("CDP870"[Substance Name] OR "CDP870"[All Fields] OR "certolizumab"[All Fields]) OR ("TNFR-Fc fusion protein"[Substance Name] OR "TNFR-Fc fusion protein"[All Fields] OR "etanercept"[All Fields]) OR ("golimumab"[Substance Name] OR "golimumab"[All Fields]) OR ("infliximab"[Substance Name] OR "infliximab"[All Fields]) OR ("monoclonal antibody CNTO 1275"[Substance Name] OR "monoclonal antibody CNTO 1275"[All Fields] OR "ustekinumab"[All Fields])) AND (("arthritis, rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "rheumatoid"[All Fields]) OR "rheumatoid arthritis"[All Fields] OR ("rheumatoid"[All Fields] AND "arthritis"[All Fields])) OR ("psoriasis"[MeSH Terms] OR "psoriasis"[All Fields]) OR ("arthritis, psoriatic"[MeSH Terms] OR ("arthritis"[All Fields] AND "psoriatic"[All Fields]) OR "psoriatic arthritis"[All Fields] OR ("psoriatic"[All Fields] AND "arthritis"[All Fields]))) OR health technology appraisal[tiab]
Date of Search	10/16/10
Total Yield	14
Total marked for retrieval	0
Notes	Loveman 09 relevant but economic analysis with 4 RCTs (duplicates)
Notes	

1: Signorovitch JE, Wu EQ, Yu AP, Gerrits CM, Kantor E, Bao Y, Gupta SR, Mulani PM. Comparative effectiveness without head-to-head trials: a method for matching-adjusted indirect comparisons applied to psoriasis treatment with adalimumab or etanercept. Pharmacoeconomics. 2010 Oct 1;28(10):935-45. doi: 10.2165/11538370-000000000-00000. PubMed PMID: 20831302.

2: Syrett K. Health technology appraisal and the courts: accountability for reasonableness and the judicial model of procedural justice. Health Econ Policy Law. 2010 Aug 12:1-20. [Epub ahead of print] PubMed PMID: 20701830.

3: Green C. Considering the value associated with innovation in health technology appraisal decisions (deliberations): a NICE thing to do? Appl Health Econ Health Policy. 2010;8(1):1-5. doi: 10.2165/11532950-000000000-00000. PubMed PMID: 20038189.

4: Loveman E, Turner D, Hartwell D, Cooper K, Clegg A. Infliximab for the treatment of adults with psoriasis. Health Technol Assess. 2009 Jun;13 Suppl 1:55-60. PubMed PMID: 19567215.

5: Green C, Gerard K. Exploring the social value of health-care interventions: a stated preference discrete choice experiment. Health Econ. 2009 Aug;18(8):951-76. PubMed PMID: 19034951.

6: Jönsson B, Kobelt G, Smolen J. The burden of rheumatoid arthritis and access to treatment: uptake of new therapies. Eur J Health Econ. 2008 Jan;8 Suppl 2:S61-86. PubMed PMID: 18097697.

7: Warren V. Health technology appraisal of interventional procedures: comparison of rapid and slow methods. J Health Serv Res Policy. 2007 Jul;12(3):142-6. PubMed PMID: 17716416.

8: Burchell M, Ruiz F, Barnett D. NICE Health Technology Appraisal Programme. Ann R Coll Surg Engl. 2005 Jul;87(4):283-4. PubMed PMID: 16884603; PubMed Central PMCID: PMC1963961.

9: Dundar Y, Dodd S, Dickson R, Walley T, Haycox A, Williamson PR. Comparison of conference abstracts and presentations with full-text articles in the health technology assessments of rapidly evolving technologies. Health Technol Assess. 2006 Feb;10(5):iii-iv, ix-145. Review. PubMed PMID: 16487455.

10: Kearney P, Stokoe G, Breithardt G, Longson C, Marco J, Morgan J, Priori S, Ruether A, Taylor R, Hertog M. Improving patient access to novel medical technologies in Europe. Eur Heart J. 2006 Apr;27(7):882-5. Epub 2006 Feb 13. PubMed PMID: 16476691.

11: Meads C, Nouwen A. Does emotional disclosure have any effects? A systematic review of the literature with meta-analyses. Int J Technol Assess Health Care. 2005 Spring;21(2):153-64. Review. PubMed PMID: 15921054.

12: Sørensen J, Andersen LS. The case of tumour necrosis factor-alpha inhibitors in the treatment of rheumatoid arthritis: a budget impact analysis. Pharmacoeconomics. 2005;23(3):289-98. PubMed PMID: 15836009.

13: Calvert MJ, Freemantle N. Use of health-related quality of life in prescribing research. Part 1: why evaluate health-related quality of life? J Clin Pharm Ther. 2003 Dec;28(6):513-21. PubMed PMID: 14651676.

14: Davies E, Littlejohns P. Views of Directors of Public Health about NICE Appraisal Guidance: results of a postal survey. National Institute for Clinical Excellence. J Public Health Med. 2002 Dec;24(4):319-25. PubMed PMID: 12546211.

SEARCH 12_all agents 2009 to aug 15 trials

Category	Description
Clinical question or focus	BIOLOGICAL AGENTS FINAL
Source	PubMed
Terms	**(adalimumab OR certolizumab OR etanercept OR golimumab OR infliximab**

	OR ustekinumab) AND (Rheumatoid arthritis OR psoriasis OR psoriatic arthritis)
Limits	Clinical trial
▪ Date limits	2009 through 8/15/2010
▪ Other limits	
Query Translation (eg, "Details" in PubMed)	(("adalimumab"[Substance Name] OR "adalimumab"[All Fields]) OR ("CDP870"[Substance Name] OR "CDP870"[All Fields] OR "certolizumab"[All Fields]) OR ("TNFR-Fc fusion protein"[Substance Name] OR "TNFR-Fc fusion protein"[All Fields] OR "etanercept"[All Fields]) OR ("golimumab"[Substance Name] OR "golimumab"[All Fields]) OR ("infliximab"[Substance Name] OR "infliximab"[All Fields]) OR ("monoclonal antibody CNTO 1275"[Substance Name] OR "monoclonal antibody CNTO 1275"[All Fields] OR "ustekinumab"[All Fields])) AND (("arthritis, rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "rheumatoid"[All Fields]) OR "rheumatoid arthritis"[All Fields] OR ("rheumatoid"[All Fields] AND "arthritis"[All Fields])) OR ("psoriasis"[MeSH Terms] OR "psoriasis"[All Fields]) OR ("arthritis, psoriatic"[MeSH Terms] OR ("arthritis"[All Fields] AND "psoriatic"[All Fields]) OR "psoriatic arthritis"[All Fields] OR ("psoriatic"[All Fields] AND "arthritis"[All Fields]))) AND (Clinical Trial[ptyp] AND ("2009/01/01"[PDAT] : "2010/08/15"[PDAT])
Date of Search	8/18/10
Total Yield	153
Total marked for retrieval	Leonardi 10, Mease 10, Menter 10, Emery 10, Kavanaugh 10, Sterry 10, Keystone 08
Exclusions	• Not focus of review: population, intervention, comparison, outcome • Superseded by more recent larger study • Lacking safety data • Wrong study type • Duplicates

1: Leonardi C, Strober B, Gottlieb AB, Elewski BE, Ortonne JP, van de Kerkhof P, Chiou CF, Dunn M, Jahreis A. Long-term safety and efficacy of etanercept in patients with psoriasis: an open-label study. J Drugs Dermatol. 2010 Aug;9(8):928-37. PubMed PMID: 20684143.

2: Brodmerkel C, Zhu Y, Jiao Q, Cornacoff J, Treacy G, Mascelli MA, Gottlieb AB. Effects of ustekinumab administration on primate/human antigen-recall and humoral immune response functions. J Drugs Dermatol. 2010 Jun;9(6):677-83. PubMed PMID: 20645530.

3: Sultanova TZh. [Evaluation of remicade efficiency for the treatment of rheumatoid arthritis]. Lik Sprava. 2010 Jan-Mar;(1-2):78-82. Russian. PubMed PMID: 20608030.

4: Coates LC, Helliwell PS. Validation of minimal disease activity criteria for psoriatic arthritis using interventional trial data. Arthritis Care Res (Hoboken). 2010 Jul;62(7):965-9. PubMed PMID: 20589696.

5: Scheinberg M, Guedes-Barbosa LS, Mangueira C, Rosseto EA, Mota L, Oliveira AC, Lima RA. Yellow fever revaccination during infliximab therapy. Arthritis Care Res (Hoboken). 2010 Jun;62(6):896-8. PubMed PMID: 20535801.

6: Schoels M, Aletaha D, Funovits J, Kavanaugh A, Baker D, Smolen JS. Application of the DAREA/DAPSA score for assessment of disease activity in psoriatic arthritis. Ann Rheum Dis. 2010 Aug;69(8):1441-7. Epub 2010 Jun 4. PubMed PMID: 20525844.

7: Visser K, Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Ronday HK, Seys PE, Kerstens PJ, Huizinga TW, Dijkmans BA, Allaart CF. A matrix risk model for the

prediction of rapid radiographic progression in patients with rheumatoid arthritis receiving different dynamic treatment strategies: post hoc analyses from the BeSt study. Ann Rheum Dis. 2010 Jul;69(7):1333-7. Epub 2010 May 24. PubMed PMID: 20498212.

8: Bissonnette R, Bolduc C, Poulin Y, Guenther L, Lynde CW, Maari C. Efficacy and safety of adalimumab in patients with plaque psoriasis who have shown an unsatisfactory response to etanercept. J Am Acad Dermatol. 2010 Aug;63(2):228-34. Epub 2010 May 21. PubMed PMID: 20494479.

9: Ingegnoli F, Fantini F, Griffini S, Soldi A, Meroni PL, Cugno M. Anti-tumor necrosis factor alpha therapy normalizes fibrinolysis impairment in patients with active rheumatoid arthritis. Clin Exp Rheumatol. 2010 Mar-Apr;28(2):254-7. Epub 2010 May 13. PubMed PMID: 20483049.

10: Aerts NE, Ebo DG, Bridts CH, Stevens WJ, De Clerck LS. T cell signal transducer and activator of transcription (STAT) 4 and 6 are affected by adalimumab therapy in rheumatoid arthritis. Clin Exp Rheumatol. 2010 Mar-Apr;28(2):208-14. Epub 2010 May 13. PubMed PMID: 20483042.

11: Klarenbeek NB, van der Kooij SM, Huizinga TJ, Goekoop-Ruiterman YP, Hulsmans HM, van Krugten MV, Speyer I, de Vries-Bouwstra JK, Kerstens PJ, Huizinga TW, Dijkmans BA, Allaart CF. Blood pressure changes in patients with recent-onset rheumatoid arthritis treated with four different treatment strategies: a post hoc analysis from the BeSt trial. Ann Rheum Dis. 2010 Jul;69(7):1342-5. Epub 2010 May 14. PubMed PMID: 20472597.

12: Vassilopoulos D, Apostolopoulou A, Hadziyannis E, Papatheodoridis GV, Manolakopoulos S, Koskinas J, Manesis EK, Archimandritis AI. Long-term safety of anti-TNF treatment in patients with rheumatic diseases and chronic or resolved hepatitis B virus infection. Ann Rheum Dis. 2010 Jul;69(7):1352-5. Epub 2010 May 14. PubMed PMID: 20472596.

13: Lisbona MP, Maymó J, Perich J, Almirall M, Carbonell J. Rapid reduction in tenosynovitis of the wrist and fingers evaluated by MRI in patients with rheumatoid arthritis after treatment with etanercept. Ann Rheum Dis. 2010 Jun;69(6):1117-22. Epub 2010 May 6. PubMed PMID: 20448287.

14: Potter C, Cordell HJ, Barton A, Daly AK, Hyrich KL, Mann DA, Morgan AW, Wilson AG; and the Biologics in Rheumatoid Arthritis Genetics and Genomics Study Syndicate (BRAGGSS), Isaacs JD. Association between anti-tumour necrosis factor treatment response and genetic variants within the TLR and NF{kappa}B signalling pathways. Ann Rheum Dis. 2010 Jul;69(7):1315-20. Epub 2010 May 6. PubMed PMID: 20448286.

15: Tan RJ, Gibbons LJ, Potter C, Hyrich KL, Morgan AW, Wilson AG, Isaacs JD; BRAGGSS, Barton A. Investigation of rheumatoid arthritis susceptibility genes identifies association of AFF3 and CD226 variants with response to anti-tumour necrosis factor treatment. Ann Rheum Dis. 2010 Jun;69(6):1029-35. Epub 2010 May 5. PubMed PMID: 20444755.

16: Keystone E, Genovese MC, Klareskog L, Hsia EC, Hall S, Miranda PC, Pazdur J, Bae SC, Palmer W, Xu S, Rahman MU. Golimumab in patients with active rheumatoid arthritis despite methotrexate therapy: 52-week results of the GO-FORWARD study. Ann Rheum Dis. 2010 Jun;69(6):1129-35. Epub 2010 May 5. PubMed PMID: 20444749.

17: Mease PJ, Woolley JM, Singh A, Tsuji W, Dunn M, Chiou CF. Patient-reported outcomes in a randomized trial of etanercept in psoriatic arthritis. J Rheumatol. 2010 Jun;37(6):1221-7. Epub 2010 Apr 15. PubMed PMID: 20395648.

18: Saad AA, Ashcroft DM, Watson KD, Symmons DP, Noyce PR, Hyrich KL; British Society for Rheumatology Biologics Register. Improvements in quality of life and

functional status in patients with psoriatic arthritis receiving anti-tumor necrosis factor therapies. Arthritis Care Res (Hoboken). 2010 Mar;62(3):345-53. PubMed PMID: 20391480; PubMed Central PMCID: PMC2909400.

19: Tanaka Y, Takeuchi T, Mimori T, Saito K, Nawata M, Kameda H, Nojima T, Miyasaka N, Koike T; RRR study investigators. Discontinuation of infliximab after attaining low disease activity in patients with rheumatoid arthritis: RRR (remission induction by Remicade in RA) study. Ann Rheum Dis. 2010 Jul;69(7):1286-91. Epub 2010 Apr 1. PubMed PMID: 20360136.

20: Scott BL, Ramakrishnan A, Fosdal M, Storer B, Becker P, Petersdorf S, Deeg HJ. Anti-thymocyte globulin plus etanercept as therapy for myelodysplastic syndromes (MDS): a phase II study. Br J Haematol. 2010 Jun;149(5):706-10. Epub 2010 Mar 16. PubMed PMID: 20331464.

21: Cui J, Saevarsdottir S, Thomson B, Padyukov L, van der Helm-van Mil AH, Nititham J, Hughes LB, de Vries N, Raychaudhuri S, Alfredsson L, Askling J, Wedrén S, Ding B, Guiducci C, Wolbink GJ, Crusius JB, van der Horst-Bruinsma IE, Herenius M, Weinblatt ME, Shadick NA, Worthington J, Batliwalla F, Kern M, Morgan AW, Wilson AG, Isaacs JD, Hyrich K, Seldin MF, Moreland LW, Behrens TW, Allaart CF, Criswell LA, Huizinga TW, Tak PP, Bridges SL Jr, Toes RE, Barton A, Klareskog L, Gregersen PK, Karlson EW, Plenge RM. Rheumatoid arthritis risk allele PTPRC is also associated with response to anti-tumor necrosis factor alpha therapy. Arthritis Rheum. 2010 Jul;62(7):1849-61. PubMed PMID: 20309874.

22: Ruperto N, Lovell DJ, Cuttica R, Woo P, Meiorin S, Wouters C, Silverman ED, Balogh Z, Henrickson M, Davidson J, Foeldvari I, Imundo L, Simonini G, Oppermann J, Xu S, Shen YK, Visvanathan S, Fasanmade A, Mendelsohn A, Martini A, Giannini EH; Paediatric Rheumatology INternational Trials Organization (PRINTO); Pediatric Rheumatology Collaborative Study Group (PRCSG). Long-term efficacy and safety of infliximab plus methotrexate for the treatment of polyarticular-course juvenile rheumatoid arthritis: findings from an open-label treatment extension. Ann Rheum Dis. 2010 Apr;69(4):718-22. PubMed PMID: 20237125.

23: Menter A, Augustin M, Signorovitch J, Yu AP, Wu EQ, Gupta SR, Bao Y, Mulani P. The effect of adalimumab on reducing depression symptoms in patients with moderate to severe psoriasis: a randomized clinical trial. J Am Acad Dermatol. 2010 May;62(5):812-8. Epub 2010 Mar 9. PubMed PMID: 20219265.

24: Wakabayashi H, Sudo A, Hasegawa M, Oka H, Uchida A, Nishioka K. Retrospective clinical study of the efficacy of lower-dose methotrexate and infliximab therapy in patients with rheumatoid arthritis. Clin Rheumatol. 2010 Jun;29(6):671-5. Epub 2010 Mar 4. PubMed PMID: 20204668.

25: Ancuţa C, Ancuţa E, Miu S, Iordache C, Belibou C, Chirieac R. Adalimumab therapy in patients with active rheumatoid arthritis. Rev Med Chir Soc Med Nat Iasi. 2009 Jul-Sep;113(3):710-5. PubMed PMID: 20191820.

26: Englbrecht M, Wang Y, Ronneberger M, Manger B, Vastesaeger N, Veale DJ, Schett G. Measuring joint involvement in polyarticular psoriatic arthritis: an introduction of alternatives. Arthritis Care Res (Hoboken). 2010 Jul;62(7):977-83. PubMed PMID: 20191568.

27: van Vollenhoven RF, Cifaldi MA, Ray S, Chen N, Weisman MH. Improvement in work place and household productivity for patients with early rheumatoid arthritis treated with adalimumab plus methotrexate: work outcomes and their correlations with clinical and radiographic measures from a randomized controlled trial companion study. Arthritis Care Res (Hoboken). 2010 Feb;62(2):226-34. PubMed PMID: 20191522.

28: Emery P, Breedveld F, van der Heijde D, Ferraccioli G, Dougados M, Robertson D, Pedersen R, Koenig AS, Freundlich B; Combination of Methotrexate and

Etanercept in Early Rheumatoid Arthritis Trial Group. Two-year clinical and radiographic results with combination etanercept-methotrexate therapy versus monotherapy in early rheumatoid arthritis: a two-year, double-blind, randomized study. Arthritis Rheum. 2010 Mar;62(3):674-82. PubMed PMID: 20187135.

29: Landells I, Paller AS, Pariser D, Kricorian G, Foehl J, Molta C, Freundlich B. Efficacy and safety of etanercept in children and adolescents aged > or = 8 years with severe plaque psoriasis. Eur J Dermatol. 2010 May-Jun;20(3):323-8. Epub 2010 Feb 25. PubMed PMID: 20185386.

30: Frühauf J, Schwantzer G, Ambros-Rudolph CM, Weger W, Ahlgrimm-Siess V, Salmhofer W, Hofmann-Wellenhof R. Pilot study using teledermatology to manage high-need patients with psoriasis. Arch Dermatol. 2010 Feb;146(2):200-1. PubMed PMID: 20157037.

31: Kavanaugh A, Lee SJ, Weng HH, Chon Y, Huang XY, Lin SL. Patient-derived joint counts are a potential alternative for determining Disease Activity Score. J Rheumatol. 2010 May;37(5):1035-41. Epub 2010 Feb 15. PubMed PMID: 20156946.

32: Kremer J, Ritchlin C, Mendelsohn A, Baker D, Kim L, Xu Z, Han J, Taylor P. Golimumab, a new human anti-tumor necrosis factor alpha antibody, administered intravenously in patients with active rheumatoid arthritis: Forty-eight-week efficacy and safety results of a phase III randomized, double-blind, placebo-controlled study. Arthritis Rheum. 2010 Apr;62(4):917-28. PubMed PMID: 20131276.

33: Sterry W, Ortonne JP, Kirkham B, Brocq O, Robertson D, Pedersen RD, Estojak J, Molta CT, Freundlich B. Comparison of two etanercept regimens for treatment of psoriasis and psoriatic arthritis: PRESTA randomised double blind multicentre trial. BMJ. 2010 Feb 2;340:c147. doi: 10.1136/bmj.c147. PubMed PMID: 20124563.

34: Mavragani CP, La DT, Stohl W, Crow MK. Association of the response to tumor necrosis factor antagonists with plasma type I interferon activity and interferon-beta/alpha ratios in rheumatoid arthritis patients: a post hoc analysis of a predominantly Hispanic cohort. Arthritis Rheum. 2010 Feb;62(2):392-401. PubMed PMID: 20112385; PubMed Central PMCID: PMC2821991.

35: Otten MH, Prince FH, Twilt M, van Rossum MA, Armbrust W, Hoppenreijs EP, Kamphuis S, Koopman-Keemink Y, Wulffraat NM, Gorter SL, Ten Cate R, van Suijlekom-Smit LW. Delayed clinical response in patients with juvenile idiopathic arthritis treated with etanercept. J Rheumatol. 2010 Mar;37(3):665-7. Epub 2010 Jan 15. PubMed PMID: 20080910.

36: Caldarola G, De Simone C, Carbone A, Tulli A, Amerio P, Feliciani C. TNFalpha and its receptors in psoriatic skin, before and after treatment with etanercept. Int J Immunopathol Pharmacol. 2009 Oct-Dec;22(4):961-6. PubMed PMID: 20074459.

37: Griffiths CE, Strober BE, van de Kerkhof P, Ho V, Fidelus-Gort R, Yeilding N, Guzzo C, Xia Y, Zhou B, Li S, Dooley LT, Goldstein NH, Menter A; ACCEPT Study Group. Comparison of ustekinumab and etanercept for moderate-to-severe psoriasis. N Engl J Med. 2010 Jan 14;362(2):118-28. PubMed PMID: 20071701.

38: Atteno M, Peluso R, Costa L, Padula S, Iervolino S, Caso F, Sanduzzi A, Lubrano E, Del Puente A, Scarpa R. Comparison of effectiveness and safety of infliximab, etanercept, and adalimumab in psoriatic arthritis patients who experienced an inadequate response to previous disease-modifying antirheumatic drugs. Clin Rheumatol. 2010 Apr;29(4):399-403. PubMed PMID: 20066450.

39: Mazzotta A, Esposito M, Schipani C, Chimenti S. Long-term experience with etanercept in psoriatic arthritis patients: a 3-year observational study. J Dermatolog Treat. 2009;20(6):354-8. PubMed PMID: 19954392.

40: Zhang W, Shi Q, Wu DH, Bao CD, Yang NP, Li ZG, Zhu P, Zhang X, Huang CB, He DY, Ye ZZ, Tao Y, Fang YF, Gu JR, Wu HX, Sun LY, Yang XY, Huang F, Xu HJ, Zhao DB, Zhang MJ, Zheng Y, Ai MX, Lu J, Zhang FC. [Efficacy and safety of infliximab in patients with rheumatoid arthritis]. Zhonghua Yi Xue Za Zhi. 2009 Jul 21;89(27):1876-80. Chinese. PubMed PMID: 19953907.

41: Ringold S, Chon Y, Singer NG. Associations between the American College of Rheumatology pediatric response measures and the continuous measures of disease activity used in adult rheumatoid arthritis: a secondary analysis of clinical trial data from children with polyarticular-course juvenile idiopathic arthritis. Arthritis Rheum. 2009 Dec;60(12):3776-83. PubMed PMID: 19950286.

42: Ban A, Inaba M, Furumitsu Y, Okamoto K, Yukioka K, Goto H, Nishizawa Y. Time-course of health status in patients with rheumatoid arthritis during the first year of treatment with infliximab. Biomed Pharmacother. 2010 Feb;64(2):107-12. Epub 2009 Nov 5. PubMed PMID: 19944558.

43: Mulleman D, Méric JC, Paintaud G, Ducourau E, Magdelaine-Beuzelin C, Valat JP, Goupille P; Centre National de la Recherche Scientifique UMR 6239 GICC. Infliximab concentration monitoring improves the control of disease activity in rheumatoid arthritis. Arthritis Res Ther. 2009;11(6):R178. Epub 2009 Nov 25. PubMed PMID: 19939280.

44: Kamishima T, Sagawa A, Tanimura K, Shimizu M, Matsuhashi M, Shinohara M, Hagiwara H, Henmi M, Narita A, Terae S, Shirato H. Semi-quantitative analysis of rheumatoid finger joint synovitis using power Doppler ultrasonography: when to perform follow-up study after treatment consisting mainly of antitumor necrosis factor alpha agent. Skeletal Radiol. 2010 May;39(5):457-65. Epub 2009 Nov 20. PubMed PMID: 19936743.

45: Peters MJ, Welsh P, McInnes IB, Wolbink G, Dijkmans BA, Sattar N, Nurmohamed MT. Tumour necrosis factor {alpha} blockade reduces circulating N-terminal pro-brain natriuretic peptide levels in patients with active rheumatoid arthritis: results from a prospective cohort study. Ann Rheum Dis. 2010 Jul;69(7):1281-5. Epub 2009 Nov 23. PubMed PMID: 19934107.

46: Zhou H, Hu C, Zhu Y, Lu M, Liao S, Yeilding N, Davis HM. Population-based exposure-efficacy modeling of ustekinumab in patients with moderate to severe plaque psoriasis. J Clin Pharmacol. 2010 Mar;50(3):257-67. Epub 2009 Nov 23. PubMed PMID: 19934030.

47: Joy MS, Gipson DS, Powell L, MacHardy J, Jennette JC, Vento S, Pan C, Savin V, Eddy A, Fogo AB, Kopp JB, Cattran D, Trachtman H. Phase 1 trial of adalimumab in Focal Segmental Glomerulosclerosis (FSGS): II. Report of the FONT (Novel Therapies for Resistant FSGS) study group. Am J Kidney Dis. 2010 Jan;55(1):50-60. Epub 2009 Nov 22. PubMed PMID: 19932542; PubMed Central PMCID: PMC2804955.

48: Klimiuk PA, Sierakowski S, Domyslawska I, Chwiecko J. Effect of etanercept on serum levels of soluble cell adhesion molecules (sICAM-1, sVCAM-1, and sE-selectin) and vascular endothelial growth factor in patients with rheumatoid arthritis. Scand J Rheumatol. 2009 Nov-Dec;38(6):439-44. PubMed PMID: 19922018.

49: Strand V, Mease P, Burmester GR, Nikaï E, Coteur G, van Vollenhoven R, Combe B, Keystone EC, Kavanaugh A. Rapid and sustained improvements in health-related quality of life, fatigue, and other patient-reported outcomes in rheumatoid arthritis patients treated with certolizumab pegol plus methotrexate over 1 year: results from the RAPID 1 randomized controlled trial. Arthritis Res Ther. 2009;11(6):R170. Epub 2009 Nov 12. PubMed PMID: 19909548.

50: Lebwohl M, Papp K, Han C, Schenkel B, Yeilding N, Wang Y, Krueger GG. Ustekinumab improves health-related quality of life in patients with moderate-to-severe psoriasis: results from the PHOENIX 1 trial. Br J Dermatol.

2010 Jan;162(1):137-46. Epub 2009 Nov 9. PubMed PMID: 19903183.

51: Zaba LC, Suárez-Fariñas M, Fuentes-Duculan J, Nograles KE, Guttman-Yassky E, Cardinale I, Lowes MA, Krueger JG. Effective treatment of psoriasis with etanercept is linked to suppression of IL-17 signaling, not immediate response TNF genes. J Allergy Clin Immunol. 2009 Nov;124(5):1022-10.e1-395. PubMed PMID: 19895991; PubMed Central PMCID: PMC2852188.

52: Kavanaugh A, Smolen JS, Emery P, Purcaru O, Keystone E, Richard L, Strand V, van Vollenhoven RF. Effect of certolizumab pegol with methotrexate on home and work place productivity and social activities in patients with active rheumatoid arthritis. Arthritis Rheum. 2009 Nov 15;61(11):1592-600. PubMed PMID: 19877104.

53: Lukas C, van der Heijde D, Fatenajad S, Landewé R. Repair of erosions occurs almost exclusively in damaged joints without swelling. Ann Rheum Dis. 2010 May;69(5):851-5. Epub 2009 Oct 21. PubMed PMID: 19846407.

54: Salemi S, Picchianti-Diamanti A, Germano V, Donatelli I, Di Martino A, Facchini M, Nisini R, Biselli R, Ferlito C, Podestà E, Cappella A, Milanetti F, Rossi F, Amodeo R, Tabacco F, Di Rosa R, Laganà B, D Amelio R. Influenza vaccine administration in rheumatoid arthritis patients under treatment with TNFalpha blockers: safety and immunogenicity. Clin Immunol. 2010 Feb;134(2):113-20. Epub 2009 Oct 21. PubMed PMID: 19846344.

55: Van den Bosch F, Manger B, Goupille P, McHugh N, Rødevand E, Holck P, van Vollenhoven RF, Leirisalo-Repo M, Fitzgerald O, Kron M, Frank M, Kary S, Kupper H. Effectiveness of adalimumab in treating patients with active psoriatic arthritis and predictors of good clinical responses for arthritis, skin and nail lesions. Ann Rheum Dis. 2010 Feb;69(2):394-9. Epub 2009 Oct 7. PubMed PMID: 19815494; PubMed Central PMCID: PMC2800202.

56: Lukina GV, Sigidin IaA, Nasonov EL. [Clinical experience with infliximab administration in patients with rheumatoid arthritis (according to Russian register data)]. Ter Arkh. 2009;81(8):65-9. Russian. PubMed PMID: 19799204.

57: Lin Q, Gu JR, Li TW, Zhang FC, Lin ZM, Liao ZT, Wei QJ, Cao SY, Li L. Value of the peripheral blood B-cells subsets in patients with ankylosing spondylitis. Chin Med J (Engl). 2009 Aug 5;122(15):1784-9. PubMed PMID: 19781326.

58: Reich K, Segaert S, Van de Kerkhof P, Durian C, Boussuge MP, Paolozzi L, Wajdula J, Boggs R. Once-weekly administration of etanercept 50 mg improves patient-reported outcomes in patients with moderate-to-severe plaque psoriasis. Dermatology. 2009;219(3):239-49. Epub 2009 Sep 10. PubMed PMID: 19752505.

59: Soubrier M, Puéchal X, Sibilia J, Mariette X, Meyer O, Combe B, Flipo RM, Mulleman D, Berenbaum F, Zarnitsky C, Schaeverbeke T, Fardellone P, Dougados M. Evaluation of two strategies (initial methotrexate monotherapy vs its combination with adalimumab) in management of early active rheumatoid arthritis: data from the GUEPARD trial. Rheumatology (Oxford). 2009 Nov;48(11):1429-34. Epub 2009 Sep 9. PubMed PMID: 19741011.

60: van Lingen RG, van Erp PE, Seyger MM, de Jong EM, de Boer-van Huizen RT, Driessen RJ, van de Kerkhof PC. Persistent expression of CD26/DPPIV after treatment with infliximab in psoriasis despite clinical improvement. Acta Derm Venereol. 2009;89(5):518-20. PubMed PMID: 19734982.

61: Galarraga B, Khan F, Kumar P, Pullar T, Belch JJ. Etanercept improves inflammation-associated arterial stiffness in rheumatoid arthritis. Rheumatology (Oxford). 2009 Nov;48(11):1418-23. Epub 2009 Sep 4. PubMed PMID: 19734293.

62: Giannini EH, Ilowite NT, Lovell DJ, Wallace CA, Rabinovich CE, Reiff A, Higgins G, Gottlieb B, Singer NG, Chon Y, Lin SL, Baumgartner SW; Pediatric

Rheumatology Collaborative Study Group. Long-term safety and effectiveness of etanercept in children with selected categories of juvenile idiopathic arthritis. Arthritis Rheum. 2009 Sep;60(9):2794-804. PubMed PMID: 19714630.

63: Anis A, Zhang W, Emery P, Sun H, Singh A, Freundlich B, Sato R. The effect of etanercept on work productivity in patients with early active rheumatoid arthritis: results from the COMET study. Rheumatology (Oxford). 2009 Oct;48(10):1283-9. Epub 2009 Aug 18. PubMed PMID: 19690125.

64: Masi L, Ricci L, Zulian F, Del Monte F, Simonini G, Capannini S, De Martino M, Brandi ML, Falcini F. Serum osteopontin as a predictive marker of responsiveness to methotrexate in juvenile idiopathic arthritis. J Rheumatol. 2009 Oct;36(10):2308-13. Epub 2009 Aug 14. PubMed PMID: 19684155.

65: D'Angelo S, Cutro MS, Lubrano E, Leccese P, Mennillo GA, Ferrara N, Olivieri I. Combination therapy with ciclosporin and etanercept in patients with psoriatic arthritis. Ann Rheum Dis. 2010 May;69(5):934-5. Epub 2009 Aug 9. PubMed PMID: 19666936.

66: van Vollenhoven RF, Ernestam S, Geborek P, Petersson IF, Cöster L, Waltbrand E, Zickert A, Theander J, Thörner A, Hellström H, Teleman A, Dackhammar C, Akre F, Forslind K, Ljung L, Oding R, Chatzidionysiou A, Wörnert M, Bratt J. Addition of infliximab compared with addition of sulfasalazine and hydroxychloroquine to methotrexate in patients with early rheumatoid arthritis (Swefot trial): 1-year results of a randomised trial. Lancet. 2009 Aug 8;374(9688):459-66. PubMed PMID: 19665644.

67: Laffitte E, Janssens JP, Roux-Lombard P, Thielen AM, Barde C, Marazza G, Panizzon RG, Saurat JH. Tuberculosis screening in patients with psoriasis before antitumour necrosis factor therapy: comparison of an interferon-gamma release assay vs. tuberculin skin test. Br J Dermatol. 2009 Oct;161(4):797-800. Epub 2009 Jun 5. PubMed PMID: 19659473.

68: Mazzotta A, Esposito M, Costanzo A, Chimenti S. Efficacy and safety of etanercept in psoriasis after switching from other treatments: an observational study. Am J Clin Dermatol. 2009;10(5):319-24. doi: 10.2165/11310770-000000000-00000. PubMed PMID: 19658444.

69: Emery P, Fleischmann RM, Moreland LW, Hsia EC, Strusberg I, Durez P, Nash P, Amante EJ, Churchill M, Park W, Pons-Estel BA, Doyle MK, Visvanathan S, Xu W, Rahman MU. Golimumab, a human anti-tumor necrosis factor alpha monoclonal antibody, injected subcutaneously every four weeks in methotrexate-naive patients with active rheumatoid arthritis: twenty-four-week results of a phase III, multicenter, randomized, double-blind, placebo-controlled study of golimumab before methotrexate as first-line therapy for early-onset rheumatoid arthritis. Arthritis Rheum. 2009 Aug;60(8):2272-83. PubMed PMID: 19644849.

70: Scrivo R, Conti F, Spinelli FR, Truglia S, Magrini L, Di Franco M, Ceccarelli F, Valesini G. Switching between TNFalpha antagonists in rheumatoid arthritis: personal experience and review of the literature. Reumatismo. 2009 Apr-Jun;61(2):107-17. Review. PubMed PMID: 19633797.

71: Takeuchi T, Miyasaka N, Inoue K, Abe T, Koike T; RISING study. Impact of trough serum level on radiographic and clinical response to infliximab plus methotrexate in patients with rheumatoid arthritis: results from the RISING study. Mod Rheumatol. 2009;19(5):478-87. Epub 2009 Jul 22. PubMed PMID: 19626391; PubMed Central PMCID: PMC2759008.

72: Sany J, Cohen JD, Combescure C, Bozonnat MC, Roch-Bras F, Lafon G, Daurès JP. Medico-economic evaluation of infliximab in rheumatoid arthritis--prospective French study of a cohort of 635 patients monitored for two years. Rheumatology (Oxford). 2009 Oct;48(10):1236-41. Epub 2009 Jul 20. PubMed PMID: 19620209.

73: Xu Z, Vu T, Lee H, Hu C, Ling J, Yan H, Baker D, Beutler A, Pendley C, Wagner C, Davis HM, Zhou H. Population pharmacokinetics of golimumab, an anti-tumor necrosis factor-alpha human monoclonal antibody, in patients with psoriatic arthritis. J Clin Pharmacol. 2009 Sep;49(9):1056-70. Epub 2009 Jul 17. PubMed PMID: 19617465.

74: van den Bemt BJ, Vos K, den Broeder AA, Blom M, Thurlings RM, Bartelds GM, Stapel SO, Barrera P, Tak PP, Nurmohamed MT, Wolbink GJ. A single course of rituximab does not abrogate anti-infliximab antibodies in patients with rheumatoid arthritis. Ann Rheum Dis. 2009 Aug;68(8):1368-9. PubMed PMID: 19605744.

75: Conti F, Scrivo R, Spinelli FR, Truglia S, Magrini L, Di Franco M, Ceccarelli F, Valesini G. Outcome in patients with rheumatoid arthritis switching TNF-alpha antagonists: a single center, observational study over an 8-year period. Clin Exp Rheumatol. 2009 May-Jun;27(3):540-1. PubMed PMID: 19604456.

76: Jin T, Bokarewa M, Amu S, Tarkowski A. Impact of short-term therapies with biologics on prothrombotic biomarkers in rheumatoid arthritis. Clin Exp Rheumatol. 2009 May-Jun;27(3):491-4. PubMed PMID: 19604443.

77: Gonzalez-Gay MA, Garcia-Unzueta MT, Berja A, Vazquez-Rodriguez TR, Miranda-Filloy JA, Gonzalez-Juanatey C, de Matias JM, Martin J, Dessein PH, Llorca J. Short-term effect of anti-TNF-alpha therapy on nitric oxide production in patients with severe rheumatoid arthritis. Clin Exp Rheumatol. 2009 May-Jun;27(3):452-8. PubMed PMID: 19604438.

78: Vastesaeger N, Xu S, Aletaha D, St Clair EW, Smolen JS. A pilot risk model for the prediction of rapid radiographic progression in rheumatoid arthritis. Rheumatology (Oxford). 2009 Sep;48(9):1114-21. Epub 2009 Jul 9. Review. PubMed PMID: 19589891.

79: Prince FH, Geerdink LM, Borsboom GJ, Twilt M, van Rossum MA, Hoppenreijs EP, Cate RT, Koopman-Keemink Y, van Santen-Hoeufft M, Raat H, van Suijlekom-Smit LW. Major improvements in health-related quality of life during the use of etanercept in patients with previously refractory juvenile idiopathic arthritis. Ann Rheum Dis. 2010 Jan;69(1):138-42. Epub . PubMed PMID: 19581280.

80: Bartelds GM, Wijbrandts CA, Nurmohamed MT, Stapel S, Lems WF, Aarden L, Dijkmans BA, Tak PP, Wolbink GJ. Anti-infliximab and anti-adalimumab antibodies in relation to response to adalimumab in infliximab switchers and anti-tumour necrosis factor naive patients: a cohort study. Ann Rheum Dis. 2010 May;69(5):817-21. Epub 2009 Jul 5. PubMed PMID: 19581278.

81: Martyn-Simmons CL, Green L, Ash G, Groves RW, Smith CH, Barker JN. Adalimumab for psoriasis patients who are non-responders to etanercept: open-label prospective evaluation. J Eur Acad Dermatol Venereol. 2009 Dec;23(12):1394-7. Epub 2009 Jul 1. PubMed PMID: 19573024.

82: Ortonne JP, Taïeb A, Ormerod AD, Robertson D, Foehl J, Pedersen R, Molta C, Freundlich B. Patients with moderate-to-severe psoriasis recapture clinical response during re-treatment with etanercept. Br J Dermatol. 2009 Nov;161(5):1190-5. Epub 2009 May 21. PubMed PMID: 19566665.

83: Kremer JM, Bloom BJ, Breedveld FC, Coombs JH, Fletcher MP, Gruben D, Krishnaswami S, Burgos-Vargas R, Wilkinson B, Zerbini CA, Zwillich SH. The safety and efficacy of a JAK inhibitor in patients with active rheumatoid arthritis: Results of a double-blind, placebo-controlled phase IIa trial of three dosage levels of CP-690,550 versus placebo. Arthritis Rheum. 2009 Jul;60(7):1895-905. PubMed PMID: 19565475.

84: Derdemezis CS, Filippatos TD, Voulgari PV, Tselepis AD, Drosos AA, Kiortsis DN. Effects of a 6-month infliximab treatment on plasma levels of leptin and adiponectin in patients with rheumatoid arthritis. Fundam Clin Pharmacol. 2009 Oct;23(5):595-600. Epub 2009 Jun 25. PubMed PMID: 19563510.

85: Daudén E, Griffiths CE, Ortonne JP, Kragballe K, Molta CT, Robertson D, Pedersen R, Estojak J, Boggs R. Improvements in patient-reported outcomes in moderate-to-severe psoriasis patients receiving continuous or paused etanercept treatment over 54 weeks: the CRYSTEL study. J Eur Acad Dermatol Venereol. 2009 Dec;23(12):1374-82. Epub 2009 Jun 26. PubMed PMID: 19563497.

86: Smolen JS, Kay J, Doyle MK, Landewé R, Matteson EL, Wollenhaupt J, Gaylis N, Murphy FT, Neal JS, Zhou Y, Visvanathan S, Hsia EC, Rahman MU; GO-AFTER study investigators. Golimumab in patients with active rheumatoid arthritis after treatment with tumour necrosis factor alpha inhibitors (GO-AFTER study): a multicentre, randomised, double-blind, placebo-controlled, phase III trial. Lancet. 2009 Jul 18;374(9685):210-21. Epub 2009 Jun 26. Erratum in: Lancet. 2009 Oct 24;374(9699):1422. PubMed PMID: 19560810.

87: Sakai Y, Sakai S, Otsuka T, Ohno D, Murasawa T, Munakata K, Mizuno K. Efficacy of high-throughput leukocytapheresis for rheumatoid arthritis with a reduced response to infliximab. Ther Apher Dial. 2009 Jun;13(3):179-85. PubMed PMID: 19527463.

88: Giannitti C, Benucci M, Caporali R, Manganelli S, Bellisai F, Sebastiani GD, Galeazzi M. Efficacy and safety of anti-TNF-alpha therapy combined with cyclosporine A in patients with rheumatoid arthritis and concomitant hepatitis C virus infection. Int J Immunopathol Pharmacol. 2009 Apr-Jun;22(2):543-6. PubMed PMID: 19505408.

89: Laganà B, Picchianti Diamanti A, Ferlito C, Germano V, Migliore A, Cremona A, Argento G, David V, Salemi S, D'Amelio R. Imaging progression despite clinical remission in early rheumatoid arthritis patients after etanercept interruption. Int J Immunopathol Pharmacol. 2009 Apr-Jun;22(2):447-54. PubMed PMID: 19505397.

90: Campanati A, Goteri G, Simonetti O, Ganzetti G, Giuliodori K, Giuliano A, Sabato S, Stramazzotti D, Gulini E, Dusi D, De Blasio S, Fabris G, Offidani A. Angiogenesis in psoriatic skin and its modifications after administration of etanercept: videocapillaroscopic, histological and immunohistochemical evaluation. Int J Immunopathol Pharmacol. 2009 Apr-Jun;22(2):371-7. PubMed PMID: 19505391.

91: Prignano F, Ricceri F, Bianchi B, Lotti T. Quantity, distribution and immunophenotypical modification of dendritic cells upon biological treatments in psoriasis. Int J Immunopathol Pharmacol. 2009 Apr-Jun;22(2):379-87. PubMed PMID: 19505376.

92: Souto-Carneiro MM, Mahadevan V, Takada K, Fritsch-Stork R, Nanki T, Brown M, Fleisher TA, Wilson M, Goldbach-Mansky R, Lipsky PE. Alterations in peripheral blood memory B cells in patients with active rheumatoid arthritis are dependent on the action of tumour necrosis factor. Arthritis Res Ther. 2009;11(3):R84. Epub 2009 Jun 5. PubMed PMID: 19500335; PubMed Central PMCID: PMC2714135.

93: Visvanathan S, Wagner C, Rojas J, Kay J, Dasgupta B, Matteson EL, Mack M, Baker DG, Rahman MU. E-selectin, interleukin 18, serum amyloid a, and matrix metalloproteinase 9 are associated with clinical response to golimumab plus methotrexate in patients with active rheumatoid arthritis despite methotrexate therapy. J Rheumatol. 2009 Jul;36(7):1371-9. Epub 2009 Jun 1. PubMed PMID: 19487269.

94: Horneff G, Ebert A, Fitter S, Minden K, Foeldvari I, Kümmerle-Deschner J, Thon A, Girschick HJ, Weller F, Huppertz HI. Safety and efficacy of once weekly

etanercept 0.8 mg/kg in a multicentre 12 week trial in active polyarticular course juvenile idiopathic arthritis. Rheumatology (Oxford). 2009 Aug;48(8):916-9. Epub 2009 May 29. PubMed PMID: 19483091.

95: Lin Q, Lin Z, Gu J, Huang F, Li T, Wei Q, Liao Z, Cao S, Jiang Y, Huang J. Abnormal high-expression of CD154 on T lymphocytes of ankylosing spondylitis patients is down-regulated by etanercept treatment. Rheumatol Int. 2010 Jan;30(3):317-23. Epub 2009 May 23. PubMed PMID: 19466423.

96: Kageyama Y, Kobayashi H, Kato N, Shimazu M. Etanercept reduces the serum levels of macrophage chemotactic protein-1 in patients with rheumatoid arthritis. Mod Rheumatol. 2009;19(4):372-8. Epub 2009 May 21. PubMed PMID: 19458908.

97: Luger TA, Barker J, Lambert J, Yang S, Robertson D, Foehl J, Molta CT, Boggs R. Sustained improvement in joint pain and nail symptoms with etanercept therapy in patients with moderate-to-severe psoriasis. J Eur Acad Dermatol Venereol. 2009 Aug;23(8):896-904. Epub 2009 May 3. PubMed PMID: 19453794.

98: Luzi G, Laganà B, Salemi S, Di Rosa R. Are glucocorticoids a consistent risk factor for infections in rheumatoid arthritis patients under treatment with methotrexate and etanercept? Clin Ter. 2009 Mar-Apr;160(2):121-3. PubMed PMID: 19452100.

99: Russo RA, Katsicas MM. Clinical remission in patients with systemic juvenile idiopathic arthritis treated with anti-tumor necrosis factor agents. J Rheumatol. 2009 May;36(5):1078-82. PubMed PMID: 19435972.

100: Aletaha D, Funovits J, Breedveld FC, Sharp J, Segurado O, Smolen JS. Rheumatoid arthritis joint progression in sustained remission is determined by disease activity levels preceding the period of radiographic assessment. Arthritis Rheum. 2009 May;60(5):1242-9. PubMed PMID: 19404938.

101: Haugeberg G, Conaghan PG, Quinn M, Emery P. Bone loss in patients with active early rheumatoid arthritis: infliximab and methotrexate compared with methotrexate treatment alone. Explorative analysis from a 12-month randomised, double-blind, placebo-controlled study. Ann Rheum Dis. 2009 Dec;68(12):1898-901. Epub 2009 Apr 21. PubMed PMID: 19386610.

102: Emery P, Genovese MC, van Vollenhoven R, Sharp JT, Patra K, Sasso EH. Less radiographic progression with adalimumab plus methotrexate versus methotrexate monotherapy across the spectrum of clinical response in early rheumatoid arthritis. J Rheumatol. 2009 Jul;36(7):1429-41. Epub 2009 Apr 15. Erratum in: J Rheumatol. 2010 May;37(5):1081. PubMed PMID: 19369462.

103: Chen DY, Chou SJ, Hsieh TY, Chen YH, Chen HH, Hsieh CW, Lan JL. Randomized, double-blind, placebo-controlled, comparative study of human anti-TNF antibody adalimumab in combination with methotrexate and methotrexate alone in Taiwanese patients with active rheumatoid arthritis. J Formos Med Assoc. 2009 Apr;108(4):310-9. PubMed PMID: 19369178.

104: Pavelka K, Jarosová K, Suchý D, Senolt L, Chroust K, Dusek L, Vencovský J. Increasing the infliximab dose in rheumatoid arthritis patients: a randomised, double blind study failed to confirm its efficacy. Ann Rheum Dis. 2009 Aug;68(8):1285-9. Epub 2009 Apr 6. PubMed PMID: 19351624.

105: Koc E, Tunca M, Akgul EO, Akar A, Kurt Y, Kurumlu Z, Erbil K, Kilic S. Effects of etanercept on urine neopterin levels in patients with psoriasis in a controlled, open-label study. J Dermatol. 2009 Apr;36(4):191-6. PubMed PMID: 19348656.

106: Kavanaugh A, McInnes I, Mease P, Krueger GG, Gladman D, Gomez-Reino J, Papp K, Zrubek J, Mudivarthy S, Mack M, Visvanathan S, Beutler A. Golimumab, a new

human tumor necrosis factor alpha antibody, administered every four weeks as a subcutaneous injection in psoriatic arthritis: Twenty-four-week efficacy and safety results of a randomized, placebo-controlled study. Arthritis Rheum. 2009 Apr;60(4):976-86. Erratum in: Arthritis Rheum.2010 Aug;62(8):2555. PubMed PMID: 19333944.

107: Horikoshi M, Ito S, Ishikawa M, Umeda N, Kondo Y, Tsuboi H, Hayashi T, Goto D, Matsumoto I, Sumida T. Efficacy of mizoribine pulse therapy in patients with rheumatoid arthritis who show a reduced or insufficient response to infliximab. Mod Rheumatol. 2009;19(3):229-34. Epub 2009 Mar 27. PubMed PMID: 19326186; PubMed Central PMCID: PMC2689357.

108: Bingham CO 3rd, Ince A, Haraoui B, Keystone EC, Chon Y, Baumgartner S. Effectiveness and safety of etanercept in subjects with RA who have failed infliximab therapy: 16-week, open-label, observational study. Curr Med Res Opin. 2009 May;25(5):1131-42. PubMed PMID: 19317607.

109: Vena GA, Galluccio A, De Simone C, Mastrandrea V, Buquicchio R, La Greca S, Dattola S, Puglisi Guerra A, Donato L, Cantoresi F, De Pità O, Pezza M, D Agostino M, Vernaci R, Miracapillo A, Valenti G, Cassano N. A multicenter open-label experience on the response of psoriasis to Adalimumab and effect of dose escalation in non-responders: the Aphrodite project. Int J Immunopathol Pharmacol. 2009 Jan-Mar;22(1):227-33. PubMed PMID: 19309570.

110: Kekow J, Moots RJ, Emery P, Durez P, Koenig A, Singh A, Pedersen R, Robertson D, Freundlich B, Sato R. Patient-reported outcomes improve with etanercept plus methotrexate in active early rheumatoid arthritis and the improvement is strongly associated with remission: the COMET trial. Ann Rheum Dis. 2010 Jan;69(1):222-5. Epub . PubMed PMID: 19293160.

111: Flint-Wagner HG, Lisse J, Lohman TG, Going SB, Guido T, Cussler E, Gates D, Yocum DE. Assessment of a sixteen-week training program on strength, pain, and function in rheumatoid arthritis patients. J Clin Rheumatol. 2009 Jun;15(4):165-71. PubMed PMID: 19279507.

112: Dwivedi RC, Dhindsa N, Krokhin OV, Cortens J, Wilkins JA, El-Gabalawy HS. The effects of infliximab therapy on the serum proteome of rheumatoid arthritis patients. Arthritis Res Ther. 2009;11(2):R32. Epub 2009 Mar 6. PubMed PMID: 19265537; PubMed Central PMCID: PMC2688177.

113: van den Hout WB, Goekoop-Ruiterman YP, Allaart CF, de Vries-Bouwstra JK, Hazes JM, Kerstens PJ, van Zeben D, Hulsmans HM, de Jonge-Bok JM, de Sonnaville PB, Dijkmans BA, Breedveld FC. Cost-utility analysis of treatment strategies in patients with recent-onset rheumatoid arthritis. Arthritis Rheum. 2009 Mar 15;61(3):291-9. PubMed PMID: 19248130.

114: Keystone E, Freundlich B, Schiff M, Li J, Hooper M. Patients with moderate rheumatoid arthritis (RA) achieve better disease activity states with etanercept treatment than patients with severe RA. J Rheumatol. 2009 Mar;36(3):522-31. Epub 2009 Feb 17. PubMed PMID: 19228659.

115: Gottlieb A, Menter A, Mendelsohn A, Shen YK, Li S, Guzzo C, Fretzin S, Kunynetz R, Kavanaugh A. Ustekinumab, a human interleukin 12/23 monoclonal antibody, for psoriatic arthritis: randomised, double-blind, placebo-controlled, crossover trial. Lancet. 2009 Feb 21;373(9664):633-40. Epub 2009 Feb 11. Erratum in: Lancet. 2009 Apr 18;373(9672):1340. PubMed PMID: 19217154.

116: Gülfe A, Kristensen LE, Geborek P. Six and 12 weeks treatment response predicts continuation of tumor necrosis factor blockade in rheumatoid arthritis: an observational cohort study from southern Sweden. J Rheumatol. 2009 Mar;36(3):517-21. Epub 2009 Jan 22. PubMed PMID: 19208596.

117: Feijóo M, Túnez I, Tasset I, Montilla P, Pérez-Guijo V, Muñoz-Gomariz E, Ruiz A, Schiotis R, Collantes E. Infliximab reduces myeloperoxidase concentration in chronic inflammatory joint diseases. Pharmacology. 2009;83(4):211-6. Epub 2009 Feb 7. PubMed PMID: 19204412.

118: Anandarajah AP, Ory P, Salonen D, Feng C, Wong RL, Ritchlin CT. Effect of adalimumab on joint disease: features of patients with psoriatic arthritis detected by magnetic resonance imaging. Ann Rheum Dis. 2010 Jan;69(1):206-9. Epub . PubMed PMID: 19204015.

119: Strangfeld A, Hierse F, Kekow J, von Hinueber U, Tony HP, Dockhorn R, Listing J, Zink A. Comparative effectiveness of tumour necrosis factor alpha inhibitors in combination with either methotrexate or leflunomide. Ann Rheum Dis. 2009 Dec;68(12):1856-62. Epub 2009 Jan 6. PubMed PMID: 19126559.

120: Eedy DJ, Griffiths CE, Chalmers RJ, Ormerod AD, Smith CH, Barker JN, Potter J, Ingham J, Lowe D, Burge S. Care of patients with psoriasis: an audit of U.K. services in secondary care. Br J Dermatol. 2009 Mar;160(3):557-64. Epub 2008 Dec 11. PubMed PMID: 19120330.

121: van der Kooij SM, de Vries-Bouwstra JK, Goekoop-Ruiterman YP, Ewals JA, Han KH, Hazes JM, Kerstens PJ, Peeters AJ, van Zeben D, Breedveld FC, Huizinga TW, Dijkmans BA, Allaart CF. Patient-reported outcomes in a randomized trial comparing four different treatment strategies in recent-onset rheumatoid arthritis. Arthritis Rheum. 2009 Jan 15;61(1):4-12. PubMed PMID: 19116965.

122: Nagasawa H, Kameda H, Sekiguchi N, Amano K, Takeuchi T. Improvement of the HAQ score by infliximab treatment in patients with RA: its association with disease activity and joint destruction. Mod Rheumatol. 2009;19(2):166-72. Epub 2008 Dec 13. PubMed PMID: 19083077.

123: Jamal S, Patra K, Keystone EC. Adalimumab response in patients with early versus established rheumatoid arthritis: DE019 randomized controlled trial subanalysis. Clin Rheumatol. 2009 Apr;28(4):413-9. Epub 2008 Dec 9. PubMed PMID: 19067101.

124: Keystone EC, Genovese MC, Klareskog L, Hsia EC, Hall ST, Miranda PC, Pazdur J, Bae SC, Palmer W, Zrubek J, Wiekowski M, Visvanathan S, Wu Z, Rahman MU; GO-FORWARD Study. Golimumab, a human antibody to tumour necrosis factor {alpha} given by monthly subcutaneous injections, in active rheumatoid arthritis despite methotrexate therapy: the GO-FORWARD Study. Ann Rheum Dis. 2009 Jun;68(6):789-96. Epub 2008 Dec 9. PubMed PMID: 19066176; PubMed Central PMCID: PMC2674549.

125: Bazzani C, Filippini M, Caporali R, Bobbio-Pallavicini F, Favalli EG, Marchesoni A, Atzeni F, Sarzi-Puttini P, Gorla R. Anti-TNFalpha therapy in a cohort of rheumatoid arthritis patients: clinical outcomes. Autoimmun Rev. 2009 Jan;8(3):260-5. Epub 2008 Nov 21. PubMed PMID: 19027090.

126: Favalli EG, Desiati F, Atzeni F, Sarzi-Puttini P, Caporali R, Pallavicini FB, Gorla R, Filippini M, Marchesoni A. Serious infections during anti-TNFalpha treatment in rheumatoid arthritis patients. Autoimmun Rev. 2009 Jan;8(3):266-73. Epub 2008 Nov 18. PubMed PMID: 19022409.

127: Radstake TR, Svenson M, Eijsbouts AM, van den Hoogen FH, Enevold C, van Riel PL, Bendtzen K. Formation of antibodies against infliximab and adalimumab strongly correlates with functional drug levels and clinical responses in rheumatoid arthritis. Ann Rheum Dis. 2009 Nov;68(11):1739-45. Epub 2008 Nov 19. PubMed PMID: 19019895.

128: Møller Døhn U, Boonen A, Hetland ML, Hansen MS, Knudsen LS, Hansen A, Madsen OR, Hasselquist M, Møller JM, Østergaard M. Erosive progression is minimal, but erosion healing rare, in patients with rheumatoid arthritis treated with

adalimumab. A 1 year investigator-initiated follow-up study using high-resolution computed tomography as the primary outcome measure. Ann Rheum Dis. 2009 Oct;68(10):1585-90. Epub 2008 Nov 19. PubMed PMID: 19019887.

129: Smolen J, Landewé RB, Mease P, Brzezicki J, Mason D, Luijtens K, van Vollenhoven RF, Kavanaugh A, Schiff M, Burmester GR, Strand V, Vencovsky J, van der Heijde D. Efficacy and safety of certolizumab pegol plus methotrexate in active rheumatoid arthritis: the RAPID 2 study. A randomised controlled trial. Ann Rheum Dis. 2009 Jun;68(6):797-804. Epub 2008 Nov 17. PubMed PMID: 19015207; PubMed Central PMCID: PMC2674556.

130: Fleischmann R, Vencovsky J, van Vollenhoven RF, Borenstein D, Box J, Coteur G, Goel N, Brezinschek HP, Innes A, Strand V. Efficacy and safety of certolizumab pegol monotherapy every 4 weeks in patients with rheumatoid arthritis failing previous disease-modifying antirheumatic therapy: the FAST4WARD study. Ann Rheum Dis. 2009 Jun;68(6):805-11. Epub 2008 Nov 17. PubMed PMID: 19015206; PubMed Central PMCID: PMC2674555.

131: Sidiropoulos PI, Siakka P, Pagonidis K, Raptopoulou A, Kritikos H, Tsetis D, Boumpas DT. Sustained improvement of vascular endothelial function during anti-TNFalpha treatment in rheumatoid arthritis patients. Scand J Rheumatol. 2009 Jan-Feb;38(1):6-10. PubMed PMID: 18991190.

132: Smolen JS, van der Heijde DM, Aletaha D, Xu S, Han J, Baker D, St Clair EW. Progression of radiographic joint damage in rheumatoid arthritis: independence of erosions and joint space narrowing. Ann Rheum Dis. 2009 Oct;68(10):1535-40. Epub 2008 Oct 28. PubMed PMID: 18957487.

133: Cañete JD, Suárez B, Hernández MV, Sanmartí R, Rego I, Celis R, Moll C, Pinto JA, Blanco FJ, Lozano F. Influence of variants of Fc gamma receptors IIA and IIIA on the American College of Rheumatology and European League Against Rheumatism responses to anti-tumour necrosis factor alpha therapy in rheumatoid arthritis. Ann Rheum Dis. 2009 Oct;68(10):1547-52. Epub 2008 Oct 17. PubMed PMID: 18930989.

134: van der Kooij SM, le Cessie S, Goekoop-Ruiterman YP, de Vries-Bouwstra JK, van Zeben D, Kerstens PJ, Hazes JM, van Schaardenburg D, Breedveld FC, Dijkmans BA, Allaart CF. Clinical and radiological efficacy of initial vs delayed treatment with infliximab plus methotrexate in patients with early rheumatoid arthritis. Ann Rheum Dis. 2009 Jul;68(7):1153-8. Epub 2008 Oct 17. PubMed PMID: 18930988.

135: Wong M, Oakley SP, Young L, Jiang BY, Wierzbicki A, Panayi G, Chowienczyk P, Kirkham B. Infliximab improves vascular stiffness in patients with rheumatoid arthritis. Ann Rheum Dis. 2009 Aug;68(8):1277-84. Epub 2008 Oct 17. PubMed PMID: 18930987; PubMed Central PMCID: PMC2703705.

136: Hoff M, Kvien TK, Kälvesten J, Elden A, Haugeberg G. Adalimumab therapy reduces hand bone loss in early rheumatoid arthritis: explorative analyses from the PREMIER study. Ann Rheum Dis. 2009 Jul;68(7):1171-6. Epub 2008 Sep 18. PubMed PMID: 18801760; PubMed Central PMCID: PMC2689520.

137: Combe B, Codreanu C, Fiocco U, Gaubitz M, Geusens PP, Kvien TK, Pavelka K, Sambrook PN, Smolen JS, Khandker R, Singh A, Wajdula J, Fatenejad S; Etanercept European Investigators Network. Efficacy, safety and patient-reported outcomes of combination etanercept and sulfasalazine versus etanercept alone in patients with rheumatoid arthritis: a double-blind randomised 2-year study. Ann Rheum Dis. 2009 Jul;68(7):1146-52. Epub 2008 Sep 15. PubMed PMID: 18794178; PubMed Central PMCID: PMC2689524.

138: Caproni M, Antiga E, Melani L, Volpi W, Del Bianco E, Fabbri P. Serum levels of IL-17 and IL-22 are reduced by etanercept, but not by acitretin, in patients

with psoriasis: a randomized-controlled trial. J Clin Immunol. 2009 Mar;29(2):210-4. Epub 2008 Sep 2. PubMed PMID: 18763027.

139: van der Heijde D, Burmester G, Melo-Gomes J, Codreanu C, Martin Mola E, Pedersen R, Robertson D, Chang D, Koenig A, Freundlich B; Etanercept Study Investigators. Inhibition of radiographic progression with combination etanercept and methotrexate in patients with moderately active rheumatoid arthritis previously treated with monotherapy. Ann Rheum Dis. 2009 Jul;68(7):1113-8. Epub 2008 Aug 21. PubMed PMID: 18718986.

140: Hu D, Bao C, Chen S, Gu J, Li Z, Sun L, Han X, Ni L. A comparison study of a recombinant tumor necrosis factor receptor:Fc fusion protein (rhTNFR:Fc) and methotrexate in treatment of patients with active rheumatoid arthritis in China. Rheumatol Int. 2009 Jan;29(3):297-303. Epub 2008 Aug 15. PubMed PMID: 18704426.

141: Mease PJ, Ory P, Sharp JT, Ritchlin CT, Van den Bosch F, Wellborne F, Birbara C, Thomson GT, Perdok RJ, Medich J, Wong RL, Gladman DD. Adalimumab for long-term treatment of psoriatic arthritis: 2-year data from the Adalimumab Effectiveness in Psoriatic Arthritis Trial (ADEPT). Ann Rheum Dis. 2009 May;68(5):702-9. Epub 2008 Aug 6. PubMed PMID: 18684743; PubMed Central PMCID: PMC2663711.

142: Mease PJ, Hobbs K, Chalmers A, El-Gabalawy H, Bookman A, Keystone E, Furst DE, Anklesaria P, Heald AE. Local delivery of a recombinant adenoassociated vector containing a tumour necrosis factor alpha antagonist gene in inflammatory arthritis: a phase 1 dose-escalation safety and tolerability study. Ann Rheum Dis. 2009 Aug;68(8):1247-54. Epub 2008 Aug 4. PubMed PMID: 18678578.

143: Trocmé C, Marotte H, Baillet A, Pallot-Prades B, Garin J, Grange L, Miossec P, Tebib J, Berger F, Nissen MJ, Juvin R, Morel F, Gaudin P. Apolipoprotein A-I and platelet factor 4 are biomarkers for infliximab response in rheumatoid arthritis. Ann Rheum Dis. 2009 Aug;68(8):1328-33. Epub 2008 Jul 29. PubMed PMID: 18664547; PubMed Central PMCID: PMC2921545.

144: van der Kooij SM, Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Güler-Yüksel M, Zwinderman AH, Kerstens PJ, van der Lubbe PA, de Beus WM, Grillet BA, Ronday HK, Huizinga TW, Breedveld FC, Dijkmans BA, Allaart CF. Drug-free remission, functioning and radiographic damage after 4 years of response-driven treatment in patients with recent-onset rheumatoid arthritis. Ann Rheum Dis. 2009 Jun;68(6):914-21. Epub 2008 Jul 28. PubMed PMID: 18662933.

145: van Kuijk AW, Gerlag DM, Vos K, Wolbink G, de Groot M, de Rie MA, Zwinderman AH, Dijkmans BA, Tak PP. A prospective, randomised, placebo-controlled study to identify biomarkers associated with active treatment in psoriatic arthritis: effects of adalimumab treatment on synovial tissue. Ann Rheum Dis. 2009 Aug;68(8):1303-9. Epub 2008 Jul 22. PubMed PMID: 18647851; PubMed Central PMCID: PMC2703703.

146: Popa C, van Tits LJ, Barrera P, Lemmers HL, van den Hoogen FH, van Riel PL, Radstake TR, Netea MG, Roest M, Stalenhoef AF. Anti-inflammatory therapy with tumour necrosis factor alpha inhibitors improves high-density lipoprotein cholesterol antioxidative capacity in rheumatoid arthritis patients. Ann Rheum Dis. 2009 Jun;68(6):868-72. Epub 2008 Jul 17. PubMed PMID: 18635596.

147: Smolen JS, Han C, van der Heijde DM, Emery P, Bathon JM, Keystone E, Maini RN, Kalden JR, Aletaha D, Baker D, Han J, Bala M, St Clair EW; Active-Controlled Study of Patients Receiving Infliximab for the Treatment of Rheumatoid Arthritis of Early Onset (ASPIRE) Study Group. Radiographic changes in rheumatoid arthritis patients attaining different disease activity states with methotrexate monotherapy and infliximab plus methotrexate: the impacts of remission and tumour necrosis factor blockade. Ann Rheum Dis. 2009 Jun;68(6):823-7. Epub 2008 Jul 1. PubMed PMID: 18593759.

148: Maksymowych WP, Mallon C, Morrow S, Shojania K, Olszynski WP, Wong RL, Sampalis J, Conner-Spady B. Development and validation of the Spondyloarthritis Research Consortium of Canada (SPARCC) Enthesitis Index. Ann Rheum Dis. 2009 Jun;68(6):948-53. Epub 2008 Jun 4. PubMed PMID: 18524792.

149: Prince FH, Twilt M, ten Cate R, van Rossum MA, Armbrust W, Hoppenreijs EP, van Santen-Hoeufft M, Koopman-Keemink Y, Wulffraat NM, van Suijlekom-Smit LW. Long-term follow-up on effectiveness and safety of etanercept in juvenile idiopathic arthritis: the Dutch national register. Ann Rheum Dis. 2009 May;68(5):635-41. Epub 2008 Apr 15. PubMed PMID: 18413443.

150: Horneff G, De Bock F, Foeldvari I, Girschick HJ, Michels H, Moebius D, Schmeling H; German and Austrian Paediatric Rheumatology Collaborative Study Group. Safety and efficacy of combination of etanercept and methotrexate compared to treatment with etanercept only in patients with juvenile idiopathic arthritis (JIA): preliminary data from the German JIA Registry. Ann Rheum Dis. 2009 Apr;68(4):519-25. Epub 2008 Apr 15. PubMed PMID: 18413440.

151: Wijbrandts CA, Klaasen R, Dijkgraaf MG, Gerlag DM, van Eck-Smit BL, Tak PP. Bone mineral density in rheumatoid arthritis patients 1 year after adalimumab therapy: arrest of bone loss. Ann Rheum Dis. 2009 Mar;68(3):373-6. Epub 2008 Apr 13. PubMed PMID: 18408246.

152: Potter C, Hyrich KL, Tracey A, Lunt M, Plant D, Symmons DP, Thomson W, Worthington J, Emery P, Morgan AW, Wilson AG, Isaacs J, Barton A; BRAGGSS. Association of rheumatoid factor and anti-cyclic citrullinated peptide positivity, but not carriage of shared epitope or PTPN22 susceptibility variants, with anti-tumour necrosis factor response in rheumatoid arthritis. Ann Rheum Dis. 2009 Jan;68(1):69-74. Epub 2008 Mar 28. PubMed PMID: 18375541; PubMed Central PMCID: PMC2596303.

153: Güler-Yüksel M, Allaart CF, Goekoop-Ruiterman YP, de Vries-Bouwstra JK, van Groenendael JH, Mallée C, de Bois MH, Breedveld FC, Dijkmans BA, Lems WF. Changes in hand and generalised bone mineral density in patients with recent-onset rheumatoid arthritis. Ann Rheum Dis. 2009 Mar;68(3):330-6. Epub 2008 Mar 28. PubMed PMID: 18375540.

SEARCH 13_register infection

Category	**Description**
Clinical question or focus	BIOLOGICAL AGENTS FINAL
Source	PubMed
Terms	**DMARDs (REGISTER or registry) serious infection**
Limits	
▪ Date limits	
▪ Other limits	
Query Translation (eg, “Details” in PubMed)	DMARDs[All Fields] AND (("Regist Ky Hist Soc"[Journal] OR "register"[All Fields]) OR ("registries"[MeSH Terms] OR "registries"[All Fields] OR "registry"[All Fields])) AND (serious[All Fields] AND ("infection"[MeSH Terms] OR "infection"[All Fields] OR "communicable diseases"[MeSH Terms] OR ("communicable"[All Fields] AND "diseases"[All Fields]) OR "communicable diseases"[All Fields]
Date of Search	9/1210
Total Yield	5
Total marked for retrieval	Furst 10, Dixon 07, Dixon 06
Exclusions	• Not focus of review: population, intervention, comparison, outcome • Superseded by more recent larger study • Wrong study type • Lacking safety data

	• Duplicates
Notes	Furst provided no comparative information.

1: Fisher MC, Greenberg JD. Assessing infection risk with biologic agents in RA: methodological challenges. Nat Rev Rheumatol. 2009 May;5(5):288-91. PubMed PMID: 19412196.

2: Furst DE. The risk of infections with biologic therapies for rheumatoid arthritis. Semin Arthritis Rheum. 2010 Apr;39(5):327-46. Epub 2008 Dec 31. Review. PubMed PMID: 19117595.

3: Dixon WG, Symmons DP, Lunt M, Watson KD, Hyrich KL; British Society for Rheumatology Biologics Register Control Centre Consortium, Silman AJ; British Society for Rheumatology Biologics Register. Serious infection following anti-tumor necrosis factor alpha therapy in patients with rheumatoid arthritis: lessons from interpreting data from observational studies. Arthritis Rheum. 2007 Sep;56(9):2896-904. PubMed PMID: 17763441; PubMed Central PMCID: PMC2435418.

4: Dixon WG, Watson K, Lunt M, Hyrich KL, Silman AJ, Symmons DP; British Society for Rheumatology Biologics Register. Rates of serious infection, including site-specific and bacterial intracellular infection, in rheumatoid arthritis patients receiving anti-tumor necrosis factor therapy: results from the British Society for Rheumatology Biologics Register. Arthritis Rheum. 2006 Aug;54(8):2368-76. PubMed PMID: 16868999.

5: Symmons DP, Silman AJ. The world of biologics. Lupus. 2006;15(3):122-6. Review. PubMed PMID: 16634363.

SEARCH 14_register infection TNF

Category	**Description**
Clinical question or focus	BIOLOGICAL AGENTS FINAL
Source	PubMed
Terms	**serious infection AND (registry or register) AND (TNF OR biological DMARD)**
Limits	
▪ Date limits	
▪ Other limits	
Query Translation (eg, “Details” in PubMed)	(serious[All Fields] AND ("infection"[MeSH Terms] OR "infection"[All Fields] OR "communicable diseases"[MeSH Terms] OR ("communicable"[All Fields] AND "diseases"[All Fields]) OR "communicable diseases"[All Fields])) AND (("registries"[MeSH Terms] OR "registries"[All Fields] OR "registry"[All Fields]) OR ("Regist Ky Hist Soc"[Journal] OR "register"[All Fields])) AND (TNF[All Fields] OR (("biology"[MeSH Terms] OR "biology"[All Fields] OR "biological"[All Fields]) AND ("antirheumatic agents"[MeSH Terms] OR ("antirheumatic"[All Fields] AND "agents"[All Fields]) OR "antirheumatic agents"[All Fields] OR "dmard"[All Fields] OR "antirheumatic agents"[Pharmacological Action]))))
Date of Search	9/13/10
Total Yield	9
Total marked for retrieval	Galloway 10, Tsiodras 08, Carmona 07, Askling 07, Listing 05
Exclusions	• Not focus of review: population, intervention, comparison, outcome • Superseded by more recent larger study • Lacking safety data • Duplicates

1: Galloway JB, Hyrich KL, Mercer LK, Dixon WG, Fu B, Ustianowski AP, Watson KD, Lunt M; BSRBR Control Centre Consortium, Symmons DP; on behalf of the British

Society for Rheumatology Biologics Register. Anti-TNF therapy is associated with an increased risk of serious infections in patients with rheumatoid arthritis especially in the first 6 months of treatment: updated results from the British Society for Rheumatology Biologics Register with special emphasis on risks in the elderly. Rheumatology (Oxford). 2010 Jul 31. [Epub ahead of print] PubMed PMID: 20675706.

2: Katikireddi VS, Whittle SL, Hill CL. Tumour necrosis factor inhibitors and risk of serious infection in rheumatoid arthritis. Int J Rheum Dis. 2010 Feb 1;13(1):12-26. Review. PubMed PMID: 20374381.

3: Furst DE. The risk of infections with biologic therapies for rheumatoid arthritis. Semin Arthritis Rheum. 2010 Apr;39(5):327-46. Epub 2008 Dec 31. Review. PubMed PMID: 19117595.

4: Tsiodras S, Samonis G, Boumpas DT, Kontoyiannis DP. Fungal infections complicating tumor necrosis factor alpha blockade therapy. Mayo Clin Proc. 2008 Feb;83(2):181-94. Review. PubMed PMID: 18241628.

5: Carmona L, Descalzo MA, Perez-Pampin E, Ruiz-Montesinos D, Erra A, Cobo T, Gómez-Reino JJ; BIOBADASER and EMECAR Groups. All-cause and cause-specific mortality in rheumatoid arthritis are not greater than expected when treated with tumour necrosis factor antagonists. Ann Rheum Dis. 2007 Jul;66(7):880-5. Epub 2007 Feb 26. PubMed PMID: 17324968; PubMed Central PMCID: PMC1955107.

6: Askling J, Fored CM, Brandt L, Baecklund E, Bertilsson L, Feltelius N, Cöster L, Geborek P, Jacobsson LT, Lindblad S, Lysholm J, Rantapää-Dahlqvist S, Saxne T, van Vollenhoven RF, Klareskog L. Time-dependent increase in risk of hospitalisation with infection among Swedish RA patients treated with TNF antagonists. Ann Rheum Dis. 2007 Oct;66(10):1339-44. Epub 2007 Jan 29. Erratum in: Ann Rheum Dis. 2007 Nov;66(11):1548. PubMed PMID: 17261532.

7: Dixon WG, Watson K, Lunt M, Hyrich KL, Silman AJ, Symmons DP; British Society for Rheumatology Biologics Register. Rates of serious infection, including site-specific and bacterial intracellular infection, in rheumatoid arthritis patients receiving anti-tumor necrosis factor therapy: results from the British Society for Rheumatology Biologics Register. Arthritis Rheum. 2006 Aug;54(8):2368-76. PubMed PMID: 16868999.

8: Symmons DP, Silman AJ. The world of biologics. Lupus. 2006;15(3):122-6. Review. PubMed PMID: 16634363.

9: Listing J, Strangfeld A, Kary S, Rau R, von Hinueber U, Stoyanova-Scholz M, Gromnica-Ihle E, Antoni C, Herzer P, Kekow J, Schneider M, Zink A. Infections in patients with rheumatoid arthritis treated with biologic agents. Arthritis Rheum. 2005 Nov;52(11):3403-12. PubMed PMID: 16255017.

SEARCH 15_CERTOLIZUMAB SR

Category	**Description**
Clinical question or focus	BIOLOGICAL AGENTS FINAL
Source	PubMed
Terms	**certolizumab**
Limits	
▪ Date limits	
▪ Other limits	Systematic review
Query Translation (eg, “Details” in PubMed)	("CDP870"[Substance Name] OR "CDP870"[All Fields] OR "certolizumab"[All Fields]) AND systematic[sb]
Date of Search	10/4/2010
Total Yield	11
Total marked for retrieval	Fleishman 10, Statkute 10

Exclusions	• Not focus of review: population, intervention, comparison, outcome • Superseded by more recent larger study • Lacking safety data • Duplicates

1: Nam JL, Winthrop KL, van Vollenhoven RF, Pavelka K, Valesini G, Hensor EM, Worthy G, Landewé R, Smolen JS, Emery P, Buch MH. Current evidence for the management of rheumatoid arthritis with biological disease-modifying antirheumatic drugs: a systematic literature review informing the EULAR recommendations for the management of RA. Ann Rheum Dis. 2010 Jun;69(6):976-86. Epub 2010 May 6. Review. PubMed PMID: 20447957.

2: Fleischmann R. The clinical efficacy and safety of certolizumab pegol in rheumatoid arthritis. Expert Opin Biol Ther. 2010 May;10(5):773-86. Review. PubMed PMID: 20230188.

3: Oussalah A, Danese S, Peyrin-Biroulet L. Efficacy of TNF antagonists beyond one year in adult and pediatric inflammatory bowel diseases: a systematic review. Curr Drug Targets. 2010 Feb;11(2):156-75. Review. PubMed PMID: 20210765.

4: Smith LS, Nelson M, Dolder CR. Certolizumab pegol: a TNF-{alpha} antagonist for the treatment of moderate-to-severe Crohn's disease. Ann Pharmacother. 2010 Feb;44(2):333-42. Epub 2010 Jan 5. Review. PubMed PMID: 20118143.

5: Statkute L, Ruderman EM. Novel TNF antagonists for the treatment of rheumatoid arthritis. Expert Opin Investig Drugs. 2010 Jan;19(1):105-15. Review. PubMed PMID: 20001558.

6: Shao LM, Chen MY, Cai JT. Meta-analysis: the efficacy and safety of certolizumab pegol in Crohn's disease. Aliment Pharmacol Ther. 2009 Mar 15;29(6):605-14. PubMed PMID: 19183161.

7: Al-Subeihe I, Nielsen OH. [Tumor necrosis factor-alpha antibody for maintenance of remission in Crohn disease. A survey of a Cochrane review]. Ugeskr Laeger. 2008 Dec 8;170(50):4130-4. Review. Danish. PubMed PMID: 19091193.

8: Peyrin-Biroulet L, Deltenre P, de Suray N, Branche J, Sandborn WJ, Colombel JF. Efficacy and safety of tumor necrosis factor antagonists in Crohn's disease: meta-analysis of placebo-controlled trials. Clin Gastroenterol Hepatol. 2008 Jun;6(6):644-53. PubMed PMID: 18550004.

9: Behm BW, Bickston SJ. Tumor necrosis factor-alpha antibody for maintenance of remission in Crohn's disease. Cochrane Database Syst Rev. 2008 Jan 23;(1):CD006893. Review. PubMed PMID: 18254120.

10: Rahimi R, Nikfar S, Abdollahi M. Do anti-tumor necrosis factors induce response and remission in patients with acute refractory Crohn's disease? A systematic meta-analysis of controlled clinical trials. Biomed Pharmacother. 2007 Jan;61(1):75-80. Epub 2006 Dec 4. PubMed PMID: 17184965.

11: D'Haens G, Daperno M. Advances in biologic therapy for ulcerative colitis and Crohn's disease. Curr Gastroenterol Rep. 2006 Dec;8(6):506-12. Review. PubMed PMID: 17105690.

SEARCH 16 all REGISTER

Category	Description
Clinical question or focus	BIOLOGICAL AGENTS FINAL
Source	PubMed
Terms	(adalimumab OR certolizumab OR etanercept OR golimumab OR infliximab

	OR ustekinumab) AND (register or registry)
Limits	none
▪ Date limits	none
▪ Other limits	none
▪ Number of hits	172
Query Translation (eg, “Details” in PubMed)	(("adalimumab"[Substance Name] OR "adalimumab"[All Fields]) OR ("CDP870"[Substance Name] OR "CDP870"[All Fields] OR "certolizumab"[All Fields]) OR ("TNFR-Fc fusion protein"[Substance Name] OR "TNFR-Fc fusion protein"[All Fields] OR "etanercept"[All Fields]) OR ("golimumab"[Substance Name] OR "golimumab"[All Fields]) OR ("infliximab"[Substance Name] OR "infliximab"[All Fields]) OR ("monoclonal antibody CNTO 1275"[Substance Name] OR "monoclonal antibody CNTO 1275"[All Fields] OR "ustekinumab"[All Fields])) AND (("Regist Ky Hist Soc"[Journal] OR "register"[All Fields]) OR ("registries"[MeSH Terms] OR "registries"[All Fields] OR "registry"[All Fields]))
Date of Search	10/6/10
Total marked for retrieval	Virrki 10, Favalli 10, Galloway 10, Uhlenhake 10, Saad 10, Askling 05, Askling 09, Hetland 10, Dixon 10, Schmitt 09, Tubach 06, Listing 08, Mariette 10, Marchesoni 09, Tubach 09, Favalli 08, Gómez-Reino 07, Wolfe 07b, Jacobsson 07, Wolfe 04
Exclusions	• Not focus of review: population, intervention, comparison, outcome • Superseded by more recent larger study • Lacking safety data • Wrong study type • Duplicates

1: van Luijn J, Danz M, Bijlsma J, Gribnau F, Leufkens H. Post-approval trials of new medicines: widening use or deepening knowledge? Analysis of 10 years of etanercept. Scand J Rheumatol. 2010 Sep 21. [Epub ahead of print] PubMed PMID: 20858147.

2: van der Velde G, Pham B, Machado M, Ieraci L, Witteman W, Bombardier C, Krahn M. Cost-effectiveness of biologic response modifiers compared to disease modifying anti-rheumatic drugs for rheumatoid arthritis: A systematic review. Arthritis Care Res (Hoboken). 2010 Aug 25. [Epub ahead of print] PubMed PMID: 20740606.

3: Virkki LM, Sumathikutty BC, Aarnio M, Valleala H, Heikkilä R, Kauppi M, Karstila K, Pirilä L, Ekman P, Salomaa S, Romu M, Seppälä J, Niinisalo H, Konttinen YT, Nordström DC. Biological Therapy for Psoriatic Arthritis in Clinical Practice: Outcomes Up to 2 Years. J Rheumatol. 2010 Aug 17. [Epub ahead of print] PubMed PMID: 20716655.

4: Warren RB, Brown BC, Lavery D, Griffiths CE. Adalimumab for psoriasis: practical experience in a U.K. tertiary referral centre. Br J Dermatol. 2010 Aug 13. [Epub ahead of print] PubMed PMID: 20716225.

5: Hetland ML. [Danish data document therapeutic effect differences of tumor necrosis factor inhibitors in patient with rheumatoid arthritis]. Ugeskr Laeger. 2010 Jun 28;172(26):2003; author reply 2003-4. Danish. PubMed PMID: 20681045.

6: Galloway JB, Hyrich KL, Mercer LK, Dixon WG, Fu B, Ustianowski AP, Watson KD, Lunt M; BSRBR Control Centre Consortium, Symmons DP; on behalf of the British Society for Rheumatology Biologics Register. Anti-TNF therapy is associated with an increased risk of serious infections in patients with rheumatoid arthritis especially in the first 6 months of treatment: updated results from the British Society for Rheumatology Biologics Register with special emphasis on risks in the

elderly. Rheumatology (Oxford). 2010 Jul 31. [Epub ahead of print] PubMed PMID: 20675706.

7: Giannini EH, Ilowite NT, Lovell DJ, Wallace CA, Rabinovich CE, Reiff A, Higgins G, Gottlieb B, Chon Y, Zhang N, Baumgartner SW; for the Pediatric Rheumatology Collaborative Study Group. Effects of long-term etanercept treatment on growth in children with selected categories of juvenile idiopathic arthritis. Arthritis Rheum. 2010 Jul 28. [Epub ahead of print] PubMed PMID: 20669280.

8: Dückers G, Niehues T. [The importance of biologicals in the treatment of SoJIA]. Z Rheumatol. 2010 Aug;69(6):505-15. German. PubMed PMID: 20668866.

9: Van Lümig PP, Lecluse LL, Driessen RJ, Spuls PI, Boezeman JB, van de Kerkhof PC, De Jong EM. Switching from etanercept to adalimumab is effective and safe: results in 30 patients with psoriasis with primary failure, secondary failure or intolerance to etanercept. Br J Dermatol. 2010 Oct;163(4):838-46. doi: 10.1111/j.1365-2133.2010.09950.x. Epub 2010 Sep 2. PubMed PMID: 20649798.

10: Collamer AN, Battafarano DF. Psoriatic Skin Lesions Induced by Tumor Necrosis Factor Antagonist Therapy: Clinical Features and Possible Immunopathogenesis. Semin Arthritis Rheum. 2010 Jun 25. [Epub ahead of print] PubMed PMID: 20580412.

11: Soubrier M, Mathieu S, Payet S, Dubost JJ, Ristori JM. Elderly-onset rheumatoid arthritis. Joint Bone Spine. 2010 Jul;77(4):290-6. Epub 2010 May 31. PubMed PMID: 20554241.

12: McCroskery P, Wallace CA, Lovell DJ, Stryker S, Chernyukhin N, Blosch C, Zack DJ. Summary of worldwide pediatric malignancies reported after exposure to etanercept. Pediatr Rheumatol Online J. 2010 Jun 14;8:18. PubMed PMID: 20546618; PubMed Central PMCID: PMC2904755.

13: Horneff G. [Malignancy and tumor necrosis factor inhibitors in juvenile idiopathic arthritis]. Z Rheumatol. 2010 Aug;69(6):516-26. German. PubMed PMID: 20532787.

14: Mercuri SR, Naldi L. Potential role of ustekinumab in the treatment of chronic plaque psoriasis. Biologics. 2010 May 25;4:119-29. PubMed PMID: 20531968; PubMed Central PMCID: PMC2880344.

15: Glintborg B, Ostergaard M, Krogh NS, Dreyer L, Kristensen HL, Hetland ML. Predictors of treatment response and drug continuation in 842 patients with ankylosing spondylitis treated with anti-tumour necrosis factor: results from 8 years' surveillance in the Danish nationwide DANBIO registry. Ann Rheum Dis. 2010 May 28. [Epub ahead of print] PubMed PMID: 20511613.

16: Blom M, Kievit W, Kuper HH, Jansen TL, Visser H, den Broeder AA, Brus HL, van de Laar MA, van Riel PL. Frequency and effectiveness of dose increase of adalimumab, etanercept, and infliximab in daily clinical practice. Arthritis Care Res (Hoboken). 2010 Sep;62(9):1335-41. PubMed PMID: 20506128.

17: Sauvain MJ, Schalm SB, Bérthet G, Bolz D, Cannizzaro E, Hofer M, Kaiser D, Saurenmann RK, Bolt IB. [Swiss registry for TNF-alpha blockers in children and adolescents with rheumatological diseases]. Praxis (Bern 1994). 2010 May 26;99(11):649-54. German. PubMed PMID: 20506089.

18: Finckh A, Dudler J, Wermelinger F, Ciurea A, Kyburz D, Gabay C, Bas S; physicians of SCQM. Influence of anti-infliximab antibodies and residual infliximab concentrations on the occurrence of acquired drug resistance to infliximab in rheumatoid arthritis patients. Joint Bone Spine. 2010 Jul;77(4):313-8. Epub 2010 May 14. PubMed PMID: 20471890.

19: Uhlenhake EE, Feldman SR. Efficacy and safety of ustekinumab and etanercept

for the treatment of psoriasis. Expert Opin Biol Ther. 2010 Jul;10(7):1105-12. Review. PubMed PMID: 20446825.

20: Singh JA, Noorbaloochi S, Singh G. Golimumab for rheumatoid arthritis: a systematic review. J Rheumatol. 2010 Jun;37(6):1096-104. Epub 2010 May 1. Review. PubMed PMID: 20436075.

21: Abrahamyan L, Beyene J, Feng J, Chon Y, Willan AR, Schmeling H, Horneff G, Keystone EC, Feldman BM. Response times follow lognormal or gamma distribution in arthritis patients. J Clin Epidemiol. 2010 Apr 28. [Epub ahead of print] PubMed PMID: 20430577.

22: Saad AA, Ashcroft DM, Watson KD, Symmons DP, Noyce PR, Hyrich KL; British Society for Rheumatology Biologics Register. Improvements in quality of life and functional status in patients with psoriatic arthritis receiving anti-tumor necrosis factor therapies. Arthritis Care Res (Hoboken). 2010 Mar;62(3):345-53. PubMed PMID: 20391480; PubMed Central PMCID: PMC2909400.

23: Lv D, Song H, Shi G. Anti-TNF-alpha treatment for pelvic pain associated with endometriosis. Cochrane Database Syst Rev. 2010 Mar 17;3:CD008088. Review. PubMed PMID: 20238362.

24: Horneff G, Hospach T, Dannecker G, Föll D, Haas JP, Girschick HJ, Huppertz HI, Keitzer R, Laws HJ, Michels H, Minden K, Trauzeddel R. [Updated statement by the German Society for Pediatric and Adolescent Rheumatology (GKJR) on the FDA's report regarding malignancies in anti-TNF-treated patients from Aug. 4, 2009]. Z Rheumatol. 2010 Aug;69(6):561-7. German. PubMed PMID: 20174926.

25: Pavelka K, Forejtová S, Stolfa J, Chroust K, Buresová L, Mann H, Vencovský J. Anti-TNF therapy of ankylosing spondylitis in clinical practice. Results from the Czech national registry ATTRA. Clin Exp Rheumatol. 2009 Nov-Dec;27(6):958-63. PubMed PMID: 20149312.

26: Giansanti F, Papucci L, Capaccioli S, Bacherini D, Vannozzi L, Witort E, Menchini U. Ocular safety of infliximab in rabbit and cell culture models. J Ocul Pharmacol Ther. 2010 Feb;26(1):65-71. PubMed PMID: 20148652.

27: Hyams JS, Lerer T, Griffiths A, Pfefferkorn M, Stephens M, Evans J, Otley A, Carvalho R, Mack D, Bousvaros A, Rosh J, Grossman A, Tomer G, Kay M, Crandall W, Oliva-Hemker M, Keljo D, LeLeiko N, Markowitz J; Pediatric Inflammatory Bowel Disease Collaborative Research Group. Outcome following infliximab therapy in children with ulcerative colitis. Am J Gastroenterol. 2010 Jun;105(6):1430-6. Epub 2010 Jan 26. PubMed PMID: 20104217.

28: Singh JA, Noorbaloochi S, Singh G. Golimumab for rheumatoid arthritis. Cochrane Database Syst Rev. 2010 Jan 20;(1):CD008341. Review. PubMed PMID: 20091667.

29: Lekander I, Borgström F, Svarvar P, Ljung T, Carli C, van Vollenhoven RF. Cost-effectiveness of real-world infliximab use in patients with rheumatoid arthritis in Sweden. Int J Technol Assess Health Care. 2010 Jan;26(1):54-61. PubMed PMID: 20059781.

30: Caporali R, Sarzi-Puttini P, Atzeni F, Gorla R, Filippini M, Marchesoni A, Favalli EG, Bobbio-Pallavicini F, Montecucco C. Switching TNF-alpha antagonists in rheumatoid arthritis: the experience of the LORHEN registry. Autoimmun Rev. 2010 Apr;9(6):465-9. Epub 2009 Dec 31. PubMed PMID: 20044040.

31: Hetland ML, Christensen IJ, Tarp U, Dreyer L, Hansen A, Hansen IT, Kollerup G, Linde L, Lindegaard HM, Poulsen UE, Schlemmer A, Jensen DV, Jensen S, Hostenkamp G, Østergaard M; All Departments of Rheumatology in Denmark. Direct comparison of treatment responses, remission rates, and drug adherence in

patients with rheumatoid arthritis treated with adalimumab, etanercept, or infliximab: results from eight years of surveillance of clinical practice in the nationwide Danish DANBIO registry. Arthritis Rheum. 2010 Jan;62(1):22-32. PubMed PMID: 20039405.

32: Puig L, Barco D, Alomar A. Treatment of psoriasis with anti-TNF drugs during pregnancy: case report and review of the literature. Dermatology. 2010;220(1):71-6. Epub 2009 Nov 25. Review. PubMed PMID: 19940453.

33: El Mourabet M, El-Hachem S, Harrison JR, Binion DG. Anti-TNF antibody therapy for inflammatory bowel disease during pregnancy: a clinical review. Curr Drug Targets. 2010 Feb;11(2):234-41. Review. PubMed PMID: 19916950.

34: Askling J, van Vollenhoven RF, Granath F, Raaschou P, Fored CM, Baecklund E, Dackhammar C, Feltelius N, Cöster L, Geborek P, Jacobsson LT, Lindblad S, Rantapää-Dahlqvist S, Saxne T, Klareskog L. Cancer risk in patients with rheumatoid arthritis treated with anti-tumor necrosis factor alpha therapies: does the risk change with the time since start of treatment? Arthritis Rheum. 2009 Nov;60(11):3180-9. PubMed PMID: 19877027.

35: Dixon WG, Hyrich KL, Watson KD, Lunt M, Galloway J, Ustianowski A; B S R B R Control Centre Consortium, Symmons DP; BSR Biologics Register. Drug-specific risk of tuberculosis in patients with rheumatoid arthritis treated with anti-TNF therapy: results from the British Society for Rheumatology Biologics Register (BSRBR). Ann Rheum Dis. 2010 Mar;69(3):522-8. Epub 2009 Oct 22. PubMed PMID: 19854715; PubMed Central PMCID: PMC2927681.

36: Mariette X, Tubach F, Bagheri H, Bardet M, Berthelot JM, Gaudin P, Heresbach D, Martin A, Schaeverbeke T, Salmon D, Lemann M, Hermine O, Raphael M, Ravaud P. Lymphoma in patients treated with anti-TNF: results of the 3-year prospective French RATIO registry. Ann Rheum Dis. 2010 Feb;69(2):400-8. Epub 2009 Oct 14. PubMed PMID: 19828563; PubMed Central PMCID: PMC2925048.

37: Doherty G, Bennett G, Patil S, Cheifetz A, Moss AC. Interventions for prevention of post-operative recurrence of Crohn's disease. Cochrane Database Syst Rev. 2009 Oct 7;(4):CD006873. Review. PubMed PMID: 19821389.

38: Jessop S, Whitelaw DA, Delamere FM. Drugs for discoid lupus erythematosus. Cochrane Database Syst Rev. 2009 Oct 7;(4):CD002954. Review. PubMed PMID: 19821298.

39: Lukina GV, Sigidin IaA, Nasonov EL. [Clinical experience with infliximab administration in patients with rheumatoid arthritis (according to Russian register data)]. Ter Arkh. 2009;81(8):65-9. Russian. PubMed PMID: 19799204.

40: Markowitz J. Early inflammatory bowel disease: different treatment response to specific or all medications? Dig Dis. 2009;27(3):358-65. Epub 2009 Sep 24. Review. PubMed PMID: 19786765.

41: Marchesoni A, Zaccara E, Gorla R, Bazzani C, Sarzi-Puttini P, Atzeni F, Caporali R, Bobbio-Pallavicini F, Favalli EG. TNF-alpha antagonist survival rate in a cohort of rheumatoid arthritis patients observed under conditions of standard clinical practice. Ann N Y Acad Sci. 2009 Sep;1173:837-46. PubMed PMID: 19758236.

42: Blom M, Kievit W, Fransen J, Kuper IH, den Broeder AA, De Gendt CM, Jansen TL, Brus HL, van de Laar MA, van Riel PL. The reason for discontinuation of the first tumor necrosis factor (TNF) blocking agent does not influence the effect of a second TNF blocking agent in patients with rheumatoid arthritis. J Rheumatol. 2009 Oct;36(10):2171-7. Epub 2009 Sep 1. PubMed PMID: 19723902.

43: Giannini EH, Ilowite NT, Lovell DJ, Wallace CA, Rabinovich CE, Reiff A,

Higgins G, Gottlieb B, Singer NG, Chon Y, Lin SL, Baumgartner SW; Pediatric Rheumatology Collaborative Study Group. Long-term safety and effectiveness of etanercept in children with selected categories of juvenile idiopathic arthritis. Arthritis Rheum. 2009 Sep;60(9):2794-804. PubMed PMID: 19714630.

44: Schmitt J, Wozel G. Targeted treatment of psoriasis with adalimumab: a critical appraisal based on a systematic review of the literature. Biologics. 2009;3:303-18. Epub 2009 Jul 13. PubMed PMID: 19707417; PubMed Central PMCID: PMC2726069.

45: Tubach F, Salmon D, Ravaud P, Allanore Y, Goupille P, Bréban M, Pallot-Prades B, Pouplin S, Sacchi A, Chichemanian RM, Bretagne S, Emilie D, Lemann M, Lortholary O, Mariette X; Research Axed on Tolerance of Biotherapies Group. Risk of tuberculosis is higher with anti-tumor necrosis factor monoclonal antibody therapy than with soluble tumor necrosis factor receptor therapy: The three-year prospective French Research Axed on Tolerance of Biotherapies registry. Arthritis Rheum. 2009 Jul;60(7):1884-94. Erratum in: Arthritis Rheum. 2009 Aug;60(8):2540. Lorthololary, O [corrected to Lortholary, O]. PubMed PMID: 19565495; PubMed Central PMCID: PMC2921546.

46: Viktil KK, Engeland A, Furu K. Use of antirheumatic drugs in mothers and fathers before and during pregnancy-a population-based cohort study. Pharmacoepidemiol Drug Saf. 2009 Aug;18(8):737-42. PubMed PMID: 19504626.

47: Horneff G, Ebert A, Fitter S, Minden K, Foeldvari I, Kümmerle-Deschner J, Thon A, Girschick HJ, Weller F, Huppertz HI. Safety and efficacy of once weekly etanercept 0.8 mg/kg in a multicentre 12 week trial in active polyarticular course juvenile idiopathic arthritis. Rheumatology (Oxford). 2009 Aug;48(8):916-9. Epub 2009 May 29. PubMed PMID: 19483091.

48: Augustsson J, Neovius M, Cullinane-Carli C, Eksborg S, van Vollenhoven RF. Patients with rheumatoid arthritis treated with tumour necrosis factor antagonists increase their participation in the workforce: potential for significant long-term indirect cost gains (data from a population-based registry). Ann Rheum Dis. 2010 Jan;69(1):126-31. Epub . PubMed PMID: 19470527.

49: Pirenne J, Kawai M. Intestinal transplantation: evolution in immunosuppression protocols. Curr Opin Organ Transplant. 2009 Jun;14(3):250-5. Review. PubMed PMID: 19373085.

50: Saad AA, Ashcroft DM, Watson KD, Hyrich KL, Noyce PR, Symmons DP; British Society for Rheumatology Biologics Register. Persistence with anti-tumour necrosis factor therapies in patients with psoriatic arthritis: observational study from the British Society of Rheumatology Biologics Register. Arthritis Res Ther. 2009;11(2):R52. Epub 2009 Apr 8. PubMed PMID: 19356232; PubMed Central

51: Prokes M. [Effectiveness of TNF antagonists in routine clinical practice and costs]. Vnitr Lek. 2009 Jan;55(1):45-53. Review. Czech. PubMed PMID: 19227955.

52: Strangfeld A, Listing J, Herzer P, Liebhaber A, Rockwitz K, Richter C, Zink A. Risk of herpes zoster in patients with rheumatoid arthritis treated with anti-TNF-alpha agents. JAMA. 2009 Feb 18;301(7):737-44. PubMed PMID: 19224750.

53: Atzeni F, Antivalle M, Pallavicini FB, Caporali R, Bazzani C, Gorla R, Favalli EG, Marchesoni A, Sarzi-Puttini P. Predicting response to anti-TNF treatment in rheumatoid arthritis patients. Autoimmun Rev. 2009 Mar;8(5):431-7. Epub 2009 Jan 27. PubMed PMID: 19211043.

54: Dreyer L, Mellemkjaer L, Hetland ML. [Cancer in arthritis patients after anti-tumour necrosis factor therapy]. Ugeskr Laeger. 2009 Feb 9;171(7):506-11. Danish. PubMed PMID: 19210932.

55: Virkki LM, Konttinen YT, Peltomaa R, Suontama K, Saario R, Immonen K, Jäntti J, Tuomiranta T, Nykänen P, Hämeenkorpi R, Heikkilä S, Isomäki P, Nordström D. Cost-effectiveness of infliximab in the treatment of rheumatoid arthritis in clinical practice. Clin Exp Rheumatol. 2008 Nov-Dec;26(6):1059-66. PubMed PMID: 19210870.

56: Driessen RJ, Boezeman JB, van de Kerkhof PC, de Jong EM. Three-year registry data on biological treatment for psoriasis: the influence of patient characteristics on treatment outcome. Br J Dermatol. 2009 Mar;160(3):670-5. Epub 2008 Jan 28. PubMed PMID: 19210502.

57: Carter JD, Ladhani A, Ricca LR, Valeriano J, Vasey FB. A safety assessment of tumor necrosis factor antagonists during pregnancy: a review of the Food and Drug Administration database. J Rheumatol. 2009 Mar;36(3):635-41. PubMed PMID: 19132789.

58: Sarzi-Puttini P, Antivalle M, Marchesoni A, Favalli EG, Gorla R, Filippini M, Caporali R, Bobbio-Pallavicini F, Montecucco C, Atzeni F. Efficacy and safety of anti-TNF agents in the Lombardy rheumatoid arthritis network (LORHEN). Reumatismo. 2008 Oct-Dec;60(4):290-5. PubMed PMID: 19132154.

59: Strangfeld A, Hierse F, Kekow J, von Hinueber U, Tony HP, Dockhorn R, Listing J, Zink A. Comparative effectiveness of tumour necrosis factor alpha inhibitors in combination with either methotrexate or leflunomide. Ann Rheum Dis. 2009 Dec;68(12):1856-62. Epub 2009 Jan 6. PubMed PMID: 19126559.

60: Furst DE. The risk of infections with biologic therapies for rheumatoid arthritis. Semin Arthritis Rheum. 2010 Apr;39(5):327-46. Epub 2008 Dec 31. Review. PubMed PMID: 19117595.

61: Hyams JS, Lerer T, Griffiths A, Pfefferkorn M, Kugathasan S, Evans J, Otley A, Carvalho R, Mack D, Bousvaros A, Rosh J, Mamula P, Kay M, Crandall W, Oliva-Hemker M, Keljo D, LeLeiko N, Markowitz J; Pediatric Inflammatory Bowel Disease Collaborative Research Group. Long-term outcome of maintenance infliximab therapy in children with Crohn's disease. Inflamm Bowel Dis. 2009 Jun;15(6):816-22. PubMed PMID: 19107783.

62: Kristensen LE, Geborek P, Saxne T. Dose escalation of infliximab therapy in arthritis patients is related to diagnosis and concomitant methotrexate treatment: observational results from the South Swedish Arthritis Treatment Group register. Rheumatology (Oxford). 2009 Mar;48(3):243-5. Epub 2008 Dec 23. PubMed PMID: 19106164.

63: Alejandro R, Barton FB, Hering BJ, Wease S; Collaborative Islet Transplant Registry Investigators. 2008 Update from the Collaborative Islet Transplant Registry. Transplantation. 2008 Dec 27;86(12):1783-8. PubMed PMID: 19104422.

64: Peña-Sagredo JL, Hernández MV, Fernandez-Llanio N, Giménez-Ubeda E, Muñoz-Fernandez S, Ortiz A, Gonzalez-Gay MA, Fariñas MC; Biobadaser group. Listeria monocytogenes infection in patients with rheumatic diseases on TNF-alpha antagonist therapy: the Spanish Study Group experience. Clin Exp Rheumatol. 2008 Sep-Oct;26(5):854-9. PubMed PMID: 19032819.

65: Keljo DJ, Markowitz J, Langton C, Lerer T, Bousvaros A, Carvalho R, Crandall W, Evans J, Griffiths A, Kay M, Kugathasan S, LeLeiko N, Mack D, Mamula P, Moyer MS, Oliva-Hemker M, Otley A, Pfefferkorn M, Rosh J, Hyams JS. Course and treatment of perianal disease in children newly diagnosed with Crohn's disease. Inflamm Bowel Dis. 2009 Mar;15(3):383-7. PubMed PMID: 19023863.

66: Favalli EG, Desiati F, Atzeni F, Sarzi-Puttini P, Caporali R, Pallavicini FB, Gorla R, Filippini M, Marchesoni A. Serious infections during anti-TNFalpha treatment in rheumatoid arthritis patients. Autoimmun Rev. 2009 Jan;8(3):266-73.

Epub 2008 Nov 18. PubMed PMID: 19022409.

67: Caporali R, Pallavicini FB, Filippini M, Gorla R, Marchesoni A, Favalli EG, Sarzi-Puttini P, Atzeni F, Montecucco C. Treatment of rheumatoid arthritis with anti-TNF-alpha agents: a reappraisal. Autoimmun Rev. 2009 Jan;8(3):274-80. Epub 2008 Nov 17. Review. PubMed PMID: 19017546.

68: Ramos-Casals M, Brito-Zerón P, Muñoz S, Soto MJ; BIOGEAS STUDY Group. A systematic review of the off-label use of biological therapies in systemic autoimmune diseases. Medicine (Baltimore). 2008 Nov;87(6):345-64. Review. PubMed PMID: 19011506.

69: Lopez-Olivo MA, Kallen MA, Ortiz Z, Skidmore B, Suarez-Almazor ME. Quality appraisal of clinical practice guidelines and consensus statements on the use of biologic agents in rheumatoid arthritis: a systematic review. Arthritis Rheum. 2008 Nov 15;59(11):1625-38. Review. PubMed PMID: 18975351.

70: Halpern MT, Cifaldi MA, Kvien TK. Impact of adalimumab on work participation in rheumatoid arthritis: comparison of an open-label extension study and a registry-based control group. Ann Rheum Dis. 2009 Jun;68(6):930-7. Epub 2008 Oct 1. PubMed PMID: 18829616; PubMed Central PMCID: PMC2674552.

71: Bejarano V, Quinn M, Conaghan PG, Reece R, Keenan AM, Walker D, Gough A, Green M, McGonagle D, Adebajo A, Jarrett S, Doherty S, Hordon L, Melsom R, Unnebrink K, Kupper H, Emery P; Yorkshire Early Arthritis Register Consortium. Effect of the early use of the anti-tumor necrosis factor adalimumab on the prevention of job loss in patients with early rheumatoid arthritis. Arthritis Rheum. 2008 Oct 15;59(10):1467-74. PubMed PMID: 18821658.

72: Stagaki E, Mountford WK, Lackland DT, Judson MA. The treatment of lupus pernio: results of 116 treatment courses in 54 patients. Chest. 2009 Feb;135(2):468-76. Epub 2008 Sep 23. PubMed PMID: 18812454.

73: Warren RB, Brown BC, Lavery D, Ashcroft DM, Griffiths CE. Biologic therapies for psoriasis: practical experience in a U.K. tertiary referral centre. Br J Dermatol. 2009 Jan;160(1):162-9. Epub 2008 Sep 19. PubMed PMID: 18808412.

74: Nielsen S, Ruperto N, Gerloni V, Simonini G, Cortis E, Lepore L, Alpigiani MG, Zulian F, Corona F, Alessio M, Barcellona R, Gallizzi R, Rossi F, Magni-Manzoni S, Lombardini G, Filocamo G, Raschetti R, Martini A, Ravelli A; Italian Pediatric Rheumatology Study Group. Preliminary evidence that etanercept may reduce radiographic progression in juvenile idiopathic arthritis. Clin Exp Rheumatol. 2008 Jul-Aug;26(4):688-92. PubMed PMID: 18799107.

75: Gupta N, Bostrom AG, Kirschner BS, Cohen SA, Abramson O, Ferry GD, Gold BD, Winter HS, Baldassano RN, Smith T, Heyman MB. Presentation and disease course in early- compared to later-onset pediatric Crohn's disease. Am J Gastroenterol. 2008 Aug;103(8):2092-8. PubMed PMID: 18796101.

76: Eshuis EJ, Bemelman WA, van Bodegraven AA, Sprangers MA, Bossuyt PM, van Milligen de Wit AW, Crolla RM, Cahen DL, Oostenbrug LE, Sosef MN, Voorburg AM, Davids PH, van der Woude CJ, Lange J, Mallant RC, Boom MJ, Lieverse RJ, van der Zaag ES, Houben MH, Vecht J, Pierik RE, van Ditzhuijsen TJ, Prins HA, Marsman WA, Stockmann HB, Brink MA, Consten EC, van der Werf SD, Marinelli AW, Jansen JM, Gerhards MF, Bolwerk CJ, Stassen LP, Spanier BW, Bilgen EJ, van Berkel AM, Cense HA, van Heukelem HA, van de Laar A, Slot WB, Eijsbouts QA, van Ooteghem NA, van Wagensveld B, van den Brande JM, van Geloven AA, Bruin KF, Maring JK, Oldenburg B, van Hillegersberg R, de Jong DJ, Bleichrodt R, van der Peet DL, Dekkers PE, Goei TH, Stokkers PC. Laparoscopic ileocolic resection versus infliximab treatment of distal ileitis in Crohn's disease: a randomized multicenter trial (LIR!C-trial). BMC Surg. 2008 Aug 22;8:15. PubMed PMID: 18721465; PubMed Central PMCID: PMC2533646.

77: Ilowite NT. Update on biologics in juvenile idiopathic arthritis. Curr Opin Rheumatol. 2008 Sep;20(5):613-8. Review. PubMed PMID: 18698187.

78: Hutfless S, Fireman B, Kane S, Herrinton LJ. Screening differences and risk of cervical cancer in inflammatory bowel disease. Aliment Pharmacol Ther. 2008 Sep 1;28(5):598-605. Epub 2008 Jun 28. PubMed PMID: 18549465.

79: Greenberg JD, Kishimoto M, Strand V, Cohen SB, Olenginski TP, Harrington T, Kafka SP, Reed G, Kremer JM; Consortium of Rheumatology Researchers of North America Investigators. Tumor necrosis factor antagonist responsiveness in a United States rheumatoid arthritis cohort. Am J Med. 2008 Jun;121(6):532-8. PubMed PMID: 18501236; PubMed Central PMCID: PMC2587326.

80: Hyrich KL, Lunt M, Dixon WG, Watson KD, Symmons DP; BSR Biologics Register. Effects of switching between anti-TNF therapies on HAQ response in patients who do not respond to their first anti-TNF drug. Rheumatology (Oxford). 2008 Jul;47(7):1000-5. Epub 2008 Apr 17. PubMed PMID: 18420660; PubMed Central PMCID: PMC2430221.

81: Prince FH, Twilt M, ten Cate R, van Rossum MA, Armbrust W, Hoppenreijs EP, van Santen-Hoeufft M, Koopman-Keemink Y, Wulffraat NM, van Suijlekom-Smit LW. Long-term follow-up on effectiveness and safety of etanercept in juvenile idiopathic arthritis: the Dutch national register. Ann Rheum Dis. 2009 May;68(5):635-41. Epub 2008 Apr 15. PubMed PMID: 18413443.

82: Horneff G, De Bock F, Foeldvari I, Girschick HJ, Michels H, Moebius D, Schmeling H; German and Austrian Paediatric Rheumatology Collaborative Study Group. Safety and efficacy of combination of etanercept and methotrexate compared to treatment with etanercept only in patients with juvenile idiopathic arthritis (JIA): preliminary data from the German JIA Registry. Ann Rheum Dis. 2009 Apr;68(4):519-25. Epub 2008 Apr 15. PubMed PMID: 18413440.

83: Toonen EJ, Coenen MJ, Kievit W, Fransen J, Eijsbouts AM, Scheffer H, Radstake TR, Creemers MC, de Rooij DJ, van Riel PL, Franke B, Barrera P. The tumour necrosis factor receptor superfamily member 1b 676T>G polymorphism in relation to response to infliximab and adalimumab treatment and disease severity in rheumatoid arthritis. Ann Rheum Dis. 2008 Aug;67(8):1174-7. Epub 2008 Apr 2. PubMed PMID: 18385279.

84: Harrison MJ, Dixon WG, Watson KD, King Y, Groves R, Hyrich KL, Symmons DP; British Society for Rheumatology Biologics Register Control Centre Consortium; BSRBR. Rates of new-onset psoriasis in patients with rheumatoid arthritis receiving anti-tumour necrosis factor alpha therapy: results from the British Society for Rheumatology Biologics Register. Ann Rheum Dis. 2009 Feb;68(2):209-15. Epub 2008 Apr 2. Review. PubMed PMID: 18385277; PubMed Central PMCID: PMC2605571.

85: Huang W, Cordoro KM, Taylor SL, Feldman SR. To test or not to test? An evidence-based assessment of the value of screening and monitoring tests when using systemic biologic agents to treat psoriasis. J Am Acad Dermatol. 2008 Jun;58(6):970-7. Epub 2008 Apr 2. Review. PubMed PMID: 18384909.

86: Wallis RS. Mathematical modeling of the cause of tuberculosis during tumor necrosis factor blockade. Arthritis Rheum. 2008 Apr;58(4):947-52. PubMed PMID: 18383389.

87: Tzaribachev N, Kuemmerle-Deschner J, Eichner M, Horneff G. Safety and efficacy of etanercept in children with juvenile idiopathic arthritis below the age of 4 years. Rheumatol Int. 2008 Aug;28(10):1031-4. Epub 2008 Mar 28. PubMed PMID: 18369626.

88: Kristensen LE, Kapetanovic MC, Gülfe A, Söderlin M, Saxne T, Geborek P. Predictors of response to anti-TNF therapy according to ACR and EULAR criteria in patients with established RA: results from the South Swedish Arthritis Treatment Group Register. Rheumatology (Oxford). 2008 Apr;47(4):495-9. Epub 2008 Mar 3. PubMed PMID: 18316338.

89: Listing J, Strangfeld A, Kekow J, Schneider M, Kapelle A, Wassenberg S, Zink A. Does tumor necrosis factor alpha inhibition promote or prevent heart failure in patients with rheumatoid arthritis? Arthritis Rheum. 2008 Mar;58(3):667-77. PubMed PMID: 18311816.

90: Karlsson JA, Kristensen LE, Kapetanovic MC, Gülfe A, Saxne T, Geborek P. Treatment response to a second or third TNF-inhibitor in RA: results from the South Swedish Arthritis Treatment Group Register. Rheumatology (Oxford). 2008 Apr;47(4):507-13. Epub 2008 Feb 27. PubMed PMID: 18304941.

91: O'Donnell S, O'Morain C. Review article: use of antitumour necrosis factor therapy in inflammatory bowel disease during pregnancy and conception. Aliment Pharmacol Ther. 2008 May;27(10):885-94. Epub 2008 Feb 14. Review. PubMed PMID: 18284649.

92: Behm BW, Bickston SJ. Tumor necrosis factor-alpha antibody for maintenance of remission in Crohn's disease. Cochrane Database Syst Rev. 2008 Jan 23;(1):CD006893. Review. PubMed PMID: 18254120.

93: Tsiodras S, Samonis G, Boumpas DT, Kontoyiannis DP. Fungal infections complicating tumor necrosis factor alpha blockade therapy. Mayo Clin Proc. 2008 Feb;83(2):181-94. Review. PubMed PMID: 18241628.

94: Heiberg MS, Koldingsnes W, Mikkelsen K, Rødevand E, Kaufmann C, Mowinckel P, Kvien TK. The comparative one-year performance of anti-tumor necrosis factor alpha drugs in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis: results from a longitudinal, observational, multicenter study. Arthritis Rheum. 2008 Feb 15;59(2):234-40. PubMed PMID: 18240258.

95: Kievit W, Adang EM, Fransen J, Kuper HH, van de Laar MA, Jansen TL, De Gendt CM, De Rooij DJ, Brus HL, Van Oijen PC, Van Riel PC. The effectiveness and medication costs of three anti-tumour necrosis factor alpha agents in the treatment of rheumatoid arthritis from prospective clinical practice data. Ann Rheum Dis. 2008 Sep;67(9):1229-34. Epub 2008 Jan 3. PubMed PMID: 18174220.

96: van Vollenhoven RF, Klareskog L. Infliximab dosage and infusion frequency in clinical practice: experiences in the Stockholm biologics registry STURE. Scand J Rheumatol. 2007 Nov-Dec;36(6):418-23. PubMed PMID: 18092261.

97: Swaminath A, Lichtiger S. Dilation of colonic strictures by intralesional injection of infliximab in patients with Crohn's colitis. Inflamm Bowel Dis. 2008 Feb;14(2):213-6. Review. PubMed PMID: 18022870.

98: Blumenstein I, Bock H, Weber C, Rambow A, Tacke W, Kihn R, Pfaff R, Orlemann S, Schaeffer R, Schröder O, Dignass A, Hartmann F, Stein J. Health care and cost of medication for inflammatory bowel disease in the Rhein-Main region, Germany: a multicenter, prospective, internet-based study. Inflamm Bowel Dis. 2008 Jan;14(1):53-60. PubMed PMID: 17973301.

99: Lim LL, Fraunfelder FW, Rosenbaum JT. Do tumor necrosis factor inhibitors cause uveitis? A registry-based study. Arthritis Rheum. 2007 Oct;56(10):3248-52. PubMed PMID: 17907169.

100: Pavelka K, Gatterová J, Tegzová D, Jarosová K, Tomasová Studýnková J, Svobodník A, Svihálek J, Dusek L, Vencovský J. Radiographic progression of rheumatoid arthritis in patients from the Czech National Registry receiving

infliximab treatment. Clin Exp Rheumatol. 2007 Jul-Aug;25(4):540-5. PubMed PMID: 17888209.

101: Schreiber S. [Crohn's disease--infliximab, adalimumab and certolizumab-pegol: clinical value of anti-TNF-alpha treatment]. Dtsch Med Wochenschr. 2007 Aug;132(34-35):1770-4. Review. German. PubMed PMID: 17713889.

102: Kristensen LE, Gülfe A, Saxne T, Geborek P. Efficacy and tolerability of anti-tumour necrosis factor therapy in psoriatic arthritis patients: results from the South Swedish Arthritis Treatment Group register. Ann Rheum Dis. 2008 Mar;67(3):364-9. Epub 2007 Jul 20. PubMed PMID: 17644547.

103: Kuemmerle-Deschner JB, Horneff G. Safety and efficacy of once-weekly application of Etanercept in children with juvenile idiopathic arthritis. Rheumatol Int. 2007 Dec;28(2):153-6. Epub 2007 Jul 20. PubMed PMID: 17641897.

104: Akobeng AK, Thomas AG. Enteral nutrition for maintenance of remission in Crohn's disease. Cochrane Database Syst Rev. 2007 Jul 18;(3):CD005984. Review. PubMed PMID: 17636816.

105: Ramos-Casals M, Brito-Zerón P, Muñoz S, Soria N, Galiana D, Bertolaccini L, Cuadrado MJ, Khamashta MA. Autoimmune diseases induced by TNF-targeted therapies: analysis of 233 cases. Medicine (Baltimore). 2007 Jul;86(4):242-51. PubMed PMID: 17632266.

106: Carmona L, Ortiz A, Abad MA. How good is to switch between biologics? A systematic review of the literature. Acta Reumatol Port. 2007 Apr-Jun;32(2):113-28. Review. PubMed PMID: 17572650.

107: Brennan A, Bansback N, Nixon R, Madan J, Harrison M, Watson K, Symmons D. Modelling the cost effectiveness of TNF-alpha antagonists in the management of rheumatoid arthritis: results from the British Society for Rheumatology Biologics Registry. Rheumatology (Oxford). 2007 Aug;46(8):1345-54. Epub 2007 Jun 11. PubMed PMID: 17562686.

108: Gómez-Reino JJ, Carmona L, Angel Descalzo M; Biobadaser Group. Risk of tuberculosis in patients treated with tumor necrosis factor antagonists due to incomplete prevention of reactivation of latent infection. Arthritis Rheum. 2007 Jun 15;57(5):756-61. PubMed PMID: 17530674.

109: Augustsson J, Eksborg S, Ernestam S, Gullström E, van Vollenhoven R. Low-dose glucocorticoid therapy decreases risk for treatment-limiting infusion reaction to infliximab in patients with rheumatoid arthritis. Ann Rheum Dis. 2007 Nov;66(11):1462-6. Epub 2007 May 14. PubMed PMID: 17502359.

110: Ostergaard M, Unkerskov J, Linde L, Krogh NS, Ravn T, Ringsdal VS, Petri A, Andersen LS, Tarp U, Hansen A, Hjardem E, Hetland ML. Low remission rates but long drug survival in rheumatoid arthritis patients treated with infliximab or etanercept: results from the nationwide Danish DANBIO database. Scand J Rheumatol. 2007 Mar-Apr;36(2):151-4. PubMed PMID: 17476624.

111: Salvarani C, Macchioni P, Manzini C, Paolazzi G, Trotta A, Manganelli P, Cimmino M, Gerli R, Catanoso MG, Boiardi L, Cantini F, Klersy C, Hunder GG. Infliximab plus prednisone or placebo plus prednisone for the initial treatment of polymyalgia rheumatica: a randomized trial. Ann Intern Med. 2007 May 1;146(9):631-9. PubMed PMID: 17470831.

112: Wolfe F, Michaud K. The effect of methotrexate and anti-tumor necrosis factor therapy on the risk of lymphoma in rheumatoid arthritis in 19,562 patients during 89,710 person-years of observation. Arthritis Rheum. 2007 May;56(5):1433-9. PubMed PMID: 17469100.

113: Radstake TR, Fransen J, Toonen EJ, Coenen MJ, Eijsbouts AE, Donn R, van den Hoogen FH, van Riel PL. Macrophage migration inhibitory factor polymorphisms do not predict therapeutic response to glucocorticoids or to tumour necrosis factor alpha-neutralising treatments in rheumatoid arthritis. Ann Rheum Dis. 2007 Nov;66(11):1525-30. Epub 2007 Apr 24. PubMed PMID: 17456524.

114: Kievit W, Fransen J, Oerlemans AJ, Kuper HH, van der Laar MA, de Rooij DJ, De Gendt CM, Ronday KH, Jansen TL, van Oijen PC, Brus HL, Adang EM, van Riel PL. The efficacy of anti-TNF in rheumatoid arthritis, a comparison between randomised controlled trials and clinical practice. Ann Rheum Dis. 2007 Nov;66(11):1473-8. Epub 2007 Apr 10. Review. PubMed PMID: 17426065.

115: Konttinen L, Tuompo R, Uusitalo T, Luosujärvi R, Laiho K, Lähteenmäki J, Puurtinen-Vilkki M, Lanteri R, Kortelainen S, Karilainen H, Varjolahti-Lehtinen T, Nordström D; ROB-FIN Study Group. Anti-TNF therapy in the treatment of ankylosing spondylitis: the Finnish experience. Clin Rheumatol. 2007 Oct;26(10):1693-700. Epub 2007 Mar 1. PubMed PMID: 17332979.

116: Lee HH, Song IH, Friedrich M, Gauliard A, Detert J, Röwert J, Audring H, Kary S, Burmester GR, Sterry W, Worm M. Cutaneous side-effects in patients with rheumatic diseases during application of tumour necrosis factor-alpha antagonists. Br J Dermatol. 2007 Mar;156(3):486-91. PubMed PMID: 17300238.

117: Kappelman MD, Bousvaros A, Hyams J, Markowitz J, Pfefferkorn M, Kugathasan S, Rosh J, Otley A, Mack D, Griffiths A, Evans J, Grand R, Langton C, Kleinman K, Finkelstein JA. Intercenter variation in initial management of children with Crohn's disease. Inflamm Bowel Dis. 2007 Jul;13(7):890-5. PubMed PMID: 17286275.

118: Dauendorffer JN, Rivet J, Allard A, Bachelez H. Sézary syndrome in a patient receiving infliximab for ankylosing spondylitis. Br J Dermatol. 2007 Apr;156(4):742-3. Epub 2007 Jan 30. PubMed PMID: 17263820.

119: Vander Cruyssen B, Ribbens C, Boonen A, Mielants H, de Vlam K, Lenaerts J, Steinfeld S, Van den Bosch F, Dewulf L, Vastesaeger N. The epidemiology of ankylosing spondylitis and the commencement of anti-TNF therapy in daily rheumatology practice. Ann Rheum Dis. 2007 Aug;66(8):1072-7. Epub 2007 Jan 29. PubMed PMID: 17261531; PubMed Central PMCID: PMC1954702.

120: Toussirot E, Streit G, Wendling D. Infectious complications with anti-TNFalpha therapy in rheumatic diseases: a review. Recent Pat Inflamm Allergy Drug Discov. 2007;1(1):39-47. Review. PubMed PMID: 19075965.

121: Hyrich KL, Lunt M, Watson KD, Symmons DP, Silman AJ; British Society for Rheumatology Biologics Register. Outcomes after switching from one anti-tumor necrosis factor alpha agent to a second anti-tumor necrosis factor alpha agent in patients with rheumatoid arthritis: results from a large UK national cohort study. Arthritis Rheum. 2007 Jan;56(1):13-20. PubMed PMID: 17195186.

122: Roux CH, Brocq O, Breuil V, Albert C, Euller-Ziegler L. Pregnancy in rheumatology patients exposed to anti-tumour necrosis factor (TNF)-alpha therapy. Rheumatology (Oxford). 2007 Apr;46(4):695-8. Epub 2006 Dec 7. Review. PubMed PMID: 17158212.

123: Gómez-Reino J, Carmona L. Recommendations to lower the risk of tuberculosis in patients treated with tumour necrosis factor alpha antagonists. Acta Reumatol Port. 2006 Jul-Sep;31(3):201-3. PubMed PMID: 17094331.

124: Zink A, Strangfeld A, Schneider M, Herzer P, Hierse F, Stoyanova-Scholz M, Wassenberg S, Kapelle A, Listing J. Effectiveness of tumor necrosis factor inhibitors in rheumatoid arthritis in an observational cohort study: comparison of patients according to their eligibility for major randomized clinical trials. Arthritis Rheum. 2006 Nov;54(11):3399-407. PubMed PMID: 17075823.

125: Tubach F, Ravaud P, Salmon-Céron D, Petitpain N, Brocq O, Grados F, Guillaume JC, Leport J, Roudaut A, Solau-Gervais E, Lemann M, Mariette X, Lortholary O; Recherce Axée sur la Tolérance des Biothérapies Group. Emergence of Legionella pneumophila pneumonia in patients receiving tumor necrosis factor-alpha antagonists. Clin Infect Dis. 2006 Nov 15;43(10):e95-100. Epub 2006 Oct 16. PubMed PMID: 17051484.

126: Kamm MA. Review article: biological drugs in Crohn's disease. Aliment Pharmacol Ther. 2006 Oct;24 Suppl 3:80-9. Review. PubMed PMID: 16961751.

127: Dixon WG, Watson K, Lunt M, Hyrich KL, Silman AJ, Symmons DP; British Society for Rheumatology Biologics Register. Rates of serious infection, including site-specific and bacterial intracellular infection, in rheumatoid arthritis patients receiving anti-tumor necrosis factor therapy: results from the British Society for Rheumatology Biologics Register. Arthritis Rheum. 2006 Aug;54(8):2368-76. PubMed PMID: 16868999.

128: Markowitz J, Hyams J, Mack D, Leleiko N, Evans J, Kugathasan S, Pfefferkorn M, Mezoff A, Rosh J, Tolia V, Otley A, Griffiths A, Moyer MS, Oliva-Hemker M, Wyllie R, Rothbaum R, Bousvaros A, Del Rosario JF, Hale S, Lerer T; Pediatric IBD Collaborative Research Group. Corticosteroid therapy in the age of infliximab: acute and 1-year outcomes in newly diagnosed children with Crohn's disease. Clin Gastroenterol Hepatol. 2006 Sep;4(9):1124-9. Epub 2006 Jul 24. PubMed PMID: 16861053.

129: Lawson MM, Thomas AG, Akobeng AK. Tumour necrosis factor alpha blocking agents for induction of remission in ulcerative colitis. Cochrane Database Syst Rev. 2006 Jul 19;3:CD005112. Review. PubMed PMID: 16856078.

130: Hyrich KL, Symmons DP, Watson KD, Silman AJ; British Society for Rheumatology Biologics Register. Comparison of the response to infliximab or etanercept monotherapy with the response to cotherapy with methotrexate or another disease-modifying antirheumatic drug in patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register. Arthritis Rheum. 2006 Jun;54(6):1786-94. PubMed PMID: 16736520.

131: Hyrich KL, Watson KD, Silman AJ, Symmons DP; British Society for Rheumatology Biologics Register. Predictors of response to anti-TNF-alpha therapy among patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register. Rheumatology (Oxford). 2006 Dec;45(12):1558-65. Epub 2006 May 16. PubMed PMID: 16705046.

132: Sidiropoulos PI, Boumpas DT. Differential drug resistance to anti-tumour necrosis factor agents in rheumatoid arthritis. Ann Rheum Dis. 2006 Jun;65(6):701-3. PubMed PMID: 16699049; PubMed Central PMCID: PMC1798160.

133: Lichtenstein GR, Feagan BG, Cohen RD, Salzberg BA, Diamond RH, Chen DM, Pritchard ML, Sandborn WJ. Serious infections and mortality in association with therapies for Crohn's disease: TREAT registry. Clin Gastroenterol Hepatol. 2006 May;4(5):621-30. Erratum in: Clin Gastroenterol Hepatol. 2006 Jul;4(7):931. PubMed PMID: 16678077.

134: Vijverman A, Piront P, Belaiche J, Louis E. Evolution of the prevalence and characteristics of anemia in inflammatory bowel diseases between 1993 and 2003. Acta Gastroenterol Belg. 2006 Jan-Mar;69(1):1-4. PubMed PMID: 16673554.

135: Carter JD, Valeriano J, Vasey FB. Tumor necrosis factor-alpha inhibition and VATER association: a causal relationship. J Rheumatol. 2006 May;33(5):1014-7. PubMed PMID: 16652431.

136: Symmons DP, Silman AJ. The world of biologics. Lupus. 2006;15(3):122-6.

Review. PubMed PMID: 16634363.

137: Carmona L, Gómez-Reino JJ; BIOBADASER Group. Survival of TNF antagonists in spondylarthritis is better than in rheumatoid arthritis. Data from the Spanish registry BIOBADASER. Arthritis Res Ther. 2006;8(3):R72. Epub 2006 Apr 18. PubMed PMID: 16620398; PubMed Central PMCID: PMC1526631.

138: Gupta N, Cohen SA, Bostrom AG, Kirschner BS, Baldassano RN, Winter HS, Ferry GD, Smith T, Abramson O, Gold BD, Heyman MB. Risk factors for initial surgery in pediatric patients with Crohn's disease. Gastroenterology. 2006 Apr;130(4):1069-77. PubMed PMID: 16618401.

139: Lichtenstein GR, Olson A, Travers S, Diamond RH, Chen DM, Pritchard ML, Feagan BG, Cohen RD, Salzberg BA, Hanauer SB, Sandborn WJ. Factors associated with the development of intestinal strictures or obstructions in patients with Crohn's disease. Am J Gastroenterol. 2006 May;101(5):1030-8. PubMed PMID: 16606351.

140: Zink A, Listing J, Strangfeld A, Gromnica-Ihle E, Demary W, Schneider M. [Dose adjustment in patients treated with infliximab in routine rheumatologic care in Germany. Results from the Biologics Register RABBIT]. Z Rheumatol. 2006 Sep;65(5):441-6. German. PubMed PMID: 16534537.

141: Gomez-Reino JJ, Carmona L; BIOBADASER Group. Switching TNF antagonists in patients with chronic arthritis: an observational study of 488 patients over a four-year period. Arthritis Res Ther. 2006;8(1):R29. Epub 2006 Jan 6. PubMed PMID: 16507128; PubMed Central PMCID: PMC1526564.

142: Smyth CM, Picha SB, Rathore O, Deasy J, Patchett SE, Murray FE. Increasing rates and changing patterns of hospital admissions for patients with inflammatory bowel disease in Ireland: 1996-2001. Ir J Med Sci. 2005 Oct-Dec;174(4):28-32. PubMed PMID: 16445157.

143: Tutuncu Z, Reed G, Kremer J, Kavanaugh A. Do patients with older-onset rheumatoid arthritis receive less aggressive treatment? Ann Rheum Dis. 2006 Sep;65(9):1226-9. Epub 2006 Jan 13. PubMed PMID: 16414968; PubMed Central PMCID: PMC1798297.

144: Söderlin M, Blomkvist C, Dahl P, Forsberg P, Fohlman J. [Increased risk of infection with biological immunomodifying antirheumatic agents. Clear guidelines are necessary as shown by case reports]. Lakartidningen. 2005 Dec 5-11;102(49):3794-6, 3799-800. Swedish. PubMed PMID: 16408703.

145: Weaver AL, Lautzenheiser RL, Schiff MH, Gibofsky A, Perruquet JL, Luetkemeyer J, Paulus HE, Xia HA, Leff JA; RADIUS Investigators. Real-world effectiveness of select biologic and DMARD monotherapy and combination therapy in the treatment of rheumatoid arthritis: results from the RADIUS observational registry. Curr Med Res Opin. 2006 Jan;22(1):185-98. PubMed PMID: 16393444.

146: Gibofsky A, Palmer WR, Goldman JA, Lautzenheiser RL, Markenson JA, Weaver A, Schiff MH, Keystone EC, Paulus HE, Harrison MJ, Whitmore JB, Leff JA. Real-world utilization of DMARDs and biologics in rheumatoid arthritis: the RADIUS (Rheumatoid Arthritis Disease-Modifying Anti-Rheumatic Drug Intervention and Utilization Study) study. Curr Med Res Opin. 2006 Jan;22(1):169-83. PubMed PMID: 16393443.

147: Hyrich K, Symmons D, Watson K, Silman A; BSRBR Control Centre Consortium; British Society for Rheumatology Biologics Register. Baseline comorbidity levels in biologic and standard DMARD treated patients with rheumatoid arthritis: results from a national patient register. Ann Rheum Dis. 2006 Jul;65(7):895-8. Epub 2005 Dec 8. PubMed PMID: 16339291; PubMed Central PMCID: PMC1798204.

148: Listing J, Strangfeld A, Kary S, Rau R, von Hinueber U, Stoyanova-Scholz M, Gromnica-Ihle E, Antoni C, Herzer P, Kekow J, Schneider M, Zink A. Infections in patients with rheumatoid arthritis treated with biologic agents. Arthritis Rheum. 2005 Nov;52(11):3403-12. PubMed PMID: 16255017.

149: Wick MC, Ernestam S, Lindblad S, Bratt J, Klareskog L, van Vollenhoven RF. Adalimumab (Humira) restores clinical response in patients with secondary loss of efficacy from infliximab (Remicade) or etanercept (Enbrel): results from the STURE registry at Karolinska University Hospital. Scand J Rheumatol. 2005 Sep-Oct;34(5):353-8. PubMed PMID: 16234182.

150: Nordström DC, Konttinen L, Korpela M, Tiippana-Kinnunen T, Eklund K, Forsberg S, Ilva K, Kaipiainen-Seppänen O, Malmi T, Ylä-Kerttula T, Honkanen V. Classic disease modifying anti-rheumatic drugs (DMARDs) in combination with infliximab. The Finnish experience. Rheumatol Int. 2006 Jun;26(8):741-8. Epub 2005 Oct 5. PubMed PMID: 16205925.

151: Kalden JR, Antoni C, Alvaro-Gracia JM, Combe B, Emery P, Kremer JM, Strand CV, Van Riel P, Smolen JS. Use of combination of leflunomide with biological agents in treatment of rheumatoid arthritis. J Rheumatol. 2005 Aug;32(8):1620-31. Review. PubMed PMID: 16078347.

152: Newby EA, Sawczenko A, Thomas AG, Wilson D. Interventions for growth failure in childhood Crohn's disease. Cochrane Database Syst Rev. 2005 Jul 20;(3):CD003873. Review. PubMed PMID: 16034910.

153: Jacobsson LT, Turesson C, Gülfe A, Kapetanovic MC, Petersson IF, Saxne T, Geborek P. Treatment with tumor necrosis factor blockers is associated with a lower incidence of first cardiovascular events in patients with rheumatoid arthritis. J Rheumatol. 2005 Jul;32(7):1213-8. PubMed PMID: 15996054.

154: Askling J, Fored CM, Brandt L, Baecklund E, Bertilsson L, Cöster L, Geborek P, Jacobsson LT, Lindblad S, Lysholm J, Rantapää-Dahlqvist S, Saxne T, Romanus V, Klareskog L, Feltelius N. Risk and case characteristics of tuberculosis in rheumatoid arthritis associated with tumor necrosis factor antagonists in Sweden. Arthritis Rheum. 2005 Jul;52(7):1986-92. PubMed PMID: 15986370.

155: Carmona L, Gómez-Reino JJ, Rodríguez-Valverde V, Montero D, Pascual-Gómez E, Mola EM, Carreño L, Figueroa M; BIOBADASER Group. Effectiveness of recommendations to prevent reactivation of latent tuberculosis infection in patients treated with tumor necrosis factor antagonists. Arthritis Rheum. 2005 Jun;52(6):1766-72. PubMed PMID: 15934089.

156: Botsios C. Safety of tumour necrosis factor and interleukin-1 blocking agents in rheumatic diseases. Autoimmun Rev. 2005 Mar;4(3):162-70. Review. PubMed PMID: 15823502.

157: Zink A, Listing J, Kary S, Ramlau P, Stoyanova-Scholz M, Babinsky K, von Hinueber U, Gromnica-Ihle E, Wassenberg S, Antoni C, Herzer P, Kekow J, Schneider M, Rau R. Treatment continuation in patients receiving biological agents or conventional DMARD therapy. Ann Rheum Dis. 2005 Sep;64(9):1274-9. Epub 2005 Feb 11. PubMed PMID: 15708884; PubMed Central PMCID: PMC1755655.

158: Geborek P, Bladström A, Turesson C, Gulfe A, Petersson IF, Saxne T, Olsson H, Jacobsson LT. Tumour necrosis factor blockers do not increase overall tumour risk in patients with rheumatoid arthritis, but may be associated with an increased risk of lymphomas. Ann Rheum Dis. 2005 May;64(5):699-703. Epub 2005 Feb 4. PubMed PMID: 15695534; PubMed Central PMCID: PMC1755491.

159: van Vollenhoven RF. Switching between biological agents. Clin Exp Rheumatol. 2004 Sep-Oct;22(5 Suppl 35):S115-21. Review. PubMed PMID: 15552524.

160: Wenzl HH, Reinisch W, Jahnel J, Stockenhuber F, Tilg H, Kirchgatterer A, Petritsch W. Austrian infliximab experience in Crohn's disease: a nationwide cooperative study with long-term follow-up. Eur J Gastroenterol Hepatol. 2004 Aug;16(8):767-73. PubMed PMID: 15256978.

161: Wolfe F, Michaud K. Lymphoma in rheumatoid arthritis: the effect of methotrexate and anti-tumor necrosis factor therapy in 18,572 patients. Arthritis Rheum. 2004 Jun;50(6):1740-51. PubMed PMID: 15188349.

162: Marshall NJ, Wilson G, Lapworth K, Kay LJ. Patients' perceptions of treatment with anti-TNF therapy for rheumatoid arthritis: a qualitative study. Rheumatology (Oxford). 2004 Aug;43(8):1034-8. Epub 2004 May 18. PubMed PMID: 15150436.

163: Colombel JF, Loftus EV Jr, Tremaine WJ, Pemberton JH, Wolff BG, Young-Fadok T, Harmsen WS, Schleck CD, Sandborn WJ. Early postoperative complications are not increased in patients with Crohn's disease treated perioperatively with infliximab or immunosuppressive therapy. Am J Gastroenterol. 2004 May;99(5):878-83. PubMed PMID: 15128354.

164: Horneff G, Schmeling H, Biedermann T, Foeldvari I, Ganser G, Girschick HJ, Hospach T, Huppertz HI, Keitzer R, Küster RM, Michels H, Moebius D, Rogalski B, Thon A; Paediatric Rheumatology Collaborative Group. The German etanercept registry for treatment of juvenile idiopathic arthritis. Ann Rheum Dis. 2004 Dec;63(12):1638-44. Epub 2004 Apr 28. Review. PubMed PMID: 15115709; PubMed Central PMCID: PMC1754849.

165: Jonsdottir T, Forslid J, van Vollenhoven A, Harju A, Brannemark S, Klareskog L, van Vollenhoven RF. Treatment with tumour necrosis factor alpha antagonists in patients with rheumatoid arthritis induces anticardiolipin antibodies. Ann Rheum Dis. 2004 Sep;63(9):1075-8. Epub 2004 Apr 5. PubMed PMID: 15066863; PubMed Central PMCID: PMC1755142.

166: Akobeng AK, Zachos M. Tumor necrosis factor-alpha antibody for induction of remission in Crohn's disease. Cochrane Database Syst Rev. 2004;(1):CD003574. Review. PubMed PMID: 14974022.

167: van Vollenhoven RF, Ernestam S, Harju A, Bratt J, Klareskog L. Etanercept versus etanercept plus methotrexate: a registry-based study suggesting that the combination is clinically more efficacious. Arthritis Res Ther. 2003;5(6):R347-51. Epub 2003 Oct 1. PubMed PMID: 14680509; PubMed Central PMCID: PMC333416.

168: van Vollenhoven R, Harju A, Brannemark S, Klareskog L. Treatment with infliximab (Remicade) when etanercept (Enbrel) has failed or vice versa: data from the STURE registry showing that switching tumour necrosis factor alpha blockers can make sense. Ann Rheum Dis. 2003 Dec;62(12):1195-8. PubMed PMID: 14644858; PubMed Central PMCID: PMC1754380.

169: Flendrie M, Creemers MC, Welsing PM, den Broeder AA, van Riel PL. Survival during treatment with tumour necrosis factor blocking agents in rheumatoid arthritis. Ann Rheum Dis. 2003 Nov;62 Suppl 2:ii30-3. PubMed PMID: 14532145; PubMed Central PMCID: PMC1766750.

170: Gómez-Reino JJ, Carmona L, Valverde VR, Mola EM, Montero MD; BIOBADASER Group. Treatment of rheumatoid arthritis with tumor necrosis factor inhibitors may predispose to significant increase in tuberculosis risk: a multicenter active-surveillance report. Arthritis Rheum. 2003 Aug;48(8):2122-7. PubMed PMID: 12905464.

171: van Vollenhoven RF, Klareskog L. Clinical responses to tumor necrosis factor alpha antagonists do not show a bimodal distribution: data from the Stockholm

tumor necrosis factor alpha followup registry. Arthritis Rheum. 2003 Jun;48(6):1500-3. PubMed PMID: 12794816.

172: Wagner CL, Schantz A, Barnathan E, Olson A, Mascelli MA, Ford J, Damaraju L, Schaible T, Maini RN, Tcheng JE. Consequences of immunogenicity to the therapeutic monoclonal antibodies ReoPro and Remicade. Dev Biol (Basel). 2003;112:37-53. PubMed PMID: 12762503.

SEARCH 17 meta all agents 9-14 update

Category	Description
Clinical question or focus	BIOLOGICAL AGENTS FINAL
Source	PubMed
Terms	(adalimumab OR certolizumab OR etanercept OR golimumab OR infliximab OR ustekinumab
Limits	none
▪ Date limits	none
▪ Other limits	Meta-analysis
▪ Number of hits	68
Query Translation (eg, “Details” in PubMed)	(("adalimumab"[Substance Name] OR "adalimumab"[All Fields]) OR ("CDP870"[Substance Name] OR "CDP870"[All Fields] OR "certolizumab"[All Fields]) OR ("TNFR-Fc fusion protein"[Substance Name] OR "TNFR-Fc fusion protein"[All Fields] OR "etanercept"[All Fields]) OR ("golimumab"[Substance Name] OR "golimumab"[All Fields]) OR ("infliximab"[Substance Name] OR "infliximab"[All Fields]) OR ("monoclonal antibody CNTO 1275"[Substance Name] OR "monoclonal antibody CNTO 1275"[All Fields] OR "ustekinumab"[All Fields])) AND Meta-Analysis[ptyp]
Date of Search	10/14/10
Marked for retrieval	Bongartz 06
Exclusions	-Not focus of review: population, intervention, comparison, outcome -Superseded by more recent larger study -Lacking safety data -Duplicates

1: Kuriya B, Arkema EV, Bykerk VP, Keystone EC. Efficacy of initial methotrexate monotherapy versus combination therapy with a biological agent in early rheumatoid arthritis: a meta-analysis of clinical and radiographic remission. Ann Rheum Dis. 2010 Jul;69(7):1298-304. Epub 2010 Apr 26. Review. PubMed PMID: 20421343.

2: Wiens A, Venson R, Correr CJ, Otuki MF, Pontarolo R. Meta-analysis of the efficacy and safety of adalimumab, etanercept, and infliximab for the treatment of rheumatoid arthritis. Pharmacotherapy. 2010 Apr;30(4):339-53. Review. PubMed PMID: 20334454.
Most recent meta for ETN, IFX, ADA [RA]; critiqued

3: Lee YH, Ji JD, Bae SC, Song GG. Associations between tumor necrosis factor-alpha (TNF-alpha) -308 and -238 G/A polymorphisms and shared epitope status and responsiveness to TNF-alpha blockers in rheumatoid arthritis: a metaanalysis update. J Rheumatol. 2010 Apr;37(4):740-6. Epub 2010 Mar 1. PubMed PMID: 20194454.

4: Singh JA, Noorbaloochi S, Singh G. Golimumab for rheumatoid arthritis. Cochrane Database Syst Rev. 2010 Jan 20;(1):CD008341. Review. PubMed PMID: 20091667.
Most recent meta for GOL [RA]; critiqued

5: Petitpain N, Gambier N, Wahl D, Chary-Valckenaere I, Loeuille D, Gillet P; French Network of Pharmacovigilance Centers. Arterial and venous thromboembolic

events during anti-TNF therapy: a study of 85 spontaneous reports in the period 2000-2006. Biomed Mater Eng. 2009;19(4-5):355-64. PubMed PMID: 20042802.

6: Yang Z, Wu Q, Wu K, Fan D. Meta-analysis: pre-operative infliximab treatment and short-term post-operative complications in patients with ulcerative colitis. Aliment Pharmacol Ther. 2010 Feb 15;31(4):486-92. Epub 2009 Nov 19. PubMed PMID: 19925496.

7: Blasco AJ, Lázaro P, Ferrándiz C, García-Díez A, Liso J. [Efficiency of biologic agents in the treatment of moderate to severe psoriasis]. Actas Dermosifiliogr. 2009 Nov;100(9):792-803. Spanish. PubMed PMID: 19889301.

8: Singh JA, Christensen R, Wells GA, Suarez-Almazor ME, Buchbinder R, Lopez-Olivo MA, Ghogomu ET, Tugwell P. A network meta-analysis of randomized controlled trials of biologics for rheumatoid arthritis: a Cochrane overview. CMAJ. 2009 Nov 24;181(11):787-96. Epub 2009 Nov 2. Erratum in: CMAJ. 2010 May 18;182(8):806. PubMed PMID: 19884297; PubMed Central PMCID: PMC2780484.

9: Singh JA, Christensen R, Wells GA, Suarez-Almazor ME, Buchbinder R, Lopez-Olivo MA, Tanjong Ghogomu E, Tugwell P. Biologics for rheumatoid arthritis: an overview of Cochrane reviews. Cochrane Database Syst Rev. 2009 Oct 7;(4):CD007848. Review. PubMed PMID: 19821440.
Most recent Cochrane meta [RA]; critiqued

10: Doherty G, Bennett G, Patil S, Cheifetz A, Moss AC. Interventions for prevention of post-operative recurrence of Crohn's disease. Cochrane Database Syst Rev. 2009 Oct 7;(4):CD006873. Review. PubMed PMID: 19821389.

11: Jessop S, Whitelaw DA, Delamere FM. Drugs for discoid lupus erythematosus. Cochrane Database Syst Rev. 2009 Oct 7;(4):CD002954. Review. PubMed PMID: 19821298.

12: Köller MD, Aletaha D, Funovits J, Pangan A, Baker D, Smolen JS. Response of elderly patients with rheumatoid arthritis to methotrexate or TNF inhibitors compared with younger patients. Rheumatology (Oxford). 2009 Dec;48(12):1575-80. Epub 2009 Oct 7. PubMed PMID: 19812228.

13: Frankel AJ, Van Voorhees AS, Hsu S, Korman NJ, Lebwohl MG, Bebo BF Jr, Gottlieb AB; National Psoriasis Foundation. Treatment of psoriasis in patients with hepatitis C: from the Medical Board of the National Psoriasis Foundation. J Am Acad Dermatol. 2009 Dec;61(6):1044-55. Epub 2009 Oct 7. Review. PubMed PMID: 19811848.

14: Poulin Y, Langley RG, Teixeira HD, Martel MJ, Cheung S. Biologics in the treatment of psoriasis: clinical and economic overview. J Cutan Med Surg. 2009 Sep-Oct;13 Suppl 2:S49-57. Review. PubMed PMID: 19799827.
Most recent review [psoriasis]; no safety data

15: Wiens A, Correr CJ, Venson R, Grochocki MC, Otuki MF, Pontarolo R. A meta-analysis of the efficacy and safety of using infliximab for the treatment of rheumatoid arthritis. Clin Rheumatol. 2009 Dec;28(12):1365-73. Epub 2009 Sep 22. Review. PubMed PMID: 19771491.

16: Wiens A, Correr CJ, Pontarolo R, Venson R, Quinalha JV, Otuki MF. A systematic review and meta-analysis of the efficacy and safety of etanercept for treating rheumatoid arthritis. Scand J Immunol. 2009 Oct;70(4):337-44. Review. PubMed PMID: 19751268.

17: Christensen R, Kristensen LE, Geborek P, Danneskiold-Samsøe B, Saxne T, Bliddal H. [The efficacy of the three available anti-tumour necrosis factor therapies in patients with rheumatoid arthritis. A meta-analytic literature review--secondary publication]. Ugeskr Laeger. 2009 Jun 22;171(26):2192-4.

Review. Danish. PubMed PMID: 19678436.

18: Bansback N, Sizto S, Sun H, Feldman S, Willian MK, Anis A. Efficacy of systemic treatments for moderate to severe plaque psoriasis: systematic review and meta-analysis. Dermatology. 2009;219(3):209-18. Epub 2009 Aug 5. Review. PubMed PMID: 19657180.
Recent meta [psoriasis] but no safety data

19: Brown BC, Warren RB, Grindlay DJ, Griffiths CE. What's new in psoriasis? Analysis of the clinical significance of systematic reviews on psoriasis published in 2007 and 2008. Clin Exp Dermatol. 2009 Aug;34(6):664-7. Epub 2009 Jun 30. Review. PubMed PMID: 19572945.

20: Sieper J, Koenig A, Baumgartner S, Wishneski C, Foehl J, Vlahos B, Freundlich B. Analysis of uveitis rates across all etanercept ankylosing spondylitis clinical trials. Ann Rheum Dis. 2010 Jan;69(1):226-9. Epub . PubMed PMID: 19465402.

21: Zhang Z, Schmitt J, Wozel G, Kirch W. [Treatment of plaque psoriasis with biologics. A meta-analysis of randomized controlled trials]. Med Klin (Munich). 2009 Feb 15;104(2):125-36. Epub 2009 Feb 26. German. PubMed PMID: 19242664.

22: Shao LM, Chen MY, Cai JT. Meta-analysis: the efficacy and safety of certolizumab pegol in Crohn's disease. Aliment Pharmacol Ther. 2009 Mar 15;29(6):605-14. PubMed PMID: 19183161.

23: Burmester GR, Mease P, Dijkmans BA, Gordon K, Lovell D, Panaccione R, Perez J, Pangan AL. Adalimumab safety and mortality rates from global clinical trials of six immune-mediated inflammatory diseases. Ann Rheum Dis. 2009 Dec;68(12):1863-9. Epub 2009 Jan 15. PubMed PMID: 19147611; PubMed Central PMCID: PMC2770105.

24: Zintzaras E, Dahabreh IJ, Giannouli S, Voulgarelis M, Moutsopoulos HM. Infliximab and methotrexate in the treatment of rheumatoid arthritis: a systematic review and meta-analysis of dosage regimens. Clin Ther. 2008 Nov;30(11):1939-55. Review. PubMed PMID: 19108784.

25: Bongartz T, Warren FC, Mines D, Matteson EL, Abrams KR, Sutton AJ. Etanercept therapy in rheumatoid arthritis and the risk of malignancies: a systematic review and individual patient data meta-analysis of randomised controlled trials. Ann Rheum Dis. 2009 Jul;68(7):1177-83. Epub 2008 Nov 19. Review. PubMed PMID: 19019889.
To SS

26: Venkateshan SP, Sidhu S, Malhotra S, Pandhi P. Efficacy of biologicals in the treatment of rheumatoid arthritis. a meta-analysis. Pharmacology. 2009;83(1):1-9. Epub 2008 Oct 28. Review. PubMed PMID: 18957873.

27: Doyle MK, Rahman MU, Han C, Han J, Giles J, Bingham CO 3rd, Bathon J. Treatment with infliximab plus methotrexate improves anemia in patients with rheumatoid arthritis independent of improvement in other clinical outcome measures-a pooled analysis from three large, multicenter, double-blind, randomized clinical trials. Semin Arthritis Rheum. 2009 Oct;39(2):123-31. Epub 2008 Sep 27. Review. PubMed PMID: 18823645.

28: Schmitt J, Zhang Z, Wozel G, Meurer M, Kirch W. Efficacy and tolerability of biologic and nonbiologic systemic treatments for moderate-to-severe psoriasis: meta-analysis of randomized controlled trials. Br J Dermatol. 2008 Sep;159(3):513-26. Epub 2008 Jul 9. Review. PubMed PMID: 18627372.
Recent review [psoriasis]; critiqued

29: Peyrin-Biroulet L, Deltenre P, de Suray N, Branche J, Sandborn WJ, Colombel

JF. Efficacy and safety of tumor necrosis factor antagonists in Crohn's disease: meta-analysis of placebo-controlled trials. Clin Gastroenterol Hepatol. 2008 Jun;6(6):644-53. PubMed PMID: 18550004.

30: Brimhall AK, King LN, Licciardone JC, Jacobe H, Menter A. Safety and efficacy of alefacept, efalizumab, etanercept and infliximab in treating moderate to severe plaque psoriasis: a meta-analysis of randomized controlled trials. Br J Dermatol. 2008 Aug;159(2):274-85. Epub 2008 Jun 10. Review. PubMed PMID: 18547300.

31: Alonso-Ruiz A, Pijoan JI, Ansuategui E, Urkaregi A, Calabozo M, Quintana A. Tumor necrosis factor alpha drugs in rheumatoid arthritis: systematic review and metaanalysis of efficacy and safety. BMC Musculoskelet Disord. 2008 Apr 17;9:52. Review. PubMed PMID: 18419803; PubMed Central PMCID: PMC2377247.

32: Saad AA, Symmons DP, Noyce PR, Ashcroft DM. Risks and benefits of tumor necrosis factor-alpha inhibitors in the management of psoriatic arthritis: systematic review and metaanalysis of randomized controlled trials. J Rheumatol. 2008 May;35(5):883-90. Epub 2008 Mar 15. Review. PubMed PMID: 18381787. Abstract review: Lacking useful safety information.

33: Behm BW, Bickston SJ. Tumor necrosis factor-alpha antibody for maintenance of remission in Crohn's disease. Cochrane Database Syst Rev. 2008 Jan 23;(1):CD006893. Review. PubMed PMID: 18254120.

34: Nelson AA, Pearce DJ, Fleischer AB Jr, Balkrishnan R, Feldman SR. Cost-effectiveness of biologic treatments for psoriasis based on subjective and objective efficacy measures assessed over a 12-week treatment period. J Am Acad Dermatol. 2008 Jan;58(1):125-35. Epub 2007 Nov 8. Review. PubMed PMID: 17996329.

35: Bravo Vergel Y, Hawkins NS, Claxton K, Asseburg C, Palmer S, Woolacott N, Bruce IN, Sculpher MJ. The cost-effectiveness of etanercept and infliximab for the treatment of patients with psoriatic arthritis. Rheumatology (Oxford). 2007 Nov;46(11):1729-35. PubMed PMID: 17956918.

36: Lee YH, Woo JH, Rho YH, Choi SJ, Ji JD, Song GG. Meta-analysis of the combination of TNF inhibitors plus MTX compared to MTX monotherapy, and the adjusted indirect comparison of TNF inhibitors in patients suffering from active rheumatoid arthritis. Rheumatol Int. 2008 Apr;28(6):553-9. Epub 2007 Oct 18. PubMed PMID: 17943257.

37: Brodszky V, Czirják L, Géher P, Hodinka L, Kárpáti K, Péntek M, Poór G, Szekanecz Z, Gulácsi L. [Rituximab in patients with rheumatoid arthritis: systematic review]. Orv Hetil. 2007 Oct 7;148(40):1883-93. Review. Hungarian. PubMed PMID: 17905683.

38: Rahimi R, Nikfar S, Abdollahi M. Meta-analysis technique confirms the effectiveness of anti-TNF-alpha in the management of active ulcerative colitis when administered in combination with corticosteroids. Med Sci Monit. 2007 Jul;13(7):PI13-8. PubMed PMID: 17599035.

39: Heiligenhaus A, Horneff G, Greiner K, Mackensen F, Zierhut M, Foeldvari I, Michels H. [Inhibitors of tumour necrosis factor-alpha for the treatment of arthritis and uveitis in childhood]. Klin Monbl Augenheilkd. 2007 Jun;224(6):526-31. Review. German. PubMed PMID: 17594625.

40: Botteman MF, Hay JW, Luo MP, Curry AS, Wong RL, van Hout BA. Cost effectiveness of adalimumab for the treatment of ankylosing spondylitis in the United Kingdom. Rheumatology (Oxford). 2007 Aug;46(8):1320-8. Epub 2007 Jun 2. PubMed PMID: 17545684.

41: Nixon R, Bansback N, Brennan A. The efficacy of inhibiting tumour necrosis

factor alpha and interleukin 1 in patients with rheumatoid arthritis: a meta-analysis and adjusted indirect comparisons. Rheumatology (Oxford). 2007 Jul;46(7):1140-7. Epub 2007 May 3. PubMed PMID: 17478472.

42: Katugampola RP, Lewis VJ, Finlay AY. The Dermatology Life Quality Index: assessing the efficacy of biological therapies for psoriasis. Br J Dermatol. 2007 May;156(5):945-50. Epub 2007 Mar 28. Review. PubMed PMID: 17388922.

43: Gisbert JP, González-Lama Y, Maté J. Systematic review: Infliximab therapy in ulcerative colitis. Aliment Pharmacol Ther. 2007 Jan 1;25(1):19-37. Review. PubMed PMID: 17229218.

44: Gartlehner G, Hansen RA, Jonas BL, Thieda P, Lohr KN. The comparative efficacy and safety of biologics for the treatment of rheumatoid arthritis: a systematic review and metaanalysis. J Rheumatol. 2006 Dec;33(12):2398-408. Review. PubMed PMID: 17225293.

45: Rahimi R, Nikfar S, Abdollahi M. Do anti-tumor necrosis factors induce response and remission in patients with acute refractory Crohn's disease? A systematic meta-analysis of controlled clinical trials. Biomed Pharmacother. 2007 Jan;61(1):75-80. Epub 2006 Dec 4. PubMed PMID: 17184965.

46: Koó E, Brodszky V, Péntek M, Ujfalussy I, Nagy MB, Gulácsi L. [The role of biological agents in the treatment of psoriatic arthritis, literature review]. Orv Hetil. 2006 Oct 15;147(41):1963-70. Review. Hungarian. PubMed PMID: 17120686.

47: Chen YF, Jobanputra P, Barton P, Jowett S, Bryan S, Clark W, Fry-Smith A, Burls A. A systematic review of the effectiveness of adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis in adults and an economic evaluation of their cost-effectiveness. Health Technol Assess. 2006 Nov;10(42):iii-iv, xi-xiii, 1-229. Review. PubMed PMID: 17049139.

48: Regueiro M, Loftus EV Jr, Steinhart AH, Cohen RD. Medical management of left-sided ulcerative colitis and ulcerative proctitis: critical evaluation of therapeutic trials. Inflamm Bowel Dis. 2006 Oct;12(10):979-94. PubMed PMID: 17012969.

49: Woolacott N, Bravo Vergel Y, Hawkins N, Kainth A, Khadjesari Z, Misso K, Light K, Asseburg C, Palmer S, Claxton K, Bruce I, Sculpher M, Riemsma R. Etanercept and infliximab for the treatment of psoriatic arthritis: a systematic review and economic evaluation. Health Technol Assess. 2006 Sep;10(31):iii-iv, xiii-xvi, 1-239. Review. PubMed PMID: 16948890.

50: Géher P, Nagy MB, Péntek M, Tóth E, Brodszky V, Gulácsi L. [The role of biologic agents in the therapy of ankylosing spondylitis]. Orv Hetil. 2006 Jul 2;147(26):1203-13. Review. Hungarian. PubMed PMID: 16898082.

51: Lawson MM, Thomas AG, Akobeng AK. Tumour necrosis factor alpha blocking agents for induction of remission in ulcerative colitis. Cochrane Database Syst Rev. 2006 Jul 19;3:CD005112. Review. PubMed PMID: 16856078.

52: Siegel CA, Hur C, Korzenik JR, Gazelle GS, Sands BE. Risks and benefits of infliximab for the treatment of Crohn's disease. Clin Gastroenterol Hepatol. 2006 Aug;4(8):1017-24; quiz 976. Epub 2006 Jul 14. PubMed PMID: 16843733.

53: Kemény L, Brodszky V, Kárpáti K, Gulácsi L. [The role of biological drugs in the treatment of psoriasis, results from 9 randomized placebo-controlled trials]. Orv Hetil. 2006 May 28;147(21):981-90. Review. Hungarian. PubMed PMID: 16812973.

54: Bongartz T, Sutton AJ, Sweeting MJ, Buchan I, Matteson EL, Montori V. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful

effects in randomized controlled trials. JAMA. 2006 May 17;295(19):2275-85. Review. Erratum in: JAMA. 2006 Jun 7;295(21):2482. PubMed PMID: 16705109.

55: Navarro-Sarabia F, Ariza-Ariza R, Hernández-Cruz B, Villanueva I. Adalimumab for treating rheumatoid arthritis. J Rheumatol. 2006 Jun;33(6):1075-81. Epub 2006 May 1. Review. PubMed PMID: 16652437.

56: Fransen J, Antoni C, Mease PJ, Uter W, Kavanaugh A, Kalden JR, Van Riel PL. Performance of response criteria for assessing peripheral arthritis in patients with psoriatic arthritis: analysis of data from randomised controlled trials of two tumour necrosis factor inhibitors. Ann Rheum Dis. 2006 Oct;65(10):1373-8. Epub 2006 Apr 27. PubMed PMID: 16644783; PubMed Central PMCID: PMC1798317.

57: Chung CP, Thompson JL, Koch GG, Amara I, Strand V, Pincus T. Are American College of Rheumatology 50% response criteria superior to 20% criteria in distinguishing active aggressive treatment in rheumatoid arthritis clinical trials reported since 1997? A meta-analysis of discriminant capacities. Ann Rheum Dis. 2006 Dec;65(12):1602-7. Epub 2006 Feb 27. Review. PubMed PMID: 16504992; PubMed Central PMCID: PMC1798472.

58: Gottlieb AB, Leonardi CL, Goffe BS, Ortonne JP, van der Kerkhof PC, Zitnik R, Nakanishi A, Jahreis A. Etanercept monotherapy in patients with psoriasis: a summary of safety, based on an integrated multistudy database. J Am Acad Dermatol. 2006 Mar;54(3 Suppl 2):S92-100. PubMed PMID: 16488335.

59: Gordon K, Korman N, Frankel E, Wang H, Jahreis A, Zitnik R, Chang T. Efficacy of etanercept in an integrated multistudy database of patients with psoriasis. J Am Acad Dermatol. 2006 Mar;54(3 Suppl 2):S101-11. PubMed PMID: 16488320.

60: Fleischmann R, Baumgartner SW, Weisman MH, Liu T, White B, Peloso P. Long term safety of etanercept in elderly subjects with rheumatic diseases. Ann Rheum Dis. 2006 Mar;65(3):379-84. Epub 2005 Sep 8. PubMed PMID: 16150792; PubMed Central PMCID: PMC1798057.

61: Navarro-Sarabia F, Ariza-Ariza R, Hernandez-Cruz B, Villanueva I. Adalimumab for treating rheumatoid arthritis. Cochrane Database Syst Rev. 2005 Jul 20;(3):CD005113. Review. PubMed PMID: 16034967.

62: Rossetti S, Actis GC, Fadda M, Rizzetto M, Palmo A. The use of the anti-tumour necrosis factor monoclonal antibody--infliximab--to treat ulcerative colitis: implications and trends beyond the available data. Dig Liver Dis. 2004 Jun;36(6):426-31. PubMed PMID: 15248385.

63: Torrance GW, Tugwell P, Amorosi S, Chartash E, Sengupta N. Improvement in health utility among patients with rheumatoid arthritis treated with adalimumab (a human anti-TNF monoclonal antibody) plus methotrexate. Rheumatology (Oxford). 2004 Jun;43(6):712-8. Epub 2004 Mar 23. PubMed PMID: 15039494.

64: Blumenauer B, Judd M, Cranney A, Burls A, Coyle D, Hochberg M, Tugwell P, Wells G. Etanercept for the treatment of rheumatoid arthritis. Cochrane Database Syst Rev. 2003;(4):CD004525. Review. PubMed PMID: 14584021.

65: Hochberg MC, Tracy JK, Hawkins-Holt M, Flores RH. Comparison of the efficacy of the tumour necrosis factor alpha blocking agents adalimumab, etanercept, and infliximab when added to methotrexate in patients with active rheumatoid arthritis. Ann Rheum Dis. 2003 Nov;62 Suppl 2:ii13-6. Review. PubMed PMID: 14532140; PubMed Central PMCID: PMC1766753.

66: Jones G, Halbert J, Crotty M, Shanahan EM, Batterham M, Ahern M. The effect of treatment on radiological progression in rheumatoid arthritis: a systematic review of randomized placebo-controlled trials. Rheumatology (Oxford). 2003 Jan;42(1):6-13. Review. PubMed PMID: 12509606.

67: Rau R. Adalimumab (a fully human anti-tumour necrosis factor alpha monoclonal antibody) in the treatment of active rheumatoid arthritis: the initial results of five trials. Ann Rheum Dis. 2002 Nov;61 Suppl 2:ii70-3. Review. PubMed PMID: 12379628; PubMed Central PMCID: PMC1766697.

68: Rodewald EJ, Housman TS, Mellen BG, Feldman SR. The efficacy of 308nm laser treatment of psoriasis compared to historical controls. Dermatol Online J. 2001 Dec;7(2):4. PubMed PMID: 12165220.

SEARCH 18 SR cert gol ustek

Category	Description
Clinical question or focus	BIOLOGICAL AGENTS FINAL
Source	PubMed
Terms	(certolizumab OR golimumab OR ustekinumab
Limits	none
▪ Date limits	none
▪ Other limits	SR
▪ Number of hits	25
Query Translation (eg, “Details” in PubMed)	("CDP870"[Substance Name] OR "CDP870"[All Fields] OR "certolizumab"[All Fields]) OR ("golimumab"[Substance Name] OR "golimumab"[All Fields]) OR ("monoclonal antibody CNTO 1275"[Substance Name] OR "monoclonal antibody CNTO 1275"[All Fields] OR "ustekinumab"[All Fields]) AND systematic[sb]
Date of Search	10/14/10
Total marked for retrieval	Fleischmann 10, Zidi 10
Exclusions	• Not focus of review: population, intervention, comparison, outcome • Superseded by more recent larger study • Lacking safety data • Wrong study type • Duplicates
Notes	Relevant studies are all duplicates.

1: Tan JY, Li S, Yang K, Ma B, Chen W, Zha C, Zhang J. Ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: a meta-analysis. J Dermatolog Treat. 2010 Oct 5. [Epub ahead of print] PubMed PMID: 20923370.

2: Papoutsaki M, Talamonti M, Giunta A, Costanzo A, Ruzzetti M, Teoli M, Chimenti S. The impact of methodological approaches for presenting long-term clinical data on estimates of efficacy in psoriasis illustrated by three-year treatment data on infliximab. Dermatology. 2010;221 Suppl 1:43-7. Epub 2010 Aug 9. PubMed PMID: 20733314.

3: Mercuri SR, Naldi L. Potential role of ustekinumab in the treatment of chronic plaque psoriasis. Biologics. 2010 May 25;4:119-29. PubMed PMID: 20531968; PubMed Central PMCID: PMC2880344.

4: Fleischmann R. The efficacy and safety of golimumab in the treatment of arthritis. Expert Opin Biol Ther. 2010 Jul;10(7):1131-43. Review. PubMed PMID: 20504106.
Most recent review golimumab; ordered

5: Gospodarevskaya E, Picot J, Cooper K, Loveman E, Takeda A. Ustekinumab for the treatment of moderate to severe psoriasis. Health Technol Assess. 2009 Oct;13 Suppl 3:61-6. Review. PubMed PMID: 19846031.

6: Nam JL, Winthrop KL, van Vollenhoven RF, Pavelka K, Valesini G, Hensor EM, Worthy G, Landewé R, Smolen JS, Emery P, Buch MH. Current evidence for the management of rheumatoid arthritis with biological disease-modifying antirheumatic drugs: a systematic literature review informing the EULAR recommendations for the management of RA. Ann Rheum Dis. 2010 Jun;69(6):976-86. Epub 2010 May 6. Review. PubMed PMID: 20447957.

7: Uhlenhake EE, Feldman SR. Efficacy and safety of ustekinumab and etanercept for the treatment of psoriasis. Expert Opin Biol Ther. 2010 Jul;10(7):1105-12. Review. PubMed PMID: 20446825.
Recent review ustekinumab; retrieved

8: Singh JA, Noorbaloochi S, Singh G. Golimumab for rheumatoid arthritis: a systematic review. J Rheumatol. 2010 Jun;37(6):1096-104. Epub 2010 May 1. Review. PubMed PMID: 20436075.
Recent golimumab; retrieved; critiqued

9: Zidi I, Bouaziz A, Mnif W, Bartegi A, Ben Amor N. Golimumab and malignancies: true or false association? Med Oncol. 2010 Apr 7. [Epub ahead of print] PubMed PMID: 20373059.

10: Fleischmann R. The clinical efficacy and safety of certolizumab pegol in rheumatoid arthritis. Expert Opin Biol Ther. 2010 May;10(5):773-86. Review. PubMed PMID: 20230188.
Most recent review certolizumab; RA; ordered

11: Oussalah A, Danese S, Peyrin-Biroulet L. Efficacy of TNF antagonists beyond one year in adult and pediatric inflammatory bowel diseases: a systematic review. Curr Drug Targets. 2010 Feb;11(2):156-75. Review. PubMed PMID: 20210765.

12: Storage SS, Agrawal H, Furst DE. Description of the efficacy and safety of three new biologics in the treatment of rheumatoid arthritis. Korean J Intern Med. 2010 Mar;25(1):1-17. Epub 2010 Feb 26. Review. PubMed PMID: 20195397; PubMed Central PMCID: PMC2829405.

13: McCluggage LK, Scholtz JM. Golimumab: a tumor necrosis factor alpha inhibitor for the treatment of rheumatoid arthritis. Ann Pharmacother. 2010 Jan;44(1):135-44. Review. PubMed PMID: 20118145.

14: Smith LS, Nelson M, Dolder CR. Certolizumab pegol: a TNF-{alpha} antagonist for the treatment of moderate-to-severe Crohn's disease. Ann Pharmacother. 2010 Feb;44(2):333-42. Epub 2010 Jan 5. Review. PubMed PMID: 20118143.

15: Singh JA, Noorbaloochi S, Singh G. Golimumab for rheumatoid arthritis. Cochrane Database Syst Rev. 2010 Jan 20;(1):CD008341. Review. PubMed PMID: 20091667.

16: Statkute L, Ruderman EM. Novel TNF antagonists for the treatment of rheumatoid arthritis. Expert Opin Investig Drugs. 2010 Jan;19(1):105-15. Review. PubMed PMID: 20001558.

17: Poulin Y, Langley RG, Teixeira HD, Martel MJ, Cheung S. Biologics in the treatment of psoriasis: clinical and economic overview. J Cutan Med Surg. 2009 Sep-Oct;13 Suppl 2:S49-57. Review. PubMed PMID: 19799827.

18: Scanlon JV, Exter BP, Steinberg M, Jarvis CI. Ustekinumab: treatment of adult moderate-to-severe chronic plaque psoriasis. Ann Pharmacother. 2009 Sep;43(9):1456-65. Epub 2009 Aug 11. Review. PubMed PMID: 19671802.

19: Shao LM, Chen MY, Cai JT. Meta-analysis: the efficacy and safety of certolizumab pegol in Crohn's disease. Aliment Pharmacol Ther. 2009 Mar

15;29(6):605-14. PubMed PMID: 19183161.

20: Al-Subeihe I, Nielsen OH. [Tumor necrosis factor-alpha antibody for maintenance of remission in Crohn disease. A survey of a Cochrane review]. Ugeskr Laeger. 2008 Dec 8;170(50):4130-4. Review. Danish. PubMed PMID: 19091193.

21: Peyrin-Biroulet L, Deltenre P, de Suray N, Branche J, Sandborn WJ, Colombel JF. Efficacy and safety of tumor necrosis factor antagonists in Crohn's disease: meta-analysis of placebo-controlled trials. Clin Gastroenterol Hepatol. 2008 Jun;6(6):644-53. PubMed PMID: 18550004.

22: Behm BW, Bickston SJ. Tumor necrosis factor-alpha antibody for maintenance of remission in Crohn's disease. Cochrane Database Syst Rev. 2008 Jan 23;(1):CD006893. Review. PubMed PMID: 18254120.

23: Hirohata S. [Fully human anti TNF-alpha monoclonal antibodies (adalimumab, golimumab)]. Nippon Rinsho. 2007 Jul;65(7):1202-8. Review. Japanese. PubMed PMID: 17642233.

24: Rahimi R, Nikfar S, Abdollahi M. Do anti-tumor necrosis factors induce response and remission in patients with acute refractory Crohn's disease? A systematic meta-analysis of controlled clinical trials. Biomed Pharmacother. 2007 Jan;61(1):75-80. Epub 2006 Dec 4. PubMed PMID: 17184965.

25: D'Haens G, Daperno M. Advances in biologic therapy for ulcerative colitis and Crohn's disease. Curr Gastroenterol Rep. 2006 Dec;8(6):506-12. Review. PubMed PMID: 17105690.

SEARCH 19 all agents condits SR update

Category	Description
Clinical question or focus	BIOLOGICAL AGENTS FINAL
Source	PubMed
Terms	(adalimumab OR certolizumab OR etanercept OR golimumab OR infliximab OR ustekinumab) AND (Rheumatoid arthritis OR psoriasis OR psoriatic arthritis)
Limits	Systematic Review
▪ Date limits	None
▪ Other limits	None
Query Translation (eg, “Details” in PubMed)	("adalimumab"[Supplementary Concept] OR "CDP870"[Supplementary Concept] OR "TNFR-Fc fusion protein"[Supplementary Concept] OR "golimumab"[Supplementary Concept] OR "infliximab"[Supplementary Concept] OR "monoclonal antibody CNTO 1275"[Supplementary Concept]) AND (("arthritis, rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "rheumatoid"[All Fields]) OR "rheumatoid arthritis"[All Fields] OR ("rheumatoid"[All Fields] AND "arthritis"[All Fields])) OR ("psoriasis"[MeSH Terms] OR "psoriasis"[All Fields]) OR ("arthritis, psoriatic"[MeSH Terms] OR ("arthritis"[All Fields] AND "psoriatic"[All Fields]) OR "psoriatic arthritis"[All Fields] OR ("psoriatic"[All Fields] AND "arthritis"[All Fields]))) AND systematic[sb]
Date of Search	1/31/11
Total Yield	142
Total marked for retrieval	No new studies
Exclusions	• Not focus of review: population, intervention, comparison, outcome • Superseded by more recent larger study • Lacking safety data • Wrong study type • Duplicates
Notes	Many duplicates Donahue 08 full text review: no additional useful AE data.

1: Papoutsaki M, Talamonti M, Giunta A, Costanzo A, Ruzzetti M, Teoli M, Chimenti

S. The impact of methodological approaches for presenting long-term clinical data on estimates of efficacy in psoriasis illustrated by three-year treatment data on infliximab. Dermatology. 2010;221 Suppl 1:43-7. Epub 2010 Aug 9. PubMed PMID: 20733314.

2: Arcese A, Aste N, Bettacchi A, Camplone G, Cantoresi F, Caproni M, D'Amico D, Fabbri P, Filosa G, Galluccio A, Hansel K, Lisi P, Micali G, Musumeci ML, Nicolini M, Parodi A, Patania M, Pezza M, Potenza C, Richetta A, Simonacci M, Trevisan P, Valenti G, Calvieri S. Treating psoriasis with etanercept in italian clinical practice: prescribing practices and duration of remission following discontinuation. Clin Drug Investig. 2010;30(8):507-16. doi: 10.2165/11537470-000000000-00000. PubMed PMID: 20586516.

3: Pedraz J, Daudén E. [Psoriatic arthritis and etanercept]. Actas Dermosifiliogr. 2010 May;101 Suppl 1:26-34. Review. Spanish. PubMed PMID: 20492877.

4: Fleischmann R. The efficacy and safety of golimumab in the treatment of arthritis. Expert Opin Biol Ther. 2010 Jul;10(7):1131-43. Review. PubMed PMID: 20504106.

5: Gospodarevskaya E, Picot J, Cooper K, Loveman E, Takeda A. Ustekinumab for the treatment of moderate to severe psoriasis. Health Technol Assess. 2009 Oct;13 Suppl 3:61-6. Review. PubMed PMID: 19846031.

6: Uhlenhake EE, Feldman SR. Efficacy and safety of ustekinumab and etanercept for the treatment of psoriasis. Expert Opin Biol Ther. 2010 Jul;10(7):1105-12. Review. PubMed PMID: 20446825.

7: Singh JA, Noorbaloochi S, Singh G. Golimumab for rheumatoid arthritis: a systematic review. J Rheumatol. 2010 Jun;37(6):1096-104. Epub 2010 May 1. Review. PubMed PMID: 20436075.

8: Pollono EN, Lopez-Olivo MA, Lopez JA, Suarez-Almazor ME. A systematic review of the effect of TNF-alpha antagonists on lipid profiles in patients with rheumatoid arthritis. Clin Rheumatol. 2010 Sep;29(9):947-55. Epub 2010 Apr 10. Review. PubMed PMID: 20383550.

9: Bojke L, Claxton K, Bravo-Vergel Y, Sculpher M, Palmer S, Abrams K. Eliciting distributions to populate decision analytic models. Value Health. 2010 Aug;13(5):557-64. Epub 2010 Mar 22. PubMed PMID: 20345548.

10: Wiens A, Venson R, Correr CJ, Otuki MF, Pontarolo R. Meta-analysis of the efficacy and safety of adalimumab, etanercept, and infliximab for the treatment of rheumatoid arthritis. Pharmacotherapy. 2010 Apr;30(4):339-53. Review. PubMed PMID: 20334454.

11: Fleischmann R. The clinical efficacy and safety of certolizumab pegol in rheumatoid arthritis. Expert Opin Biol Ther. 2010 May;10(5):773-86. Review. PubMed PMID: 20230188.

12: Storage SS, Agrawal H, Furst DE. Description of the efficacy and safety of three new biologics in the treatment of rheumatoid arthritis. Korean J Intern Med. 2010 Mar;25(1):1-17. Epub 2010 Feb 26. Review. PubMed PMID: 20195397; PubMed Central PMCID: PMC2829405.

13: Lee YH, Ji JD, Bae SC, Song GG. Associations between tumor necrosis factor-alpha (TNF-alpha) -308 and -238 G/A polymorphisms and shared epitope status and responsiveness to TNF-alpha blockers in rheumatoid arthritis: a metaanalysis update. J Rheumatol. 2010 Apr;37(4):740-6. Epub 2010 Mar 1. PubMed PMID: 20194454.

14: McCluggage LK, Scholtz JM. Golimumab: a tumor necrosis factor alpha inhibitor for the treatment of rheumatoid arthritis. Ann Pharmacother. 2010 Jan;44(1):135-44. Review. PubMed PMID: 20118145.

15: D'Haens GR. Top-down therapy for Crohn's disease: rationale and evidence. Acta Clin Belg. 2009 Nov-Dec;64(6):540-6. Review. PubMed PMID: 20101879.

16: Singh JA, Noorbaloochi S, Singh G. Golimumab for rheumatoid arthritis. Cochrane Database Syst Rev. 2010 Jan 20;(1):CD008341. Review. PubMed PMID: 20091667.

17: Yokota S, Mori M, Imagawa T, Murata T, Tomiita M, Itoh Y, Fujikawa S, Takei S; Pediatric Rheumatology Association of Japan. Guidelines on the use of etanercept for juvenile idiopathic arthritis in Japan. Mod Rheumatol. 2010 Apr;20(2):107-13. Epub 2010 Jan 20. Review. PubMed PMID: 20087751.

18: Ferrándiz C, Carrascosa JM, Boada A. A new era in the management of psoriasis? The biologics: facts and controversies. Clin Dermatol. 2010 Jan-Feb;28(1):81-7. Review. PubMed PMID: 20082956.

19: Statkute L, Ruderman EM. Novel TNF antagonists for the treatment of rheumatoid arthritis. Expert Opin Investig Drugs. 2010 Jan;19(1):105-15. Review. PubMed PMID: 20001558.

20: Sockolov ME, Alikhan A, Zargari O. Non-psoriatic dermatologic uses of monoclonal antibody therapy. J Dermatolog Treat. 2009;20(6):319-27. Review. PubMed PMID: 19954387.

21: Turner D, Picot J, Cooper K, Loveman E. Adalimumab for the treatment of psoriasis. Health Technol Assess. 2009 Sep;13 Suppl 2:49-54. Review. PubMed PMID: 19804689.

22: Leeb BF, Böttcher E, Brezinschek HP, Czerwenka C, Herold M, Hitzelhammer H, Mayrhofer F, Puchner R, Rainer F, Rintelen B, Schirmer M, Stuby U, Bröll H. The use of tumour necrosis factor alpha-blockers in daily routine. An Austrian consensus project. Clin Rheumatol. 2010 Feb;29(2):167-74. Epub 2009 Nov 11. PubMed PMID: 19904485; PubMed Central PMCID: PMC2797412.

23: Blasco AJ, Lázaro P, Ferrándiz C, García-Díez A, Liso J. [Efficiency of biologic agents in the treatment of moderate to severe psoriasis]. Actas Dermosifiliogr. 2009 Nov;100(9):792-803. Spanish. PubMed PMID: 19889301.

24: Leboime A, Berthelot JM, Allanore Y, Khalil-Kallouche L, Herman P, Orcel P, Lioté F. Sinus aspergilloma in rheumatoid arthritis before or during tumor necrosis factor-alpha antagonist therapy. Arthritis Res Ther. 2009;11(6):R164. Epub 2009 Nov 3. PubMed PMID: 19886992; PubMed Central PMCID: PMC3003503.

25: Alivernini S, Laria A, Gremese E, Zoli A, Ferraccioli G. ACR70-disease activity score remission achievement from switches between all the available biological agents in rheumatoid arthritis: a systematic review of the literature. Arthritis Res Ther. 2009;11(6):R163. Epub 2009 Nov 3. Review. PubMed PMID: 19886983; PubMed Central PMCID: PMC3003527.

26: Singh JA, Christensen R, Wells GA, Suarez-Almazor ME, Buchbinder R, Lopez-Olivo MA, Ghogomu ET, Tugwell P. A network meta-analysis of randomized controlled trials of biologics for rheumatoid arthritis: a Cochrane overview. CMAJ. 2009 Nov 24;181(11):787-96. Epub 2009 Nov 2. Erratum in: CMAJ. 2010 May 18;182(8):806. PubMed PMID: 19884297; PubMed Central PMCID: PMC2780484.

27: Singh JA, Christensen R, Wells GA, Suarez-Almazor ME, Buchbinder R, Lopez-Olivo MA, Tanjong Ghogomu E, Tugwell P. Biologics for rheumatoid arthritis: an overview of Cochrane reviews. Cochrane Database Syst Rev. 2009 Oct

7;(4):CD007848. Review. PubMed PMID: 19821440.

28: Köller MD, Aletaha D, Funovits J, Pangan A, Baker D, Smolen JS. Response of elderly patients with rheumatoid arthritis to methotrexate or TNF inhibitors compared with younger patients. Rheumatology (Oxford). 2009 Dec;48(12):1575-80. Epub 2009 Oct 7. PubMed PMID: 19812228.

29: Wiens A, Correr CJ, Venson R, Grochocki MC, Otuki MF, Pontarolo R. A meta-analysis of the efficacy and safety of using infliximab for the treatment of rheumatoid arthritis. Clin Rheumatol. 2009 Dec;28(12):1365-73. Epub 2009 Sep 22. Review. PubMed PMID: 19771491.

30: Wiens A, Correr CJ, Pontarolo R, Venson R, Quinalha JV, Otuki MF. A systematic review and meta-analysis of the efficacy and safety of etanercept for treating rheumatoid arthritis. Scand J Immunol. 2009 Oct;70(4):337-44. Review. PubMed PMID: 19751268.

31: Pathirana D, Ormerod AD, Saiag P, Smith C, Spuls PI, Nast A, Barker J, Bos JD, Burmester GR, Chimenti S, Dubertret L, Eberlein B, Erdmann R, Ferguson J, Girolomoni G, Gisondi P, Giunta A, Griffiths C, Hönigsmann H, Hussain M, Jobling R, Karvonen SL, Kemeny L, Kopp I, Leonardi C, Maccarone M, Menter A, Mrowietz U, Naldi L, Nijsten T, Ortonne JP, Orzechowski HD, Rantanen T, Reich K, Reytan N, Richards H, Thio HB, van de Kerkhof P, Rzany B. European S3-guidelines on the systemic treatment of psoriasis vulgaris. J Eur Acad Dermatol Venereol. 2009 Oct;23 Suppl 2:1-70. Erratum in: J Eur Acad Dermatol Venereol. 2010 Jan;24(1):117-8. PubMed PMID: 19712190.

32: Wiens A, Correr CJ, Venson R, Otuki MF, Pontarolo R. A systematic review and meta-analysis of the efficacy and safety of adalimumab for treating rheumatoid arthritis. Rheumatol Int. 2010 Jun;30(8):1063-70. Epub 2009 Aug 26. Review. PubMed PMID: 19707765.

33: Christensen R, Kristensen LE, Geborek P, Danneskiold-Samsøe B, Saxne T, Bliddal H. [The efficacy of the three available anti-tumour necrosis factor therapies in patients with rheumatoid arthritis. A meta-analytic literature review--secondary publication]. Ugeskr Laeger. 2009 Jun 22;171(26):2192-4. Review. Danish. PubMed PMID: 19678436.

34: Scanlon JV, Exter BP, Steinberg M, Jarvis CI. Ustekinumab: treatment of adult moderate-to-severe chronic plaque psoriasis. Ann Pharmacother. 2009 Sep;43(9):1456-65. Epub 2009 Aug 11. Review. PubMed PMID: 19671802.

35: Bansback N, Sizto S, Sun H, Feldman S, Willian MK, Anis A. Efficacy of systemic treatments for moderate to severe plaque psoriasis: systematic review and meta-analysis. Dermatology. 2009;219(3):209-18. Epub 2009 Aug 5. Review. PubMed PMID: 19657180.

36: Vastesaeger N, Xu S, Aletaha D, St Clair EW, Smolen JS. A pilot risk model for the prediction of rapid radiographic progression in rheumatoid arthritis. Rheumatology (Oxford). 2009 Sep;48(9):1114-21. Epub 2009 Jul 9. Review. PubMed PMID: 19589891.

37: Loveman E, Turner D, Hartwell D, Cooper K, Clegg A. Infliximab for the treatment of adults with psoriasis. Health Technol Assess. 2009 Jun;13 Suppl 1:55-60. PubMed PMID: 19567215.

38: Puig L, Carrascosa JM, Daudén E, Sánchez-Carazo JL, Ferrándiz C, Sánchez-Regaña M, García-Bustinduy M, Bordas X, Moreno JC, Hernanz JM, Laguarda S, García-Patos V; Grupo Español de Psoriasis de la Academia Española de Dermatología y Venereología. [Spanish evidence-based guidelines on the treatment of moderate-to-severe psoriasis with biologic agents]. Actas Dermosifiliogr. 2009 Jun;100(5):386-413. Spanish. PubMed PMID: 19558918.

39: Takeuchi T. [Present status and problems in biologics for treatment of rheumatoid arthritis in Japan]. Nippon Naika Gakkai Zasshi. 2009 Apr 10;98(4):883-9. Review. Japanese. PubMed PMID: 19469079.

40: Puig Sanz L, Sáez E, Lozano MJ, Bordas X, Carrascosa JM, Gallardo F, Luelmo J, Sánchez-Regaña M, Alsina M, García-Patos V; Grupo Español de Psoriasis de la Academia Española de Dermatología y Venereología. [Reactions to infliximab infusions in dermatologic patients: consensus statement and treatment protocol. Working Group of the Grupo Español de Psoriasis de la Academia Española de Dermatología y Venereología]. Actas Dermosifiliogr. 2009 Mar;100(2):103-12. Review. Spanish. PubMed PMID: 19445874.

41: Bourré-Tessier J, Fortin C, Belisle A, Desmarais E, Choquette D, Senécal JL. Disseminated Histoplasma capsulatum infection presenting with panniculitis and focal myositis in rheumatoid arthritis treated with etanercept. Scand J Rheumatol. 2009;38(4):311-6. Review. PubMed PMID: 19444717.

42: Takeuchi T. [Indications for and use of biologics in early rheumatoid arthritis based on the evidence]. Nippon Rinsho. 2009 May;67(5):1043-9. Review. Japanese. PubMed PMID: 19432131.

43: Borah BJ, Huang X, Zarotsky V, Globe D. Trends in RA patients' adherence to subcutaneous anti-TNF therapies and costs. Curr Med Res Opin. 2009 Jun;25(6):1365-77. PubMed PMID: 19425902.

44: Rubbert-Roth A, Finckh A. Treatment options in patients with rheumatoid arthritis failing initial TNF inhibitor therapy: a critical review. Arthritis Res Ther. 2009;11 Suppl 1:S1. Epub 2009 Apr 6. Review. PubMed PMID: 19368701; PubMed Central PMCID: PMC2669237.

45: Levy-Roy A, Porcher R, de Fonclare AL, Morel P, Dupuy A. [Efficacy of TNF-alpha antagonists for plaque-type psoriasis: a systematic review and graphical presentation]. Ann Dermatol Venereol. 2009 Apr;136(4):315-22. Epub 2009 Jan 30. Review. French. PubMed PMID: 19361697.

46: Zhang Z, Schmitt J, Wozel G, Kirch W. [Treatment of plaque psoriasis with biologics. A meta-analysis of randomized controlled trials]. Med Klin (Munich). 2009 Feb 15;104(2):125-36. Epub 2009 Feb 26. German. PubMed PMID: 19242664.

47: Burmester GR, Mease P, Dijkmans BA, Gordon K, Lovell D, Panaccione R, Perez J, Pangan AL. Adalimumab safety and mortality rates from global clinical trials of six immune-mediated inflammatory diseases. Ann Rheum Dis. 2009 Dec;68(12):1863-9. Epub 2009 Jan 15. PubMed PMID: 19147611; PubMed Central PMCID: PMC2770105.

48: Menter A, Reich K, Gottlieb AB, Bala M, Li S, Hsu MC, Guzzo C, Diels J, Gelfand JM. Adverse drug events in infliximab-treated patients compared with the general and psoriasis populations. J Drugs Dermatol. 2008 Dec;7(12):1137-46. PubMed PMID: 19137767.

49: Zintzaras E, Dahabreh IJ, Giannouli S, Voulgarelis M, Moutsopoulos HM. Infliximab and methotrexate in the treatment of rheumatoid arthritis: a systematic review and meta-analysis of dosage regimens. Clin Ther. 2008 Nov;30(11):1939-55. Review. PubMed PMID: 19108784.

50: Bongartz T, Warren FC, Mines D, Matteson EL, Abrams KR, Sutton AJ. Etanercept therapy in rheumatoid arthritis and the risk of malignancies: a systematic review and individual patient data meta-analysis of randomised controlled trials. Ann Rheum Dis. 2009 Jul;68(7):1177-83. Epub 2008 Nov 19. Review. PubMed PMID: 19019889.

51: Roundtree AK, Kallen MA, Lopez-Olivo MA, Kimmel B, Skidmore B, Ortiz Z, Cox V, Suarez-Almazor ME. Poor reporting of search strategy and conflict of interest in over 250 narrative and systematic reviews of two biologic agents in arthritis: a systematic review. J Clin Epidemiol. 2009 Feb;62(2):128-37. Epub 2008 Nov 14. Review. PubMed PMID: 19013763.

52: Guignard S, Gossec L, Bandinelli F, Dougados M. Comparison of the clinical characteristics of vasculitis occurring during anti-tumor necrosis factor treatment or not in rheumatoid arthritis patients. A systematic review of 2707 patients, 18 vasculitis. Clin Exp Rheumatol. 2008 May-Jun;26(3 Suppl 49):S23-9. PubMed PMID: 18799049.

53: Doyle MK, Rahman MU, Han C, Han J, Giles J, Bingham CO 3rd, Bathon J. Treatment with infliximab plus methotrexate improves anemia in patients with rheumatoid arthritis independent of improvement in other clinical outcome measures-a pooled analysis from three large, multicenter, double-blind, randomized clinical trials. Semin Arthritis Rheum. 2009 Oct;39(2):123-31. Epub 2008 Sep 27. Review. PubMed PMID: 18823645.

54: Reich K, Griffiths C, Barker J, Chimenti S, Daudén E, Giannetti A, Gniadecki R, Katsambas A, Langley R, Mrowietz U, Ogilvie A, Ortonne JP, Reider N, Saurat JH. Recommendations for the long-term treatment of psoriasis with infliximab: a dermatology expert group consensus. Dermatology. 2008;217(3):268-75. Epub 2008 Aug 6. PubMed PMID: 18685261.

55: Lecluse LL, Piskin G, Mekkes JR, Bos JD, de Rie MA. Review and expert opinion on prevention and treatment of infliximab-related infusion reactions. Br J Dermatol. 2008 Sep;159(3):527-36. Epub 2008 Jul 9. Review. PubMed PMID: 18627374.

56: Schmitt J, Zhang Z, Wozel G, Meurer M, Kirch W. Efficacy and tolerability of biologic and nonbiologic systemic treatments for moderate-to-severe psoriasis: meta-analysis of randomized controlled trials. Br J Dermatol. 2008 Sep;159(3):513-26. Epub 2008 Jul 9. Review. PubMed PMID: 18627372.

57: Smith N, Ding T, Butt S, Gadsby K, Deighton C. The importance of the baseline Disease Activity Score 28 in determining responders and non-responders to anti-TNF in UK clinical practice. Rheumatology (Oxford). 2008 Sep;47(9):1389-91. Epub 2008 Jul 4. PubMed PMID: 18603597.

58: Brimhall AK, King LN, Licciardone JC, Jacobe H, Menter A. Safety and efficacy of alefacept, efalizumab, etanercept and infliximab in treating moderate to severe plaque psoriasis: a meta-analysis of randomized controlled trials. Br J Dermatol. 2008 Aug;159(2):274-85. Epub 2008 Jun 10. Review. PubMed PMID: 18547300.

59: Doherty SD, Van Voorhees A, Lebwohl MG, Korman NJ, Young MS, Hsu S, National Psoriasis Foundation. National Psoriasis Foundation consensus statement on screening for latent tuberculosis infection in patients with psoriasis treated with systemic and biologic agents. J Am Acad Dermatol. 2008 Aug;59(2):209-17. Epub 2008 May 15. PubMed PMID: 18485527.

60: Babić-Naglić D, Laktasić N, Jajić Z, Anić B, Morović-Vergles J, Curković B; Croatian Society for Rheumatology. [Proposal of Croatian Society for Rheumatology for anti-TNF-alpha therapy in adult patients with spondyloarthritides]. Reumatizam. 2007;54(1):20-30. Croatian. PubMed PMID: 18450273.

61: Gottlieb A, Korman NJ, Gordon KB, Feldman SR, Lebwohl M, Koo JY, Van Voorhees AS, Elmets CA, Leonardi CL, Beutner KR, Bhushan R, Menter A. Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 2. Psoriatic arthritis: overview and guidelines of care for treatment with an emphasis on the biologics. J Am Acad Dermatol. 2008 May;58(5):851-64. PubMed PMID: 18423261.

62: Menter A, Gottlieb A, Feldman SR, Van Voorhees AS, Leonardi CL, Gordon KB, Lebwohl M, Koo JY, Elmets CA, Korman NJ, Beutner KR, Bhushan R. Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 1. Overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics. J Am Acad Dermatol. 2008 May;58(5):826-50. PubMed PMID: 18423260.

63: Alonso-Ruiz A, Pijoan JI, Ansuategui E, Urkaregi A, Calabozo M, Quintana A. Tumor necrosis factor alpha drugs in rheumatoid arthritis: systematic review and metaanalysis of efficacy and safety. BMC Musculoskelet Disord. 2008 Apr 17;9:52. Review. PubMed PMID: 18419803; PubMed Central PMCID: PMC2377247.

64: Saad AA, Symmons DP, Noyce PR, Ashcroft DM. Risks and benefits of tumor necrosis factor-alpha inhibitors in the management of psoriatic arthritis: systematic review and metaanalysis of randomized controlled trials. J Rheumatol. 2008 May;35(5):883-90. Epub 2008 Mar 15. Review. PubMed PMID: 18381787.

65: Reich K, Sinclair R, Roberts G, Griffiths CE, Tabberer M, Barker J. Comparative effects of biological therapies on the severity of skin symptoms and health-related quality of life in patients with plaque-type psoriasis: a meta-analysis. Curr Med Res Opin. 2008 May;24(5):1237-54. Epub 2008 Mar 19. Review. PubMed PMID: 18355421.

66: Kristensen LE, Christensen R, Bliddal H, Geborek P, Danneskiold-Samsøe B, Saxne T. The number needed to treat for adalimumab, etanercept, and infliximab based on ACR50 response in three randomized controlled trials on established rheumatoid arthritis: a systematic literature review. Scand J Rheumatol. 2007 Nov-Dec;36(6):411-7. Review. PubMed PMID: 18092260.

67: Koike R, Takeuchi T, Eguchi K, Miyasaka N; Japan College of Rheumatology. Update on the Japanese guidelines for the use of infliximab and etanercept in rheumatoid arthritis. Mod Rheumatol. 2007;17(6):451-8. Epub 2007 Dec 20. Review. PubMed PMID: 18084695.

68: Nelson AA, Pearce DJ, Fleischer AB Jr, Balkrishnan R, Feldman SR. Cost-effectiveness of biologic treatments for psoriasis based on subjective and objective efficacy measures assessed over a 12-week treatment period. J Am Acad Dermatol. 2008 Jan;58(1):125-35. Epub 2007 Nov 8. Review. PubMed PMID: 17996329.

69: Bravo Vergel Y, Hawkins NS, Claxton K, Asseburg C, Palmer S, Woolacott N, Bruce IN, Sculpher MJ. The cost-effectiveness of etanercept and infliximab for the treatment of patients with psoriatic arthritis. Rheumatology (Oxford). 2007 Nov;46(11):1729-35. PubMed PMID: 17956918.

70: Lee YH, Woo JH, Rho YH, Choi SJ, Ji JD, Song GG. Meta-analysis of the combination of TNF inhibitors plus MTX compared to MTX monotherapy, and the adjusted indirect comparison of TNF inhibitors in patients suffering from active rheumatoid arthritis. Rheumatol Int. 2008 Apr;28(6):553-9. Epub 2007 Oct 18. PubMed PMID: 17943257.

71: Brodszky V, Czirják L, Géher P, Hodinka L, Kárpáti K, Péntek M, Poór G, Szekanecz Z, Gulácsi L. [Rituximab in patients with rheumatoid arthritis: systematic review]. Orv Hetil. 2007 Oct 7;148(40):1883-93. Review. Hungarian. PubMed PMID: 17905683.

72: Tilg H, Feichtenschlager T, Knoflach P, Petritsch W, Schöfl R, Vogelsang H, Reinisch W. [Use of infliximab in ulcerative colitis]. Z Gastroenterol. 2007 Aug;45(8):907-11. German. PubMed PMID: 17701864.

73: Bertele' V, Assisi A, Di Muzio V, Renzo D, Garattini S. New antirheumatic drugs: any real added value? A critical overview of regulatory criteria for their marketing approval. Eur J Clin Pharmacol. 2007 Sep;63(9):879-89. Epub 2007 Jul 24. PubMed PMID: 17646975.

74: Fujikawa K, Kawakami A, Eguchi K. [Etanercept: recombinant human soluble tumor necrosis factor receptor fusion protein]. Nippon Rinsho. 2007 Jul;65(7):1211-7. Review. Japanese. PubMed PMID: 17642234.

75: Hirohata S. [Fully human anti TNF-alpha monoclonal antibodies (adalimumab, golimumab)]. Nippon Rinsho. 2007 Jul;65(7):1202-8. Review. Japanese. PubMed PMID: 17642233.

76: Amano K. [Anti-TNF-alpha chimeric antibody (infliximab)]. Nippon Rinsho. 2007 Jul;65(7):1197-201. Review. Japanese. PubMed PMID: 17642232.

77: Tanaka Y. [Biologics: current therapeutic strategies for rheumatoid arthritis]. Nippon Rinsho. 2007 Jul;65(7):1179-84. Review. Japanese. PubMed PMID: 17642229.

78: Nixon R, Bansback N, Brennan A. The efficacy of inhibiting tumour necrosis factor alpha and interleukin 1 in patients with rheumatoid arthritis: a meta-analysis and adjusted indirect comparisons. Rheumatology (Oxford). 2007 Jul;46(7):1140-7. Epub 2007 May 3. PubMed PMID: 17478472.

79: Kim J, Remick DG. Tumor necrosis factor inhibitors for the treatment of asthma. Curr Allergy Asthma Rep. 2007 May;7(2):151-6. Review. PubMed PMID: 17437686.

80: Kievit W, Fransen J, Oerlemans AJ, Kuper HH, van der Laar MA, de Rooij DJ, De Gendt CM, Ronday KH, Jansen TL, van Oijen PC, Brus HL, Adang EM, van Riel PL. The efficacy of anti-TNF in rheumatoid arthritis, a comparison between randomised controlled trials and clinical practice. Ann Rheum Dis. 2007 Nov;66(11):1473-8. Epub 2007 Apr 10. Review. PubMed PMID: 17426065; PubMed Central PMCID: PMC2111629.

81: Katugampola RP, Lewis VJ, Finlay AY. The Dermatology Life Quality Index: assessing the efficacy of biological therapies for psoriasis. Br J Dermatol. 2007 May;156(5):945-50. Epub 2007 Mar 28. Review. PubMed PMID: 17388922.

82: Leon A, Nguyen A, Letsinger J, Koo J. An attempt to formulate an evidence-based strategy in the management of moderate-to-severe psoriasis: a review of the efficacy and safety of biologics and prebiologic options. Expert Opin Pharmacother. 2007 Apr;8(5):617-32. Review. PubMed PMID: 17376017.

83: Meyer O, de Bandt M, Berthelot JM, Cantagrel A, Combe B, Fautrel B, Flipo RM, Lioté F, Maillefert JF, Saraux A, Wendling D, Guillemin F, Le Loët X; Working Group for Therapeutic Strategies for Rheumatoid Arthritis. Clinical practice format for choosing a second-line disease modifying anti-rheumatic drug in early rheumatoid arthritis after failure of 6 months' first-line DMARD therapy. Joint Bone Spine. 2007 Jan;74(1):73-8. Epub 2006 Nov 29. PubMed PMID: 17194614.

84: Woolacott NF, Khadjesari ZC, Bruce IN, Riemsma RP. Etanercept and infliximab for the treatment of psoriatic arthritis: a systematic review. Clin Exp Rheumatol. 2006 Sep-Oct;24(5):587-93. Review. PubMed PMID: 17181932.

85: Roux CH, Brocq O, Breuil V, Albert C, Euller-Ziegler L. Pregnancy in rheumatology patients exposed to anti-tumour necrosis factor (TNF)-alpha therapy. Rheumatology (Oxford). 2007 Apr;46(4):695-8. Epub 2006 Dec 7. Review. PubMed PMID: 17158212.

86: Koó E, Brodszky V, Péntek M, Ujfalussy I, Nagy MB, Gulácsi L. [The role of biological agents in the treatment of psoriatic arthritis, literature review]. Orv Hetil. 2006 Oct 15;147(41):1963-70. Review. Hungarian. PubMed PMID: 17120686.

87: Woolacott N, Hawkins N, Mason A, Kainth A, Khadjesari Z, Vergel YB, Misso K,

Light K, Chalmers R, Sculpher M, Riemsma R. Etanercept and efalizumab for the treatment of psoriasis: a systematic review. Health Technol Assess. 2006 Nov;10(46):1-233, i-iv. Review. PubMed PMID: 17083854.

88: Chen YF, Jobanputra P, Barton P, Jowett S, Bryan S, Clark W, Fry-Smith A, Burls A. A systematic review of the effectiveness of adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis in adults and an economic evaluation of their cost-effectiveness. Health Technol Assess. 2006 Nov;10(42):iii-iv, xi-xiii, 1-229. Review. PubMed PMID: 17049139.

89: Takeuchi T. [TNF targetting therapy for rheumatoid arthritis]. Nippon Naika Gakkai Zasshi. 2006 Sep 10;95(9):1787-94. Review. Japanese. PubMed PMID: 17037316.

90: Cohen JD, Bournerias I, Buffard V, Paufler A, Chevalier X, Bagot M, Claudepierre P. Psoriasis induced by tumor necrosis factor-alpha antagonist therapy: a case series. J Rheumatol. 2007 Feb;34(2):380-5. Epub 2006 Oct 1. PubMed PMID: 17013997.

91: Ariza-Ariza R, Navarro-Sarabia F, Hernández-Cruz B, Rodríguez-Arboleya L, Navarro-Compán V, Toyos J. Dose escalation of the anti-TNF-alpha agents in patients with rheumatoid arthritis. A systematic review. Rheumatology (Oxford). 2007 Mar;46(3):529-32. Epub 2006 Sep 29. Review. PubMed PMID: 17012439.

92: Pedersen SJ, Hetland ML, Østergaard M. [Treatment of rheumatoid arthritis with adalimumab. Results from a Cochrane review]. Ugeskr Laeger. 2006 Aug 28;168(35):2899-903. Review. Danish. PubMed PMID: 16982019.

93: Doan QV, Chiou CF, Dubois RW. Review of eight pharmacoeconomic studies of the value of biologic DMARDs (adalimumab, etanercept, and infliximab) in the management of rheumatoid arthritis. J Manag Care Pharm. 2006 Sep;12(7):555-69. Review. PubMed PMID: 16981801.

94: de Groot M, Appelman M, Spuls PI, de Rie MA, Bos JD. Initial experience with routine administration of etanercept in psoriasis. Br J Dermatol. 2006 Oct;155(4):808-14. PubMed PMID: 16965432.

95: Woolacott N, Bravo Vergel Y, Hawkins N, Kainth A, Khadjesari Z, Misso K, Light K, Asseburg C, Palmer S, Claxton K, Bruce I, Sculpher M, Riemsma R. Etanercept and infliximab for the treatment of psoriatic arthritis: a systematic review and economic evaluation. Health Technol Assess. 2006 Sep;10(31):iii-iv, xiii-xvi, 1-239. Review. PubMed PMID: 16948890.

96: Boehncke WH, Brasie RA, Barker J, Chimenti S, Daudén E, de Rie M, Dubertret L, Giannetti A, Katsambas A, Kragballe K, Naeyaert JM, Ortonne JP, Peyrí J, Prinz JC, Saurat JH, Strohal R, van de Kerkhof P, Sterry W; European Dermatology Expert Group. Recommendations for the use of etanercept in psoriasis: a European dermatology expert group consensus. J Eur Acad Dermatol Venereol. 2006 Sep;20(8):988-98. PubMed PMID: 16922950.

97: Farahani P, Levine M, Goeree R. A comparison between integrating clinical practice setting and randomized controlled trial setting into economic evaluation models of therapeutics. J Eval Clin Pract. 2006 Aug;12(4):463-70. PubMed PMID: 16907691.

98: Salliot C, Gossec L, Ruyssen-Witrand A, Luc M, Duclos M, Guignard S, Dougados M. Infections during tumour necrosis factor-alpha blocker therapy for rheumatic diseases in daily practice: a systematic retrospective study of 709 patients. Rheumatology (Oxford). 2007 Feb;46(2):327-34. Epub 2006 Jul 31. PubMed PMID: 16880188.

99: Kemény L, Brodszky V, Kárpáti K, Gulácsi L. [The role of biological drugs in

the treatment of psoriasis, results from 9 randomized placebo-controlled trials]. Orv Hetil. 2006 May 28;147(21):981-90. Review. Hungarian. PubMed PMID: 16812973.

100: Helliwell PS. Therapies for dactylitis in psoriatic arthritis. A systematic review. J Rheumatol. 2006 Jul;33(7):1439-41. Epub 2006 May 15. Review. PubMed PMID: 16724369.

101: Boehncke WH, Prinz J, Gottlieb AB. Biologic therapies for psoriasis. A systematic review. J Rheumatol. 2006 Jul;33(7):1447-51. Epub 2006 May 15. Review. PubMed PMID: 16724367.

102: Bongartz T, Sutton AJ, Sweeting MJ, Buchan I, Matteson EL, Montori V. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. JAMA. 2006 May 17;295(19):2275-85. Review. Erratum in: JAMA. 2006 Jun 7;295(21):2482. PubMed PMID: 16705109.

103: Navarro-Sarabia F, Ariza-Ariza R, Hernández-Cruz B, Villanueva I. Adalimumab for treating rheumatoid arthritis. J Rheumatol. 2006 Jun;33(6):1075-81. Epub 2006 May 1. Review. PubMed PMID: 16652437.

104: Fransen J, Antoni C, Mease PJ, Uter W, Kavanaugh A, Kalden JR, Van Riel PL. Performance of response criteria for assessing peripheral arthritis in patients with psoriatic arthritis: analysis of data from randomised controlled trials of two tumour necrosis factor inhibitors. Ann Rheum Dis. 2006 Oct;65(10):1373-8. Epub 2006 Apr 27. PubMed PMID: 16644783; PubMed Central PMCID: PMC1798317.

105: Gottlieb AB, Leonardi CL, Goffe BS, Ortonne JP, van der Kerkhof PC, Zitnik R, Nakanishi A, Jahreis A. Etanercept monotherapy in patients with psoriasis: a summary of safety, based on an integrated multistudy database. J Am Acad Dermatol. 2006 Mar;54(3 Suppl 2):S92-100. PubMed PMID: 16488335.

106: Gordon K, Korman N, Frankel E, Wang H, Jahreis A, Zitnik R, Chang T. Efficacy of etanercept in an integrated multistudy database of patients with psoriasis. J Am Acad Dermatol. 2006 Mar;54(3 Suppl 2):S101-11. PubMed PMID: 16488320.

107: Dundar Y, Dodd S, Dickson R, Walley T, Haycox A, Williamson PR. Comparison of conference abstracts and presentations with full-text articles in the health technology assessments of rapidly evolving technologies. Health Technol Assess. 2006 Feb;10(5):iii-iv, ix-145. Review. PubMed PMID: 16487455.

108: Horneff G. [Biologics for treatment of juvenile idiopathic arthritis. Consensus statement of the 7th Wörlitzer Expertengespräche 2004 for the German Arbeitsgemeinschaft Kinder- und Jugendrheumatologie]. Z Rheumatol. 2006 Mar;65(2):152-6, 158. German. PubMed PMID: 16372138.

109: Finckh A, Simard JF, Gabay C, Guerne PA; SCQM physicians. Evidence for differential acquired drug resistance to anti-tumour necrosis factor agents in rheumatoid arthritis. Ann Rheum Dis. 2006 Jun;65(6):746-52. Epub 2005 Dec 8. PubMed PMID: 16339288; PubMed Central PMCID: PMC1798167.

110: Jacobi A, Manger B, Schuler G, Hertl M. [Therapeutic application of TNF-alpha inhibitors infliximab and etanercept in inflammatory skin disorders]. J Dtsch Dermatol Ges. 2003 Apr;1(4):259-72. Review. German. PubMed PMID: 16285480.

111: Fleischmann R, Baumgartner SW, Weisman MH, Liu T, White B, Peloso P. Long term safety of etanercept in elderly subjects with rheumatic diseases. Ann Rheum Dis. 2006 Mar;65(3):379-84. Epub 2005 Sep 8. PubMed PMID: 16150792; PubMed Central PMCID: PMC1798057.

112: Smith CH, Anstey AV, Barker JN, Burden AD, Chalmers RJ, Chandler D, Finlay

AY, Griffiths CE, Jackson K, McHugh NJ, McKenna KE, Reynolds NJ, Ormerod AD; British Association of Dermatologists. British Association of Dermatologists guidelines for use of biological interventions in psoriasis 2005. Br J Dermatol. 2005 Sep;153(3):486-97. Erratum in: Br J Dermatol. 2005 Nov;153(5):1092. Grifitths, C E M [corrected to Griffiths, C E M]. PubMed PMID: 16120132.

113: Navarro-Sarabia F, Ariza-Ariza R, Hernandez-Cruz B, Villanueva I. Adalimumab for treating rheumatoid arthritis. Cochrane Database Syst Rev. 2005 Jul 20;(3):CD005113. Review. PubMed PMID: 16034967.

114: Hochberg MC, Lebwohl MG, Plevy SE, Hobbs KF, Yocum DE. The benefit/risk profile of TNF-blocking agents: findings of a consensus panel. Semin Arthritis Rheum. 2005 Jun;34(6):819-36. Review. PubMed PMID: 15942917.

115: Guenther L, Langley RG, Shear NH, Bissonnette R, Ho V, Lynde C, Murray E, Papp K, Poulin Y, Zip C. Integrating biologic agents into management of moderate-to-severe psoriasis: a consensus of the Canadian Psoriasis Expert Panel. February 27, 2004. J Cutan Med Surg. 2004 Sep-Oct;8(5):321-37. PubMed PMID: 15868311.

116: Suzuki Y, Wakabayashi T, Jackson K. [Methotrexate for therapy of rheumatoid arthritis]. Nippon Rinsho. 2005 Jan;63 Suppl 1:498-502. Review. Japanese. PubMed PMID: 15799406.

117: Kyle S, Chandler D, Griffiths CE, Helliwell P, Lewis J, McInnes I, Oliver S, Symmons D, McHugh N; British Society for Rheumatology Standards Guidelines Audit Working Group (SGAWG). Guideline for anti-TNF-alpha therapy in psoriatic arthritis. Rheumatology (Oxford). 2005 Mar;44(3):390-7. Epub 2005 Feb 3. Review. Erratum in: Rheumatology (Oxford). 2005 Apr;44(4):569. Rheumatology (Oxford). 2005 May;44(5):701. PubMed PMID: 15695305.

118: Ledingham J, Deighton C; British Society for Rheumatology Standards, Guidelines and Audit Working Group. Update on the British Society for Rheumatology guidelines for prescribing TNFalpha blockers in adults with rheumatoid arthritis (update of previous guidelines of April 2001). Rheumatology (Oxford). 2005 Feb;44(2):157-63. Epub 2005 Jan 5. Erratum in: Rheumatology (Oxford). 2006 Sep;45(9):1170. PubMed PMID: 15637039.

119: Salvarani C, Olivieri I, Cantini F, Marchesoni A, Punzi L, Scarpa R, Matucci-Cerinic M. [Recommendations for the appropriate use of anti-TNFalpha therapy in patients with psoriatic arthritis. Italian Rheumatology Society]. Reumatismo. 2004 Jul-Sep;56(3):133-4, 136-8. Italian. PubMed PMID: 15470517.

120: Homik JE, Suarez-Almazor M. An economic approach to health care. Best Pract Res Clin Rheumatol. 2004 Apr;18(2):203-18. Review. PubMed PMID: 15121040.

121: Cutolo M. The addition of adalimumab to methotrexate reduces rheumatoid arthritis activity in patients with longstanding disease. Clin Exp Rheumatol. 2004 Mar-Apr;22(2):144. PubMed PMID: 15083879.

122: Torrance GW, Tugwell P, Amorosi S, Chartash E, Sengupta N. Improvement in health utility among patients with rheumatoid arthritis treated with adalimumab (a human anti-TNF monoclonal antibody) plus methotrexate. Rheumatology (Oxford). 2004 Jun;43(6):712-8. Epub 2004 Mar 23. PubMed PMID: 15039494.

123: Barton P, Jobanputra P, Wilson J, Bryan S, Burls A. The use of modelling to evaluate new drugs for patients with a chronic condition: the case of antibodies against tumour necrosis factor in rheumatoid arthritis. Health Technol Assess. 2004 Mar;8(11):iii, 1-91. Review. PubMed PMID: 14982655.

124: Blumenauer B, Judd M, Cranney A, Burls A, Coyle D, Hochberg M, Tugwell P, Wells G. Etanercept for the treatment of rheumatoid arthritis. Cochrane Database

Syst Rev. 2003;(4):CD004525. Review. PubMed PMID: 14584021.

125: Hochberg MC, Tracy JK, Hawkins-Holt M, Flores RH. Comparison of the efficacy of the tumour necrosis factor alpha blocking agents adalimumab, etanercept, and infliximab when added to methotrexate in patients with active rheumatoid arthritis. Ann Rheum Dis. 2003 Nov;62 Suppl 2:ii13-6. Review. PubMed PMID: 14532140; PubMed Central PMCID: PMC1766753.

126: Nahar IK, Shojania K, Marra CA, Alamgir AH, Anis AH. Infliximab treatment of rheumatoid arthritis and Crohn's disease. Ann Pharmacother. 2003 Sep;37(9):1256-65. Review. PubMed PMID: 12921510.

127: Maksymowych WP, Inman RD, Gladman D, Thomson G, Stone M, Karsh J, Russell AS; Spondyloarthritis Research Consortium of Canada (SPARCC). Canadian Rheumatology Association Consensus on the use of anti-tumor necrosis factor-alpha directed therapies in the treatment of spondyloarthritis. J Rheumatol. 2003 Jun;30(6):1356-63. Review. PubMed PMID: 12784417.

128: Salmon-Ceron D; Groupe Recherche Anti-TNF et Infections Opportunistes; Agence Française de Sécurité Sanitaire des Produits de Santé. Recommendations for the prevention and management of tuberculosis in patients taking infliximab. Ann Med Interne (Paris). 2002 Nov;153(7):429-31. PubMed PMID: 12598827.

129: Schnabel A, Gross WL. [Evidence-based treatment of methotrexate-resistant rheumatoid arthritis. Cytokine antagonists]. Dtsch Med Wochenschr. 2003 Jan 31;128(5):201-3. Review. German. PubMed PMID: 12557112.

130: Obrador A, López San Román A, Muñoz P, Fortún J, Gassull MA; Grupo Español de Trabajo de Enfermedad de Crohn y Colitis Ulcerosa (GETECCU). [Consensus guideline on tuberculosis and treatment of inflammatory bowel disease with infliximab. Spanish Working Group on Crohn Disease and Ulcerative Colitis]. Gastroenterol Hepatol. 2003 Jan;26(1):29-33. Review. Spanish. PubMed PMID: 12525326.

131: Jobanputra P, Barton P, Bryan S, Burls A. The effectiveness of infliximab and etanercept for the treatment of rheumatoid arthritis: a systematic review and economic evaluation. Health Technol Assess. 2002;6(21):1-110. Review. PubMed PMID: 12387732.

132: Rau R. Adalimumab (a fully human anti-tumour necrosis factor alpha monoclonal antibody) in the treatment of active rheumatoid arthritis: the initial results of five trials. Ann Rheum Dis. 2002 Nov;61 Suppl 2:ii70-3. Review. PubMed PMID: 12379628; PubMed Central PMCID: PMC1766697.

133: Cummins C, Connock M, Fry-Smith A, Burls A. A systematic review of effectiveness and economic evaluation of new drug treatments for juvenile idiopathic arthritis: etanercept. Health Technol Assess. 2002;6(17):1-43. Review. PubMed PMID: 12234456.

134: Rodewald EJ, Housman TS, Mellen BG, Feldman SR. The efficacy of 308nm laser treatment of psoriasis compared to historical controls. Dermatol Online J. 2001 Dec;7(2):4. PubMed PMID: 12165220.

135: Blumenauer B, Judd M, Wells G, Burls A, Cranney A, Hochberg M, Tugwell P. Infliximab for the treatment of rheumatoid arthritis. Cochrane Database Syst Rev. 2002;(3):CD003785. Review. PubMed PMID: 12137712.

136: Hochberg MC, Tracy JK, Flores RH. "Stepping-up" from methotrexate: a systematic review of randomised placebo controlled trials in patients with rheumatoid arthritis with an incomplete response to methotrexate. Ann Rheum Dis. 2001 Nov;60 Suppl 3:iii51-4. Review. PubMed PMID: 11890654; PubMed Central PMCID: PMC1766673.

137: Schattenkirchner M. [New basic therapeutic drugs from the viewpoint of evidence-based therapy]. Z Rheumatol. 2001 Dec;60(6):473-6. German. PubMed PMID: 11826744.

138: Nuijten MJ, Engelfriet P, Duijn K, Bruijn G, Wierz D, Koopmanschap M. A cost-cost study comparing etanercept with infliximab in rheumatoid arthritis. Pharmacoeconomics. 2001;19(10):1051-64. PubMed PMID: 11735673.

139: Moreland LW, Russell AS, Paulus HE. Management of rheumatoid arthritis: the historical context. J Rheumatol. 2001 Jun;28(6):1431-52. Review. PubMed PMID: 11409142.

140: Johnson CJ, Reilly KM, Murray KM. Etanercept in juvenile rheumatoid arthritis. Ann Pharmacother. 2001 Apr;35(4):464-71. Review. PubMed PMID: 11302411.

141: Moder KG. New medications for use in patients with rheumatoid arthritis. Ann Allergy Asthma Immunol. 2000 Mar;84(3):280-4; quiz 284, 287. Review. PubMed PMID: 10752910.

142: Luong BT, Chong BS, Lowder DM. Treatment options for rheumatoid arthritis: celecoxib, leflunomide, etanercept, and infliximab. Ann Pharmacother. 2000 Jun;34(6):743-60. Review. PubMed PMID: 10860137.

SEARCH 20 all agent FUNGAL NOT TB

Category	Description
Clinical question or focus	BIOLOGICAL AGENTS FINAL
Source	PubMed
Terms	**fungal infections AND (adalimumab OR certolimumab OR etanercept OR golimumab OR infliximab OR ustekinumab) AND english [lang]**
Limits	NONE
▪ Date limits	None
▪ Other limits	None
Query Translation (eg, "Details" in PubMed)	("mycoses"[MeSH Terms] OR "mycoses"[All Fields] OR ("fungal"[All Fields] AND "infections"[All Fields]) OR "fungal infections"[All Fields]) AND (("adalimumab"[Substance] OR "adalimumab"[All Fields]) OR certolimumab[All Fields] OR ("TNFR-Fc fusion protein"[Substance] OR "TNFR-Fc fusion protein"[All Fields] OR "etanercept"[All Fields]) OR ("golimumab"[Substance] OR "golimumab"[All Fields]) OR ("infliximab"[Substance] OR "infliximab"[All Fields]) OR ("monoclonal antibody CNTO 1275"[Substance] OR "monoclonal antibody CNTO 1275"[All Fields] OR "ustekinumab"[All Fields])) AND english[lang]
Date of Search	1/7/11
Total Yield	116
Marked for retireval	Weinblatt 10, Salmon-Ceron 10, Gottlieb 03
Exclusions	• Not focus of review: population, intervention, comparison, outcome • Superseded by more recent larger study • Lacking safety data • Wrong study type • Duplicates

1: Weinblatt ME, Bathon JM, Kremer JM, Fleischmann RM, Schiff MH, Martin RW, Baumgartner SW, Park GS, Mancini EL, Genovese MC. Safety and efficacy of etanercept beyond 10 years of therapy in North American patients with early and long-standing rheumatoid arthritis. Arthritis Care Res (Hoboken). 2010 Oct 18. [Epub ahead of print] PubMed PMID: 20957659.

2: Osawa R, Singh N. Colitis as a manifestation of infliximab-associated

disseminated cryptococcosis. Int J Infect Dis. 2010 May;14(5):e436-40. Epub 2009 Aug 6. PubMed PMID: 19660974.

3: Ben Said B, Kanitakis J, Graber I, Berard F, Nicolas JF, Saurin JC, Augey F. Severe sporotrichoid fishtank granuloma following infliximab therapy for Crohn's disease. Inflamm Bowel Dis. 2010 Mar;16(3):375-6. PubMed PMID: 19639559.

4: Sitapati AM, Kao CL, Cachay ER, Masoumi H, Wallis RS, Mathews WC. Treatment of HIV-related inflammatory cerebral cryptococcoma with adalimumab. Clin Infect Dis. 2010 Jan 15;50(2):e7-10. PubMed PMID: 20001539.

5: Kamili QA, Menter A. Atypical presentation of histoplasmosis in a patient with psoriasis and psoriatic arthritis on infliximab therapy. J Drugs Dermatol. 2010 Jan;9(1):57-60. PubMed PMID: 20120426.

6: Salmon-Ceron D, Tubach F, Lortholary O, Chosidow O, Bretagne S, Nicolas N, Cuillerier E, Fautrel B, Michelet C, Morel J, Puéchal X, Wendling D, Lemann M, Ravaud P, Mariette X; for the RATIO group. Drug-specific risk of non-tuberculosis opportunistic infections in patients receiving anti-TNF therapy reported to the 3-year prospective French RATIO registry. Ann Rheum Dis. 2010 Dec 21. [Epub ahead of print] PubMed PMID: 21177290.

7: Ciralsky J, Papaliodis GN, Foster CS, Dohlman CH, Chodosh J. Keratoprosthesis in autoimmune disease. Ocul Immunol Inflamm. 2010 Aug;18(4):275-80. Review. PubMed PMID: 20662659.

8: Mehta BM, Hashkes PJ, Avery R, Deal CL. A 21-year-old man with Still's disease with fever, rash, and pancytopenia. Arthritis Care Res (Hoboken). 2010 Apr;62(4):575-9. PubMed PMID: 20391515.

9: Mitter SS, Derhovanessian A, Hillman JD, Uslan DZ. Disseminated coccidioidomycosis in a patient managed with adalimumab for Crohn's disease. Nat Rev Gastroenterol Hepatol. 2010 Apr;7(4):231-5. PubMed PMID: 20376095.

10: Gupta N, Fox CM, Grisolano SW. Disseminated histoplasmosis with colonic ulcers in a patient receiving infliximab. Gastrointest Endosc. 2009 Sep;70(3):597-8. Epub 2009 Jul 1. PubMed PMID: 19573865.

11: Kluger N, Poirier P, Guilpain P, Baixench MT, Cohen P, Paugam A. Cryptococcal meningitis in a patient treated with infliximab and mycophenolate mofetil for Behcet's disease. Int J Infect Dis. 2009 Sep;13(5):e325. Epub 2009 Jan 20. PubMed PMID: 19157948.

12: Dare JA, Jahan S, Hiatt K, Torralba KD. Reintroduction of etanercept during treatment of cutaneous Mycobacterium marinum infection in a patient with ankylosing spondylitis. Arthritis Rheum. 2009 May 15;61(5):583-6. PubMed PMID: 19405014.

13: Judson MA. Allergic bronchopulmonary aspergillosis after infliximab therapy for sarcoidosis: a potential mechanism related to T-helper cytokine balance. Chest. 2009 May;135(5):1358-9. PubMed PMID: 19420205.

14: Thavarajah K, Wu P, Rhew EJ, Yeldandi AK, Kamp DW. Pulmonary complications of tumor necrosis factor-targeted therapy. Respir Med. 2009 May;103(5):661-9. Epub 2009 Feb 7. Review. PubMed PMID: 19201589; PubMed Central PMCID: PMC2743303.

15: Luzi G, Laganà B, Salemi S, Di Rosa R. Are glucocorticoids a consistent risk factor for infections in rheumatoid arthritis patients under treatment with methotrexate and etanercept? Clin Ter. 2009 Mar-Apr;160(2):121-3. PubMed PMID: 19452100.

16: Komano Y, Harigai M, Koike R, Sugiyama H, Ogawa J, Saito K, Sekiguchi N, Inoo

M, Onishi I, Ohashi H, Amamoto F, Miyata M, Ohtsubo H, Hiramatsu K, Iwamoto M, Minota S, Matsuoka N, Kageyama G, Imaizumi K, Tokuda H, Okochi Y, Kudo K, Tanaka Y, Takeuchi T, Miyasaka N. Pneumocystis jiroveci pneumonia in patients with rheumatoid arthritis treated with infliximab: a retrospective review and case-control study of 21 patients. Arthritis Rheum. 2009 Mar 15;61(3):305-12. PubMed PMID: 19248121.

17: Rao K, Rao A, Karlsson H, Jagani M, Veys P, Amrolia PJ. Improved survival and preserved antiviral responses after combination therapy with daclizumab and infliximab in steroid-refractory graft-versus-host disease. J Pediatr Hematol Oncol. 2009 Jun;31(6):456-61. PubMed PMID: 19648797.

18: Cadena J, Thompson GR 3rd, Ho TT, Medina E, Hughes DW, Patterson TF. Immune reconstitution inflammatory syndrome after cessation of the tumor necrosis factor alpha blocker adalimumab in cryptococcal pneumonia. Diagn Microbiol Infect Dis. 2009 Jul;64(3):327-30. PubMed PMID: 19501793.

19: Fuchs HA, Tanner SB. Granulomatous disorders of the nose and paranasal sinuses. Curr Opin Otolaryngol Head Neck Surg. 2009 Feb;17(1):23-7. Review. PubMed PMID: 19225301.

20: Narayana N, Gifford R, Giannini P, Casey J. Oral histoplasmosis: an unusual presentation. Head Neck. 2009 Feb;31(2):274-7. PubMed PMID: 18798316.

21: Estrada S, García-Campos F, Calderón R, Delgado E, Bengoa R, Enciso C. Pneumocystis jiroveci (carinii) pneumonia following a second infusion of infliximab in a patient with ulcerative colitis. Inflamm Bowel Dis. 2009 Feb;15(2):315-6. PubMed PMID: 19058233.

22: Arnaud L, Sene D, Costedoat-Chalumeau N, Cacoub P, Chapelon-Abric C, Piette JC. Disseminated cryptococcal infection and anti-tumor necrosis factor-alpha treatment for refractory sarcoidosis: an expected association? J Rheumatol. 2009 Feb;36(2):462-3. PubMed PMID: 19208587.

23: Ngai JC, Lam R, Ko FW, To KW, Hui DS. Pulmonary scedosporium infection as a complication of infliximab therapy for ankylosing spondylitis. Thorax. 2009 Feb;64(2):184. PubMed PMID: 19176849.

24: Thin L, Macquillan G, Adams L, Garas G, Seow C, Cannell P, Augustson B, Mitchell A, Delriveire L, Jeffrey G. Acute graft-versus-host disease after liver transplant: novel use of etanercept and the role of tumor necrosis factor alpha inhibitors. Liver Transpl. 2009 Apr;15(4):421-6. PubMed PMID: 19326415.

25: Leboime A, Berthelot JM, Allanore Y, Khalil-Kallouche L, Herman P, Orcel P, Lioté F. Sinus aspergilloma in rheumatoid arthritis before or during tumor necrosis factor-alpha antagonist therapy. Arthritis Res Ther. 2009;11(6):R164. Epub 2009 Nov 3. PubMed PMID: 19886992; PubMed Central PMCID: PMC3003503.

26: Wall GC, Leman BI. Mucormycosis in a Crohn's disease patient treated with infliximab. Digestion. 2009;80(3):182-4. Epub 2009 Sep 16. PubMed PMID: 19776582.

27: Bourré-Tessier J, Fortin C, Belisle A, Desmarais E, Choquette D, Senécal JL. Disseminated Histoplasma capsulatum infection presenting with panniculitis and focal myositis in rheumatoid arthritis treated with etanercept. Scand J Rheumatol. 2009;38(4):311-6. Review. PubMed PMID: 19444717.

28: Kuehn BM. Severe fungal infections linked to drugs. JAMA. 2008 Oct 8;300(14):1639. PubMed PMID: 18840827.

29: Asrani NS. Disseminated histoplasmosis associated with the treatment of rheumatoid arthritis with anticytokine therapy. Ann Intern Med. 2008 Oct 21;149(8):594-5. PubMed PMID: 18936512.

30: Rehman T, Ali J, Lopez FA. A 61-year-old man with asymptomatic, bilateral lung masses. J La State Med Soc. 2008 Nov-Dec;160(6):309-14; quiz 349. PubMed PMID: 19283977.

31: Levy MS, Polsky D, Davidson A, Strober BE. Tinea versicolor associated with etanercept therapy. J Am Acad Dermatol. 2008 May;58(5 Suppl 1):S99-100. PubMed PMID: 18489062.

32: Kozic H, Riggs K, Ringpfeil F, Lee JB. Disseminated Cryptococcus neoformans after treatment with infliximab for rheumatoid arthritis. J Am Acad Dermatol. 2008 May;58(5 Suppl 1):S95-6. PubMed PMID: 18489059.

33: Galandiuk S, Davis BR. Infliximab-induced disseminated histoplasmosis in a patient with Crohn's disease. Nat Clin Pract Gastroenterol Hepatol. 2008 May;5(5):283-7. Epub 2008 Apr 8. PubMed PMID: 18398409.

34: Slusher JR, Maldonado ME, Mousavi F, Lozada CJ. Central nervous system Aspergillus fumigatus presenting as cranial nerve palsy in a patient with ankylosing spondylitis on anti-TNF therapy. Rheumatology (Oxford). 2008 May;47(5):739-40. Epub 2008 Apr 1. PubMed PMID: 18381385.

35: Hamadani M, Hofmeister CC, Jansak B, Phillips G, Elder P, Blum W, Penza S, Lin TS, Klisovic R, Marcucci G, Farag SS, Devine SM. Addition of infliximab to standard acute graft-versus-host disease prophylaxis following allogeneic peripheral blood cell transplantation. Biol Blood Marrow Transplant. 2008 Jul;14(7):783-9. PubMed PMID: 18541197.

36: Wilson ML, Sewell LD, Mowad CM. Primary cutaneous Cryptococcosis during therapy with methotrexate and adalimumab. J Drugs Dermatol. 2008 Jan;7(1):53-4. PubMed PMID: 18246698.

37: Tsiodras S, Samonis G, Boumpas DT, Kontoyiannis DP. Fungal infections complicating tumor necrosis factor alpha blockade therapy. Mayo Clin Proc. 2008 Feb;83(2):181-94. Review. PubMed PMID: 18241628.

38: Odessey E, Cohn A, Beaman K, Schechter L. Invasive mucormycosis of the maxillary sinus: extensive destruction with an indolent presentation. Surg Infect (Larchmt). 2008 Feb;9(1):91-8. Review. PubMed PMID: 18363473.

39: Booker MJ, Flint J, Saravana S. Aseptic meningitis in a patient taking etanercept for rheumatoid arthritis: a case report. Cases J. 2008 Dec 1;1(1):364. PubMed PMID: 19046446; PubMed Central PMCID: PMC2612655.

40: Davaine AC, Saraux A, Prigent S, Kupfer-Bessaguet I, Roswag D, Plantin P, Schoenlaub P, Talarmin F, Zagnoli A, Misery L. Cutaneous events during treatment of chronic inflammatory joint disorders with anti-tumour necrosis factor alpha: a cross-sectional study. J Eur Acad Dermatol Venereol. 2008 Dec;22(12):1471-7. Epub 2008 Aug 18. PubMed PMID: 18713230.

41: Arriola-Villalobos P, Díaz-Valle D, Alejandre-Alba N, López-Abad C, Méndez-Fernández R, Benítez-del-Castillo JM. Bilateral Candida chorioretinitis following etanercept treatment for hidradenitis suppurativa. Eye (Lond). 2008 Apr;22(4):599-600. Epub 2008 Feb 1. PubMed PMID: 18239677.

42: Kaiser J. Gene therapy. Questions remain on cause of death in arthritis trial. Science. 2007 Sep 21;317(5845):1665. PubMed PMID: 17885103.

43: Mertz LE, Blair JE. Coccidioidomycosis in rheumatology patients: incidence and potential risk factors. Ann N Y Acad Sci. 2007 Sep;1111:343-57. Epub 2007 Mar 15. PubMed PMID: 17363440.

44: Sleight BS, Chan KW, Braun TM, Serrano A, Gilman AL. Infliximab for GVHD therapy in children. Bone Marrow Transplant. 2007 Sep;40(5):473-80. Epub 2007 Jul 9. PubMed PMID: 17618323.

45: Devlin SM, Hu B, Ippoliti A. Mucormycosis presenting as recurrent gastric perforation in a patient with Crohn's disease on glucocorticoid, 6-mercaptopurine, and infliximab therapy. Dig Dis Sci. 2007 Sep;52(9):2078-81. Epub 2007 Apr 4. PubMed PMID: 17406841.

46: Wadman M. Poor trial design leaves gene therapy death a mystery. Nat Med. 2007 Oct;13(10):1124. PubMed PMID: 17917642.

47: Harigai M, Koike R, Miyasaka N; Pneumocystis Pneumonia under Anti-Tumor Necrosis Factor Therapy (PAT) Study Group. Pneumocystis pneumonia associated with infliximab in Japan. N Engl J Med. 2007 Nov 1;357(18):1874-6. PubMed PMID: 17978303.

48: Hoang JK, Burruss J. Localized cutaneous Cryptococcus albidus infection in a 14-year-old boy on etanercept therapy. Pediatr Dermatol. 2007 May-Jun;24(3):285-8. PubMed PMID: 17542882.

49: Filler SG, Solis NV, Guo J, Doellgast G, Ruiz-Garcia A, Pan WJ. Pharmacokinetics of murine p75-Fc fusion protein and MP6-XT22 anti-murine TNF-alpha mAb in mice. J Investig Dermatol Symp Proc. 2007 May;12(1):52-6. PubMed PMID: 17502872.

50: Dweik M, Baethge BA, Duarte AG. Coccidioidomycosis pneumonia in a nonendemic area associated with infliximab. South Med J. 2007 May;100(5):517-8. PubMed PMID: 17534091.

51: Lowther AL, Somani AK, Camouse M, Florentino FT, Somach SC. Invasive Trichophyton rubrum infection occurring with infliximab and long-term prednisone treatment. J Cutan Med Surg. 2007 Mar-Apr;11(2):84-8. PubMed PMID: 17374319.

52: Lee HH, Song IH, Friedrich M, Gauliard A, Detert J, Röwert J, Audring H, Kary S, Burmester GR, Sterry W, Worm M. Cutaneous side-effects in patients with rheumatic diseases during application of tumour necrosis factor-alpha antagonists. Br J Dermatol. 2007 Mar;156(3):486-91. PubMed PMID: 17300238.

53: Sharma K, Rao P, Krishnamurthy P, Ali SA, Beck G. Pneumocystis carinii jiroveci pneumonia following infliximab infusion for Crohn disease: emphasis on prophylaxis. South Med J. 2007 Mar;100(3):331-2. PubMed PMID: 17402149.

54: Kaur N, Mahl TC. Pneumocystis jiroveci (carinii) pneumonia after infliximab therapy: a review of 84 cases. Dig Dis Sci. 2007 Jun;52(6):1481-4. Epub 2007 Apr 11. PubMed PMID: 17429728.

55: Itaba S, Iwasa T, Sadamoto Y, Nasu T, Misawa T, Inoue K, Shimokawa H, Nakamura K, Takayanagi R. Pneumocystis pneumonia during combined therapy of infliximab, corticosteroid, and azathioprine in a patient with Crohn's disease. Dig Dis Sci. 2007 Jun;52(6):1438-41. Epub 2007 Apr 3. PubMed PMID: 17404870.

56: Horcajada JP, Peña JL, Martínez-Taboada VM, Pina T, Belaustegui I, Cano ME, García-Palomo D, Fariñas MC. Invasive Cryptococcosis and adalimumab treatment. Emerg Infect Dis. 2007 Jun;13(6):953-5. PubMed PMID: 17582908; PubMed Central PMCID: PMC2792838.

57: Busca A, Locatelli F, Marmont F, Ceretto C, Falda M. Recombinant human soluble tumor necrosis factor receptor fusion protein as treatment for steroid refractory graft-versus-host disease following allogeneic hematopoietic stem cell transplantation. Am J Hematol. 2007 Jan;82(1):45-52. PubMed PMID: 16937391.

58: Weinblatt M, Schiff M, Goldman A, Kremer J, Luggen M, Li T, Chen D, Becker JC. Selective costimulation modulation using abatacept in patients with active rheumatoid arthritis while receiving etanercept: a randomised clinical trial. Ann Rheum Dis. 2007 Feb;66(2):228-34. Epub 2006 Aug 25. PubMed PMID: 16935912; PubMed Central PMCID: PMC1798511.

59: Kaiser J. Clinical trials. Gene transfer an unlikely contributor to patient's death. Science. 2007 Dec 7;318(5856):1535. PubMed PMID: 18063761.

60: Lahiff C, Khiaron OB, Nolan N, Chadwick GA. Pneumocystis carinii pneumonia in a patient on etanercept for psoriatic arthritis. Ir J Med Sci. 2007 Dec;176(4):309-11. Epub 2007 Sep 29. PubMed PMID: 17906888.

61: Gadadhar H, Hawkins S, Huffstutter JE, Panda M. Cutaneous mucormycosis complicating methotrexate, prednisone, and infliximab therapy. J Clin Rheumatol. 2007 Dec;13(6):361-2. PubMed PMID: 18176152.

62: Chou LS, Lewis RE, Ippoliti C, Champlin RE, Kontoyiannis DP. Caspofungin as primary antifungal prophylaxis in stem cell transplant recipients. Pharmacotherapy. 2007 Dec;27(12):1644-50. PubMed PMID: 18041885.

63: Ahmed MM, Mubashir E, Dossabhoy NR. Isolated renal sarcoidosis: a rare presentation of a rare disease treated with infliximab. Clin Rheumatol. 2007 Aug;26(8):1346-9. Epub 2006 Jul 19. PubMed PMID: 16850114.

64: Singh P, Taylor SF, Murali R, Gomes LJ, Kanthan GL, Maloof AJ. Disseminated mucormycosis and orbital ischaemia in combination immunosuppression with a tumour necrosis factor alpha inhibitor. Clin Experiment Ophthalmol. 2007 Apr;35(3):275-80. PubMed PMID: 17430516.

65: Muñoz P, Giannella M, Valerio M, Soria T, Díaz F, Longo JL, Bouza E. Cryptococcal meningitis in a patient treated with infliximab. Diagn Microbiol Infect Dis. 2007 Apr;57(4):443-6. Epub 2007 Jan 19. Review. PubMed PMID: 17240111.

66: Kalyoncu U, Karadag O, Akdogan A, Kisacik B, Erman M, Erguven S, Ertenli AI. Pneumocystis carinii pneumonia in a rheumatoid arthritis patient treated with adalimumab. Scand J Infect Dis. 2007;39(5):475-8. PubMed PMID: 17464877.

67: D'Amore M, Minenna G, Favoino E, D'Amore S. Phlegmonous abscess associated with etanercept therapy. Panminerva Med. 2006 Sep;48(3):199-200. PubMed PMID: 17122757.

68: Finn S, Bond J, McCarthy D, Sheahan K, Quinn C. Angioinvasive aspergillosis presenting as neutropenic colitis. Histopathology. 2006 Oct;49(4):440-1. PubMed PMID: 16978214.

69: Winthrop KL. Risk and prevention of tuberculosis and other serious opportunistic infections associated with the inhibition of tumor necrosis factor. Nat Clin Pract Rheumatol. 2006 Nov;2(11):602-10. Review. PubMed PMID: 17075599.

70: Jain VV, Evans T, Peterson MW. Reactivation histoplasmosis after treatment with anti-tumor necrosis factor alpha in a patient from a nonendemic area. Respir Med. 2006 Jul;100(7):1291-3. Epub 2006 Mar 20. PubMed PMID: 16545951.

71: Keijzer A, van der Valk P, Ossenkoppele GJ, van de Loosdrecht AA. Mucormycosis in a patient with low risk myelodysplasia treated with anti-TNF-alpha. Haematologica. 2006 Dec;91(12 Suppl):ECR51. PubMed PMID: 17194657.

72: Braun J, Targan SR. Multiparameter analysis of immunogenetic mechanisms in clinical diagnosis and management of inflammatory bowel disease. Adv Exp Med

Biol. 2006;579:209-18. Review. PubMed PMID: 16620020.

73: Amano K. Pulmonary infections in patients with rheumatoid arthritis who have received anti-TNF therapy. Intern Med. 2006;45(17):991-2. Epub 2006 Oct 2. PubMed PMID: 17015997.

74: Imaizumi K, Sugishita M, Usui M, Kawabe T, Hashimoto N, Hasegawa Y. Pulmonary infectious complications associated with anti-TNFalpha therapy (infliximab) for rheumatoid arthritis. Intern Med. 2006;45(10):685-8. Epub 2006 Jun 15. PubMed PMID: 16778341.

75: Oda S, Fujinaga H, Takahashi K. Infectious myositis involving the piriformis in a patient with rheumatoid arthritis. Mod Rheumatol. 2006;16(4):260-3. PubMed PMID: 16906380.

76: Mori S, Imamura F, Kiyofuji C, Ito K, Koga Y, Honda I, Sugimoto M. Pneumocystis jiroveci pneumonia in a patient with rheumatoid arthritis as a complication of treatment with infliximab, anti-tumor necrosis factor alpha neutralizing antibody. Mod Rheumatol. 2006;16(1):58-62. PubMed PMID: 16622728.

77: Alderson JW, Van Dinter TG Jr, Opatowsky MJ, Burton EC. Disseminated aspergillosis following infliximab therapy in an immunosuppressed patient with Crohn's disease and chronic hepatitis C: a case study and review of the literature. MedGenMed. 2005 Sep 21;7(3):7. Review. PubMed PMID: 16369233; PubMed Central PMCID: PMC1681636.

78: Crum NF, Lederman ER, Wallace MR. Infections associated with tumor necrosis factor-alpha antagonists. Medicine (Baltimore). 2005 Sep;84(5):291-302. Review. PubMed PMID: 16148729.

79: Rychly DJ, DiPiro JT. Infections associated with tumor necrosis factor-alpha antagonists. Pharmacotherapy. 2005 Sep;25(9):1181-92. Review. PubMed PMID: 16164393.

80: van der Meer JW, Popa C, Netea MG. Side effects of anticytokine strategies. Neth J Med. 2005 Mar;63(3):78-80. PubMed PMID: 15813418.

81: Seddik M, Melliez H, Seguy D, Viget N, Cortot A, Colombel JF. Pneumocystis jiroveci (carinii) pneumonia after initiation of infliximab and azathioprine therapy in a patient with Crohn's disease. Inflamm Bowel Dis. 2005 Jun;11(6):618-20. Erratum in: Inflamm Bowel Dis. 2005 Aug;11(8):705. PubMed PMID: 15905713.

82: Bakleh M, Tleyjeh I, Matteson EL, Osmon DR, Berbari EF. Infectious complications of tumor necrosis factor-alpha antagonists. Int J Dermatol. 2005 Jun;44(6):443-8. Review. PubMed PMID: 15941429.

83: Baughman RP, Lower EE. Fungal infections as a complication of therapy for sarcoidosis. QJM. 2005 Jun;98(6):451-6. Epub 2005 May 6. PubMed PMID: 15879444.

84: Scheinfeld N. Adalimumab: a review of side effects. Expert Opin Drug Saf. 2005 Jul;4(4):637-41. Review. PubMed PMID: 16011443.

85: Goulet CJ, Moseley RH, Tonnerre C, Sandhu IS, Saint S. Clinical problem-solving. The unturned stone. N Engl J Med. 2005 Feb 3;352(5):489-94. Erratum in: N Engl J Med. 2005 Apr 21;352(16):1731. PubMed PMID: 15689588.

86: Tai YJ, Kelly R. Pyoderma gangrenosum complicated by herpes simplex virus infection. Australas J Dermatol. 2005 Aug;46(3):161-4. PubMed PMID: 16008647.

87: Stratakos G, Kalomenidis I, Papas V, Malagari K, Kollintza A, Roussos C, Anagnostopoulou M, Paniara O, Zakynthinos S, Papiris SA. Cough and fever in a

female with Crohn's disease receiving infliximab. Eur Respir J. 2005 Aug;26(2):354-7. PubMed PMID: 16055885.

88: Lamprecht P, Voswinkel J, Gross WL. TNF-inhibitors in Wegener's granulomatosis. Kidney Blood Press Res. 2005;28(1):62. Epub 2005 Nov 18. PubMed PMID: 15557770.

89: Kaur N, Mahl TC. Pneumocystis carinii pneumonia with oral candidiasis after infliximab therapy for Crohn's disease. Dig Dis Sci. 2004 Sep;49(9):1458-60. Review. PubMed PMID: 15481319.

90: Velayos FS, Sandborn WJ. Pneumocystis carinii pneumonia during maintenance anti-tumor necrosis factor-alpha therapy with infliximab for Crohn's disease. Inflamm Bowel Dis. 2004 Sep;10(5):657-60. PubMed PMID: 15472531.

91: Giles JT, Bathon JM. Serious infections associated with anticytokine therapies in the rheumatic diseases. J Intensive Care Med. 2004 Nov-Dec;19(6):320-34. Review. PubMed PMID: 15523118.

92: Patriarca F, Sperotto A, Damiani D, Morreale G, Bonifazi F, Olivieri A, Ciceri F, Milone G, Cesaro S, Bandini G, Dini G, Corradini P, Fanin R. Infliximab treatment for steroid-refractory acute graft-versus-host disease. Haematologica. 2004 Nov;89(11):1352-9. PubMed PMID: 15531458.

93: Lassoued S, Sire S, Farny M, Billey T, Lassoued K. Pulmonary aspergillosis in a patient with rheumatoid arthritis treated by etanercept. Clin Exp Rheumatol. 2004 Mar-Apr;22(2):267-8. PubMed PMID: 15083902.

94: Bergstrom L, Yocum DE, Ampel NM, Villanueva I, Lisse J, Gluck O, Tesser J, Posever J, Miller M, Araujo J, Kageyama DM, Berry M, Karl L, Yung CM. Increased risk of coccidioidomycosis in patients treated with tumor necrosis factor alpha antagonists. Arthritis Rheum. 2004 Jun;50(6):1959-66. PubMed PMID: 15188373.

95: Shrestha RK, Stoller JK, Honari G, Procop GW, Gordon SM. Pneumonia due to Cryptococcus neoformans in a patient receiving infliximab: possible zoonotic transmission from a pet cockatiel. Respir Care. 2004 Jun;49(6):606-8. PubMed PMID: 15165294.

96: Coyle CM, Weiss LM, Rhodes LV 3rd, Cali A, Takvorian PM, Brown DF, Visvesvara GS, Xiao L, Naktin J, Young E, Gareca M, Colasante G, Wittner M. Fatal myositis due to the microsporidian Brachiola algerae, a mosquito pathogen. N Engl J Med. 2004 Jul 1;351(1):42-7. PubMed PMID: 15229306.

97: Seddik M, Meliez H, Seguy D, Viget N, Cortot A, Colombel JF. Pneumocystis jiroveci (carinii) pneumonia following initiation of infliximab and azathioprine therapy in a patient with Crohn's disease. Inflamm Bowel Dis. 2004 Jul;10(4):436-7. Erratum in: Inflamm Bowel Dis. 2005 Aug;11(8):705. PubMed PMID: 15475754.

98: Couriel D, Saliba R, Hicks K, Ippoliti C, de Lima M, Hosing C, Khouri I, Andersson B, Gajewski J, Donato M, Anderlini P, Kontoyiannis DP, Cohen A, Martin T, Giralt S, Champlin R. Tumor necrosis factor-alpha blockade for the treatment of acute GVHD. Blood. 2004 Aug 1;104(3):649-54. Epub 2004 Apr 6. PubMed PMID: 15069017.

99: Arend SM, Kuijper EJ, Allaart CF, Muller WH, Van Dissel JT. Cavitating pneumonia after treatment with infliximab and prednisone. Eur J Clin Microbiol Infect Dis. 2004 Aug;23(8):638-41. Epub 2004 Jul 23. PubMed PMID: 15278730.

100: Gottlieb GS, Lesser CF, Holmes KK, Wald A. Disseminated sporotrichosis associated with treatment with immunosuppressants and tumor necrosis factor-alpha antagonists. Clin Infect Dis. 2003 Sep 15;37(6):838-40. Epub 2003 Aug 23. PubMed

PMID: 12955647.

101: Marty FM, Lee SJ, Fahey MM, Alyea EP, Soiffer RJ, Antin JH, Baden LR. Infliximab use in patients with severe graft-versus-host disease and other emerging risk factors of non-Candida invasive fungal infections in allogeneic hematopoietic stem cell transplant recipients: a cohort study. Blood. 2003 Oct 15;102(8):2768-76. Epub 2003 Jul 10. PubMed PMID: 12855583.

102: Jacobsohn DA, Hallick J, Anders V, McMillan S, Morris L, Vogelsang GB. Infliximab for steroid-refractory acute GVHD: a case series. Am J Hematol. 2003 Oct;74(2):119-24. PubMed PMID: 14508798.

103: Zandman-Goddard G. Infection and anti-tumor necrosis factor-alpha therapy. Isr Med Assoc J. 2003 Nov;5(11):814-6. Review. PubMed PMID: 14650109.

104: Wood KL, Hage CA, Knox KS, Kleiman MB, Sannuti A, Day RB, Wheat LJ, Twigg HL 3rd. Histoplasmosis after treatment with anti-tumor necrosis factor-alpha therapy. Am J Respir Crit Care Med. 2003 May 1;167(9):1279-82. Epub 2003 Feb 13. PubMed PMID: 12615627.

105: Netea MG, Radstake T, Joosten LA, van der Meer JW, Barrera P, Kullberg BJ. Salmonella septicemia in rheumatoid arthritis patients receiving anti-tumor necrosis factor therapy: association with decreased interferon-gamma production and Toll-like receptor 4 expression. Arthritis Rheum. 2003 Jul;48(7):1853-7. PubMed PMID: 12847679.

106: De Rosa FG, Shaz D, Campagna AC, Dellaripa PE, Khettry U, Craven DE. Invasive pulmonary aspergillosis soon after therapy with infliximab, a tumor necrosis factor-alpha-neutralizing antibody: a possible healthcare-associated case? Infect Control Hosp Epidemiol. 2003 Jul;24(7):477-82. Review. PubMed PMID: 12887234.

107: Hage CA, Wood KL, Winer-Muram HT, Wilson SJ, Sarosi G, Knox KS. Pulmonary cryptococcosis after initiation of anti-tumor necrosis factor-alpha therapy. Chest. 2003 Dec;124(6):2395-7. PubMed PMID: 14665529.

108: van der Klooster JM, Bosman RJ, Oudemans-van Straaten HM, van der Spoel JI, Wester JP, Zandstra DF. Disseminated tuberculosis, pulmonary aspergillosis and cutaneous herpes simplex infection in a patient with infliximab and methotrexate. Intensive Care Med. 2003 Dec;29(12):2327-9. Epub 2003 Nov 5. PubMed PMID: 14600805.

109: Fleishmann RM. Safety of anakinra, a recombinant interleukin-1 receptor antagonist (r-metHuIL-1ra), in patients with rheumatoid arthritis and comparison to anti-TNF-alpha agents. Clin Exp Rheumatol. 2002 Sep-Oct;20(5 Suppl 27):S35-41. Review. PubMed PMID: 14989428.

110: Lee JH, Slifman NR, Gershon SK, Edwards ET, Schwieterman WD, Siegel JN, Wise RP, Brown SL, Udall JN Jr, Braun MM. Life-threatening histoplasmosis complicating immunotherapy with tumor necrosis factor alpha antagonists infliximab and etanercept. Arthritis Rheum. 2002 Oct;46(10):2565-70. PubMed PMID: 12384912.

111: True DG, Penmetcha M, Peckham SJ. Disseminated cryptococcal infection in rheumatoid arthritis treated with methotrexate and infliximab. J Rheumatol. 2002 Jul;29(7):1561-3. PubMed PMID: 12136922.

112: Nakelchik M, Mangino JE. Reactivation of histoplasmosis after treatment with infliximab. Am J Med. 2002 Jan;112(1):78. PubMed PMID: 11812415.

113: Zhang Z, Correa H, Bégué RE. Tuberculosis and treatment with infliximab. N Engl J Med. 2002 Feb 21;346(8):623-6. PubMed PMID: 11859880.

114: Tai TL, O'Rourke KP, McWeeney M, Burke CM, Sheehan K, Barry M. Pneumocystis carinii pneumonia following a second infusion of infliximab. Rheumatology (Oxford). 2002 Aug;41(8):951-2. PubMed PMID: 12154220.

115: Estey E. Reducing mortality associated with immediate treatment complications of adult leukemias. Semin Hematol. 2001 Oct;38(4 Suppl 10):32-7. PubMed PMID: 11694950.

116: Warris A, Bjørneklett A, Gaustad P. Invasive pulmonary aspergillosis associated with infliximab therapy. N Engl J Med. 2001 Apr 5;344(14):1099-100. PubMed PMID: 11291675.

SEARCH 21_ ustekinumab_ psoriatic arthritis trials

Category	Description
Clinical question or focus	BIOLOGICAL AGENTS FINAL
Source	PubMed
Terms	**ustekinumab** AND psoriatic arthritis
Limits	Systematic Review
▪ Date limits	
▪ Other limits	Clinical trials
Query Translation (eg, “Details” in PubMed)	(("monoclonal antibody CNTO 1275"[Substance] OR "monoclonal antibody CNTO 1275"[All Fields] OR "ustekinumab"[All Fields]) AND ("arthritis, psoriatic"[MeSH Terms] OR ("arthritis"[All Fields] AND "psoriatic"[All Fields]) OR "psoriatic arthritis"[All Fields] OR ("psoriatic"[All Fields] AND "arthritis"[All Fields]))) AND Clinical Trial[ptyp]
Date of Search	1/14/11
Total Yield	2
Total marked for retrieval	Gottlieb 09
Exclusions	• Not focus of review: population, intervention, comparison, outcome • Superseded by more recent larger study • Lacking safety data • Duplicates

Primary Studies: Yield and Dispositions

1: Zhu YW, Mendelsohn A, Pendley C, Davis HM, Zhou H. Population pharmacokinetics of ustekinumab in patients with active psoriatic arthritis. Int J Clin Pharmacol Ther. 2010 Dec;48(12):830-46. PubMed PMID: 21084039.

2: Gottlieb A, Menter A, Mendelsohn A, Shen YK, Li S, Guzzo C, Fretzin S, Kunynetz R, Kavanaugh A. Ustekinumab, a human interleukin 12/23 monoclonal antibody, for psoriatic arthritis: randomised, double-blind, placebo-controlled, crossover trial. Lancet. 2009 Feb 21;373(9664):633-40. Epub 2009 Feb 11. Erratum in: Lancet. 2010 Nov 6;376(9752):1542. Lancet. 2009 Apr 18;373(9672):1340. PubMed PMID: 19217154.

SEARCH 22_5 agents_ psoriatic arthritis RCTs

Category	Description
Clinical question or focus	BIOLOGICAL AGENTS FINAL
Source	PubMed
Terms	**(Adalimumab OR Etanercept OR Golimumab OR Infliximab OR Ustekinumab) AND psoriatic arthritis AND english [lang]**
Limits	RCT
▪ Date limits	
▪ Other limits	Clinical trials
Query Translation (eg, “Details” in PubMed)	(("adalimumab"[Substance] OR "adalimumab"[All Fields]) OR ("TNFR-Fc

	fusion protein"[Substance] OR "TNFR-Fc fusion protein"[All Fields] OR "etanercept"[All Fields]) OR ("golimumab"[Substance] OR "golimumab"[All Fields]) OR ("infliximab"[Substance] OR "infliximab"[All Fields]) OR ("monoclonal antibody CNTO 1275"[Substance] OR "monoclonal antibody CNTO 1275"[All Fields] OR "ustekinumab"[All Fields])) AND ("arthritis, psoriatic"[MeSH Terms] OR ("arthritis"[All Fields] AND "psoriatic"[All Fields]) OR "psoriatic arthritis"[All Fields] OR ("psoriatic"[All Fields] AND "arthritis"[All Fields])) AND english[lang] AND Randomized Controlled Trial[ptyp]
Date of Search	1/14/11
Total Yield	40
Total marked for retrieval	Sterry 10, Mease 08, Kavanaugh 09, Antoni 08, Menter 06
Exclusions	• Not focus of review: population, intervention, comparison, outcome • Superseded by more recent larger study • Wrong study type • Lacking safety data • Duplicates

Primary Studies: Yield and Dispositions

1: Zhu YW, Mendelsohn A, Pendley C, Davis HM, Zhou H. Population pharmacokinetics of ustekinumab in patients with active psoriatic arthritis. Int J Clin Pharmacol Ther. 2010 Dec;48(12):830-46. PubMed PMID: 21084039.

2: Torii H, Nakagawa H; Japanese Infliximab Study investigators. Infliximab monotherapy in Japanese patients with moderate-to-severe plaque psoriasis and psoriatic arthritis. A randomized, double-blind, placebo-controlled multicenter trial. J Dermatol Sci. 2010 Jul;59(1):40-9. Epub 2010 May 4. PubMed PMID: 20547039.

3: Gladman DD, Mease PJ, Choy EH, Ritchlin CT, Perdok RJ, Sasso EH. Risk factors for radiographic progression in psoriatic arthritis: subanalysis of the randomized controlled trial ADEPT. Arthritis Res Ther. 2010;12(3):R113. Epub 2010 Jun 10. PubMed PMID: 20537151; PubMed Central PMCID: PMC2911906.

4: Schoels M, Aletaha D, Funovits J, Kavanaugh A, Baker D, Smolen JS. Application of the DAREA/DAPSA score for assessment of disease activity in psoriatic arthritis. Ann Rheum Dis. 2010 Aug;69(8):1441-7. Epub 2010 Jun 4. PubMed PMID: 20525844.

5: Mease PJ, Woolley JM, Singh A, Tsuji W, Dunn M, Chiou CF. Patient-reported outcomes in a randomized trial of etanercept in psoriatic arthritis. J Rheumatol. 2010 Jun;37(6):1221-7. Epub 2010 Apr 15. PubMed PMID: 20395648.

6: Englbrecht M, Wang Y, Ronneberger M, Manger B, Vastesaeger N, Veale DJ, Schett G. Measuring joint involvement in polyarticular psoriatic arthritis: an introduction of alternatives. Arthritis Care Res (Hoboken). 2010 Jul;62(7):977-83. PubMed PMID: 20191568.

7: Sterry W, Ortonne JP, Kirkham B, Brocq O, Robertson D, Pedersen RD, Estojak J, Molta CT, Freundlich B. Comparison of two etanercept regimens for treatment of psoriasis and psoriatic arthritis: PRESTA randomised double blind multicentre trial. BMJ. 2010 Feb 2;340:c147. doi: 10.1136/bmj.c147. PubMed PMID: 20124563.

8: Atteno M, Peluso R, Costa L, Padula S, Iervolino S, Caso F, Sanduzzi A, Lubrano E, Del Puente A, Scarpa R. Comparison of effectiveness and safety of infliximab, etanercept, and adalimumab in psoriatic arthritis patients who experienced an inadequate response to previous disease-modifying antirheumatic

drugs. Clin Rheumatol. 2010 Apr;29(4):399-403. PubMed PMID: 20066450.

9: Peters MJ, Watt P, Cherry L, Welsh P, Henninger E, Dijkmans BA, McInnes IB, Nurmohamed MT, Sattar N. Lack of effect of TNFalpha blockade therapy on circulating adiponectin levels in patients with autoimmune disease: results from two independent prospective studies. Ann Rheum Dis. 2010 Sep;69(9):1687-90. Epub 2009 Jul 28. PubMed PMID: 19640853.

10: Xu Z, Vu T, Lee H, Hu C, Ling J, Yan H, Baker D, Beutler A, Pendley C, Wagner C, Davis HM, Zhou H. Population pharmacokinetics of golimumab, an anti-tumor necrosis factor-alpha human monoclonal antibody, in patients with psoriatic arthritis. J Clin Pharmacol. 2009 Sep;49(9):1056-70. Epub 2009 Jul 17. PubMed PMID: 19617465.

11: Kavanaugh A, McInnes I, Mease P, Krueger GG, Gladman D, Gomez-Reino J, Papp K, Zrubek J, Mudivarthy S, Mack M, Visvanathan S, Beutler A. Golimumab, a new human tumor necrosis factor alpha antibody, administered every four weeks as a subcutaneous injection in psoriatic arthritis: Twenty-four-week efficacy and safety results of a randomized, placebo-controlled study. Arthritis Rheum. 2009 Apr;60(4):976-86. Erratum in: Arthritis Rheum.2010 Aug;62(8):2555. PubMed PMID: 19333944.

12: Gottlieb A, Menter A, Mendelsohn A, Shen YK, Li S, Guzzo C, Fretzin S, Kunynetz R, Kavanaugh A. Ustekinumab, a human interleukin 12/23 monoclonal antibody, for psoriatic arthritis: randomised, double-blind, placebo-controlled, crossover trial. Lancet. 2009 Feb 21;373(9664):633-40. Epub 2009 Feb 11. Erratum in: Lancet. 2010 Nov 6;376(9752):1542. Lancet. 2009 Apr 18;373(9672):1340. PubMed PMID: 19217154.

13: Mease PJ, Ory P, Sharp JT, Ritchlin CT, Van den Bosch F, Wellborne F, Birbara C, Thomson GT, Perdok RJ, Medich J, Wong RL, Gladman DD. Adalimumab for long-term treatment of psoriatic arthritis: 2-year data from the Adalimumab Effectiveness in Psoriatic Arthritis Trial (ADEPT). Ann Rheum Dis. 2009 May;68(5):702-9. Epub 2008 Aug 6. PubMed PMID: 18684743; PubMed Central PMCID: PMC2663711.

14: van Kuijk AW, Gerlag DM, Vos K, Wolbink G, de Groot M, de Rie MA, Zwinderman AH, Dijkmans BA, Tak PP. A prospective, randomised, placebo-controlled study to identify biomarkers associated with active treatment in psoriatic arthritis: effects of adalimumab treatment on synovial tissue. Ann Rheum Dis. 2009 Aug;68(8):1303-9. Epub 2008 Jul 22. PubMed PMID: 18647851; PubMed Central PMCID: PMC2703703.

15: Feldman SR, Gottlieb AB, Bala M, Wu Y, Eisenberg D, Guzzo C, Li S, Dooley LT, Menter A. Infliximab improves health-related quality of life in the presence of comorbidities among patients with moderate-to-severe psoriasis. Br J Dermatol. 2008 Sep;159(3):704-10. Epub 2008 Jul 9. PubMed PMID: 18627375.

16: Strober B, Teller C, Yamauchi P, Miller JL, Hooper M, Yang YC, Dann F. Effects of etanercept on C-reactive protein levels in psoriasis and psoriatic arthritis. Br J Dermatol. 2008 Aug;159(2):322-30. Epub 2008 May 22. PubMed PMID: 18503600.

17: van der Heijde D, Landewé R, Einstein S, Ory P, Vosse D, Ni L, Lin SL, Tsuji W, Davis JC Jr. Radiographic progression of ankylosing spondylitis after up to two years of treatment with etanercept. Arthritis Rheum. 2008 May;58(5):1324-31. PubMed PMID: 18438853.

18: Antoni CE, Kavanaugh A, van der Heijde D, Beutler A, Keenan G, Zhou B, Kirkham B, Tutuncu Z, Burmester GR, Schneider U, Furst DE, Molitor J, Keystone E, Gladman DD, Manger B, Wassenberg S, Weier R, Wallace DJ, Weisman MH, Kalden JR, Smolen JS. Two-year efficacy and safety of infliximab treatment in patients with active psoriatic arthritis: findings of the Infliximab Multinational Psoriatic

Arthritis Controlled Trial (IMPACT). J Rheumatol. 2008 May;35(5):869-76. Epub 2008 Mar 15. PubMed PMID: 18381786.

19: Revicki D, Willian MK, Saurat JH, Papp KA, Ortonne JP, Sexton C, Camez A. Impact of adalimumab treatment on health-related quality of life and other patient-reported outcomes: results from a 16-week randomized controlled trial in patients with moderate to severe plaque psoriasis. Br J Dermatol. 2008 Mar;158(3):549-57. Epub 2007 Nov 28. PubMed PMID: 18047521.

20: van der Heijde D, Kavanaugh A, Gladman DD, Antoni C, Krueger GG, Guzzo C, Zhou B, Dooley LT, de Vlam K, Geusens P, Birbara C, Halter D, Beutler A. Infliximab inhibits progression of radiographic damage in patients with active psoriatic arthritis through one year of treatment: Results from the induction and maintenance psoriatic arthritis clinical trial 2. Arthritis Rheum. 2007 Aug;56(8):2698-707. PubMed PMID: 17665424.

21: Genovese MC, Mease PJ, Thomson GT, Kivitz AJ, Perdok RJ, Weinberg MA, Medich J, Sasso EH; M02-570 Study Group. Safety and efficacy of adalimumab in treatment of patients with psoriatic arthritis who had failed disease modifying antirheumatic drug therapy. J Rheumatol. 2007 May;34(5):1040-50. Epub 2007 Apr 15. Erratum in: J Rheumatol. 2007 Jun;34(6):1439. PubMed PMID: 17444593.

22: Gladman DD, Mease PJ, Ritchlin CT, Choy EH, Sharp JT, Ory PA, Perdok RJ, Sasso EH. Adalimumab for long-term treatment of psoriatic arthritis: forty-eight week data from the adalimumab effectiveness in psoriatic arthritis trial. Arthritis Rheum. 2007 Feb;56(2):476-88. PubMed PMID: 17265483.

23: Kavanaugh A, Krueger GG, Beutler A, Guzzo C, Zhou B, Dooley LT, Mease PJ, Gladman DD, de Vlam K, Geusens PP, Birbara C, Halter DG, Antoni C; IMPACT 2 Study Group. Infliximab maintains a high degree of clinical response in patients with active psoriatic arthritis through 1 year of treatment: results from the IMPACT 2 trial. Ann Rheum Dis. 2007 Apr;66(4):498-505. Epub 2006 Nov 17. PubMed PMID: 17114188; PubMed Central PMCID: PMC1856065.

24: Menter A, Feldman SR, Weinstein GD, Papp K, Evans R, Guzzo C, Li S, Dooley LT, Arnold C, Gottlieb AB. A randomized comparison of continuous vs. intermittent infliximab maintenance regimens over 1 year in the treatment of moderate-to-severe plaque psoriasis. J Am Acad Dermatol. 2007 Jan;56(1):31.e1-15. Epub 2006 Sep 6. PubMed PMID: 17097378.

25: Gladman DD, Mease PJ, Cifaldi MA, Perdok RJ, Sasso E, Medich J. Adalimumab improves joint-related and skin-related functional impairment in patients with psoriatic arthritis: patient-reported outcomes of the Adalimumab Effectiveness in Psoriatic Arthritis Trial. Ann Rheum Dis. 2007 Feb;66(2):163-8. Epub 2006 Oct 17. PubMed PMID: 17046964; PubMed Central PMCID: PMC1798491.

26: Kavanaugh A, Antoni C, Mease P, Gladman D, Yan S, Bala M, Zhou B, Dooley LT, Beutler A, Guzzo C, Krueger GG. Effect of infliximab therapy on employment, time lost from work, and productivity in patients with psoriatic arthritis. J Rheumatol. 2006 Nov;33(11):2254-9. Epub 2006 Sep 1. PubMed PMID: 16960923.

27: Ritchlin C. Efficacy and safety of infliximab for the treatment of psoriatic arthritis. Nat Clin Pract Rheumatol. 2006 Jun;2(6):300-1. PubMed PMID: 16932707.

28: Mease PJ, Kivitz AJ, Burch FX, Siegel EL, Cohen SB, Ory P, Salonen D, Rubenstein J, Sharp JT, Dunn M, Tsuji W. Continued inhibition of radiographic progression in patients with psoriatic arthritis following 2 years of treatment with etanercept. J Rheumatol. 2006 Apr;33(4):712-21. Epub 2006 Feb 1. PubMed PMID: 16463435.

29: Kavanaugh A, Antoni CE, Gladman D, Wassenberg S, Zhou B, Beutler A, Keenan G, Burmester G, Furst DE, Weisman MH, Kalden JR, Smolen J, van der Heijde D. The

Infliximab Multinational Psoriatic Arthritis Controlled Trial (IMPACT): results of radiographic analyses after 1 year. Ann Rheum Dis. 2006 Aug;65(8):1038-43. Epub 2006 Jan 26. PubMed PMID: 16439444; PubMed Central PMCID: PMC1798249.

30: Mease PJ, Gladman DD, Ritchlin CT, Ruderman EM, Steinfeld SD, Choy EH, Sharp JT, Ory PA, Perdok RJ, Weinberg MA; Adalimumab Effectiveness in Psoriatic Arthritis Trial Study Group. Adalimumab for the treatment of patients with moderately to severely active psoriatic arthritis: results of a double-blind, randomized, placebo-controlled trial. Arthritis Rheum. 2005 Oct;52(10):3279-89. PubMed PMID: 16200601.

31: Kavanaugh A, Antoni C, Krueger GG, Yan S, Bala M, Dooley LT, Beutler A, Guzzo C, Gladman D. Infliximab improves health related quality of life and physical function in patients with psoriatic arthritis. Ann Rheum Dis. 2006 Apr;65(4):471-7. Epub 2005 Aug 11. PubMed PMID: 16096330; PubMed Central PMCID: PMC1798094.

32: Antoni CE, Kavanaugh A, Kirkham B, Tutuncu Z, Burmester GR, Schneider U, Furst DE, Molitor J, Keystone E, Gladman D, Manger B, Wassenberg S, Weier R, Wallace DJ, Weisman MH, Kalden JR, Smolen J. Sustained benefits of infliximab therapy for dermatologic and articular manifestations of psoriatic arthritis: results from the infliximab multinational psoriatic arthritis controlled trial (IMPACT). Arthritis Rheum. 2005 Apr;52(4):1227-36. Erratum in: Arthritis Rheum. 2005 Sep;52(9):2951. PubMed PMID: 15818699.

33: Antoni C, Krueger GG, de Vlam K, Birbara C, Beutler A, Guzzo C, Zhou B, Dooley LT, Kavanaugh A; IMPACT 2 Trial Investigators. Infliximab improves signs and symptoms of psoriatic arthritis: results of the IMPACT 2 trial. Ann Rheum Dis. 2005 Aug;64(8):1150-7. Epub 2005 Jan 27. PubMed PMID: 15677701; PubMed Central PMCID: PMC1755609.

34: Mease PJ, Kivitz AJ, Burch FX, Siegel EL, Cohen SB, Ory P, Salonen D, Rubenstein J, Sharp JT, Tsuji W. Etanercept treatment of psoriatic arthritis: safety, efficacy, and effect on disease progression. Arthritis Rheum. 2004 Jul;50(7):2264-72. PubMed PMID: 15248226.

35: Mease PJ, Ritchlin CT, Martin RW, Gottlieb AB, Baumgartner SW, Burge DJ, Whitmore JB. Pneumococcal vaccine response in psoriatic arthritis patients during treatment with etanercept. J Rheumatol. 2004 Jul;31(7):1356-61. PubMed PMID: 15229957.

36: Goedkoop AY, Kraan MC, Teunissen MB, Picavet DI, de Rie MA, Bos JD, Tak PP. Early effects of tumour necrosis factor alpha blockade on skin and synovial tissue in patients with active psoriasis and psoriatic arthritis. Ann Rheum Dis. 2004 Jul;63(7):769-73. PubMed PMID: 15194570; PubMed Central PMCID: PMC1755073.

37: Davis JC Jr, Van Der Heijde D, Braun J, Dougados M, Cush J, Clegg DO, Kivitz A, Fleischmann R, Inman R, Tsuji W; Enbrel Ankylosing Spondylitis Study Group. Recombinant human tumor necrosis factor receptor (etanercept) for treating ankylosing spondylitis: a randomized, controlled trial. Arthritis Rheum. 2003 Nov;48(11):3230-6. PubMed PMID: 14613288.

38: Mease PJ. Etanercept, a TNF antagonist for treatment for psoriatic arthritis and psoriasis. Skin Therapy Lett. 2003 Jan;8(1):1-4. PubMed PMID: 12728284.

39: Mease PJ. Cytokine blockers in psoriatic arthritis. Ann Rheum Dis. 2001 Nov;60 Suppl 3:iii37-40. PubMed PMID: 11890650; PubMed Central PMCID: PMC1766666.

40: Mease PJ, Goffe BS, Metz J, VanderStoep A, Finck B, Burge DJ. Etanercept in the treatment of psoriatic arthritis and psoriasis: a randomised trial. Lancet. 2000 Jul 29;356(9227):385-90. PubMed PMID: 10972371.

SEARCH 23_5 agents_ psoriatic arthritis SR

Category	Description
Clinical question or focus	BIOLOGICAL AGENTS FINAL
Source	PubMed
Terms	**(Adalimumab OR Etanercept OR Golimumab OR Infliximab OR Ustekinumab) AND psoriatic arthritis AND english [lang]**
Limits	Systematic Review
▪ Date limits	
▪ Other limits	Systematic Review
Query Translation (eg, "Details" in PubMed)	(("adalimumab"[Substance] OR "adalimumab"[All Fields]) OR ("TNFR-Fc fusion protein"[Substance] OR "TNFR-Fc fusion protein"[All Fields] OR "etanercept"[All Fields]) OR ("golimumab"[Substance] OR "golimumab"[All Fields]) OR ("infliximab"[Substance] OR "infliximab"[All Fields]) OR ("monoclonal antibody CNTO 1275"[Substance] OR "monoclonal antibody CNTO 1275"[All Fields] OR "ustekinumab"[All Fields])) AND ("arthritis, psoriatic"[MeSH Terms] OR ("arthritis"[All Fields] AND "psoriatic"[All Fields]) OR "psoriatic arthritis"[All Fields] OR ("psoriatic"[All Fields] AND "arthritis"[All Fields])) AND english[lang] AND systematic[sb]
Date of Search	1/14/11
Total Yield	26
Total marked for retrieval	0
Exclusions	• Not focus of review: population, intervention, comparison, outcome • Superseded by more recent larger study • Lacking safety data • Duplicates

Secondary Studies: Yield and Dispositions

1: Boyce EG, Halilovic J, Stan-Ugbene O. Golimumab: Review of the efficacy and tolerability of a recently approved tumor necrosis factor-α inhibitor. Clin Ther. 2010 Sep;32(10):1681-703. PubMed PMID: 21194591.

2: Collamer AN, Battafarano DF. Psoriatic skin lesions induced by tumor necrosis factor antagonist therapy: clinical features and possible immunopathogenesis. Semin Arthritis Rheum. 2010 Dec;40(3):233-40. Epub 2010 Jun 26. PubMed PMID: 20580412.

3: Fleischmann R. The efficacy and safety of golimumab in the treatment of arthritis. Expert Opin Biol Ther. 2010 Jul;10(7):1131-43. Review. PubMed PMID: 20504106.

4: Bojke L, Claxton K, Bravo-Vergel Y, Sculpher M, Palmer S, Abrams K. Eliciting distributions to populate decision analytic models. Value Health. 2010 Aug;13(5):557-64. Epub 2010 Mar 22. PubMed PMID: 20345548.

5: Leeb BF, Böttcher E, Brezinschek HP, Czerwenka C, Herold M, Hitzelhammer H, Mayrhofer F, Puchner R, Rainer F, Rintelen B, Schirmer M, Stuby U, Bröll H. The use of tumour necrosis factor alpha-blockers in daily routine. An Austrian consensus project. Clin Rheumatol. 2010 Feb;29(2):167-74. Epub 2009 Nov 11. PubMed PMID: 19904485; PubMed Central PMCID: PMC2797412.

6: Schmitt J, Wozel G. Targeted treatment of psoriasis with adalimumab: a critical appraisal based on a systematic review of the literature. Biologics. 2009;3:303-18. Epub 2009 Jul 13. PubMed PMID: 19707417; PubMed Central PMCID: PMC2726069.

7: Braun J, Baraliakos X. Treatment of ankylosing spondylitis and other

spondyloarthritides. Curr Opin Rheumatol. 2009 Jul;21(4):324-34. Review. PubMed PMID: 19461519.

8: Burmester GR, Mease P, Dijkmans BA, Gordon K, Lovell D, Panaccione R, Perez J, Pangan AL. Adalimumab safety and mortality rates from global clinical trials of six immune-mediated inflammatory diseases. Ann Rheum Dis. 2009 Dec;68(12):1863-9. Epub 2009 Jan 15. PubMed PMID: 19147611; PubMed Central PMCID: PMC2770105.

9: Lecluse LL, Piskin G, Mekkes JR, Bos JD, de Rie MA. Review and expert opinion on prevention and treatment of infliximab-related infusion reactions. Br J Dermatol. 2008 Sep;159(3):527-36. Epub 2008 Jul 9. Review. PubMed PMID: 18627374.

10: Doherty SD, Van Voorhees A, Lebwohl MG, Korman NJ, Young MS, Hsu S, National Psoriasis Foundation. National Psoriasis Foundation consensus statement on screening for latent tuberculosis infection in patients with psoriasis treated with systemic and biologic agents. J Am Acad Dermatol. 2008 Aug;59(2):209-17. Epub 2008 May 15. PubMed PMID: 18485527.

11: Gottlieb A, Korman NJ, Gordon KB, Feldman SR, Lebwohl M, Koo JY, Van Voorhees AS, Elmets CA, Leonardi CL, Beutner KR, Bhushan R, Menter A. Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 2. Psoriatic arthritis: overview and guidelines of care for treatment with an emphasis on the biologics. J Am Acad Dermatol. 2008 May;58(5):851-64. PubMed PMID: 18423261.

12: Menter A, Gottlieb A, Feldman SR, Van Voorhees AS, Leonardi CL, Gordon KB, Lebwohl M, Koo JY, Elmets CA, Korman NJ, Beutner KR, Bhushan R. Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 1. Overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics. J Am Acad Dermatol. 2008 May;58(5):826-50. PubMed PMID: 18423260.

13: Huang W, Cordoro KM, Taylor SL, Feldman SR. To test or not to test? An evidence-based assessment of the value of screening and monitoring tests when using systemic biologic agents to treat psoriasis. J Am Acad Dermatol. 2008 Jun;58(6):970-7. Epub 2008 Apr 2. Review. PubMed PMID: 18384909.

14: Saad AA, Symmons DP, Noyce PR, Ashcroft DM. Risks and benefits of tumor necrosis factor-alpha inhibitors in the management of psoriatic arthritis: systematic review and metaanalysis of randomized controlled trials. J Rheumatol. 2008 May;35(5):883-90. Epub 2008 Mar 15. Review. PubMed PMID: 18381787.

15: Pham T, Fautrel B, Dernis E, Goupille P, Guillemin F, Le Loët X, Ravaud P, Claudepierre P, Miceli-Richard C, de Bandt M, Breban M, Maillefert JF, Masson C, Saraux A, Schaeverbeke T, Wendling D, Mariette X, Combe B; Club Rhumatismes et Inflammation (CRI/SFR). Recommendations of the French Society for Rheumatology regarding TNFalpha antagonist therapy in patients with ankylosing spondylitis or psoriatic arthritis: 2007 update. Joint Bone Spine. 2007 Dec;74(6):638-46. Epub 2007 Nov 8. PubMed PMID: 18065252.

16: Lebwohl M, Bagel J, Gelfand JM, Gladman D, Gordon KB, Hsu S, Kalb RE, Kimball AB, Korman NJ, Krueger GG, Mease P, Morison WL, Paller A, Pariser DM, Ritchlin C, Strober B, Van Voorhees A, Weinstein GD, Young M, Horn L. From the Medical Board of the National Psoriasis Foundation: monitoring and vaccinations in patients treated with biologics for psoriasis. J Am Acad Dermatol. 2008 Jan;58(1):94-105. Epub 2007 Nov 5. PubMed PMID: 17980456.

17: Bravo Vergel Y, Hawkins NS, Claxton K, Asseburg C, Palmer S, Woolacott N, Bruce IN, Sculpher MJ. The cost-effectiveness of etanercept and infliximab for the treatment of patients with psoriatic arthritis. Rheumatology (Oxford). 2007 Nov;46(11):1729-35. PubMed PMID: 17956918.

18: Woolacott NF, Khadjesari ZC, Bruce IN, Riemsma RP. Etanercept and infliximab for the treatment of psoriatic arthritis: a systematic review. Clin Exp

Rheumatol. 2006 Sep-Oct;24(5):587-93. Review. PubMed PMID: 17181932.

19: Roux CH, Brocq O, Breuil V, Albert C, Euller-Ziegler L. Pregnancy in rheumatology patients exposed to anti-tumour necrosis factor (TNF)-alpha therapy. Rheumatology (Oxford). 2007 Apr;46(4):695-8. Epub 2006 Dec 7. Review. PubMed PMID: 17158212.

20: Woolacott N, Bravo Vergel Y, Hawkins N, Kainth A, Khadjesari Z, Misso K, Light K, Asseburg C, Palmer S, Claxton K, Bruce I, Sculpher M, Riemsma R. Etanercept and infliximab for the treatment of psoriatic arthritis: a systematic review and economic evaluation. Health Technol Assess. 2006 Sep;10(31):iii-iv, xiii-xvi, 1-239. Review. PubMed PMID: 16948890.

21: Soriano ER, McHugh NJ. Therapies for peripheral joint disease in psoriatic arthritis. A systematic review. J Rheumatol. 2006 Jul;33(7):1422-30. Epub 2006 May 15. Review. PubMed PMID: 16724372.

22: Helliwell PS. Therapies for dactylitis in psoriatic arthritis. A systematic review. J Rheumatol. 2006 Jul;33(7):1439-41. Epub 2006 May 15. Review. PubMed PMID: 16724369.

23: Fransen J, Antoni C, Mease PJ, Uter W, Kavanaugh A, Kalden JR, Van Riel PL. Performance of response criteria for assessing peripheral arthritis in patients with psoriatic arthritis: analysis of data from randomised controlled trials of two tumour necrosis factor inhibitors. Ann Rheum Dis. 2006 Oct;65(10):1373-8. Epub 2006 Apr 27. PubMed PMID: 16644783; PubMed Central PMCID: PMC1798317.

24: Fleischmann R, Baumgartner SW, Weisman MH, Liu T, White B, Peloso P. Long term safety of etanercept in elderly subjects with rheumatic diseases. Ann Rheum Dis. 2006 Mar;65(3):379-84. Epub 2005 Sep 8. PubMed PMID: 16150792; PubMed Central PMCID: PMC1798057.

25: Kyle S, Chandler D, Griffiths CE, Helliwell P, Lewis J, McInnes I, Oliver S, Symmons D, McHugh N; British Society for Rheumatology Standards Guidelines Audit Working Group (SGAWG). Guideline for anti-TNF-alpha therapy in psoriatic arthritis. Rheumatology (Oxford). 2005 Mar;44(3):390-7. Epub 2005 Feb 3. Review. Erratum in: Rheumatology (Oxford). 2005 Apr;44(4):569. Rheumatology (Oxford). 2005 May;44(5):701. PubMed PMID: 15695305.

26: Fisher VS. Clinical monograph for drug formulary review: systemic agents for psoriasis/psoriatic arthritis. J Manag Care Pharm. 2005 Jan-Feb;11(1):33-55. Review. PubMed PMID: 15667232.

SEARCH 24 all infus inject

Category	Description
Clinical question or focus	BIOLOGICAL AGENTS FINAL
Source	PubMed
Terms	rheumatoid arthritis OR psoriasis OR psoriatic AND injection site reaction OR infusion reaction (etanercept OR adalimumab OR infliximab OR certolizumab OR golimumab OR ustekinumab OR etanercept)
Limits	
▪ Date limits	None
▪ Other limits	None
Query Translation (eg, “Details” in PubMed)	("arthritis, rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "rheumatoid"[All Fields]) OR "rheumatoid arthritis"[All Fields] OR ("rheumatoid"[All Fields] AND "arthritis"[All Fields])) OR ("psoriasis"[MeSH Terms] OR "psoriasis"[All Fields]) OR psoriatic[All Fields] AND (("injections"[MeSH Terms] OR "injections"[All Fields] OR "injection"[All Fields]) AND site[All Fields] AND reaction[All Fields]) OR (infusion[All Fields] AND reaction[All Fields]) AND (("TNFR-Fc fusion protein"[Substance] OR "TNFR-Fc fusion protein"[All Fields] OR "etanercept"[All Fields]) OR ("adalimumab"[Substance] OR "adalimumab"[All Fields]) OR ("infliximab"[Substance] OR "infliximab"[All Fields]) OR ("CDP870"[Substance] OR "CDP870"[All Fields] OR "certolizumab"[All Fields]) OR

	("golimumab"[Substance] OR "golimumab"[All Fields]) OR ("monoclonal antibody CNTO 1275"[Substance] OR "monoclonal antibody CNTO 1275"[All Fields] OR "ustekinumab"[All Fields]) OR ("TNFR-Fc fusion protein"[Substance] OR "TNFR-Fc fusion protein"[All Fields] OR "etanercept"[All Fields]))
Date of Search	1/21/11
Total Yield	134
Total marked for retrieval	Thaler 09
Duplicates	Multiple
Notes	Usual exclusions

1: Elliott E, Campbell H, Escudier M, Poate T, Nunes C, Lomer M, Mentzer A, Patel P, Shirlaw P, Brostoff J, Challacombe S, Sanderson J. Experience with anti-TNF-α therapy for orofacial granulomatosis. J Oral Pathol Med. 2011 Jan;40(1):14-9. PubMed PMID: 21249727.

2: Kaneko U, Kishi T, Kikuchi M, Hara R, Shinoki T, Miyamae T, Imagawa T, Mori M, Yokota S. [Infliximab therapy for three adolescent patients with refractory Takayasu's arteritis]. Nihon Rinsho Meneki Gakkai Kaishi. 2010;33(6):317-23. Japanese. PubMed PMID: 21212584.

3: de Vries HS, van Oijen MG, Driessen RJ, de Jong EM, Creemers MC, Kievit W, de Jong DJ. Appropriate infliximab infusion dosage and monitoring: results of a panel meeting of rheumatologists, dermatologists and gastroenterologists. Br J Clin Pharmacol. 2011 Jan;71(1):7-19. doi: 10.1111/j.1365-2125.2010.03760.x. PubMed PMID: 21143496; PubMed Central PMCID: PMC3018021.

4: Van Assche G, Vermeire S, Noman M, Amant C, Weyts E, Vleminckx A, Vermeyen MJ, Rutgeerts P. Infliximab administered with shortened infusion times in a specialized IBD infusion unit: a prospective cohort study. J Crohns Colitis. 2010 Sep;4(3):329-33. Epub 2010 Jan 18. PubMed PMID: 21122522.

5: Lönnkvist MH, Theodorsson E, Holst M, Ljung T, Hellström PM. Blood chemistry markers for evaluation of inflammatory activity in Crohn's disease during infliximab therapy. Scand J Gastroenterol. 2010 Nov 30. [Epub ahead of print] PubMed PMID: 21114432.

6: Chouliaras G, Panayiotou J, Dimakou C, Pachoula J, Orfanou I, Chrousos GP, Roma-Giannikou E. Biological agents in paediatric inflammatory bowel disease: a clinical observation study from Greece. Acta Gastroenterol Belg. 2010 Jul-Sep;73(3):342-8. PubMed PMID: 21086936.

7: Shen CH, Tsai RY, Shih MS, Lin SL, Tai YH, Chien CC, Wong CS. Etanercept restores the antinociceptive effect of morphine and suppresses spinal neuroinflammation in morphine-tolerant rats. Anesth Analg. 2011 Feb;112(2):454-9. Epub 2010 Nov 16. PubMed PMID: 21081778.

8: Okuyama A, Nagasawa H, Suzuki K, Kameda H, Kondo H, Amano K, Takeuchi T. Fc{gamma} receptor IIIb polymorphism and use of glucocorticoids at baseline are associated with infusion reactions to infliximab in patients with rheumatoid arthritis. Ann Rheum Dis. 2011 Feb;70(2):299-304. Epub 2010 Oct 27. PubMed PMID: 20980704; PubMed Central PMCID: PMC3015102.

9: Hamzaoglu H, Cooper J, Alsahli M, Falchuk KR, Peppercorn MA, Farrell RJ. Safety of infliximab in Crohn's disease: a large single-center experience. Inflamm Bowel Dis. 2010 Dec;16(12):2109-16. doi: 10.1002/ibd.21290. PubMed PMID: 20848473.

10: Bhat S, Sharma D, Doherty P, Tham TC, Caddy GR. Are accelerated infliximab infusions safe in patients with inflammatory bowel disease? Inflamm Bowel Dis. 2010 Nov;16(11):1922-5. PubMed PMID: 20848465.

11: Guarneri C, Polimeni G. Nicolau syndrome following etanercept administration. Am J Clin Dermatol. 2010;11 Suppl 1:51-2. doi: 10.2165/1153426-S0-000000000-00000. PubMed PMID: 20586511.

12: Kling MC, Larian AA, Scordi-Bello I, Emer J, Lebwohl MG. Fatal influenza A(H1N1) respiratory tract infection in a patient having psoriasis treated with infliximab. Arch Dermatol. 2010 Jun;146(6):651-4. PubMed PMID: 20566928.

13: Yamamoto S, Nakase H, Matsuura M, Honzawa Y, Masuda S, Inui K, Chiba T. Efficacy and safety of infliximab as rescue therapy for ulcerative colitis refractory to tacrolimus. J Gastroenterol Hepatol. 2010 May;25(5):886-91. PubMed PMID: 20546441.

14: Lahdenne P, Wikström AM, Aalto K, Kolho KL. Prevention of acute adverse events related to infliximab infusions in pediatric patients. Arthritis Care Res (Hoboken). 2010 Jun;62(6):785-90. PubMed PMID: 20535789.

15: Ducharme J, Pelletier C, Zacharias R. The safety of infliximab infusions in the community setting. Can J Gastroenterol. 2010 May;24(5):307-11. PubMed PMID: 20485705; PubMed Central PMCID: PMC2886572.

16: Li Z, Arijs I, De Hertogh G, Vermeire S, Noman M, Bullens D, Coorevits L, Sagaert X, Schuit F, Rutgeerts P, Ceuppens JL, Van Assche G. Reciprocal changes of Foxp3 expression in blood and intestinal mucosa in IBD patients responding to infliximab. Inflamm Bowel Dis. 2010 Aug;16(8):1299-310. PubMed PMID: 20196149.

17: Herrlinger KR, Barthel DN, Schmidt KJ, Büning J, Barthel CS, Wehkamp J, Stange EF, Fellermann K. Infliximab as rescue medication for patients with severe ulcerative/indeterminate colitis refractory to tacrolimus. Aliment Pharmacol Ther. 2010 May;31(9):1036-41. Epub 2010 Feb 18. PubMed PMID: 20175769.

18: Veres G, Szabó D, Várkonyi A, Tari B, Polgár M, B Kovács J, Horváth A, Tomsits E, Tokodi I, Bodánszky H, Dezsofi A, Szakos E, Vass N, Ruszinkó V, Kovács M, Müller KE, Arató A. [Analysis of infliximab treated pediatric patients with Crohn disease in Hungary]. Orv Hetil. 2010 Jan 31;151(5):179-83. Hungarian. PubMed PMID: 20083466.

19: Zheng JJ, Wang YM, Zhu F, Gu W, Xing YC, Zhou CL, Shen BW. [A study of efficiacy of infliximab treatment for Crohn's disease.]. Zhonghua Nei Ke Za Zhi. 2009 Nov;48(11):922-5. Chinese. PubMed PMID: 20079322.

20: Thaler K, Chandiramani DV, Hansen RA, Gartlehner G. Efficacy and safety of anakinra for the treatment of rheumatoid arthritis: an update of the Oregon Drug Effectiveness Review Project. Biologics. 2009;3:485-98. Epub 2009 Dec 29. PubMed PMID: 20054439; PubMed Central PMCID: PMC2802074.

21: Vultaggio A, Matucci A, Nencini F, Pratesi S, Parronchi P, Rossi O, Romagnani S, Maggi E. Anti-infliximab IgE and non-IgE antibodies and induction of infusion-related severe anaphylactic reactions. Allergy. 2010 May;65(5):657-61. Epub 2009 Nov 27. PubMed PMID: 19951375.

22: Su KY, Lee HT, Chou CT, Tsai ST, Chen WS, Tsai CY. Improvement of active rheumatoid arthritis after etanercept injection: a single-center experience. J Chin Med Assoc. 2009 Nov;72(11):581-7. Erratum in: J Chin Med Assoc. 2010 Jan;73(1):56. PubMed PMID: 19948435.

23: Chung SJ, Kim JK, Park MC, Park YB, Lee SK. Reactivation of hepatitis B viral infection in inactive HBsAg carriers following anti-tumor necrosis factor-alpha therapy. J Rheumatol. 2009 Nov;36(11):2416-20. Epub 2009 Oct 1. Erratum in: J Rheumatol. 2010 Jan;37(1):216. PubMed PMID: 19797507.

24: Lissia M, Mulas P, Bulla A, Rubino C. Toxic epidermal necrolysis (Lyell's

disease). Burns. 2010 Mar;36(2):152-63. Epub 2009 Sep 18. Review. PubMed PMID: 19766401.

25: Rosh JR, Lerer T, Markowitz J, Goli SR, Mamula P, Noe JD, Pfefferkorn MD, Kelleher KT, Griffiths AM, Kugathasan S, Keljo D, Oliva-Hemker M, Crandall W, Carvalho RS, Mack DR, Hyams JS. Retrospective Evaluation of the Safety and Effect of Adalimumab Therapy (RESEAT) in pediatric Crohn's disease. Am J Gastroenterol. 2009 Dec;104(12):3042-9. Epub 2009 Sep 1. PubMed PMID: 19724267.

26: Kim SH, Yang S, Kim KJ, Kim EH, Yoon SM, Ye BD, Byeon JS, Myung SJ, Kim JH. [Efficacy of infliximab in the treatment of korean patients with crohns disease]. Korean J Gastroenterol. 2009 Aug;54(2):108-16. Korean. PubMed PMID: 19696538.

27: Yamada Y, Sugita S, Tanaka H, Kamoi K, Kawaguchi T, Mochizuki M. Comparison of infliximab versus ciclosporin during the initial 6-month treatment period in Behçet disease. Br J Ophthalmol. 2010 Mar;94(3):284-8. Epub 2009 Aug 18. PubMed PMID: 19692382.

28: Bremmer MS, Bremmer SF, Baig-Lewis S, Simpson EL. Are biologics safe in the treatment of atopic dermatitis? A review with a focus on immediate hypersensitivity reactions. J Am Acad Dermatol. 2009 Oct;61(4):666-76. Epub 2009 Jul 31. Review. PubMed PMID: 19646779.

29: Yeckes AR, Hoffenberg EJ. Rapid infliximab infusions in pediatric inflammatory bowel disease. J Pediatr Gastroenterol Nutr. 2009 Jul;49(1):151-4. PubMed PMID: 19516188.

30: Uppal SS, Hayat SJ, Raghupathy R. Efficacy and safety of infliximab in active SLE: a pilot study. Lupus. 2009 Jul;18(8):690-7. PubMed PMID: 19502264.

31: Puig Sanz L, Sáez E, Lozano MJ, Bordas X, Carrascosa JM, Gallardo F, Luelmo J, Sánchez-Regaña M, Alsina M, García-Patos V; Grupo Español de Psoriasis de la Academia Española de Dermatología y Venereología. [Reactions to infliximab infusions in dermatologic patients: consensus statement and treatment protocol. Working Group of the Grupo Español de Psoriasis de la Academia Española de Dermatología y Venereología]. Actas Dermosifiliogr. 2009 Mar;100(2):103-12. Review. Spanish. PubMed PMID: 19445874.

32: Desai D, Goldbach-Mansky R, Milner JD, Rabin RL, Hull K, Pucino F, Colburn N. Anaphylactic reaction to anakinra in a rheumatoid arthritis patient intolerant to multiple nonbiologic and biologic disease-modifying antirheumatic drugs. Ann Pharmacother. 2009 May;43(5):967-72. PubMed PMID: 19417117; PubMed Central PMCID: PMC2938799.

33: Lichtenstein GR, Diamond RH, Wagner CL, Fasanmade AA, Olson AD, Marano CW, Johanns J, Lang Y, Sandborn WJ. Clinical trial: benefits and risks of immunomodulators and maintenance infliximab for IBD-subgroup analyses across four randomized trials. Aliment Pharmacol Ther. 2009 Aug;30(3):210-26. Epub 2009 Apr 21. PubMed PMID: 19392858.

34: Koike T, Harigai M, Inokuma S, Inoue K, Ishiguro N, Ryu J, Takeuchi T, Tanaka Y, Yamanaka H, Fujii K, Freundlich B, Suzukawa M. Postmarketing surveillance of the safety and effectiveness of etanercept in Japan. J Rheumatol. 2009 May;36(5):898-906. Epub 2009 Mar 30. PubMed PMID: 19332630.

35: Komano Y, Harigai M, Koike R, Sugiyama H, Ogawa J, Saito K, Sekiguchi N, Inoo M, Onishi I, Ohashi H, Amamoto F, Miyata M, Ohtsubo H, Hiramatsu K, Iwamoto M, Minota S, Matsuoka N, Kageyama G, Imaizumi K, Tokuda H, Okochi Y, Kudo K, Tanaka Y, Takeuchi T, Miyasaka N. Pneumocystis jiroveci pneumonia in patients with rheumatoid arthritis treated with infliximab: a retrospective review and case-control study of 21 patients. Arthritis Rheum. 2009 Mar 15;61(3):305-12. PubMed PMID: 19248121.

36: Lees CW, Ali AI, Thompson AI, Ho GT, Forsythe RO, Marquez L, Cochrane CJ, Aitken S, Fennell J, Rogers P, Shand AG, Penman ID, Palmer KR, Wilson DC, Arnott ID, Satsangi J. The safety profile of anti-tumour necrosis factor therapy in inflammatory bowel disease in clinical practice: analysis of 620 patient-years follow-up. Aliment Pharmacol Ther. 2009 Feb 1;29(3):286-97. PubMed PMID: 19132970.

37: Gorovoy I, Berghoff A, Ferris L. Successful Treatment of Recalcitrant Hidradenitis Suppurativa with Adalimumab. Case Rep Dermatol. 2009 Oct 27;1(1):71-77. PubMed PMID: 20652119; PubMed Central PMCID: PMC2895215.

38: Richetta A, Mattozzi C, Carlomagno V, Maiani E, Carboni V, Giancristoforo S, D'Epiro S, Bruni F, Calvieri S. A case of infliximab-induced psoriasis. Dermatol Online J. 2008 Nov 15;14(11):9. PubMed PMID: 19094847.

39: Puig L. [Efficacy of treatment with infliximab in patients with moderate-severe psoriasis and high needs of therapy. A retrospective study of 43 patients]. Actas Dermosifiliogr. 2008 Jul;99 Suppl 4:30-5. Spanish. PubMed PMID: 19080989.

40: Clare DF, Alexander FC, Mike S, Dan G, Allan F, Lisa W, Peter HJ. Accelerated infliximab infusions are safe and well tolerated in patients with inflammatory bowel disease. Eur J Gastroenterol Hepatol. 2009 Jan;21(1):71-5. PubMed PMID: 19060632.

41: Lees CW, Ali A, Thompson AI, Ho GT, Forsythe RO, Marquez L, Cochrane CJ, Aitken S, Fennell J, Rogers P, Shand AG, Penman ID, Palmer KR, Wilson DC, Arnott ID, Satsangi J. The safety profile of anti-TNF therapy in inflammatory bowel disease in clinical practice: analysis of 620 patient-years follow-up. Aliment Pharmacol Ther. 2008 Nov 4. [Epub ahead of print] PubMed PMID: 19006536.

42: Calogiuri G, Ventura MT, Mason L, Valacca A, Buquicchio R, Cassano N, Vena GA. Hypersensitivity reactions to last generation chimeric, humanized [correction of umanized] and human recombinant monoclonal antibodies for therapeutic use. Curr Pharm Des. 2008;14(27):2883-91. Review. PubMed PMID: 18991706.

43: Shahid M, Francis J, Majid DS. Tumor necrosis factor-alpha induces renal vasoconstriction as well as natriuresis in mice. Am J Physiol Renal Physiol. 2008 Dec;295(6):F1836-44. Epub 2008 Oct 15. PubMed PMID: 18922887; PubMed Central PMCID: PMC2604828.

44: Toki H, Momohara S, Tsukahara S, Ikari K. Infusion reaction to infliximab in a patient with rheumatoid arthritis after discontinuation over 1 year and readministration. J Rheumatol. 2008 Sep;35(9):1896-7; author reply 1897. PubMed PMID: 18785300.

45: van der Laken CJ, Voskuyl AE, Roos JC, Stigter van Walsum M, de Groot ER, Wolbink GJ, Dijkmans BA, Aarden LA. [The formation of infliximab and anti-infliximab immune complexes as an explanation for non-responding to infliximab treatment of rheumatoid arthritis: observational study in 4 patients]. Ned Tijdschr Geneeskd. 2008 Jul 26;152(30):1672-7. Dutch. PubMed PMID: 18714521.

46: Rajakulendran S, Deighton C. Adverse dermatological reactions in rheumatoid arthritis patients treated with etanercept, an anti-TNFalpha drug. Curr Drug Saf. 2006 Aug;1(3):259-64. PubMed PMID: 18690936.

47: Al-Rayes H, Al-Swailem R, Al-Balawi M, Al-Dohayan N, Al-Zaidi S, Tariq M. Safety and efficacy of infliximab therapy in active behcet's uveitis: an open-label trial. Rheumatol Int. 2008 Nov;29(1):53-7. Epub 2008 May 22. PubMed PMID: 18496694.

48: Moss AC, Fernandez-Becker N, Jo Kim K, Cury D, Cheifetz AS. The impact of infliximab infusion reactions on long-term outcomes in patients with Crohn's disease. Aliment Pharmacol Ther. 2008 Jul;28(2):221-7. Epub 2008 May 12. PubMed PMID: 18485127.

49: Hellwig K, Schimrigk S, Fischer M, Haghikia A, Müller T, Chan A, Gold R. Allergic and nonallergic delayed infusion reactions during natalizumab therapy. Arch Neurol. 2008 May;65(5):656-8. PubMed PMID: 18474743.

50: Sekiguchi N, Kawauchi S, Furuya T, Inaba N, Matsuda K, Ando S, Ogasawara M, Aburatani H, Kameda H, Amano K, Abe T, Ito S, Takeuchi T. Messenger ribonucleic acid expression profile in peripheral blood cells from RA patients following treatment with an anti-TNF-alpha monoclonal antibody, infliximab. Rheumatology (Oxford). 2008 Jun;47(6):780-8. Epub 2008 Apr 3. PubMed PMID: 18388148.

51: Figueiredo IT, Morel J, Sany J, Combe B. Maintenance and tolerability of infliximab in a cohort of 152 patients with rheumatoid arthritis. Clin Exp Rheumatol. 2008 Jan-Feb;26(1):18-23. PubMed PMID: 18328142.

52: Hengstman GJ, De Bleecker JL, Feist E, Vissing J, Denton CP, Manoussakis MN, Slott Jensen H, van Engelen BG, van den Hoogen FH. Open-label trial of anti-TNF-alpha in dermato- and polymyositis treated concomitantly with methotrexate. Eur Neurol. 2008;59(3-4):159-63. Epub 2008 Jan 29. PubMed PMID: 18230873.

53: Mocciaro F, Orlando A, Scimeca D, Cottone M. [Infliximab in moderate to severe steroid-dependent or steroid-refractory ulcerative colitis]. Recenti Prog Med. 2007 Nov;98(11):560-4. Italian. PubMed PMID: 18044405.

54: Pachot A, Arnaud B, Marrote H, Cazalis MA, Diasparra J, Gouraud A, Mougin B, Miossec P. Increased tumor necrosis factor-alpha mRNA expression in whole blood from patients with rheumatoid arthritis: reduction after infliximab treatment does not predict response. J Rheumatol. 2007 Nov;34(11):2158-61. Epub 2007 Sep 15. PubMed PMID: 17896807.

55: Fernández-Vozmediano JM, Armario-Hita JC. Infliximab for the treatment of hidradenitis suppurativa. Dermatology. 2007;215(1):41-4. PubMed PMID: 17587838.

56: Augustsson J, Eksborg S, Ernestam S, Gullström E, van Vollenhoven R. Low-dose glucocorticoid therapy decreases risk for treatment-limiting infusion reaction to infliximab in patients with rheumatoid arthritis. Ann Rheum Dis. 2007 Nov;66(11):1462-6. Epub 2007 May 14. PubMed PMID: 17502359; PubMed Central PMCID: PMC2111638.

57: Haitz KA, Kalb RE. Infliximab in the treatment of psoriasis in patients previously treated with etanercept. J Am Acad Dermatol. 2007 Jul;57(1):120-5. Epub 2007 May 7. PubMed PMID: 17482715.

58: Hansen RA, Gartlehner G, Powell GE, Sandler RS. Serious adverse events with infliximab: analysis of spontaneously reported adverse events. Clin Gastroenterol Hepatol. 2007 Jun;5(6):729-35. Epub 2007 May 4. PubMed PMID: 17481964.

59: de Vries MK, Wolbink GJ, Stapel SO, de Vrieze H, van Denderen JC, Dijkmans BA, Aarden LA, van der Horst-Bruinsma IE. Decreased clinical response to infliximab in ankylosing spondylitis is correlated with anti-infliximab formation. Ann Rheum Dis. 2007 Sep;66(9):1252-4. Epub 2007 May 1. PubMed PMID: 17472991; PubMed Central PMCID: PMC1955152.

60: Arvidson NG, Larsen A, Aaseth J, Larsson A. Short-term effects of the TNFalpha antagonist infliximab on the acute phase reaction and activities of daily life in patients with rheumatoid arthritis. Scand J Clin Lab Invest. 2007;67(3):337-42. PubMed PMID: 17454848.

61: Kaur N, Mahl TC. Pneumocystis jiroveci (carinii) pneumonia after infliximab therapy: a review of 84 cases. Dig Dis Sci. 2007 Jun;52(6):1481-4. Epub 2007 Apr 11. PubMed PMID: 17429728.

62: Dore RK, Mathews S, Schechtman J, Surbeck W, Mandel D, Patel A, Zhou L, Peloso P. The immunogenicity, safety, and efficacy of etanercept liquid administered once weekly in patients with rheumatoid arthritis. Clin Exp Rheumatol. 2007 Jan-Feb;25(1):40-6. PubMed PMID: 17417989.

63: Jeudy G, Dutronc Y, Galliot-Repkat C, Dupuis J, Jolimoy G, Lambert D, Collet E. [Infliximab-induced skin reaction with visceral manifestations and high levels of anti-DNA antibodies]. Ann Dermatol Venereol. 2007 Mar;134(3 Pt 1):268-71. French. PubMed PMID: 17389855.

64: Lavagna A, Bergallo M, Daperno M, Sostegni R, Costa C, Leto R, Crocellà L, Molinaro G, Rocca R, Cavallo R, Pera A. Infliximab and the risk of latent viruses reactivation in active Crohn's disease. Inflamm Bowel Dis. 2007 Jul;13(7):896-902. PubMed PMID: 17345605.

65: Thonhofer R, Soleiman A, Kriessmayr M, Thonhofer U, Wipfler E, Gaugg M, Eder S, Erlacher L. Decrease of proteinuria in a patient with adult-onset Still's disease and glomerulonephritis after anti-TNFalpha therapy. Scand J Rheumatol. 2006 Nov-Dec;35(6):485-8. PubMed PMID: 17343260.

66: Fardet L, Dupuy A, Kerob D, Levy A, Allez M, Begon E, Bachelez H, Morel P, Lebbé C. Infliximab for severe hidradenitis suppurativa: transient clinical efficacy in 7 consecutive patients. J Am Acad Dermatol. 2007 Apr;56(4):624-8. Epub 2007 Jan 22. PubMed PMID: 17240478.

67: Bendtzen K, Geborek P, Svenson M, Larsson L, Kapetanovic MC, Saxne T. Individualized monitoring of drug bioavailability and immunogenicity in rheumatoid arthritis patients treated with the tumor necrosis factor alpha inhibitor infliximab. Arthritis Rheum. 2006 Dec;54(12):3782-9. PubMed PMID: 17133559.

68: Mayer L, Young Y. Infusion reactions and their management. Gastroenterol Clin North Am. 2006 Dec;35(4):857-66. Review. PubMed PMID: 17129817.

69: Montané E, Sallés M, Barriocanal A, Riera E, Costa J, Tena X. Antitumor necrosis factor-induced neutropenia: a case report with double positive rechallenges. Clin Rheumatol. 2007 Sep;26(9):1527-9. Epub 2006 Oct 10. PubMed PMID: 17031483.

70: Sugiura F, Kojima T, Oba M, Tsuchiya H, Ishiguro N. Anaphylactic reaction to infliximab in two rheumatoid arthritis patients who had previously received infliximab and resumed. Mod Rheumatol. 2005;15(3):201-3. PubMed PMID: 17029063.

71: Saleh S, Ghodsian S, Yakimova V, Henderson J, Sharma OP. Effectiveness of infliximab in treating selected patients with sarcoidosis. Respir Med. 2006 Nov;100(11):2053-9. Epub 2006 Aug 28. PubMed PMID: 16935484.

72: Duburque C, Lelong J, Iacob R, Seddik M, Desreumaux P, Fournier C, Wallaert B, Cortot A, Colombel JF. Successful induction of tolerance to infliximab in patients with Crohn's disease and prior severe infusion reactions. Aliment Pharmacol Ther. 2006 Sep 1;24(5):851-8. PubMed PMID: 16918890.

73: Kapetanovic MC, Larsson L, Truedsson L, Sturfelt G, Saxne T, Geborek P. Predictors of infusion reactions during infliximab treatment in patients with arthritis. Arthritis Res Ther. 2006;8(4):R131. PubMed PMID: 16869978; PubMed Central PMCID: PMC1779374.

74: Toh ML, Marotte H, Blond JL, Jhumka U, Eljaafari A, Mougin B, Miossec P. Overexpression of synoviolin in peripheral blood and synoviocytes from rheumatoid arthritis patients and continued elevation in nonresponders to infliximab treatment. Arthritis Rheum. 2006 Jul;54(7):2109-18. PubMed PMID: 16802346.

75: van der Laken CJ, Voskuyl AE, Roos JC, Stigter van Walsum M, de Groot ER, Wolbink G, Dijkmans BA, Aarden LA. Imaging and serum analysis of immune complex formation of radiolabelled infliximab and anti-infliximab in responders and non-responders to therapy for rheumatoid arthritis. Ann Rheum Dis. 2007 Feb;66(2):253-6. Epub 2006 Jun 22. PubMed PMID: 16793840; PubMed Central PMCID: PMC1798492.

76: Lequerré T, Vittecoq O, Klemmer N, Goëb V, Pouplin S, Menard JF, Daragon A, Mejjad O, Le Loët X. Management of infusion reactions to infliximab in patients with rheumatoid arthritis or spondyloarthritis: experience from an immunotherapy unit of rheumatology. J Rheumatol. 2006 Jul;33(7):1307-14. Epub 2006 Jun 1. PubMed PMID: 16758513.

77: Huang F, Zhang LY, Zhang JL, Zhang FC, Liang DF, Deng XH, Guo JH, Zhu J, Zhao W, Li XF, Hou Y. [A short-term efficacy and safety study of infliximab in active ankylosing spondylitis]. Zhonghua Nei Ke Za Zhi. 2006 Feb;45(2):122-6. Chinese. PubMed PMID: 16624120.

78: Wolbink GJ, Vis M, Lems W, Voskuyl AE, de Groot E, Nurmohamed MT, Stapel S, Tak PP, Aarden L, Dijkmans B. Development of antiinfliximab antibodies and relationship to clinical response in patients with rheumatoid arthritis. Arthritis Rheum. 2006 Mar;54(3):711-5. PubMed PMID: 16508927.

79: Winfield H, Lain E, Horn T, Hoskyn J. Eosinophilic cellulitislike reaction to subcutaneous etanercept injection. Arch Dermatol. 2006 Feb;142(2):218-20. PubMed PMID: 16490850.

80: Rajaraman RT, Kimura Y, Li S, Haines K, Chu DS. Retrospective case review of pediatric patients with uveitis treated with infliximab. Ophthalmology. 2006 Feb;113(2):308-14. Epub 2006 Jan 10. PubMed PMID: 16406545.

81: Clelland S, Hunek JR. Etanercept injection site reaction. Dermatol Nurs. 2005 Oct;17(5):375-. PubMed PMID: 16294944.

82: Chávez-López MA, Delgado-Villafaña J, Gallaga A, Huerta-Yáñez G. Severe anaphylactic reaction during the second infusion of infliximab in a patient with psoriatic arthritis. Allergol Immunopathol (Madr). 2005 Sep-Oct;33(5):291-2. PubMed PMID: 16287551.

83: Hlavaty T, Pierik M, Henckaerts L, Ferrante M, Joossens S, van Schuerbeek N, Noman M, Rutgeerts P, Vermeire S. Polymorphisms in apoptosis genes predict response to infliximab therapy in luminal and fistulizing Crohn's disease. Aliment Pharmacol Ther. 2005 Oct 1;22(7):613-26. PubMed PMID: 16181301.

84: Mastroianni A, Minutilli E, Mussi A, Bordignon V, Trento E, D'Agosto G, Cordiali-Fei P, Berardesca E. Cytokine profiles during infliximab monotherapy in psoriatic arthritis. Br J Dermatol. 2005 Sep;153(3):531-6. PubMed PMID: 16120138.

85: Aries PM, Reinhold-Keller E. [Symmetric polyarthritis in a patient with Churg-Strauss syndrome]. Dtsch Med Wochenschr. 2005 Aug 19;130(33):1871-3. German. PubMed PMID: 16118729.

86: Sidiropoulos P, Kritikos HD, Siakka P, Mamoulaki M, Kouroumali H, Voudouris K, Boumpas DT. Low dose of infliximab is inadequate in most patients with spondylarthropathies. Clin Exp Rheumatol. 2005 Jul-Aug;23(4):513-6. PubMed PMID: 16095121.

87: Lelong J, Duburque C, Fournier C, Colombel JF, Desreumaux P, Tonnel AB, Wallaert B. [Desensitisation to infliximab in patients with Crohn's disease]. Rev Mal Respir. 2005 Apr;22(2 Pt 1):239-46. French. PubMed PMID: 16092162.

88: Romero Crespo I, Antón Torres R, Borrás Blasco J, Navarro Ruiz A. [Pharmaceutical care of patients with rheumatoid and psoriatic arthritis receiving etanercept]. Farm Hosp. 2005 May-Jun;29(3):171-6. Spanish. PubMed PMID: 16013943.

89: Suhler EB, Smith JR, Wertheim MS, Lauer AK, Kurz DE, Pickard TD, Rosenbaum JT. A prospective trial of infliximab therapy for refractory uveitis: preliminary safety and efficacy outcomes. Arch Ophthalmol. 2005 Jul;123(7):903-12. PubMed PMID: 16009830.

90: Torre-Cisneros J, Del Castillo M, Castón JJ, Castro MC, Pérez V, Collantes E. Infliximab does not activate replication of lymphotropic herpesviruses in patients with refractory rheumatoid arthritis. Rheumatology (Oxford). 2005 Sep;44(9):1132-5. Epub 2005 May 31. PubMed PMID: 15927999.

91: Favalli EG, Varenna M, Sinigaglia L. Drug-induced agranulocytosis during treatment with infliximab in enteropathic spondyloarthropathy. Clin Exp Rheumatol. 2005 Mar-Apr;23(2):247-50. PubMed PMID: 15895899.

92: Sánchez JM, Maldonado JC, Torres EA, Rivera C. Infliximab in Hispanics: characterization of response to infliximab in an ethnic minority with Crohn's disease. P R Health Sci J. 2005 Mar;24(1):11-7. PubMed PMID: 15895872.

93: Botsios C, Ostuni P, Todesco S. [Incidence and management of infusion reactions to infliximab in 186 italian patients with rheumatoid arthritis: the Padua experience]. Reumatismo. 2005 Jan-Mar;57(1):44-51. Italian. PubMed PMID: 15776146.

94: Ringheanu M, Daum F, Markowitz J, Levine J, Katz S, Lin X, Silver J. Effects of infliximab on apoptosis and reverse signaling of monocytes from healthy individuals and patients with Crohn's disease. Inflamm Bowel Dis. 2004 Nov;10(6):801-10. PubMed PMID: 15626899.

95: Lamireau T, Cézard JP, Dabadie A, Goulet O, Lachaux A, Turck D, Maurage C, Morali A, Sokal E, Belli D, Stoller J, Cadranel S, Ginies JL, Viola S, Huet F, Languepin J, Lenaerts C, Bury F, Sarles J; French-Speaking Group for Pediatric Gastroenterology Nutrition. Efficacy and tolerance of infliximab in children and adolescents with Crohn's disease. Inflamm Bowel Dis. 2004 Nov;10(6):745-50. PubMed PMID: 15626892.

96: Becker M, Rosé CD, McIlvain-Simpson G. Niacin-like reaction to infliximab infusion in systemic juvenile rheumatoid arthritis. J Rheumatol. 2004 Dec;31(12):2529-30. PubMed PMID: 15570667.

97: Rajakulendran S, Deighton C. Delayed multiple injection site reaction in a rheumatoid arthritis patient treated with etanercept. Rheumatology (Oxford). 2004 Dec;43(12):1588-9. PubMed PMID: 15564639.

98: Losco A, Gianelli U, Cassani B, Baldini L, Conte D, Basilisco G. Epstein-Barr virus-associated lymphoma in Crohn's disease. Inflamm Bowel Dis. 2004 Jul;10(4):425-9. PubMed PMID: 15475752.

99: Winterfield L, Menter A. Psoriasis and its treatment with infliximab-mediated tumor necrosis factor alpha blockade. Dermatol Clin. 2004 Oct;22(4):437-47, ix. Review. PubMed PMID: 15450339.

100: Scheinfeld N. A comprehensive review and evaluation of the side effects of the tumor necrosis factor alpha blockers etanercept, infliximab and adalimumab. J

Dermatolog Treat. 2004 Sep;15(5):280-94. Review. PubMed PMID: 15370396.

101: Ryan BM, Romberg M, Wolters F, Stockbrugger RW. Extensive forearm deep venous thrombosis following a severe infliximab infusion reaction. Eur J Gastroenterol Hepatol. 2004 Sep;16(9):941-2. PubMed PMID: 15316423.

102: Seiderer J, Göke B, Ochsenkühn T. Safety aspects of infliximab in inflammatory bowel disease patients. A retrospective cohort study in 100 patients of a German University Hospital. Digestion. 2004;70(1):3-9. Epub 2004 Aug 3. PubMed PMID: 15297773.

103: de Ridder L, Escher JC, Bouquet J, Schweizer JJ, Rings EH, Tolboom JJ, Houwen RH, Norbruis OF, Derkx BH, Taminiau JA. Infliximab therapy in 30 patients with refractory pediatric crohn disease with and without fistulas in The Netherlands. J Pediatr Gastroenterol Nutr. 2004 Jul;39(1):46-52. PubMed PMID: 15187780.

104: Reijasse D, Le Pendeven C, Cosnes J, Dehee A, Gendre JP, Nicolas JC, Beaugerie L. Epstein-Barr virus viral load in Crohn's disease: effect of immunosuppressive therapy. Inflamm Bowel Dis. 2004 Mar;10(2):85-90. PubMed PMID: 15168806.

105: Stallmach A, Giese T, Schmidt C, Meuer SC, Zeuzem SS. Severe anaphylactic reaction to infliximab: successful treatment with adalimumab - report of a case. Eur J Gastroenterol Hepatol. 2004 Jun;16(6):627-30. PubMed PMID: 15167167.

106: Beuthien W, Mellinghoff HU, von Kempis J. Skin reaction to adalimumab. Arthritis Rheum. 2004 May;50(5):1690-2. PubMed PMID: 15146441.

107: Di Rocco P, Manco M, Rosa G, Greco AV, Mingrone G. Lowered tumor necrosis factor receptors, but not increased insulin sensitivity, with infliximab. Obes Res. 2004 Apr;12(4):734-9. PubMed PMID: 15090644.

108: van de Putte LB, Atkins C, Malaise M, Sany J, Russell AS, van Riel PL, Settas L, Bijlsma JW, Todesco S, Dougados M, Nash P, Emery P, Walter N, Kaul M, Fischkoff S, Kupper H. Efficacy and safety of adalimumab as monotherapy in patients with rheumatoid arthritis for whom previous disease modifying antirheumatic drug treatment has failed. Ann Rheum Dis. 2004 May;63(5):508-16. PubMed PMID: 15082480; PubMed Central PMCID: PMC1755008.

109: Mamula P, Markowitz JE, Cohen LJ, von Allmen D, Baldassano RN. Infliximab in pediatric ulcerative colitis: two-year follow-up. J Pediatr Gastroenterol Nutr. 2004 Mar;38(3):298-301. PubMed PMID: 15076630.

110: Colombel JF, Loftus EV Jr, Tremaine WJ, Egan LJ, Harmsen WS, Schleck CD, Zinsmeister AR, Sandborn WJ. The safety profile of infliximab in patients with Crohn's disease: the Mayo clinic experience in 500 patients. Gastroenterology. 2004 Jan;126(1):19-31. PubMed PMID: 14699483.

111: Sandborn WJ. Optimizing anti-tumor necrosis factor strategies in inflammatory bowel disease. Curr Gastroenterol Rep. 2003 Dec;5(6):501-5. Review. PubMed PMID: 14602060.

112: Alho HS, Maasilta PK, Harjula AL, Hämmäinen P, Salminen J, Salminen US. Tumor necrosis factor-alpha in a porcine bronchial model of obliterative bronchiolitis. Transplantation. 2003 Aug 15;76(3):516-23. PubMed PMID: 12923437.

113: Baeten D, Kruithof E, Van den Bosch F, Van den Bossche N, Herssens A, Mielants H, De Keyser F, Veys EM. Systematic safety follow up in a cohort of 107 patients with spondyloarthropathy treated with infliximab: a new perspective on the role of host defence in the pathogenesis of the disease? Ann Rheum Dis. 2003 Sep;62(9):829-34. PubMed PMID: 12922954; PubMed Central PMCID: PMC1754658.

114: Regueiro M, Valentine J, Plevy S, Fleisher MR, Lichtenstein GR. Infliximab for treatment of pyoderma gangrenosum associated with inflammatory bowel disease. Am J Gastroenterol. 2003 Aug;98(8):1821-6. PubMed PMID: 12907338.

115: Arnold EL, Khanna D, Paulus H, Goodman MP. Acute injection site reaction to intraarticular etanercept administration. Arthritis Rheum. 2003 Jul;48(7):2078-9. PubMed PMID: 12847708.

116: Cheifetz A, Smedley M, Martin S, Reiter M, Leone G, Mayer L, Plevy S. The incidence and management of infusion reactions to infliximab: a large center experience. Am J Gastroenterol. 2003 Jun;98(6):1315-24. PubMed PMID: 12818276.

117: Klapman JB, Ene-Stroescu D, Becker MA, Hanauer SB. A lupus-like syndrome associated with infliximab therapy. Inflamm Bowel Dis. 2003 May;9(3):176-8. PubMed PMID: 12792223.

118: Baert F, Noman M, Vermeire S, Van Assche G, D' Haens G, Carbonez A, Rutgeerts P. Influence of immunogenicity on the long-term efficacy of infliximab in Crohn's disease. N Engl J Med. 2003 Feb 13;348(7):601-8. PubMed PMID: 12584368.

119: Stephens MC, Shepanski MA, Mamula P, Markowitz JE, Brown KA, Baldassano RN. Safety and steroid-sparing experience using infliximab for Crohn's disease at a pediatric inflammatory bowel disease center. Am J Gastroenterol. 2003 Jan;98(1):104-11. PubMed PMID: 12526944.

120: Crandall WV, Mackner LM. Infusion reactions to infliximab in children and adolescents: frequency, outcome and a predictive model. Aliment Pharmacol Ther. 2003 Jan;17(1):75-84. PubMed PMID: 12492735.

121: Steinfeld SD, Demols P, Appelboom T. Infliximab in primary Sjögren's syndrome: one-year followup. Arthritis Rheum. 2002 Dec;46(12):3301-3. PubMed PMID: 12483735.

122: Yacyshyn BR, Barish C, Goff J, Dalke D, Gaspari M, Yu R, Tami J, Dorr FA, Sewell KL. Dose ranging pharmacokinetic trial of high-dose alicaforsen (intercellular adhesion molecule-1 antisense oligodeoxynucleotide) (ISIS 2302) in active Crohn's disease. Aliment Pharmacol Ther. 2002 Oct;16(10):1761-70. PubMed PMID: 12269969.

123: Kugathasan S, Levy MB, Saeian K, Vasilopoulos S, Kim JP, Prajapati D, Emmons J, Martinez A, Kelly KJ, Binion DG. Infliximab retreatment in adults and children with Crohn's disease: risk factors for the development of delayed severe systemic reaction. Am J Gastroenterol. 2002 Jun;97(6):1408-14. PubMed PMID: 12094858.

124: Riegert-Johnson DL, Godfrey JA, Myers JL, Hubmayr RD, Sandborn WJ, Loftus EV Jr. Delayed hypersensitivity reaction and acute respiratory distress syndrome following infliximab infusion. Inflamm Bowel Dis. 2002 May;8(3):186-91. PubMed PMID: 11979139.

125: Mamula P, Markowitz JE, Brown KA, Hurd LB, Piccoli DA, Baldassano RN. Infliximab as a novel therapy for pediatric ulcerative colitis. J Pediatr Gastroenterol Nutr. 2002 Mar;34(3):307-11. PubMed PMID: 11964959.

126: Shergy WJ, Isern RA, Cooley DA, Harshbarger JL, Huffstutter JE, Hughes GM, Spencer-Smith EA, Goldman AL, Roth SH, Toder JS, Warner D, Quinn A, Keenan GF, Schaible TF; PROMPT Study Group. Profiling Remicade Onset with MTX in a Prospective Trial. Open label study to assess infliximab safety and timing of onset of clinical benefit among patients with rheumatoid arthritis. J Rheumatol. 2002 Apr;29(4):667-77. PubMed PMID: 11950005.

127: Sample C, Bailey RJ, Todoruk D, Sadowski D, Gramlich L, Milan M, Cherry R, Ma M, Lalor E, McKaigney J, Sherbaniuk R, Matic K, Switzer C, Fedorak RN. Clinical experience with infliximab for Crohn's disease: the first 100 patients in Edmonton, Alberta. Can J Gastroenterol. 2002 Mar;16(3):165-70. PubMed PMID: 11930194.

128: Kraetsch HG, Antoni C, Kalden JR, Manger B. Successful treatment of a small cohort of patients with adult onset of Still's disease with infliximab: first experiences. Ann Rheum Dis. 2001 Nov;60 Suppl 3:iii55-7. PubMed PMID: 11890655; PubMed Central PMCID: PMC1766667.

129: Marotte H, Charrin JE, Miossec P. Infliximab-induced aseptic meningitis. Lancet. 2001 Nov 24;358(9295):1784. PubMed PMID: 11734240.

130: Sandborn WJ, Hanauer SB, Katz S, Safdi M, Wolf DG, Baerg RD, Tremaine WJ, Johnson T, Diehl NN, Zinsmeister AR. Etanercept for active Crohn's disease: a randomized, double-blind, placebo-controlled trial. Gastroenterology. 2001 Nov;121(5):1088-94. PubMed PMID: 11677200.

131: Zeltser R, Valle L, Tanck C, Holyst MM, Ritchlin C, Gaspari AA. Clinical, histological, and immunophenotypic characteristics of injection site reactions associated with etanercept: a recombinant tumor necrosis factor alpha receptor: Fc fusion protein. Arch Dermatol. 2001 Jul;137(7):893-9. PubMed PMID: 11453808.

132: Koh ET. New disease modifying agents in adult rheumatoid arthritis. Ann Acad Med Singapore. 2001 Mar;30(2):170-3. Review. PubMed PMID: 11379415.

133: Puchner TC, Kugathasan S, Kelly KJ, Binion DG. Successful desensitization and therapeutic use of infliximab in adult and pediatric Crohn's disease patients with prior anaphylactic reaction. Inflamm Bowel Dis. 2001 Feb;7(1):34-7. PubMed PMID: 11233658.

134: Franklin CM. Clinical experience with soluble TNF p75 receptor in rheumatoid arthritis. Semin Arthritis Rheum. 1999 Dec;29(3):172-81. Review. PubMed PMID: 10622681.

VII. REFERENCES

Notes

- References are alphabetically arranged; reference number applies to the order in this table only.

Number	Reference	Citation NLM
1.	Alonso-Ruiz 08	Alonso-Ruiz A, Pijoan JI, Ansuategui E, Urkaregi A, Calabozo M, Quintana A. Tumor necrosis factor alpha drugs in rheumatoid arthritis: systematic review and metaanalysis of efficacy and safety. BMC Musculoskelet Disord. 2008 Apr 17;9:52. Review. PubMed PMID: 18419803.
2.	Antoni 08	Antoni CE, Kavanaugh A, van der Heijde D, Beutler A, Keenan G, Zhou B, Kirkham B, Tutuncu Z, Burmester GR, Schneider U, Furst DE, Molitor J, Keystone E, Gladman DD, Manger B, Wassenberg S, Weier R, Wallace DJ, Weisman MH, Kalden JR, Smolen JS. Two-year efficacy and safety of infliximab treatment in patients with active psoriatic arthritis: findings of the Infliximab Multinational Psoriatic Arthritis Controlled Trial (IMPACT). J Rheumatol. 2008 May;35(5):869-76. Epub 2008 Mar 15. PubMed PMID: 18381786.
3.	Askling 05	Askling J, Fored CM, Brandt L, Baecklund E, Bertilsson L, Cöster L, Geborek P, Jacobsson LT, Lindblad S, Lysholm J, Rantapää-Dahlqvist S, Saxne T, Romanus V, Klareskog L, Feltelius N. Risk and case characteristics of tuberculosis in rheumatoid arthritis associated with tumor necrosis factor antagonists in Sweden. Arthritis Rheum. 2005 Jul;52(7):1986-92. PubMed PMID: 15986370.
4.	Askling 09	Askling J, Baecklund E, Granath F, Geborek P, Fored M, Backlin C, Bertilsson L, Cöster L, Jacobsson LT, Lindblad S, Lysholm J, Rantapää-Dahlqvist S, Saxne T, van Vollenhoven R, Klareskog L, Feltelius N. Anti-tumour necrosis factor therapy in rheumatoid arthritis and risk of malignant lymphomas: relative risks and time trends in the Swedish Biologics Register. Ann Rheum Dis. 2009 May;68(5):648-53. Epub 2008 May 8. PubMed PMID: 18467516.
5.	Bongartz 06	Bongartz T, Sutton AJ, Sweeting MJ, Buchan I, Matteson EL, Montori V. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. JAMA. 2006 May 17;295(19):2275-85. Review. Erratum in: JAMA. 2006 Jun 7;295(21):2482. PubMed PMID: 16705109.
6.	Bongartz 09	Bongartz T, Warren FC, Mines D, Matteson EL, Abrams KR, Sutton AJ. Etanercept therapy in rheumatoid arthritis and the risk of malignancies: a systematic review and individual patient data meta-analysis of randomised controlled trials. Ann Rheum Dis. 2009 Jul;68(7):1177-83. Epub 2008 Nov 19. Review. PubMed PMID: 19019889.
7.	Breedveld 04	Breedveld FC, Emery P, Keystone E, Patel K, Furst DE, Kalden JR, St Clair EW, Weisman M, Smolen J, Lipsky PE, Maini RN. Infliximab in active early rheumatoid arthritis. Ann Rheum Dis. 2004 Feb;63(2):149-55. PubMed PMID: 14722203; PubMed Central PMCID: PMC1754899.
8.	Burmester 09	Burmester GR, Mease P, Dijkmans BA, et al. Adalimumab safety and mortality rates from global clinical trials of six immune-mediated inflammatory diseases. Ann Rheum Dis 2009;68:1863-9.PMID: 1914761
9.	Carmona 07	Carmona L, Descalzo MA, Perez-Pampin E, Ruiz-Montesinos D, Erra A, Cobo T, Gómez-Reino JJ; BIOBADASER and EMECAR Groups. All-cause and cause-specific mortality in rheumatoid arthritis are not greater than expected when treated with tumour necrosis factor antagonists. Ann Rheum Dis. 2007 Jul;66(7):880-5. Epub 2007 Feb 26. PubMed PMID: 17324968.
10.	Chaudhari 01	Chaudhari U, Romano P, Mulcahy LD, Dooley LT, Baker DG, Gottlieb AB. Efficacy and safety of infliximab monotherapy for plaque-type psoriasis: a randomised trial. Lancet. 2001 Jun 9;357(9271):1842-7. PubMed PMID: 11410193.
11.	Curtis 07	Curtis JR, Patkar N, Xie A, Martin C, Allison JJ, Saag M, Shatin D, Saag KG. Risk of serious bacterial infections among rheumatoid arthritis patients exposed to tumor necrosis factor alpha antagonists. Arthritis Rheum2007 Apr;56(4):1125-33. PMID: 17393394
12.	Dharamsi 09	Dharamsi JW, Bhosle M, Balkrishnan R, Yentzer BA, Feldman SR. Using 'number needed to treat' to help conceptualize the magnitude of benefit and risk of tumour necrosis factor-alpha inhibitors for patients with severe psoriasis. Br J Dermatol 2009;161:605-16. PMID: 19438475
13.	Dixon 06	Dixon WG, Watson K, Lunt M, Hyrich KL, Silman AJ, Symmons DP; British Society for Rheumatology Biologics Register. Rates of serious infection, including site-specific and bacterial intracellular infection, in rheumatoid arthritis patients receiving anti-tumor necrosis factor therapy: results from the British Society for Rheumatology Biologics Register. Arthritis Rheum. 2006 Aug;54(8):2368-76. PubMed PMID: 16868999.
14.	Dixon 07	Dixon WG, Symmons DP, Lunt M, Watson KD, Hyrich KL, Silman AJ. Serious infection following anti-tumor necrosis factor alpha therapy in patients with rheumatoid arthritis: lessons from interpreting data from observational studies. Arthritis Rheum2007 Sep;56(9):2896-904. PMID: 17763441
15.	Dixon 10	Dixon WG, Hyrich KL, Watson KD, Lunt M, Galloway J, Ustianowski A, Symmons DP. Drug-specific risk of tuberculosis in patients with rheumatoid arthritis treated with anti-TNF therapy: results from the British Society for Rheumatology Biologics Register (BSRBR). Ann Rheum Dis 2010 Mar;69(3):522-8. PMID: 19854715
16.	Emery 09	Emery P, Fleischmann RM, Moreland LW, Hsia EC, Strusberg I, Durez P, Nash P, Amante EJ, Churchill M,

		Park W, Pons-Estel BA, Doyle MK, Visvanathan S, Xu W, Rahman MU. Golimumab, a human anti-tumor necrosis factor alpha monoclonal antibody, injected subcutaneously every four weeks in methotrexate-naive patients with active rheumatoid arthritis: twenty-four-week results of a phase III, multicenter, randomized, double-blind, placebo-controlled study of golimumab before methotrexate as first-line therapy for early-onset rheumatoid arthritis. Arthritis Rheum. 2009 Aug;60(8):2272-83. Erratum in: Arthritis Rheum. 2010 Oct;62(10):3005. PubMed PMID: 19644849.
17.	Favalli 09	Favalli EG, Desiati F, Atzeni F, Sarzi-Puttini P, Caporali R, Pallavicini FB, Gorla R, Filippini M, Marchesoni A. Serious infections during anti-TNFalpha treatment in rheumatoid arthritis patients. Autoimmun Rev2009 Jan;8(3):266-73.PMID: 19022409
18.	Fleischmann 06	Fleischmann R, Baumgartner SW, Weisman MH, Liu T, White B, Peloso P. Long term safety of etanercept in elderly subjects with rheumatic diseases. Ann Rheum Dis. 2006 Mar;65(3):379-84. Epub 2005 Sep 8. PubMed PMID: 16150792; PubMed Central PMCID: PMC1798057.
19.	Fleischmann 09	Fleischmann R, Vencovsky J, van Vollenhoven RF, Borenstein D, Box J, Coteur G, Goel N, Brezinschek HP, Innes A, Strand V. Efficacy and safety of certolizumab pegol monotherapy every 4 weeks in patients with rheumatoid arthritis failing previous disease-modifying antirheumatic therapy: the FAST4WARD study. Ann Rheum Dis. 2009 Jun;68(6):805-11. Epub 2008 Nov 17. PubMed PMID: 19015206; PubMed Central PMCID: PMC2674555.
20.	Galloway 10	Galloway JB, Hyrich KL, Mercer LK, Dixon WG, Fu B, Ustianowski AP, Watson KD, Lunt M; BSRBR Control Centre Consortium, Symmons DP; on behalf of the British Society for Rheumatology Biologics Register. Anti-TNF therapy is associated with an increased risk of serious infections in patients with rheumatoid arthritis especially in the first 6 months of treatment: updated results from the British Society for Rheumatology Biologics Register with special emphasis on risks in the elderly. Rheumatology (Oxford). 2010 Jul 31. [Epub ahead of print] PubMed PMID: 20675706.
21.	Gartlehner 06	Gartlehner G, Hansen RA, Jonas BL, Thieda P, Lohr KN. The comparative efficacy and safety of biologics for the treatment of rheumatoid arthritis: a systematic review and metaanalysis. J Rheumatol. 2006 Dec;33(12):2398-408. Review. PubMed PMID: 17225293.
22.	Gomez-Reino 07	Gomez-Gallego M, Meca-Lallana J, Fernandez-Barreiro A. Multiple sclerosis onset during etanercept treatment. Eur Neurol. 2008;59(1-2):91-3. Epub 2007 Oct 11. PubMed PMID: 17934280.
23.	Gottlieb 04	Gottlieb AB, Evans R, Li S, Dooley LT, Guzzo CA, Baker D, Bala M, Marano CW, Menter A. Infliximab induction therapy for patients with severe plaque-type psoriasis: a randomized, double-blind, placebo-controlled trial. J Am Acad Dermatol. 2004 Oct;51(4):534-42. PubMed PMID: 15389187.
24.	Gottlieb 09	Gottlieb A, Menter A, Mendelsohn A, Shen YK, Li S, Guzzo C, Fretzin S, Kunynetz R, Kavanaugh A. Ustekinumab, a human interleukin 12/23 monoclonal antibody, for psoriatic arthritis: randomised, double-blind, placebo-controlled, crossover trial. Lancet. 2009 Feb 21;373(9664):633-40. Epub 2009 Feb 11. Erratum in: Lancet. 2009 Apr 18;373(9672):1340. PubMed PMID: 19217154.
25.	Griffiths 10	Griffiths CE, Strober BE, van de Kerkhof P, Ho V, Fidelus-Gort R, Yeilding N, Guzzo C, Xia Y, Zhou B, Li S, Dooley LT, Goldstein NH, Menter A; ACCEPT Study Group. Comparison of ustekinumab and etanercept for moderate-to-severe psoriasis. N Engl J Med. 2010 Jan 14;362(2):118-28. PubMed PMID: 20071701.
26.	Hetland 09	Hetland ML, Christensen IJ, Tarp U, Dreyer L, Hansen A, Hansen IT, Kollerup G, Linde L, Lindegaard HM, Poulsen UE, Schlemmer A, Jensen DV, Jensen S, Hostenkamp G, Østergaard M; All Departments of Rheumatology in Denmark. Direct comparison of treatment responses, remission rates, and drug adherence in patients with rheumatoid arthritis treated with adalimumab, etanercept, or infliximab: results from eight years of surveillance of clinical practice in the nationwide Danish DANBIO registry. Arthritis Rheum. 2010 Jan;62(1):22-32. PubMed PMID: 20039405.
27.	Jacobsson 05	Jacobsson LT, Turesson C, Gülfe A, Kapetanovic MC, Petersson IF, Saxne T, Geborek P. Treatment with tumor necrosis factor blockers is associated with a lower incidence of first cardiovascular events in patients with rheumatoid arthritis. J Rheumatol. 2005 Jul;32(7):1213-8. PubMed PMID: 15996054.
28.	Kavanaugh 09	Kavanaugh A, McInnes I, Mease P, Krueger GG, Gladman D, Gomez-Reino J, Papp K, Zrubek J, Mudivarthy S, Mack M, Visvanathan S, Beutler A. Golimumab, a new human tumor necrosis factor alpha antibody, administered every four weeks as a subcutaneous injection in psoriatic arthritis: Twenty-four-week efficacy and safety results of a randomized, placebo-controlled study. Arthritis Rheum. 2009 Apr;60(4):976-86. Erratum in: Arthritis Rheum.2010 Aug;62(8):2555. PubMed PMID: 19333944.
29.	Kay 08	Kay J, Matteson EL, Dasgupta B, Nash P, Durez P, Hall S, Hsia EC, Han J, Wagner C, Xu Z, Visvanathan S, Rahman MU. Golimumab in patients with active rheumatoid arthritis despite treatment with methotrexate: a randomized, double-blind, placebo-controlled, dose-ranging study. Arthritis Rheum. 2008 Apr;58(4):964-75. Erratum in: Arthritis Rheum. 2010 Nov;62(11):3518. PubMed PMID: 18383539.
30.	Keystone 08a	Keystone E, Heijde D, Mason D Jr, Landewé R, Vollenhoven RV, Combe B, Emery P, Strand V, Mease P, Desai C, Pavelka K. Certolizumab pegol plus methotrexate is significantly more effective than placebo plus methotrexate in active rheumatoid arthritis: findings of a fifty-two-week, phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Arthritis Rheum. 2008 Nov;58(11):3319-29. Erratum in: Arthritis Rheum. 2009 May;60(5):1249. PubMed PMID: 18975346.
31.	Keystone 08b (referenced in Singh	Keystone EC, Genovese MC, Klareskog L, Hsia EC, Hall ST, Miranda PC, Pazdur J, Bae SC, Palmer W, Zrubek J, Wiekowski M, Visvanathan S, Wu Z, Rahman MU; GO-FORWARD Study. Golimumab, a human

	10 as Keystone 09)	antibody to tumour necrosis factor {alpha} given by monthly subcutaneous injections, in active rheumatoid arthritis despite methotrexate therapy: the GO-FORWARD Study. Ann Rheum Dis. 2009 Jun;68(6):789-96. Epub 2008 Dec 9. Erratum in: Ann Rheum Dis. 2011 Jan;70(1):238. PubMed PMID: 19066176.
32.	Keystone 10	Keystone E, Genovese MC, Klareskog L, Hsia EC, Hall S, Miranda PC, Pazdur J, Bae SC, Palmer W, Xu S, Rahman MU. Golimumab in patients with active rheumatoid arthritis despite methotrexate therapy: 52-week results of the GO-FORWARD study. Ann Rheum Dis2010 Jun;69(6):1129-35.
33.	Klareskog 04	Klareskog L, van der Heijde D, de Jager JP, Gough A, Kalden J, Malaise M, Martín Mola E, Pavelka K, Sany J, Settas L, Wajdula J, Pedersen R, Fatenejad S, Sanda M; TEMPO (Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes) study investigators. Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. Lancet. 2004 Feb 28;363(9410):675-81. PubMed PMID: 15001324.
34.	Kremer 10	Kremer J, Ritchlin C, Mendelsohn A, Baker D, Kim L, Xu Z, Han J, Taylor P. Golimumab, a new human anti-tumor necrosis factor alpha antibody, administered intravenously in patients with active rheumatoid arthritis: Forty-eight-week efficacy and safety results of a phase III randomized, double-blind, placebo-controlled study. Arthritis Rheum. 2010 Apr;62(4):917-28. Erratum in: Arthritis Rheum. 2010 Oct;62(10):3130. PubMed PMID: 20131276.
35.	Krueger 07	Krueger GG, Langley RG, Leonardi C, Yeilding N, Guzzo C, Wang Y, Dooley LT, Lebwohl M; CNTO 1275 Psoriasis Study Group. A human interleukin-12/23 monoclonal antibody for the treatment of psoriasis. N Engl J Med. 2007 Feb 8;356(6):580-92. PubMed PMID: 17287478.
36.	Leonardi 08	Leonardi CL, Kimball AB, Papp KA, Yeilding N, Guzzo C, Wang Y, Li S, Dooley LT, Gordon KB; PHOENIX 1 study investigators. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). Lancet. 2008 May 17;371(9625):1665-74. Erratum in: Lancet. 2008 May 31;371(9627):1838. PubMed PMID: 18486739.
37.	Listing 05	Listing J, Strangfeld A, Kary S, Rau R, von Hinueber U, Stoyanova-Scholz M, Gromnica-Ihle E, Antoni C, Herzer P, Kekow J, Schneider M, Zink A. Infections in patients with rheumatoid arthritis treated with biologic agents. Arthritis Rheum2005 Nov;52(11):3403-12. PMID: 16255017
38.	Lunt 10	Lunt M, Watson KD, Dixon WG, Symmons DP, Hyrich KL. No evidence of association between anti-TNF treatment and mortality in patients with rheumatoid arthritis: Results from the British Society for Rheumatology Biologics Register. Arthritis Rheum2010 Jul 26. PMID: 20662063
39.	Magnano 04	Magnano MD, Robinson WH, Genovese MC. Demyelination and inhibition of tumor necrosis factor (TNF). Clin Exp Rheumatol. 2004 Sep-Oct;22(5 Suppl 35):S134-40. Review. PubMed PMID: 15552527.
40.	Maini 99	Maini R, St Clair EW, Breedveld F, Furst D, Kalden J, Weisman M, Smolen J, Emery P, Harriman G, Feldmann M, Lipsky P. Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. Lancet. 1999 Dec 4;354(9194):1932-9. PubMed PMID: 10622295.
41.	Marchesoni 09	Marchesoni A, Zaccara E, Gorla R, Bazzani C, Sarzi-Puttini P, Atzeni F, Caporali R, Bobbio-Pallavicini F, Favalli EG. TNF-alpha antagonist survival rate in a cohort of rheumatoid arthritis patients observed under conditions of standard clinical practice. Ann N Y Acad Sci. 2009 Sep;1173:837-46. PubMed PMID: 19758236.
42.	Mariette 10	Mariette X, Tubach F, Bagheri H, Bardet M, Berthelot JM, Gaudin P, Heresbach D, Martin A, Schaeverbeke T, Salmon D, Lemann M, Hermine O, Raphael M, Ravaud P. Lymphoma in patients treated with anti-TNF: results of the 3-year prospective French RATIO registry. Ann Rheum Dis. 2010 Feb;69(2):400-8. Epub 2009 Oct 14. PubMed PMID: 19828563
43.	Mease 08	Mease PJ, Ory P, Sharp JT, Ritchlin CT, Van den Bosch F, Wellborne F, Birbara C, Thomson GT, Perdok RJ, Medich J, Wong RL, Gladman DD. Adalimumab for long-term treatment of psoriatic arthritis: 2-year data from the Adalimumab Effectiveness in Psoriatic Arthritis Trial (ADEPT). Ann Rheum Dis. 2009 May;68(5):702-9. Epub 2008 Aug 6. PubMed PMID: 18684743; PubMed Central PMCID: PMC2663711.
44.	Menter 06	Menter A, Feldman SR, Weinstein GD, Papp K, Evans R, Guzzo C, Li S, Dooley LT, Arnold C, Gottlieb AB. A randomized comparison of continuous vs. intermittent infliximab maintenance regimens over 1 year in the treatment of moderate-to-severe plaque psoriasis. J Am Acad Dermatol. 2007 Jan;56(1):31.e1-15. Epub 2006 Sep 6. PubMed PMID: 17097378.
45.	Mohan 04	Mohan AK, Coté TR, Block JA, Manadan AM, Siegel JN, Braun MM. Tuberculosis following the use of etanercept, a tumor necrosis factor inhibitor. Clin Infect Dis. 2004 Aug 1;39(3):295-9. Epub 2004 Jul 16. PubMed PMID: 15306993.
46.	Nam 10	Nam JL, Winthrop KL, van Vollenhoven RF, Pavelka K, Valesini G, Hensor EM, Worthy G, Landewe R, Smolen JS, Emery P, Buch MH. Current evidence for the management of rheumatoid arthritis with biological disease-modifying antirheumatic drugs: a systematic literature review informing the EULAR recommendations for the management of RA. Ann Rheum Dis2010 Jun;69(6):976-86.PMID: 20447957
47.	Owens 09	Owens DK, Lohr KN, Atkins D, Treadwell JR, Reston JT, Bass EB, Chang S, Helfand M. AHRQ series paper

		5: grading the strength of a body of evidence when comparing medical interventions--agency for healthcare research and quality and the effective health-care program. J Clin Epidemiol. 2010 May;63(5):513-23. PubMed PMID: 19595577.
48.	Papp 08,	Papp KA, Langley RG, Lebwohl M, Krueger GG, Szapary P, Yeilding N, Guzzo C, Hsu MC, Wang Y, Li S, Dooley LT, Reich K; PHOENIX 2 study investigators. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2). Lancet. 2008 May 17;371(9625):1675-84. PubMed PMID: 18486740.
49.	Reich 05	Reich K, Nestle FO, Papp K, Ortonne JP, Evans R, Guzzo C, Li S, Dooley LT, Griffiths CE; EXPRESS study investigators. Infliximab induction and maintenance therapy for moderate-to-severe psoriasis: a phase III, multicentre, double-blind trial. Lancet. 2005 Oct 15-21;366(9494):1367-74. PubMed PMID: 16226614.
50.	Saad 08	Saad AA, Ashcroft DM, Watson KD, Hyrich KL, Noyce PR, Symmons DP; British Society for Rheumatology Biologics Register. Persistence with anti-tumour necrosis factor therapies in patients with psoriatic arthritis: observational study from the British Society of Rheumatology Biologics Register. Arthritis Res Ther. 2009;11(2):R52. Epub 2009 Apr 8. PubMed PMID: 19356232;
51.	Salmon-Ceron 10	Salmon-Ceron D, Tubach F, Lortholary O, Chosidow O, Bretagne S, Nicolas N, Cuillerier E, Fautrel B, Michelet C, Morel J, Puéchal X, Wendling D, Lemann M, Ravaud P, Mariette X; for the RATIO group. Drug-specific risk of non-tuberculosis opportunistic infections in patients receiving anti-TNF therapy reported to the 3-year prospective French RATIO registry. Ann Rheum Dis. 2010 Dec 21. [Epub ahead of print] PubMed PMID: 21177290.
52.	Scanlon 09	Scanlon JV, Exter BP, Steinberg M, Jarvis CI. Ustekinumab: treatment of adult moderate-to-severe chronic plaque psoriasis. Ann Pharmacother. 2009 Sep;43(9):1456-65. Epub 2009 Aug 11. Review. PubMed PMID: 19671802.
53.	Schiff 06	Schiff MH, Burmester GR, Kent JD, Pangan AL, Kupper H, Fitzpatrick SB, Donovan C. Safety analyses of adalimumab (HUMIRA) in global clinical trials and US postmarketing surveillance of patients with rheumatoid arthritis. Ann Rheum Dis. 2006 Jul;65(7):889-94. Epub 2006 Jan 26. PubMed PMID: 16439435.
54.	Schmitt 08	Schmitt J, Zhang Z, Wozel G, Meurer M, Kirch W. Efficacy and tolerability of biologic and nonbiologic systemic treatments for moderate-to-severe psoriasis: meta-analysis of randomized controlled trials. Br J Dermatol. 2008 Sep;159(3):513-26. Epub 2008 Jul 9. Review. PubMed PMID: 18627372.
55.	Seong 07	Seong SS, Choi CB, Woo JH, Bae KW, Joung CL, Uhm WS, Kim TH, Jun JB, Yoo DH, Lee JT, Bae SC. Incidence of tuberculosis in Korean patients with rheumatoid arthritis (RA): effects of RA itself and of tumor necrosis factor blockers. J Rheumatol. 2007 Apr;34(4):706-11. Epub 2007 Feb 15. PubMed PMID: 17309133.
56.	Singh 09	Singh JA, Christensen R, Wells GA, Suarez-Almazor ME, Buchbinder R, Lopez-Olivo MA, Tanjong Ghogomu E, Tugwell P. Biologics for rheumatoid arthritis: an overview of Cochrane reviews. Cochrane Database Syst Rev. 2009 Oct 7;(4):CD007848. Review. PubMed PMID: 19821440.
57.	Singh 10	Singh JA, Noorbaloochi S, Singh G. Golimumab for rheumatoid arthritis. Cochrane Database of Systematic Reviews 2010, Issue 1. Art. No.: CD008341. DOI: 10.1002/14651858.CD008341.
58.	Singh 11	Singh JA, Wells GA, Christensen R, Tanjong Ghogomu E, Maxwell L, MacDonald JK, Filippini G, Skoetz N, Francis D, Lopes LC, Guyatt GH, Schmitt J, La Mantia L, Weberschock T, Roos JF, Siebert H, Hershan S, Lunn MPT, Tugwell P, Buchbinder R. Adverse effects of biologics: a network meta-analysis and Cochrane overview. Cochrane Database of Systematic Reviews 2011, Issue 2. Art. No.: CD008794. DOI: 10.1002/14651858.CD008794.pub2.. PubMed PMID: not yet filed
59.	Smolen 09	Smolen J, Landewé RB, Mease P, Brzezicki J, Mason D, Luijtens K, van Vollenhoven RF, Kavanaugh A, Schiff M, Burmester GR, Strand V, Vencovsky J, van der Heijde D. Efficacy and safety of certolizumab pegol plus methotrexate in active rheumatoid arthritis: the RAPID 2 study. A randomised controlled trial. Ann Rheum Dis. 2009 Jun;68(6):797-804. Epub 2008 Nov 17. PubMed PMID: 19015207.
60.	St. Clair 04	St Clair EW, van der Heijde DM, Smolen JS, Maini RN, Bathon JM, Emery P, Keystone E, Schiff M, Kalden JR, Wang B, Dewoody K, Weiss R, Baker D; Active-Controlled Study of Patients Receiving Infliximab for the Treatment of Rheumatoid Arthritis of Early Onset Study Group. Combination of infliximab and methotrexate therapy for early rheumatoid arthritis: a randomized, controlled trial. Arthritis Rheum. 2004 Nov;50(11):3432-43. PubMed PMID: 15529377.
61.	Sterry 10	Sterry W, Ortonne JP, Kirkham B, Brocq O, Robertson D, Pedersen RD, Estojak J, Molta CT, Freundlich B. Comparison of two etanercept regimens for treatment of psoriasis and psoriatic arthritis: PRESTA randomised double blind multicentre trial. BMJ. 2010 Feb 2;340:c147. doi: 10.1136/bmj.c147. PubMed PMID: 20124563.
62.	Tan 10	Tan JY, Li S, Yang K, Ma B, Chen W, Zha C, Zhang J. Ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: a meta-analysis. J Dermatolog Treat. 2010 Oct 5. [Epub ahead of print] PubMed PMID: 20923370.
63.	Thaler 09	Thaler K, Chandiramani DV, Hansen RA, Gartlehner G. Efficacy and safety of anakinra for the treatment of rheumatoid arthritis: an update of the Oregon Drug Effectiveness Review Project. Biologics.

		2009;3:485-98. Epub 2009 Dec 29. PubMed PMID: 20054439.
64.	Tsiodras 08	Tsiodras S, Samonis G, Boumpas DT, Kontoyiannis DP. Fungal infections complicating tumor necrosis factor alpha blockade therapy. Mayo Clin Proc. 2008 Feb;83(2):181-94. Review. PubMed PMID: 18241628.
65.	Tubach 09	Tubach F, Salmon D, Ravaud P, Allanore Y, Goupille P, Bréban M, Pallot-Prades B, Pouplin S, Sacchi A, Chichemanian RM, Bretagne S, Emilie D, Lemann M, Lortholary O, Mariette X; Research Axed on Tolerance of Biotherapies Group. Risk of tuberculosis is higher with anti-tumor necrosis factor monoclonal antibody therapy than with soluble tumor necrosis factor receptor therapy: The three-year prospective French Research Axed on Tolerance of Biotherapies registry. Arthritis Rheum. 2009 Jul;60(7):1884-94. Erratum in: Arthritis Rheum. 2009 Aug;60(8):2540. Lorthololary, O [corrected to Lortholary, O]. PubMed PMID: 19565495.
66.	Uhlenhake 10	Uhlenhake EE, Feldman SR. Efficacy and safety of ustekinumab and etanercept for the treatment of psoriasis. Expert Opin Biol Ther. 2010 Jul;10(7):1105-12. Review. PubMed PMID: 20446825.
67.	Weinblatt 10	Weinblatt ME, Bathon JM, Kremer JM, Fleischmann RM, Schiff MH, Martin RW, Baumgartner SW, Park GS, Mancini EL, Genovese MC. Safety and efficacy of etanercept beyond 10 years of therapy in North American patients with early and long-standing rheumatoid arthritis. Arthritis Care Res (Hoboken). 2010 Oct 18. [Epub ahead of print] PubMed PMID: 20957659.
68.	Westhovens 06	Westhovens R, Yocum D, Han J, Berman A, Strusberg I, Geusens P, Rahman MU; START Study Group. The safety of infliximab, combined with background treatments, among patients with rheumatoid arthritis and various comorbidities: a large, randomized, placebo-controlled trial. Arthritis Rheum. 2006 Apr;54(4):1075-86. Erratum in: Arthritis Rheum. 2007 May;56(5):1675. Dosage error in article text. PubMed PMID: 16572442.
69.	Wiens 10	Wiens A, Venson R, Correr CJ, Otuki MF, Pontarolo R. Meta-analysis of the efficacy and safety of adalimumab, etanercept, and infliximab for the treatment of rheumatoid arthritis. Pharmacotherapy. 2010 Apr;30(4):339-53. Review. PubMed PMID: 20334454.
70.	Wolfe 04	Wolfe F, Michaud K, Anderson J, Urbansky K. Tuberculosis infection in patients with rheumatoid arthritis and the effect of infliximab therapy. Arthritis Rheum. 2004 Feb;50(2):372-9. PubMed PMID: 14872478.
71.	Wolfe 07a	Wolfe F, Michaud K. Biologic treatment of rheumatoid arthritis and the risk of malignancy: analyses from a large US observational study. Arthritis Rheum. 2007 Sep;56(9):2886-95. PubMed PMID: 17729297.
72.	Wolfe 07b	Wolfe F, Michaud K. The effect of methotrexate and anti-tumor necrosis factor therapy on the risk of lymphoma in rheumatoid arthritis in 19,562 patients during 89,710 person-years of observation. Arthritis Rheum. 2007 May;56(5):1433-9. PubMed PMID: 17469100.
73.	Zidi 10	Zidi I, Bouaziz A, Mnif W, Bartegi A, Ben Amor N. Golimumab and malignancies: true or false association? Med Oncol2010 Apr 7.PMID: 20373059

