Summary Hightlights of Review

Abbreviations at Summary's End

Systematic Safety Review of Five Biologic Antirheumatic Drugs

Funding for Original Review Provided by Amgen, Inc*

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*Delfini had complete control over all aspects of the review except for the choice of biologic 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.

Agents and Key Question

What is the evidence regarding the comparative safety of the following five anti-TNF biologic agents (biologics) as used in the treatment of rheumatoid arthritis (RA), psoriasis and psoriatic arthritis? What is the evidence regarding the comparative safety of the human interleukin-12 and -23 antagonist ustekinumbab (Stelara)?

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

EXECUTIVE SUMMARY

Comparative safety of the various biological agents is complicated by the lack of head-to-head studies, the relative rarity of adverse events, relatively small study size and substantial heterogeneity in the study populations, study designs and multiple other contextual issues. For example, there is heterogeneity in disease activity, previous and concomitant treatments, co-interventions, study settings and study duration. Furthermore there are biases in all study designs (see outline below). However, certain compelling patterns emerge which are robust across study designs and locations.

Reviewers

Michael E. Stuart MD
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Date

June 2011

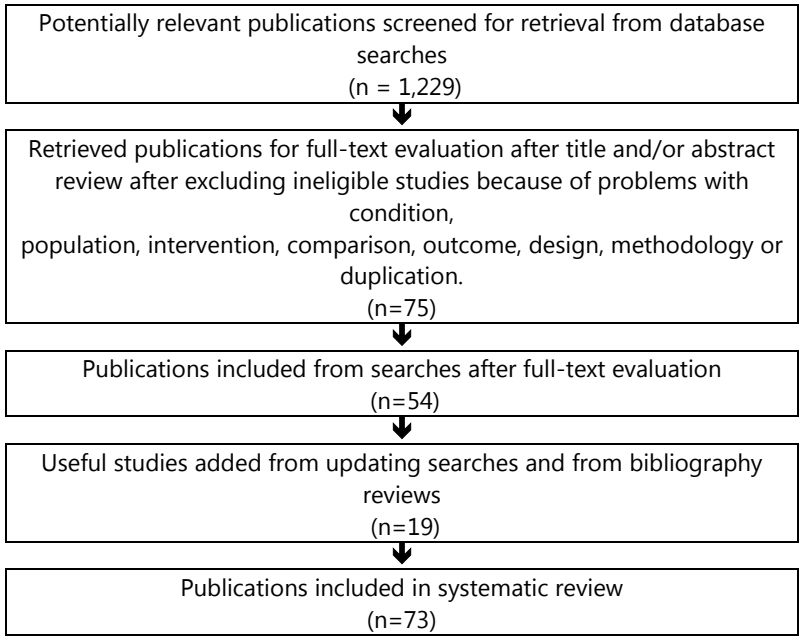
METHODS

Searching

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."

Flowchart Summarizing Search and Application of Relevance and Inclusion Criteria

We screened 1,229 potentially relevant publications from our 24 database searches. We retrieved75 studies for further abstract and/or full text evaluation after excluding ineligible studies because ofproblems 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.

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.

A full report is available along with critical appraisals of individual studies and search documentation.

Important Considerations by Study Type

- **RCTs**
  - Evidence is indirect (lack of head-to-head trials)
  - Small trials not powered to detect statistically significant differences
  - Differences in study populations, dosing, study duration, co-interventions, safety outcomes and assessments
  - Differences in study quality (selection, performance, attrition, assessment biases)
  - Lack of formal or standardized or complete reporting of adverse events
- **Meta-analyses of RCTs**
  - Larger N, but also potentially underpowered to detect some statistically significant differences
  - Heterogeneity of studies
  - Low quality studies included
- **Observational Studies and Registries**
  - Differences in populations, reporting, dosing, study duration, co-interventions, other patient choices, experiences and assessments
  - Lack of blinding
  - "Survival bias" (drop-out or removal of patients with AEs or who are deemed to be at higher risk of AEs)

CONCLUSIONS

Comparative safety of the various biologic 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. **NOTE**: Row numbers are used for navigating references in tables and differ from reference numbers.

Comparative Safety Estimates From Evidence Review of The Antirheumatic 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%*

SUMMARY OF COMPARATIVE SAFETY OF THE ANTIRHEUMATIC AGENTS OF INTEREST

The evidence is suggestive that...

SAFETY ISSUE	LOWER RISK	DIRECTION	HIGHER RISK	
Serious Infections In RA	ADA ETN IFX 3 to 4 serious infections/100 patients treated for 6 to 12 months	<	CZP 8.6 serious infections/100 patients treated for 6 months	
Tuberculosis	ETN 0.4 TB cases/1000 pt-years.	<	IFX and ADA 1.4 TB cases/1000 pt-years	
Infections (OIs) in Studied Populations	ETN 0.07 OIs/1000 pt-years	<	ADA 0.61 OIs /1000 pt-years	IFX 2.9 OIs /1000 pt-years
Lymphoma in Studied Populations	ETN 0.07 lymphomas/1000 pt-years	<	IFX or ADA 0.62 to 2.91 lymphomas/1000 pt-years	
Withdrawals and Withdrawals due to Adverse Events in RA	ETN 4-5 per 100 patients for 12 mo	<	ADA 7-9 per 100 patients for 12 mos	IFX 11-12 per 100 patients for 12 mos

Table 1. Serious Infections

SERIOUS INFECTIONS DISCUSSION	Row	Reference/Design/Outcome/ Summary	Findings		
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 DMARDs. Consistent patterns across study types and locations increase robustness of findings (LOE: borderline). Evidence synthesis suggests that ETN is associated with a decreased risk of serious infections of 1 to 2 fewer serious infections per 100 patients (3 to 12 months) when compared to the pooled risk for IFX and ADA. 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. (LOE: inconclusive). Evidence suggests that between 1 and 2 fewer serious infections per 100 patients treated with ADA, ETN, GLM or IFX for 6 months will occur when compared to CZP. Larger, high quality studies with longer follow-up are needed to more fully assess the relative safety of these agents compared to other agents.	1	Wien 10/Meta/Serious Infection in RA Indirect evidence suggestive of decreased risk of serious infection with ETN compared to ADA and IFX	RR Compared to Placebo +/- MTX		
			ADA N=2300		2.22 (95% CI 0.83 to 5.99)
			IFX N=2017		0.96 (95% CI 0.39 to 2.38
			ETN N=1302		0.89 (95% CI 0.54 to1.48)
	2	Bongartz 06/Meta/Serious Infection in RA Indirect evidence suggestive of significantly higher risk of infection with ADA and IFX compared to placebo.	Pooled ORs of ADA and IFX compared to placebo		
			ADA + IFX N=5005		2.01 (95% CI 1.31 to 3.09)
			Absolute difference 3-12 months: 1.7% (95% CI 0.8 to 2.6) NNH within 3-12 months: 59 (95% CI 39 to 125)		
	3	Singh 11/Meta/Serious Infections (3 RA trials, 1 Crohn's Disease Trial) Risk of serious infections with CZP appears to be approximately 3 times greater than with control treatments (placebo and non-biological DMARDs): Cochrane Level of Evidence : Moderate	Risk of Serious Infections CZP Compared To Controls		
			N=1929 OR 3.51 (95% CI 1.59 to 7.79) ARI=5.9% NNH=17 (95% CI 7 to 68)		
			Risk of Serious Infections CZP Compared To ADA, ETN, GLM, IFX and Placebo		
			Agent	Comparator	Odds Ratio
			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)
	4	Galloway 10/British Registry/Serious Infection RA Indirect evidence suggestive of decreased risk of serious infection with ETN compared to ADA and IFX	INCIDENCE RATES PER 1000 PY 11,798 anti-TNF-treated RA patients 3,598 traditional DMARDs		
			IFX 46/1,000 (95% CI 42 to 50)		
			ADA 43/1,000 (95% CI 39 to 47)		
			ETN 38/1,000 (95% CI 35 to 42)		
			TRADITIONAL DMARDs 32/1000 (95% CI 28 to 36)		
	5	Favalli 09/Italian Registry/Serious Infection RA Suggestive of decreased risk of serious infection with ETN compared to ADA and IFX	INCIDENCE RATES PER 1000 PY 519 IFX patients 303 ADA patients 242 ETN patients		
			IFX 38.91 (95% CI 27.14 to 50.67)		
			ADA 38.17 (95% CI 21.44 to 54.90)		
			ETN 25.58 (95% CI 10.46 to 40.69)		
	6	Curtis 07/Retrospective Cohort US/Serious Infection RA	INCIDENCE RATE RATIO (COMPARATOR IS MTX)		

SERIOUS INFECTIONS DISCUSSION	Row	Reference/Design/Outcome/ Summary	Findings		
		Suggestive of decreased risk of serious infection with ETN compared to ADA and IFX	ADA N=118 IFX N=850 ETN N=1412		
			IFX+ADA 2.4 (95% CI 1.4 to 5.2)		
			ETN 1.2 (95% CI 0.5 to 2.5)		
	7	Listing 05/German Registry/Serious Infection RA Suggestive of decreased risk of lower respiratory infections with ETN compared to IFX	RR OF LOWER RESPIRATORY INFECTION (COMPARATOR IS NON-BIOLOGIC DMARDs)		
			IFX 4.82 (95% CI 1.4 to 20.8)		
			ETN 2.66 (95% CI 0.7 to 11.8)		
	8	Dixon 07/British Registry/Serious Infections RA Inconclusive evidence suggesting possible higher risk of serious infections with IFX	Incidence Rate Ratios (IRR) of Serious Infections in RA Patients Ever Received ADA, ETN and IFX (Comparator is Traditional DMARDs)		
			IFX 1.41 (1.02 to 1.97 405/5,874=6.9%	ADA 1.25 (0.88 to 1.77) 138/2,548=5.4%	ETN 1.34 (0.97 to 1.86) 432/6,998=6.2%

Table 2. TUBERCULOSIS

TUBERCULOSIS DISCUSSION	Row	Reference/Design/Outcome/Summary	Findings
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 DMARDs in patients being treated for rheumatoid arthritis and possibly other conditions (LOE: borderline). The estimated risk difference is 1 less case of tuberculosis per 1000 RA patient-years with ETN than with the monoclonal antibodies. 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 agents (LOE: inconclusive).	1	Bongartz 06/Meta/TB	ADA or IFX N=3493 10 cases TB
	2	Fleischmann 06/Meta/TB	ETN N=4322 0 cases TB
	3	Dixon 10/British Registry/TB Suggestive of lower incidence TB with ETN	IRR Tuberculosis in RA Patients Treated with IFX, ADA and ETN Drug / Cases / Rate TB / IRR compared to ETN ADA N=3504 / 11 / 144/100,000 / 3.1 (95% CI 1.0 to 9.5) IFX N=3259 / 11 / 136/100,000 / 4.2 (95% CI 1.4 to 12.4) ETN N=3913 / 5 / 39/100,000 / Reference Agent
	4	Tubach 09/French Registry/TB Suggestive of lower incidence TB with ETN	Agent / N / SIR (95% CI) with French Population as Reference / Odds Ratio of Agent Compared to ETN Only IFX / 34 / 18.6 (13.4 to 25.8) / 13.3 (95% CI 2.6 to 69.0) Only ADA / 23 / 29.3 (20.3 to 42.4) / 17.1 (95% CI 3.6 to 80.6) Only ETN / 1 / 1.8 (0.7 to 4.3) / Reference agent
	5	Gomez-Reino 07/Spanish Registry/TB Suggestive of lower incidence TB with ETN	Agent / Cases/Subjects (Time-to-Develop) / Incidence per 100,000/yr (95% CI) IFX / 5/1303 (1.2 to 8.7 mos) / 383 (159 to 921) ADA / 1/565 (14 mos) / 176 (24 to 1245) ETN / 2/1740 (<2.5 mos) / 114 (28 to 459)
	6	Seong 07/Korean Registry/TB Suggestive of lower incidence TB with ETN	TB by Biologic Agent 2001 to 2005 N=1285 78.17 patient-years (PY) of Follow-up 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 Estimated mean risk of TB in the Korean population was 67.2 per 100,000 PY. Incidence in the IFX RA group was 2,558 per 100,000 PY.
	7	Asking 05/Swedish Registry/TB Suggestive of lower incidence TB with ETN	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)
	8	Mohan 04/Observational Study/TB Suggestive of lower incidence TB with ETN	ADEs Associated with ETN Reported to FDA between Nov 1998 and March 2002 Incidence of TB / 100,000 PY ETN 10 (95% CI not provided)
	9	Wolfe 04/Prospective Cohort Study/TB Indirect evidence suggestive of higher incidence of TB with IFX	Incidence of TB / 100,000 PY 2 Yrs N=6,460 IFX 52.5 (95% CI 14.3 to 134.4)

Table 3. Non-TB Opportunistic Infections (OI) In Studied Populations

<table>
<tr><th>NON-TB OPPORTUNISTIC INFECTIONS IN STUDIED POPULATIONS DISCUSSION</th><th>Reference/Design/Outcome</th><th colspan="3">Findings
Inconclusive evidence suggesting lower incidence non-TB opportunistic infections with ETN than with monoclonal antibodies IFX and ADA</th></tr>
<tr><td rowspan="15">Evidence from observational studies (lack of adequately powered RCTs) suggests 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 estimated risk difference is 1 less case of opportunistic infection per 1000 RA patient-years with ETN than with the monoclonal antibodies.

The evidence is insufficient to determine the relative risk for non-TB opportunistic infections 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).</td><td rowspan="15">Salmon-Ceron 10/French Registry/Non-TB Opportunistic Infections (OI)</td><td>Agent</td><td colspan="2">Annual Rate OI/100,000 PY</td></tr>
<tr><td>IFX</td><td colspan="2">290.9 (95% CI 0.0 to 835.8)</td></tr>
<tr><td>ADA</td><td colspan="2">61.8 (95% CI 0.0 to 162.5)</td></tr>
<tr><td>ETN</td><td colspan="2">7.1 (95% CI 0.0 to 24.2)</td></tr>
<tr><td colspan="3">Odds Ratio (Comparator was French population receiving TNFIs without OI)</td></tr>
<tr><td>Treatment with IFX versus treatment with ETN</td><td colspan="2">17.6 (95% CI 4.3 to 72.9)</td></tr>
<tr><td>Treatment with ADA versus treatment with ETN</td><td colspan="2">10.28 (95% CI 2.35 to 44.94)</td></tr>
<tr><td>Treatment with steroids >10 mg/day or intravenous boluses during the previous year</td><td colspan="2">10.0 (95% CI 2.3 to 44.4)</td></tr>
<tr><td colspan="3">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</td></tr>
<tr><td colspan="2">Category; N</td><td>Incidence Rate OIs per 100,000 PY</td></tr>
<tr><td colspan="2">All TNFIs; N=45</td><td>151.6 (95% CI 0 to 468.3)</td></tr>
<tr><td colspan="2">Last TNFI IFX; N=31</td><td>290.9 (95% CI 0 to 835.8)</td></tr>
<tr><td colspan="2">Last TNFI ADA; N=10</td><td>61.8 (95% CI 0 to 162.5)</td></tr>
<tr><td colspan="2">Last TNFI ETN; N=4</td><td>7.1 (95% CI 0 to 24.2)</td></tr>
<tr><td colspan="2">Only IFX; N=27</td><td>245.2 (95% CI 0 to 728.7)</td></tr>
</table>

Table 4. Lymphoma

LYMPHOMA DISCUSSION	Row	Reference/Design/ Outcome	Findings Inconclusive evidence suggesting that the risk of lymphoma in patients treated with IFX or ADA for any indication may be greater than in patients treated with ETN		
There is insufficient evidence from RCTs to reliably determine the relative risk of lymphoma in RA patients treated with IFX, ADA and ETN. Although evidence from RCTs and meta-analyses of RCTs is inconclusive, evidence from a 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). The estimated risk difference (predominantly studied in RA patients) is 1 less case of lymphoma per 1000 patient-years with ETN treatment than with the monoclonal antibodies ADA and IFX. 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 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).	1	Burmester 09/Meta/Lymphoma	Agent	Number Lymphomas per 100 PY	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
			IFX or ADA	Number of Cases	Incidence (Up to 34 Wks)
	2	Bongartz 06/Meta/Lymphoma	IFX or ADA (9 RA Trials) N=3,493	10 per 3,493 Patients	0.29%
			Agent (without restriction for underlying disease)	SIR (95% CI) with French Population as Reference	Odds Ratio of Agent Compared to ETN
	3	Mariette 10/French Registry/Lymphoma	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

Table 5. Withdrawals and Withdrawals Due to Adverse Events

WITHDRAWALS DISCUSSION **Withdrawals Due To Adverse Events in Patients with RA and Psoriasis Receiving IFX, ADA, ETN, GLM, CZP or UST**	**Row**	**Reference/Design/Outcome**	**Findings** Inconclusive evidence suggesting an increased risk of withdrawal with IFX compared to ADA, ETN, GLM	
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). The estimated risk difference in withdrawal rates is 2 fewer withdrawals per 100 patients per year with ETN treatment compared to ADA and 6 fewer withdrawals per 100 patients per year with ETN compared to IFX. 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). The estimated risk difference is 1 to 6 fewer withdrawals per 100 patients per year with ADA or GLM compared to IFX.	1	Singh 11/Meta/Withdrawals AEs RA	Agents (N)	Withdrawals
			Comparisons 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)
			Comparisons ADA Compared to Control ETN Compared to Control IFX Compared to Control	OR Withdrawal (AE) of Agents Compared to Controls 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) 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
	2	Wiens 10/Meta/Withdrawals AEs RA	Agent	RR of Withdrawal Due To AE Compared to Controls
			IFX (7 trials) ADA (8 trials) ETN (6 trials)	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)
	3	Singh 09/Meta/Withdrawals AE RA	Agent	NNH (Withdrawal due to AE Versus Controls)
			ADA (8 trials) IFX (4 trials) ETN (4 trials)	39 (95% CI 19 to 162) 18 (95% CI 8 to 72) NS
	4	Hetland 09/Danish Registry/Withdrawals RA	Comparisons IFX Compared to ETN IFX Compared to ADA ADA Compared to ETN	RR of Withdrawal 1.98 (95% CI 1.63 to 2.40) 1.35 (95% CI 1.15 to 1.58) 1.47 (95% CI 1.20 to 1.80)
	5	Marchesoni 09/Italian Registry/Withdrawals RA	Agents ETN ADA IFX	Likelihood of Continuing Agent ("Survival") (3 Years) 62.5% 53.6% 49.1% (P<0.05 for difference between ETN and other agents)
	6	Saad 08/Meta/Withdrawal for Any Reason PsA	Agent IFX ADA ETN	RR of Withdrawal (3 Years) 1.50 (95% CI 0.26 to 8.61) 0.83 (95% CI 0.39 to 1.74) 0.24 (95% CI 0.12 to 0.49)

Table 6. Mortality Predominantly RA

MORTALITY IN RA, PSORIASIS AND PsA DISCUSSION	Row	Mortality Reference	Agent (N)	RR Mortality Compared to Controls	Summary
There is insufficient evidence to determine the relative risk of mortality associated with the agents of interest. 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 DMARD therapy (LOE: Borderline).	1	Wiens 10/Meta	ADA (2428) ETN (1178) IFX (1042)	2.52 ((95% CI 0.72 to 8.86) 1.54 ((95% CI 0.19 to 12.48) 0.71 ((95% CI 0.11 to 4.85)	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. However, 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
	2	Alonso-Ruiz 08/Meta	ADA ETN IFX	1.3 ((95% CI 0.4 to 4.7) 1.5 ((95% CI 0.2 to 9.5) 0.5 ((95% CI 0.2 to 1.4) Control =Placebo +/- MTX	
	3	Lunt 10/British Registry	ADA (N=4091) ETN (N=4420) IFX (N=4161)	No overall difference in mortality rates between the biologic DMARD and the non-biologic DMARD cohorts (weighted HR 0.86 (95% CI 0.64 to 1.16)	
	4	Carmona 07/Spanish Registry	Not specified	Mortality Rate Ratio RA Pts Receiving Biologic DMARDs Versus RA Pts Receiving Non-biologic DMARDS: 0.32 (95% CI 0.20 to 0.53)	
	5	Jacobsson 05/ Swedish Registry	ETN or IFX	3 deaths/531 exposed (2 CVD, one lymphoma) in patients receiving biologic DMARDs and 29 deaths/543 exposed (12 CVD) in those not receiving biologic DMARDs	
	6	Burmester 09/Meta	• Meta-analysis, N=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 standardized mortality ratio (SMR) was 1.07 (95% CI, 0.75 to 1.49) – Data from the World Health Organization used for estimating risk in the general population for SMR calculation – 35 deaths observed compared with 32.6 deaths expected in the general population		
	7	Singh 10/Meta	• Cochrane review of 4 RCTs N=1,231 RA patients treated with GLM and 483 patients treated with placebo (with or without MTX) - No significant mortality differences between GLM and the placebo groups		

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 antirheumatic 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).

DEMYELINATING DISEASE

There is insufficient evidence to determine the relative risk of developing demyelinating disease in patients receiving the agents of interest (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 biologic agents.

Table 7. Demyelinating Disease RA

The Following 3 Trials Included in Dharamsi 09 Systematic Review				
Reference	Intervention/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	1.3
* From Incidence of Multiple Sclerosis and Optic Neuritis in US population ^95% CI not reported				

Table 8. Infusion and Injection Site Reactions

INFUSION REACTIONS & INJECTION SITE REACTIONS DISCUSSION

INFUSION REACTIONS

Infusion reactions occur in approximately 20% of patients (meta-analysis,RCT and FDA data). 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. RCT data is not specific regarding time from drug initiation to infusion reaction. 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). The evidence is sufficient to conclude that the risk of infusion reactions in patients treated with IFX is higher than in patients treated with placebo (LOE: borderline).

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).

Reported injection site reaction rates are listed below. 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. 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.

- 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%

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

Reference	Design	Agent	Condition	Type of Reaction	Crude Incidence or Range
Saad 08	Meta-analysis	IFX	PsA	Infusion	7.4% (16 weeks)
Alonso-Ruiz 08	Meta-analysis	IFX	RA	Infusion	17.9% (46 weeks)
Gottlieb 04	RCT	IFX	Psoriasis	Infusion	18% to 22% (30 weeks)
Thaler 09	Meta-analysis	ADA	RA	Injection	17.5% (95% CI 7.1 to 27.9) (24 to 36 weeks)
Saad 08	Meta-analysis	ADA	PsA	Injection	5.2% (24 weeks)
Thaler 09	Meta-analysis	ETN	RA	Injection	22.4% (95% CI 8.5 to 36.3) (24 to 36 weeks)
Saad 08	Meta-analysis	ETN	PsA	Injection	32% (12 to 48 weeks)
Smolen09, Keystone 08a, Fleishman 09	RCTs	CZP	RA	Injection	1.6% to 4.5% (24 to 52 weeks)
Keystone 10, Kavanaugh 09	RCTs	GLM	Psoriasis and PsA	Injection	5% to 20% (52 weeks)
Leonardi 08, Papp 08, Krueger 07, Griffiths 10	RCTs	UST	Psoriasis	Injection	<1% to 24.8% (36 to 76 weeks)

SUMMARY AND 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 the agents of interest 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, differing half-lives of agents, loss to follow-up and unblinded or biased assessments. It is possible that only observational studies of sufficient size and 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 various 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.

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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.
JIA	Juvenile idiopathic arthritis
LOE	Level of evidence
LRA	Long-standing RA

Abbreviation	Definition
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)