

The Comparative Efficacy and Safety of Biologics for the Treatment of Rheumatoid Arthritis: A Systematic Review and Metaanalysis

GERALD GARTLEHNER, RICHARD A. HANSEN, BETH L. JONAS, PATRICIA THIEDA, and KATHLEEN N. LOHR

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)

Key Indexing Terms:

RHEUMATOID ARTHRITIS
SYSTEMATIC REVIEW

BIOLOGICS

TARGETED IMMUNE MODULATORS
METAANALYSIS

Over the past decade, the treatment of rheumatoid arthritis (RA) has changed considerably with the advent of biologic agents such as abatacept, adalimumab, anakinra, etanercept, infliximab, and rituximab. Traditional disease modifying

antirheumatic drugs (DMARD), in particular methotrexate (MTX), are still the cornerstone of most RA treatment regimens. However, toxicity may limit their use, and many patients do not respond adequately to traditional DMARD therapy. Thus, in patients with persistent disease despite aggressive management with oral agents, biologics, often in combination with MTX, are now considered the standard of care.

Biologics work by selectively blocking the effects of cytokines. For example, tumor necrosis factor (TNF) inhibitors, e.g., adalimumab, etanercept, infliximab, produce their primary effect by blocking the interaction of TNF- α with cell-surface receptors. Anakinra blocks interleukin 1 (IL-1), another naturally occurring cytokine. Abatacept inhibits T lymphocyte activation by binding to CD80 and CD86, thereby blocking interactions with CD28. Rituximab binds specifically to the antigen CD20, resulting in the depletion of B cells. All these actions greatly reduce various inflammatory and immunological responses.

Biologics differ considerably in dosing regimens and routes of administration. Abatacept, infliximab, and rituximab require intravenous administration. Abatacept infusions are

From the Cecil G. Sheps Center for Health Services; School of Pharmacy, Division of Pharmaceutical Policy and Evaluative Sciences; School of Medicine, Thurston Arthritis Research Center; and School of Public Health, Health Policy and Administration, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA.

Funding for this research was provided to the Cecil G. Sheps Center for Health Services Research through a subcontract with the Center for Evidence-Based Policy, Oregon Health & Science University. Dr. Hansen is supported by grant K12 RR023248.

G. Gartlehner, MD, MPH, Cecil G. Sheps Center for Health Services Research; R.A. Hansen, PhD, RPh, School of Pharmacy, Division of Pharmaceutical Policy and Evaluative Sciences; B.L. Jonas, MD, School of Medicine, Thurston Arthritis Research Center; P. Thieda, MA, Cecil G. Sheps Center for Health Services Research; K.N. Lohr, PhD, School of Public Health, Health Policy and Administration.

Address reprint requests to Dr. G. Gartlehner, Cecil G. Sheps Center for Health Services, University of North Carolina at Chapel Hill—Research, 725 Martin Luther King Jr Blvd., Chapel Hill, NC 27599.

E-mail: gartlehner@schsr.unc.edu

Accepted for publication July 28, 2006.

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2006. All rights reserved.

repeated at 2 and 4 weeks and then every 4 weeks thereafter, and infliximab infusions are repeated every 4 to 8 weeks, while rituximab is given at weekly intervals for a course of 4 to 8 weeks; adalimumab, anakinra, and etanercept can be administered subcutaneously by the patient. Administration intervals also differ substantially: adalimumab is administered once every other week, etanercept once a week, and anakinra daily. Table 1 summarizes biologics currently approved for the treatment of RA in the United States, including trade names, manufacturers, routes of administration, therapeutic mechanisms of action, and approved (labeled) uses.

To date, no head-to-head, double-blinded randomized controlled trials (RCT) comparing one biologic to another have been published. Five metaanalyses of RCT provide good evidence about the general efficacy of anti-TNF drugs and anakinra for treating patients with RA¹⁻⁵. Only one systematic review conducted indirect comparisons of anti-TNF drugs, but this study included only 4 RCT⁶. None of these metaanalyses included observational studies to document adverse events. In the case of biologics, RCT are compromised by small sample sizes and limited study durations to determine reliably rare but potentially fatal adverse events such as serious infections, lymphoma, autoimmunity, heart failure, or hepatotoxicity. Thus, they cannot reliably assess the risk-benefit profiles of biologics for this condition.

Our objective was to systematically review the comparative efficacy and safety of biologic agents for the treatment of RA in patients who have failed to respond to traditional DMARD therapy. To our knowledge, this is the first systematic review to combine the evidence of RCT and observational studies to determine the comparative risk-benefit profiles of biologic agents. This study is part of a larger systematic

review of biologics conducted for the Drug Effectiveness Review Project⁷.

MATERIALS AND METHODS

Literature search. To identify relevant articles we searched Medline®, Embase, The Cochrane Library, and the International Pharmaceutical Abstracts from 1980 to 2006 (up to May 2006); we used either Medical Subject Headings (MeSH) as search terms when available or key words when appropriate. We combined terms for RA [“arthritis” (MeSH), “arthritis, rheumatoid” (MeSH)] and adverse events (“adverse events,” “harms,” “drug reactions,” “toxicity”) with a list of 4 specific biologics and their trade names (“abatacept,” “adalimumab,” “anakinra,” “etanercept,” “infliximab,” “rituximab,” or their respective trade names) from manually searched reference lists of pertinent review articles and letters to the editor. In addition, we explored the Center for Drug Evaluation and Research (CDER) database to identify unpublished research submitted to the US Food and Drug Administration (FDA). Pharmaceutical manufacturers were invited to submit dossiers, including citations, as outlined by the Drug Effectiveness Review Project⁸.

Study selection. Two persons independently reviewed abstracts and full-text articles. Records were considered for exclusion if they did not meet pre-established eligibility criteria for study design or duration, patient population, interventions, outcomes, and comparisons to medications outside our scope of interest. The outcome of interest was clinical improvement as measured on a variety of scales. These included the Disease Activity Score (DAS-28), criteria from the American College of Rheumatology (ACR 20; ACR 50; ACR 70; Paulus criteria), radiographic progression, functional capacity, and quality of life. We included controlled trials lasting at least 12 weeks to determine comparative efficacy. For adverse events we included both experimental and observational studies. We limited observational studies to those with large sample sizes (> 100 patients) that lasted at least 3 months and reported an included outcome. We designed and used a structured data abstraction form to ensure consistency in appraisal for each study.

Data abstraction and quality assessment. Trained reviewers abstracted data from each study and assigned an initial quality rating. We assessed the internal validity (quality) of trials based on predefined criteria developed by the US Preventive Services Task Force (ratings: good, fair, poor)⁹ and the National Health Service Center for Reviews and Dissemination¹⁰. We also

Table 1. Biologic agents approved for the treatment of RA.

Generic Name	US Trade Name	Manufacturer	Route and Dosing	Half-life	Onset of Action	Mechanism of Action
Abatacept	Orencia®	Bristol-Myers Squibb	Intravenous: 500 mg to 1000 mg dosed by weight; repeat at 2 and 4 weeks and then every 4 weeks thereafter	8-25 days	≥ 15 days	Cytotoxic T lymphocyte antigen immunoglobulin (CTLA-4Ig)
Adalimumab	Humira®	Abbott	Subcutaneous: 40 mg every other week as subcutaneous injection; may increase to 40 mg per week	10-18 days	1-14 days	TNF inhibitor
Anakinra	Kineret®	Amgen	Subcutaneous: 100 mg daily as subcutaneous injection; dose should be decreased to 100 mg every other day in renal insufficiency	7-8 hours	7-21 days	IL-1 receptor antagonist
Etanercept	Enbrel®	Amgen Wyeth	Subcutaneous: 50 mg per week given as 1 or 2 subcutaneous injections	4.8 days	1-28 days	TNF inhibitor
Infliximab	Remicade®	Immunex Centocor	Intravenous: 3 mg/kg infusion at 0, 2, and 6 weeks followed by maintenance every 8 weeks thereafter; may increase to maximum of 10 mg/kg every 4 weeks	9.8 days	7-14 days	TNF inhibitor
Rituximab	Rituxan®	Biogen Idec and Genentech	Intravenous: 375 mg/m ² infusion once weekly for 4 to 8 weeks	3-4 days	21-288 days	Anti-CD-20a

assessed external validity (generalizability), but this did not influence quality ratings.

Data synthesis. Because only limited head-to-head evidence on biologics was available, we conducted adjusted indirect comparisons of placebo-controlled trials (employing the method proposed by Bucher, *et al*¹¹ and metaregression). Evidence suggests that indirect comparisons agree with head-to-head trials if component studies are similar and if treatment effects are expected to be consistent across patients in different trials¹².

Using random effects models, we calculated the pooled relative risks of achieving an ACR 20 or ACR 50 response for each biologic relative to placebo. ACR responses are defined as improvements on the 20%, 50%, or 70% level in counts of tender or swollen joints, pain score, patients' and physicians' global activity score, Health Assessment Questionnaire-Disability Index (HAQ-DI), and erythrocyte sedimentation rate¹³. For one study¹⁴, we assumed that Paulus criteria¹⁵ are comparable to ACR criteria. To reduce potential heterogeneity, we limited these analyses to populations that had remained symptomatic despite MTX treatment (i.e., we excluded MTX-naïve populations). Further, we limited included data to FDA approved dosage ranges to achieve better equivalency across drugs. Data were insufficient to conduct quantitative analyses on any other outcomes than ACR 20 and ACR 50.

For each metaanalysis we assessed heterogeneity using the I^2 statistic. We explored heterogeneity with metaregression. We assessed publication bias using funnel plots and Kendall's tests. Given the small number of component studies, results of these tests must be viewed cautiously. All statistical analyses were conducted using StatsDirect, version 2.3.8, and Stata 9.1.

Role of funding source. The funding source had no role in the study design, data collection, data analysis, data interpretation, or writing of this report. The corresponding author (GG) had full access to all data in the study and had final responsibility for the decision to submit for publication.

RESULTS

We identified 1419 citations from searches and reviews of reference lists. Figure 1 depicts the results of the literature search, showing disposition of articles and individual exclusion criteria. Overall, we included 26 controlled studies for efficacy and 18 additional studies of both experimental and observational designs for adverse events assessment. No RCT was a head-to-head trial. Efficacy studies were conducted in narrowly defined populations often limited to less than 1 year of followup. The mean age of study participants was 53.4 years; the majority was female (76.3%) and Caucasian (88.5%). All efficacy studies, except a nonrandomized trial¹⁶, were funded by the pharmaceutical industry.

Head-to-head evidence. The only evidence directly comparing 2 biologic agents was a nonrandomized, open-label trial from Europe that assessed the longterm (2 years) effectiveness and safety of etanercept, infliximab, and the DMARD leflunomide¹⁶. This study can be characterized as an effectiveness trial, with high generalizability of results. Etanercept had significantly greater response rates than infliximab at 3 months ($p < 0.02$; data not shown) and 6 months ($p < 0.05$; data not shown); no differences existed after 1 year. Otherwise, no evidence directly comparing the efficacy and safety of one biologic to another could be found.

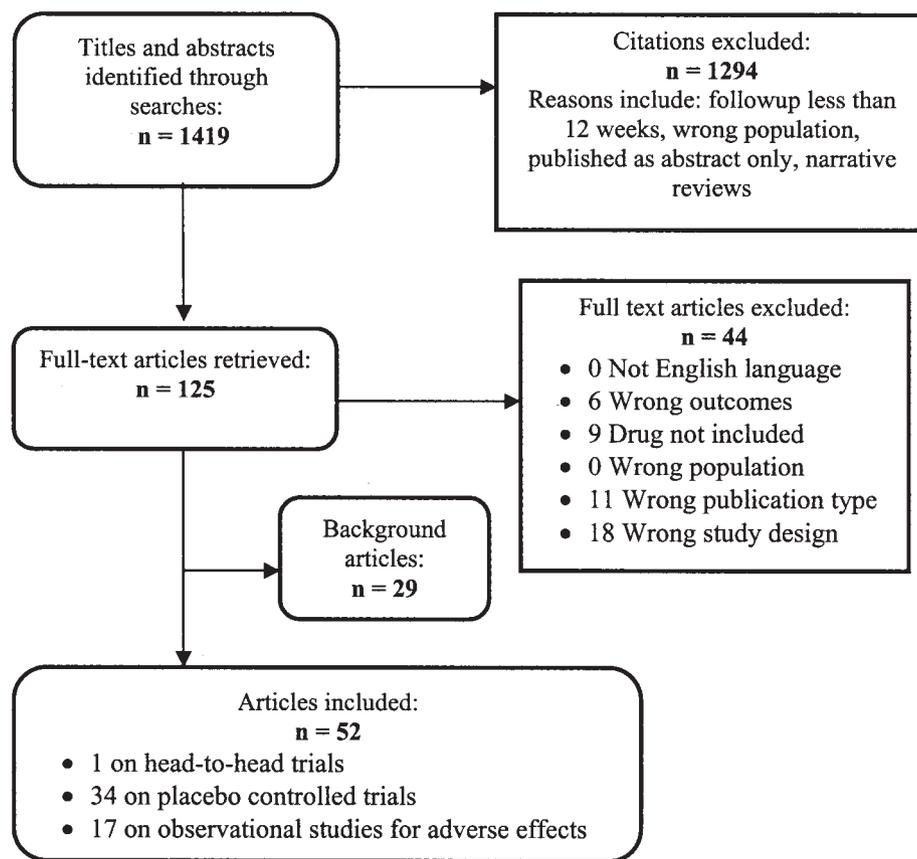


Figure 1. Results of the literature search and disposition of the articles. Numbers here differ from numbers of included studies because a single study can lead to multiple publications.

Indirect comparisons. Given the paucity of direct head-to-head evidence, we conducted indirect comparisons of randomized placebo-controlled trials. As stated above, we limited analyses to MTX-resistant populations. We pooled data from 5 studies on adalimumab (n = 2354), 5 on etanercept (n = 1151), 4 on infliximab (n = 704), and 3 on anakinra (n = 1039). Table 2 summarizes characteristics of these studies; Table 3 presents studies not included. Data were insufficient to conduct indirect comparisons on abatacept and rituximab.

Overall, results of indirect comparisons indicate that efficacy does not differ substantially among anti-TNF drugs (adalimumab, etanercept, and infliximab). Table 4 presents relative risks for improvements on ACR 20 and ACR 50 measures. Given the wide confidence intervals we cannot exclude clinically significant differences with certainty.

Point estimates of comparative ACR 20 and ACR 50 responses consistently favor adalimumab, etanercept, and infliximab over anakinra. With 2 exceptions, however, differences did not reach statistical significance. Indirect comparisons of infliximab and of anti-TNF drugs as a class compared to anakinra yielded a statistically significantly greater efficacy on ACR 20 [relative risk 0.58 (95% CI 0.38–0.90) and RR 0.61 (95% CI 0.39–0.96), respectively], but not ACR 50.

Figures 2A and 2B depict ACR 20 and ACR 50 comparisons of anakinra with anti-TNF drugs as a class and individually. Sensitivity analyses (based on different study durations, concomitant MTX treatment, and disease durations) did not change the overall conclusions.

Few studies assessed longterm radiographic outcomes^{18,22,38,47,48}. In general, the rate of radiographic progression (e.g., Sharp score, joint erosions, joint space narrowing) was significantly lower in patients treated with biologics than in placebo-treated patients, regardless of concomitant DMARD therapy. Similarly, quality of life improved significantly for patients treated with biologics. Reported data for radiographic outcomes and quality of life, however, were insufficient for indirect comparisons.

Adverse events

Most studies that examined the efficacy of biologics also determined how well patients tolerated them. Some RCT had an open-label extension phase of up to 2 years^{36,49}, but their methods of adverse event assessment differed greatly. Few studies used objective scales such as the adverse reaction terminology from the World Health Organization (WHO). Most trials combined patient-reported adverse events with a regular

Table 2. Characteristics and effect sizes of studies included for adjusted indirect comparisons of efficacy.

Study	N	Study Duration, wks	Drug	MTX	Mean Disease Duration, yrs	Radiographic Outcomes (biologic vs placebo)	ACR Response (%) of FDA Approved Doses Compared to Placebo			Quality Rating
							ACR 20	ACR 50	ACR 70	
Furst 2003 ¹⁷	636	24	ADA	Yes	10.5	NR	53 vs 35	29 vs 11	15 vs 3	Fair
Keystone 2004 ¹⁸	619	52	ADA	Yes	11.0	Mean Sharp Score 0.45 vs 2.70	57 vs 24	40 vs 10	22 vs 5	Fair
Van de Putte 2003 ¹⁹	284	12	ADA	No	10.0	NR	50 vs 10	24 vs 1	11 vs 0	Fair
Van de Putte 2004 ²⁰	544	26	ADA	No	11.0	NR	43 vs 19	21 vs 8	11 vs 2	Fair
Weinblatt 2003 ²¹	271	24	ADA	Yes	12.0	NR	67 vs 15	55 vs 8	27 vs 5	Fair
Klareskog 2004 ²²	682	52	ETA	Yes	6.5	Mean Sharp Score -0.54 vs 2.80	85 vs 75	69 vs 43	40 vs 17	Good
Lan 2004 ²³	58	12	ETA	Yes	NR	NR	90 vs 34	66 vs 10	24 vs 0	Fair
Moreland 1999 ^{24,25}	234	12	ETA	No	12	NR	59 vs 11	40 vs 5	15 vs 1	Fair
Moreland 1997 ²⁶	180*	12	ETA	No	NR	NR	75 vs 14	57 vs 7	NR	Fair
Weinblatt 1999 ²⁷	89	24	ETA	Yes	13	NR	71 vs 27	39 vs 3	15 vs 0	Fair
Abe 2006 ²⁸	147	14	INF	Yes	7.9	NR	57 vs 23	33 vs 4	13 vs 0	Fair
Kavanaugh 2000 ²⁹	28*	12	INF	Yes	6.2	NR	50 vs 14	21 vs 14	NR	Fair
Maini 1999 ^{30,31}	428	30	INF	Yes	8.4	NR	52 vs 17	33 vs 8	18 vs 2	Fair
Maini 1998 ¹⁴	101*	26	INF	Yes	10.0	NR	52 vs 7	47 vs 4	NR	Fair
Bresnihan 1998 ³²	472*	24	ANA	No	3.9	NR	38 vs 27	15 vs 8	1 vs 1	Fair
Cohen 2002 ³³	419	24	ANA	Yes	7.1	NR	42 vs 15	19 vs 3	7 vs 0	Fair
Cohen 2004 ³⁴	501	24	ANA	Yes	10.5	NR	38 vs 22	17 vs 8	6 vs 2	Fair

* We included only results of FDA-approved dosing ranges. ADA: adalimumab, INF: infliximab, ANA: anakinra, MTX: methotrexate, ETA: etanercept. NR: not reported.

Table 3. Trials excluded from adjusted indirect comparisons.

	Drug	Reason for Exclusion
Bathon 2000 ³⁵⁻³⁷	ETA	No placebo comparison; MTX-naive population
Breedveld 2006 ³⁸	ADA	MTX-naive population
Elliot 1994 ³⁹	INF	Study duration too short (4 weeks)
Edwards 2004 ⁴⁰	RIT	Insufficient data
Emery 2006 ⁴¹	RIT	Insufficient data
Geborek 2002 ¹⁶	INF vs ETA vs Leflunomide	Nonrandomized, open-label trial
Genovese 2004 ⁴²	ETA, ANA	Combination therapy
Genovese 2005 ⁴³	ABA	Anti-TNF treatment-refractory population
Keystone 2004 ⁴⁴	ETA	Study duration too short (8 weeks)
Kremer 2003 ⁴⁵	ABA	Insufficient data
Moreland 2002 ⁴⁶	ABA	Insufficient data
St. Clair 2004 ⁴⁷	INF	MTX-naive population

ANA: anakinra, MTX: methotrexate, ABA: abatacept, RIT: rituximab, ETA: etanercept, INF: infliximab.

Table 4. Adjusted indirect comparisons of biologics for treatment of RA.

Comparison	Relative Risk (95% CI)
ACR 20 Response	
Adalimumab vs etanercept	0.90 (0.33–2.43)
Adalimumab vs infliximab	0.90 (0.53–1.53)
Etanercept vs infliximab	1.00 (0.38–2.66)
Anakinra vs adalimumab	0.67 (0.41–1.08)
Anakinra vs etanercept	0.60 (0.23–1.55)
Anakinra vs infliximab	0.58 (0.38–0.90)
ACR 50 Response	
Adalimumab vs etanercept	0.68 (0.20–2.30)
Adalimumab vs infliximab	0.93 (0.46–1.89)
Etanercept vs infliximab	1.39 (0.39–4.93)
Anakinra vs adalimumab	0.61 (0.32–1.17)
Anakinra vs etanercept	0.42 (0.12–1.44)
Anakinra vs infliximab	0.58 (0.28–1.20)

clinical examination by an investigator. Determining whether assessment methods were unbiased and adequate was often difficult. Adverse events were rarely prespecified and defined. Only 2 RCT were designed to assess adverse events as primary outcomes^{17,50-52}.

In addition to efficacy trials, we included 18 studies of both experimental and observational designs for adverse event assessment (Table 5). Many observational studies derived findings from the MedWatch adverse events reporting system of the FDA. It relies on voluntary reporting of adverse events, and underreporting is likely⁵³. In addition, an adequate denominator to draw inferences about causation and the comparative risks of any drugs is lacking. Because data were insufficient to pool, we summarized the evidence qualitatively.

General tolerability. Overall, in efficacy trials, biologics

appeared to have a good tolerability profile; rare but serious adverse events such as infections, lymphoma, or neutropenia were of concern but could not be assessed reliably in trials^{50-52,56,70,71}. Discontinuation rates because of adverse events in patients treated with biologics ranged from 3% to 16%, and generally did not differ significantly from those in patients treated with placebo. Table 6 summarizes the adverse events most commonly reported in clinical trials.

The only head-to-head efficacy study¹⁶ also assessed differences in tolerability and safety between etanercept and infliximab, using the WHO adverse reaction terminology. Overall, etanercept and infliximab did not differ significantly in adverse events reported.

Injection site reactions (adalimumab, etanercept, anakinra) and infusion reactions (abatacept, infliximab, rituximab) were the most commonly and consistently reported adverse events. Injection site reactions were mainly erythema, pruritus, rash, and pain of mild to moderate severity. Nevertheless, these reactions were the most common reason for discontinuation attributable to adverse events. The mean, crude incidence of injection site reactions in RCT reviewed for this study was 19.0% (95% CI 9.2–28.8) for adalimumab, 25.0% (95% CI 11.2–38.1) for etanercept, and 55.8% (95% CI 4.9–100) for anakinra. The higher incidence of injection site reactions for anakinra than for adalimumab and etanercept is consistent with data reported in the respective package inserts⁷²⁻⁷⁴.

Some infusion reactions appeared to be more serious than injection site reactions. In clinical trials of infliximab, 17% of patients experienced infusion reactions consisting of mostly nonspecific symptoms such as headache, dizziness, nausea, pruritus, chills, or fever⁵⁶. However, 0.5% of patients had severe acute reactions that resembled acute anaphylactic conditions or led to convulsions⁵⁶. In the open-label effectiveness study, 3.7% of patients treated with infliximab had a severe infusion reaction¹⁶; in a case series of 165 consecutive patients receiving infliximab this number was 1.0%⁵⁴. Nevertheless, less than 2% of patients in clinical trials discontinued because of infusion reactions.

The rituximab studies reported infusion reactions in 35% to 45% of patients^{40,41}; glucocorticoid premedication reduced this rate to 24%⁴¹. Infusion reactions in abatacept studies ranged from 5%⁴³ to 29%⁴⁶.

Specific adverse events. Serious infections. In efficacy trials, the incidence of serious infections was consistently higher in biologic- than in placebo-treated patients. However, clinically significant differences rarely reached statistical significance. For example, in a large safety RCT (n = 1414), a trend toward an increased risk of serious infections in anakinra-treated patients was apparent during the 6 months of treatment (2.1% anakinra vs 0.4% placebo; p = 0.068), but was not statistically significant⁵⁰⁻⁵². A recent metaanalysis, pooling data of adalimumab and infliximab RCT, reported a 2-fold increase of serious infections (i.e., infections that required antimicrobial therapy and/or hospitalization) among patients treated with

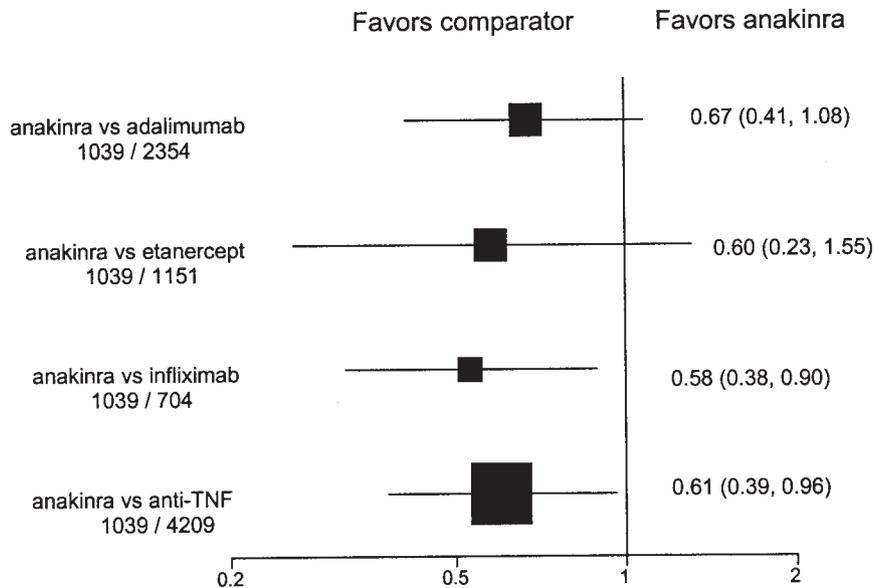


Figure 2A. Adjusted indirect comparisons of anakinra with anti-TNF drugs for the treatment of RA: ACR 20.

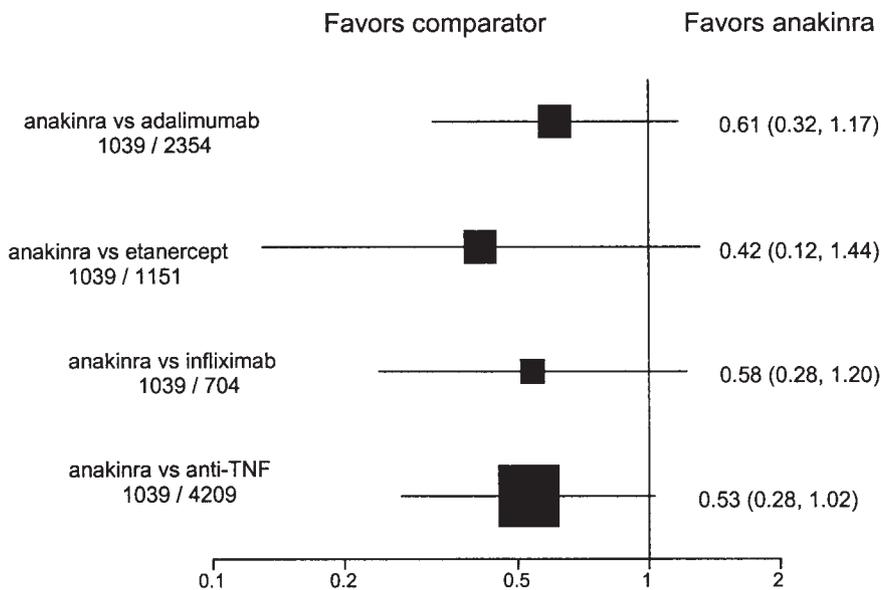


Figure 2B. Adjusted indirect comparisons of anakinra with anti-TNF drugs for the treatment of RA: ACR 50.

anti-TNF drugs compared with those taking placebo (OR 2.0, 95% CI 1.3–3.1)⁷⁵.

Longterm observational studies limited to assessments of infliximab and etanercept^{56,70,76} support these findings. The most common serious infection was tuberculosis⁵⁹. A safety analysis of a Spanish registry of RA patients reported a more than 50 times greater risk of tuberculosis (RR 53.0, 95% CI 34.5–89.0) for RA patients treated with infliximab than for RA patients who did not receive anti-TNF drugs⁵⁸.

Several observational studies indicate that infliximab might lead to a higher risk of tuberculosis or other granulomatous infections, and may lead to a faster outbreak of tuberculosis than etanercept^{57,59-63}. In one study, the median interval from start of infliximab therapy to diagnosis of tuberculosis was 3 months⁵⁹. By contrast, a different analysis of safety data, published in abstract form only, concerning etanercept and tuberculosis reported a median time of 11.5 months from start of etanercept therapy to diagnosis of tuberculosis⁷⁷.

Table 5. Characteristics of studies included for adverse events assessment.

Study	Study Design	N	Duration	Drug	Population	Quality Rating
General Tolerability						
Cheifetz 2003 ⁵⁴	Case series	165	NR	INF	Patients treated with INF	Fair
Fleischmann 2003 ⁵⁰⁻⁵²	RCT	1,414	6 mo	AKA	Patients with RA	Fair
Maini 2004 ⁵⁵	Open-label extension of RCT	259	2 yrs	INF	Patients with RA	Fair
Nuki 2002 ⁴⁹	Uncontrolled extension of RCT	309	76 wks	ANA	Patients with RA	Fair
Schaible 2000 ⁵⁶	Retrospective data analysis of clinical trials	913	12 wks-3 yrs	INF	Patients with CD or RA	NA
Serious Infections						
Bergstrom 2004 ⁵⁷	Retrospective cohort study: coccidioidomycosis	985	NR	INF, ETA	Patients with inflammatory arthritis	Fair
Gomez-Reino 2003 ⁵⁸	D-base analysis BIOBADASER: Tuberculosis	3118	Any duration	INF, ETA	Patients treated with INF or ETA	NA
Keane 2001 ⁵⁹	D-base analysis AERS: Tuberculosis	70 cases	NA	INF	Patients treated with INF	NA
Lee 2002 ⁶⁰	D-base analysis AERS: Immune deficiencies	10 cases	NA	INF, ETA	Patients treated with INF or ETA	NA
Slifman 2003 ⁶¹	D-base analysis AERS: Listeria monocytogenes	15 cases	NA	INF, ETA	Patients treated with INF or ETA	NA
Wallis 2004 ⁶²	D-base analysis Granulomatous infections	622 cases	NA	INF, ETA	Patients treated with INF or ETA	NA
Wolfe 2004 ⁶³	Prospective cohort study	15,940	3 yrs	INF	Patients treated with INF	Fair
Lymphoma and Other Malignancies						
Brown 2002 ⁶⁴	D-base analysis AERS: Lymphoma	26 cases	NA	INF, ETA	Patients with RA or CD	NA
Lebwohl 2005 ⁶⁵	D-base review: Squamous cell carcinoma	4 cases /1,442	3.7 yrs	ETA	Patients with RA	NA
Wolfe 2004 ⁶⁶	Prospective cohort study	18,572	Up to 3 yrs	INF, ETA	Patients with RA	Good
Congestive Heart Failure						
Chung 2003 ⁶⁷	RCT	150	28 wks	INF	Patients with CHF	Fair
Kwon 2003 ⁶⁸	D-base review AERS: Heart failure	47 cases	NA	ETA, INF	Patients on ETA or INF therapy	NA
Other Adverse Events						
Mohan 2001 ⁶⁹	D-base analysis AERS: Demyelination	19 cases	NA	Anti-TNF	Patients with inflammatory arthritis	NA

AERS: Adverse Events Reporting System, AKA: anakinra, D-base: database, ETA: etanercept, INF: infliximab, NA: not applicable, NR: not reported, RA: rheumatoid arthritis, RCT: randomized controlled trial, TNF: tumor necrosis factor, RCT: randomized controlled trial, CD: Crohn's disease.

Table 6. Weighted mean incidence (percentage) of reported specific adverse events across trials. Data are mean (95% confidence interval).

Drug	Diarrhea	Headache	Injection Site	Nausea	Rhinitis	URTI
Abatacept	6.91 (2.18-11.64)	11.79 (8.58-15.00)	NA	7.94 (2.38-13.50)	NR	8.98 (0-19.48)
Adalimumab	8.16 (4.44-11.88)	18.23 (6.51-29.95)	18.98 (9.21-28.76)	8.84 (5.55-12.13)	14.8 (7.26-22.35)	17.05 (9.5-24.59)
Anakinra	NR	NR	55.83 (4.91-100)	NR	NR	NR
Etanercept	18.14 (3.45-32.84)	17.54 (1.9-33.18)	24.67 (11.21-38.13)	20.86 (2.65-39.08)	18.42 (6.97-35.71)	20.89 (6.97-34.82)
Infliximab	9.31 (7.94-10.68)	17.7 (3.03-33.36)	NA	NR	7.77 (0-18.12)	24.05 (0-49.81)
Rituximab*	4.11	11.08	NA	8.54	NR	6.96

* Data limited to one trial. NA: not applicable, NR: not reported, URTI: upper respiratory tract infection.

Some of these findings, however, were derived from the MedWatch spontaneous reporting system of the FDA and must be interpreted cautiously. Nevertheless, the higher incidence of granulomatous infections in infliximab-treated patients is consistent across multiple studies.

Lymphoma. The risk of both Hodgkin's disease and non-

Hodgkin's lymphoma is generally increased in patients with RA⁷⁸. Data from controlled trials do not provide sufficient evidence concerning the comparative risk attributable to either biologics or a combination of biologics and MTX.

A large prospective cohort study followed 18,572 patients with RA registered in the National Data Bank for Rheumatic

Diseases for up to 3 years⁶⁶. Lymphomas were more common in patients undergoing anti-TNF therapies, but confidence intervals for treatment groups overlapped. MedWatch identified 26 reported cases of lymphoproliferative disorders in patients treated with infliximab or etanercept for Crohn's disease or RA as of 2002⁶⁴. In some cases, lymphoma developed shortly after starting therapy; regression occurred in 2 patients after discontinuing therapy.

A recent metaanalysis pooled data on malignancy rates in efficacy trials of adalimumab and infliximab. The results presented a more than 3-fold increase of malignancies in patients treated with adalimumab or infliximab compared to those receiving placebo (OR 3.3, 95% CI 1.2–9.1)⁷⁵.

Existing evidence is insufficient to draw conclusions about an increased risk of specific malignancies other than lymphoma for patients receiving biologics. A clinical trial database review did not detect an increased incidence of squamous cell carcinoma in 1442 RA patients (4257 patient-years) treated with etanercept (crude rate 2.8 cases per 1000 patients)⁶⁵. However, the median followup time was only 3.7 years.

Congestive heart failure. A MedWatch analysis reported that half the patients who developed new-onset congestive heart failure (CHF) under etanercept or infliximab treatment had no identifiable risk factors⁶⁸. No direct evidence on the comparative risk of CHF exists. Indirect evidence comes from 3 trials, 2 on etanercept⁷⁹ and one on infliximab⁶⁷, that evaluated the efficacy of these drugs for the treatment of CHF. Study populations had no rheumatic diseases. At least one etanercept study presented an increased risk of worsening heart failure. Similarly, the infliximab study presented higher mortality rates in the 10 mg/kg arm than in the placebo and 5 mg/kg arms⁶⁷. The infliximab package insert contains contraindication for use in patients with CHF; the package inserts for etanercept and adalimumab emphasize caution.

Other adverse events. Evidence from randomized trials and observational studies is insufficient to draw conclusions regarding the risk of rare but serious adverse events such as demyelination, autoimmunity, neutropenia, and hepatotoxicity. A case series based on MedWatch data indicated that infliximab and etanercept might be associated with demyelination⁶⁹. Similar cases have been seen in regulatory trials of adalimumab⁷³. All neurologic events were partially or completely resolved after discontinuation of treatment.

Controlled trials and observational studies have not confirmed reports of autoimmunity. However, case reports suggest an association between infliximab and drug-induced lupus erythematosus and other autoimmune diseases^{56,70,80}. The infliximab package insert reports that 34% of patients treated with infliximab and MTX experienced transient elevations of liver function measures⁸¹. Severe liver injury, including acute liver failure, has been reported⁸¹. Hepatotoxicity has not been reported for other biologics.

DISCUSSION

In this systematic review, we combined clinical trial data of 17 placebo-controlled studies including 5248 patients with MTX-resistant RA. Indirect comparisons indicate that no substantial differences in efficacy exist among anti-TNF drugs. These findings are consistent with a nonrandomized, open-label effectiveness trial comparing etanercept to infliximab, the only direct evidence to date. Further, an earlier metaanalysis based on 4 trials reached a similar conclusion⁸².

By contrast, results also indicate that anakinra is less efficacious than anti-TNF drugs. Although most comparisons do not reach statistical significance because of wide confidence intervals, a trend favoring anti-TNF drugs over anakinra is obvious. In addition, this finding is largely consistent with a metaanalysis and adjusted indirect comparisons conducted by the UK Health Technology Assessment Programme⁸³, which found anakinra to be less efficacious than anti-TNF drugs as a class (limited to infliximab and etanercept).

Data were insufficient to conduct indirect comparisons on abatacept and rituximab.

An important challenge for our systematic review was the lack of longterm studies with the methodological strength to assess rare but severe adverse events. Currently, no conclusions can be drawn regarding the comparative safety of biologics, although observational evidence indicates that some differences might exist. Biologics do not appear to differ substantially in short-term tolerability and safety. Differences in tolerability exist primarily with respect to adverse events caused by the route of administration. Anakinra has a substantially higher rate of injection site reactions than anti-TNF drugs. Abatacept, infliximab, and rituximab carry the risk of severe infusion reactions that cannot occur in drugs administered subcutaneously. Observational studies indicate possible differences among biologics with respect to serious infections, hepatotoxicity, or chronic heart failure. However, the evidence is weak and must be interpreted cautiously.

Our study has several limitations. First, indirect comparisons have methodological drawbacks and do not possess the validity of direct head-to-head trials. Further, because indirect comparisons are low in power, confidence intervals for all comparisons are wide and encompass differences that would be clinically significant. Although results of our adjusted indirect comparisons can be viewed as the best available comparative evidence, inferences must be drawn cautiously. Because of the methodological limitations, we did not attempt to calculate numbers needed to treat to illustrate differences in effect sizes.

Second, owing to limitations in reported data, we had to constrain our analyses to ACR 20 and ACR 50 response rates. Physicians need to keep in mind that, despite a clinical response, joint damage might progress. Radiographic and other measures of joint destruction and functional capacity would be necessary to assess the comparative efficacy on disease progression. Because biologics are relatively new agents,

longterm, controlled studies are generally lacking — a fact that also severely limits the comparative safety assessment. Existing data on rare but severe adverse events stem mainly from voluntary adverse event reporting systems, which cannot assess causation or the comparative safety of drugs. This lack of sufficient data severely compromises any assessment of the risk-benefit profile of biologic agents.

Third, most included efficacy trials were conducted in highly selected populations. Further, we limited our analyses to patients who failed traditional DMARD treatment. Therefore, our results may have limited generalizability and cannot be extrapolated to DMARD-naive patients with early disease.

Decisions about the choice of a biologic for the treatment of RA include not only efficacy and safety but also dosing regimens, routes of administration, comorbidities, costs, and insurance coverage. Given similar efficacy among anti-TNF drugs, such factors can guide clinical decisions.

An important contribution of any systematic review is its ability to highlight gaps in the scientific evidence. In the case of biologics, the lack of head-to-head and controlled longterm studies significantly limits our knowledge about their comparative risk-benefit profiles. When high quality evidence is missing, “weaker” evidence such as case reports should be taken into consideration. Future research must clarify the remaining questions and clearly address the longterm safety issues of biologics.

ACKNOWLEDGMENT

We thank Timothy Carey, MD, MPH, and Marian McDonagh, PharmD, for insightful comments on earlier versions of this report. Many thanks also to Laura Morgan for help with database management and word processing.

REFERENCES

1. 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;6:1-110.
2. Blumenauer B, Burls A, Cranney A, et al. Infliximab for the treatment of rheumatoid arthritis. *The Cochrane Database of Systematic Reviews* 2002: CD003785.
3. Blumenauer B, Judd M, Cranney A, et al. Etanercept for the treatment of rheumatoid arthritis. *Cochrane Database Syst Rev* 2003:CD004525.
4. 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;8:iii-iv, ix-x, 1-105.
5. Navarro-Sarabia F, Ariza-Ariza R, Hernandez-Cruz B, Villanueva I. Adalimumab for treating rheumatoid arthritis. *The Cochrane Database of Systematic Reviews* 2005:CD005113.
6. 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;60 Suppl 3:iii51-4.
7. Gartlehner G, Hansen RA, Thieda P, Jonas B, Lohr KN, Carey T. Drug class review on targeted immune modulators. *Drug Effectiveness Review Project* 2005. Internet. Available from: www.ohsu.edu/drugeffectiveness/reports. Accessed Oct 10, 2006.
8. Fox DM. Evidence of evidence-based health policy: the politics of systematic reviews in coverage decisions. *Health Aff Millwood* 2005;24:114-22.
9. Harris RP, Helfand M, Woolf SH, et al. Current methods of the US Preventive Services Task Force: a review of the process. *Am J Prev Med* 2001;20 Suppl:21-35.
10. Anonymous. Undertaking systematic reviews of research on effectiveness: CRD’s guidance for those carrying out or commissioning reviews. *CRD Report Number 4*; 2nd ed. York, UK: NHS Centre for Reviews and Dissemination, University of York; 2001. [Internet. Accessed September 8, 2006.] Available from: <http://www.york.ac.uk/inst/crd/report4.htm>.
11. Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. *J Clin Epidemiol* 1997;50:683-91.
12. Glenny AM, Altman DG, Song F, et al. Indirect comparisons of competing interventions. *Health Technol Assess* 2005;9:1-148.
13. Felson DT, Anderson JJ, Boers M, et al. The American College of Rheumatology preliminary core set of disease activity measures for rheumatoid arthritis clinical trials. The Committee on Outcome Measures in Rheumatoid Arthritis Clinical Trials. *Arthritis Rheum* 1993;36:729-40.
14. Maini RN, Breedveld FC, Kalden JR, et al. Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor alpha monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. *Arthritis Rheum* 1998;41:1552-63.
15. Paulus HE, Egger MJ, Ward JR, Williams HJ. Analysis of improvement in individual rheumatoid arthritis patients treated with disease-modifying antirheumatic drugs, based on the findings in patients treated with placebo. The Cooperative Systematic Studies of Rheumatic Diseases Group. *Arthritis Rheum* 1990;33:477-84.
16. Geborek P, Crnkic M, Petersson IF, Saxne T. Etanercept, infliximab, and leflunomide in established rheumatoid arthritis: clinical experience using a structured follow up programme in southern Sweden. *Ann Rheum Dis* 2002;61:793-8.
17. 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). *J Rheumatol* 2003;30:2563-71.
18. 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, placebo-controlled, 52-week trial. *Arthritis Rheum* 2004;50:1400-11.
19. van de Putte LB, Rau R, Breedveld FC, et al. Efficacy and safety of the fully human anti-tumour necrosis factor alpha monoclonal antibody adalimumab (D2E7) in DMARD refractory patients with rheumatoid arthritis: a 12 week, phase II study. *Ann Rheum Dis* 2003;62:1168-77.
20. 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.
21. Weinblatt ME, Keystone EC, Furst DE, et al. 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 Rheum* 2003;48:35-45.
22. Klareskog L, van der Heijde D, de Jager JP, et al. 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;363:675-81.
23. 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.
24. Moreland LW, Schiff MH, Baumgartner SW, et al. Etanercept therapy in rheumatoid arthritis. A randomized, controlled trial. *Ann Intern Med* 1999;130:478-86.
 25. Mathias SD, Colwell HH, Miller DP, Moreland LW, Buatti M, Wanke L. Health-related quality of life and functional status of patients with rheumatoid arthritis randomly assigned to receive etanercept or placebo. *Clin Ther* 2000;22:128-39.
 26. Moreland LW, Baumgartner SW, Schiff MH, et al. Treatment of rheumatoid arthritis with a recombinant human tumor necrosis factor receptor (p75)-Fc fusion protein. *N Engl J Med* 1997;337:141-7.
 27. 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.
 28. Abe T, Takeuchi T, Miyasaka N, et al. A multicenter, double-blind, randomized, placebo controlled trial of infliximab combined with low dose methotrexate in Japanese patients with rheumatoid arthritis. *J Rheumatol* 2006;33:37-44.
 29. Kavanaugh A, St. Clair EW, McCune WJ, Braakman T, Lipsky P. Chimeric anti-tumor necrosis factor-alpha monoclonal antibody treatment of patients with rheumatoid arthritis receiving methotrexate therapy. *J Rheumatol* 2000;27:841-50.
 30. Maini R, St. Clair EW, Breedveld F, et al. 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;354:1932-9.
 31. Lipsky PE, van der Heijde DM, St. Clair EW, et al. Infliximab and methotrexate in the treatment of rheumatoid arthritis. Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. *N Engl J Med* 2000;343:1594-602.
 32. Bresnihan B, Alvaro-Gracia JM, Cobby M, et al. Treatment of rheumatoid arthritis with recombinant human interleukin-1 receptor antagonist. *Arthritis Rheum* 1998;41:2196-204.
 33. Cohen S, Hurd E, Cush J, et al. Treatment of rheumatoid arthritis with anakinra, a recombinant human interleukin-1 receptor antagonist, in combination with methotrexate: results of a twenty-four-week, multicenter, randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2002;46:614-24.
 34. Cohen SB, Moreland LW, Cush JJ, et al. A multicentre, double blind, randomised, placebo controlled trial of anakinra (Kineret), a recombinant interleukin 1 receptor antagonist, in patients with rheumatoid arthritis treated with background methotrexate. *Ann Rheum Dis* 2004;63:1062-8.
 35. Bathon JM, Martin RW, Fleischmann RM, et al. A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. *N Engl J Med* 2000;343:1586-93.
 36. Genovese MC, Bathon JM, Martin RW, et al. Etanercept versus methotrexate in patients with early rheumatoid arthritis: two-year radiographic and clinical outcomes. *Arthritis Rheum* 2002;46:1443-50.
 37. Kosinski M, Kujawski SC, Martin R, et al. Health-related quality of life in early rheumatoid arthritis: impact of disease and treatment response. *Am J Manag Care* 2002;8:231-40.
 38. Breedveld FC, Weisman MH, Kavanaugh AF, et al. 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 Rheum* 2006;54:26-37.
 39. Elliott MJ, Maini RN, Feldmann M, et al. Randomised double-blind comparison of chimeric monoclonal antibody to tumour necrosis factor alpha (cA2) versus placebo in rheumatoid arthritis. *Lancet* 1994;344:1105-10.
 40. Edwards JC, Szczepanski L, Szechinski J, et al. Efficacy of B-cell-targeted therapy with rituximab in patients with rheumatoid arthritis. *N Engl J Med* 2004;350:2572-81.
 41. Emery P, Fleischmann R, Filipowicz-Sosnowska A, et al. The efficacy and safety of rituximab in patients with active rheumatoid arthritis despite methotrexate treatment: Results of a phase IIB randomized, double-blind, placebo-controlled, dose-ranging trial. *Arthritis Rheum* 2006;54:1390-400.
 42. Genovese MC, Cohen S, Moreland L, et al. Combination therapy with etanercept and anakinra in the treatment of patients with rheumatoid arthritis who have been treated unsuccessfully with methotrexate. *Arthritis Rheum* 2004;50:1412-9.
 43. Genovese MC, Becker JC, Schiff M, et al. Abatacept for rheumatoid arthritis refractory to tumor necrosis factor alpha inhibition. *N Engl J Med* 2005;353:1114-23.
 44. Keystone EC, Schiff MH, Kremer JM, et al. Once-weekly administration of 50 mg etanercept in patients with active rheumatoid arthritis: results of a multicenter, randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2004;50:353-63.
 45. Kremer JM, Westhovens R, Leon M, et al. Treatment of rheumatoid arthritis by selective inhibition of T-cell activation with fusion protein CTLA4Ig. *N Engl J Med* 2003;349:1907-15.
 46. Moreland LW, Alten R, van den Bosch F, et al. Costimulatory blockade in patients with rheumatoid arthritis: a pilot, dose-finding, double-blind, placebo-controlled clinical trial evaluating CTLA-4Ig and LEA29Y eighty-five days after the first infusion. *Arthritis Rheum* 2002;46:1470-9.
 47. 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.
 48. Smolen JS, Han C, Bala M, et al. Evidence of radiographic benefit of treatment with infliximab plus methotrexate in rheumatoid arthritis patients who had no clinical improvement: a detailed subanalysis of data from the anti-tumor necrosis factor trial in rheumatoid arthritis with concomitant therapy study. *Arthritis Rheum* 2005;52:1020-30.
 49. Nuki G, Bresnihan B, Bear MB, McCabe D. Long-term safety and maintenance of clinical improvement following treatment with anakinra (recombinant human interleukin-1 receptor antagonist) in patients with rheumatoid arthritis: extension phase of a randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2002;46:2838-46.
 50. Fleischmann RM, Schechtman J, Bennett R, et al. Anakinra, a recombinant human interleukin-1 receptor antagonist (r-metHuIL-1ra), in patients with rheumatoid arthritis: A large, international, multicenter, placebo-controlled trial. *Arthritis Rheum* 2003;48:927-34.
 51. Tesser J, Fleischmann R, Dore R, et al. Concomitant medication use in a large, international, multicenter, placebo controlled trial of anakinra, a recombinant interleukin 1 receptor antagonist, in patients with rheumatoid arthritis. *J Rheumatol* 2004;31:649-54.
 52. Schiff MH, DiVittorio G, Tesser J, et al. The safety of anakinra in high-risk patients with active rheumatoid arthritis: six-month observations of patients with comorbid conditions. *Arthritis Rheum* 2004;50:1752-60.
 53. Wood AJ. Thrombotic thrombocytopenic purpura and clopidogrel — a need for new approaches to drug safety. *N Engl J Med* 2000;342:1824-6.
 54. Cheifetz A, Smedley M, Martin S, et al. The incidence and management of infusion reactions to infliximab: a large center

- experience. *Am J Gastroenterol* 2003;98:1315-24.
55. Maini RN, Breedveld FC, Kalden JR, et al. Sustained improvement over two years in physical function, structural damage, and signs and symptoms among patients with rheumatoid arthritis treated with infliximab and methotrexate. *Arthritis Rheum* 2004;50:1051-65.
 56. Schaible TF. Long term safety of infliximab. *Can J Gastroenterol* 2000;14 Suppl C:29C-32C.
 57. Bergstrom L, Yocum DE, Ampel NM, et al. Increased risk of coccidioidomycosis in patients treated with tumor necrosis factor alpha antagonists. *Arthritis Rheum* 2004;50:1959-66.
 58. Gomez-Reino JJ, Carmona L, Valverde VR, Mola EM, Montero MD. 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;48:2122-7.
 59. Keane J, Gershon S, Wise RP, et al. Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. *N Engl J Med* 2001;345:1098-104.
 60. Lee JH, Slifman NR, Gershon SK, et al. Life-threatening histoplasmosis complicating immunotherapy with tumor necrosis factor alpha antagonists infliximab and etanercept. *Arthritis Rheum* 2002;46:2565-70.
 61. Slifman NR, Gershon SK, Lee JH, Edwards ET, Braun MM. *Listeria monocytogenes* infection as a complication of treatment with tumor necrosis factor alpha-neutralizing agents. *Arthritis Rheum* 2003;48:319-24.
 62. Wallis RS, Broder M, Wong J, Beenhouwer D. Granulomatous infections due to tumor necrosis factor blockade: correction. *Clin Infect Dis* 2004;39:1254-5.
 63. Wolfe F, Michaud K, Anderson J, Urbansky K. Tuberculosis infection in patients with rheumatoid arthritis and the effect of infliximab therapy. *Arthritis Rheum* 2004;50:372-9.
 64. Brown SL, Greene MH, Gershon SK, Edwards ET, Braun MM. Tumor necrosis factor antagonist therapy and lymphoma development: twenty-six cases reported to the Food and Drug Administration. *Arthritis Rheum* 2002;46:3151-8.
 65. Lebowitz M, Blum R, Berkowitz E, et al. No evidence for increased risk of cutaneous squamous cell carcinoma in patients with rheumatoid arthritis receiving etanercept for up to 5 years. *Arch Dermatol* 2005;141:861-4.
 66. 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;50:1740-51.
 67. Chung ES, Packer M, Lo KH, Fasanmade AA, Willerson JT. Randomized, double-blind, placebo-controlled, pilot trial of infliximab, a chimeric monoclonal antibody to tumor necrosis factor-alpha, in patients with moderate-to-severe heart failure: results of the anti-TNF Therapy Against Congestive Heart Failure (ATTACH) trial. *Circulation* 2003;107:3133-40.
 68. Kwon HJ, Cote TR, Cuffe MS, Kramer JM, Braun MM. Case reports of heart failure after therapy with a tumor necrosis factor antagonist. *Ann Intern Med* 2003;138:807-11.
 69. Mohan N, Edwards ET, Cupps TR, et al. Demyelination occurring during anti-tumor necrosis factor alpha therapy for inflammatory arthritides. *Arthritis Rheum* 2001;44:2862-9.
 70. Colombel JF, Loftus EV Jr, Tremaine WJ, et al. The safety profile of infliximab in patients with Crohn's disease: the Mayo Clinic experience in 500 patients. *Gastroenterology* 2004;126:19-31.
 71. Ljung T, Karlen P, Schmidt D, et al. Infliximab in inflammatory bowel disease: clinical outcome in a population based cohort from Stockholm County. *Gut* 2004;53:849-53.
 72. Anonymous. Enbrel package insert. 2005.
 73. Anonymous. Humira package insert. 2005.
 74. Anonymous. Kineret package insert. 2005.
 75. 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;295:2275-85.
 76. Baeten D, Kruithof E, van den Bosch F, et al. Systematic safety follow up in a cohort of 107 patients with spondyloarthritis treated with infliximab: a new perspective on the role of host defence in the pathogenesis of the disease? *Ann Rheum Dis* 2003;62:829-34.
 77. Manadan AM, Mohan AK. Tuberculosis and etanercept treatment [abstract]. *Arthritis Rheum* 2002;46 Suppl:S166.
 78. Baecklund E, Ekblom A, Sparen P, Feltelius N, Klareskog L. Disease activity and risk of lymphoma in patients with rheumatoid arthritis: nested case-control study. *BMJ* 1998;317:180-1.
 79. Coletta AP, Clark AL, Banarjee P, Cleland JG. Clinical trials update: RENEWAL (RENAISSANCE and RECOVER) and ATTACH. *Eur J Heart Fail* 2002;4:559-61.
 80. Shakoor N, Michalska M, Harris CA, Block JA. Drug-induced systemic lupus erythematosus associated with etanercept therapy. *Lancet* 2002;359:579-80.
 81. Anonymous. Remicade package insert. 2005.
 82. 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;62 Suppl 2:ii13-6.
 83. Clark W, Raftery J, Song F, et al. Systematic review and economic evaluation of the effectiveness of infliximab for the treatment of Crohn's disease. *Health Technol Assess* 2003;7:1-67.