

Efficacy and safety of anakinra for the treatment of rheumatoid arthritis: an update of the Oregon Drug Effectiveness Review Project

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Objective: To systematically review the general and comparative efficacy and safety of anakinra for rheumatoid arthritis.

Methods: We searched MEDLINE®, Embase, The Cochrane Library, and the International Pharmaceutical Abstracts from 1980 to April 2009. We manually searched reference lists of pertinent review articles and explored the Center for Drug Evaluation and Research database. For efficacy we included randomized controlled trials (RCTs) comparing anakinra with placebo or other biologics. For safety both experimental and observational studies were eligible. Two persons independently reviewed abstracts and full text articles and extracted relevant data.

Results: We included data from 3 RCTs comparing anakinra with placebo for rheumatoid arthritis (RA). The pooled relative risk (RR) of an ACR50 (American College of Rheumatology) response for anakinra compared with placebo is 2.28 (95% CI 1.41 to 3.67). Adjusted indirect comparisons of ACR50 response rates of anakinra and anti-TNF agents showed a RR of 0.67 (95% CI 0.38 to 1.17) favoring the anti-TNF drugs. This result did not reach statistical significance. For safety, we included 9 experimental and observational studies of 24 weeks to 3 years duration. Up to 30% of patients withdrew from the studies due to adverse events. 67.2% (95% CI 38.7 to 95.7) of patients experienced an injection site reaction.

Conclusions: Anakinra is an effective drug for treating RA. Indirect comparisons with adalimumab, etanercept and infliximab, however, showed a trend towards greater efficacy for the anti-TNF drugs. Anakinra also seems to be associated with comparably high rates of injection site reactions. These results should be taken into account when considering biologic therapy for patients with RA.

Keywords: anakinra, rheumatoid arthritis, infection

Introduction

Biologic agents have been approved for the treatment of rheumatic diseases, plaque psoriasis and inflammatory bowel diseases and have tremendously changed treatment strategies for these debilitating diseases.¹ These agents include abatacept (Orencia®), adalimumab (Humira®), alefacept (Amevive®), anakinra (Kineret®), certolizumab pegol (Cimzia®), etanercept (Enbrel®), golimumab (Simponi®), infliximab (Remicade®), natalizumab (Tysabri®), and rituximab (Rituxan®). Evidence suggests that biologics are highly effective, although adverse events such as serious infections, lymphoma, leucopenia, malignancies, or demyelinations are of concern.²⁻⁹ Furthermore, they are considerably more expensive than standard treatment options.^{10,11} The cost of biologic drugs is expected to exceed US\$60 billion in

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the US by 2010, representing a significant portion of the US drug industry.¹²

In general, biologic agents work by selectively blocking mechanisms involved in the inflammatory and immune response. For example, the biologics adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab block tumor necrosis factor (TNF).^{13–15} In contrast, abatacept and alefacept interfere with T-lymphocyte activation.¹⁶ Natalizumab binds the alpha(4) integrin, which results in partial blockade of immune-cell adhesion to vascular endothelium and subsequent tissue migration of lymphocytes.¹⁷ Rituximab binds to the CD20 antigen on the surface of B lymphocytes,¹⁸ which are involved in autoimmune anti-inflammatory processes, such as those involved in rheumatoid arthritis (RA). Finally, anakinra is a recombinant IL-1 (interleukin-1) receptor antagonist and has the same properties as the human IL-1 receptor agonist. Anakinra binds to the IL-1 receptor and inhibits pro-inflammatory effects by blocking signal transduction.^{4–6,19}

Dosing regimens and route of administration vary considerably among the various agents. Abatacept, infliximab, and rituximab are administered intravenously; adalimumab, anakinra and etanercept are administered subcutaneously. Abatacept is infused in doses of 500 to 1000 mg repeated at 2 and 4 weeks and every 4 weeks thereafter. Infliximab infusions are administered in doses of 3 mg/kg at 0, 2, and 6 weeks followed by maintenance every 8 weeks and rituximab is dosed at 1000 mg on days 1 and 15. Adalimumab is injected subcutaneously at 40 mg every other week, and etanercept is administered at 50 mg per week.¹¹ In comparison, anakinra is administered in doses of 100 mg subcutaneously every day. The burden of daily subcutaneous administration of anakinra might disadvantage it compared with the other biologic agents. Table 1 presents a summary of dosing and administration of the biologics.

Considering the high cost and differing regimes of the biologics, it is important to ascertain their comparative effectiveness. This systematic review and meta-analysis is a result of work conducted for the Oregon Drug Effectiveness Review Project (DERP) on the comparative efficacy and safety of 10 specific biologics for rheumatoid arthritis (RA), ankylosing spondylitis, psoriatic arthritis, Crohn's disease, ulcerative colitis, plaque psoriasis, and juvenile idiopathic arthritis in adult out-patients and subgroups including children. In a meta-analysis of studies up to January 2005 indirect comparisons suggested that anakinra is inferior to the anti-TNF biologics for RA.²⁰ In this report we focus on the general

and comparative benefits and risks of anakinra and provide an update of this result with several newer studies included in the analysis.

Methods

Data sources

We searched MEDLINE®, Embase, Cochrane Library, and International Pharmaceutical Abstracts from 1980 up to April 2009. We used either Medical Subject Headings (MeSH) as search terms when available or key words when appropriate. In the original DERP report,¹¹ we combined terms for RA, ankylosing spondylitis, psoriatic arthritis, Crohn's disease, ulcerative colitis, plaque psoriasis, and juvenile idiopathic arthritis with a list of ten specific biologics-abatacept (Orencia®), adalimumab (Humira®), alefacept (Amevive®), anakinra (Kineret®), certolizumab (Cimzia®)*, etanercept (Enbrel®), infliximab (Remicade®), natalizumab (Tysabri®), rituximab (Rituxan®). For this review we limited results to literature identified for anakinra. For the other biologics, we present comparisons with anakinra only. We did not review data on golimumab because it was not on the market at the time of this review, and excluded efalizumab because it was voluntarily withdrawn from the market. We limited electronic searches to “human” and “English language.”

We manually searched reference lists of pertinent review articles and letters to the editor and used the Center for Drug Evaluation and Research database to identify unpublished research submitted to the FDA. The Scientific Resource Center of the Oregon Health and Science University invited pharmaceutical manufacturers to submit dossiers on completed research for each drug.

Study selection

Two persons independently reviewed abstracts and relevant full-text articles. To assess efficacy or effectiveness for response and quality of life we included randomized controlled trials (RCTs) and prospective controlled observational studies of at least 12 weeks duration that compared anakinra with placebo or another biologic. To assess harms (specific adverse events, rates of adverse events, and discontinuations attributable to adverse events), we also examined data from retrospective observational studies with ≥ 100 participants and follow-up of at least 6 months. Table 2 summarizes the eligibility criteria.

If both reviewers agreed that the study did not meet eligibility criteria, we excluded it. We also excluded studies that met eligibility criteria but were reported only

Table I Administration and dosing

Drug	Mechanism	Route	Dose
Abatacept	CTLA 4-Ig	IV	Adult: dosed according to body weight (<60 kg = 500 mg; 60–100 kg = 750 mg; >100 kg = 1000 mg); dose repeated at 2 weeks and 4 weeks after initial dose, and every 4 weeks thereafter Pediatric: for children ≥6 years and <75 kg dose is 10 mg/kg, repeat dose at 2 and 4 weeks after initial infusion, and every 4 weeks thereafter. For children ≥6 years and >75 kg the dose is 750 mg if child is 75–100 kg; dose is 1000 mg if child >100 kg
Adalimumab	TNF inhibitor	SQ	RA: 40 mg every other week; patients not taking methotrexate may increase to 40 mg per week for adalimumab monotherapy PsA, AS: 40 mg every other week Plaque psoriasis: initial 80 mg as a single dose; maintenance dose is 40 mg every other week beginning 1 week after initial dose Crohn's disease: initial dose of 160 mg given as 4 injections on day 1 or over 2 days, then 80 mg 2 weeks later (day 15); Maintenance dose is 40 mg every other week beginning day 29 Pediatric: 15 kg to <30 kg: 20 mg every other week; ≥30 kg: 40 mg every other week
Alefacept	CD2 antagonist	IM	15 mg given once weekly, treatment should be continued for 12 weeks; re-treatment with an additional 12 week course may be initiated provided that CD4+ T lymphocytes counts are >250 cells/μL and a 12-week interval has passed since the end of the initial treatment cycle
Anakinra	IL-1 receptor antagonist	SQ	RA: 100 mg once daily; dose maybe decreased to 100 mg every other day in cases of renal impairment
Certolizumab pegol	TNF inhibitor	SQ	RA: Initial dose is 400 mg, repeat dose 2 and 4 weeks after initial dose. Maintenance dose is 200 mg every other week. May consider maintenance dose of 400 mg every 4 weeks Crohn's disease: Initial dose is 400 mg, repeat dose 2 and 4 weeks after initial dose. Maintenance dose is 400 mg every other week
Etanercept	TNF inhibitor	SQ	RA, PsA, AS: 25 mg twice weekly or 50 once weekly Plaque psoriasis: Initial dose of 50 mg twice weekly, 3–4 days apart, maintain initial dose for 3 months, Maintenance dose is 50 mg once weekly Pediatric: 0.8 mg once weekly or 0.4 mg twice weekly (maximum of 50 mg)
Golimumab	TNF inhibitor	SQ	RA, PsA, AS: 50 mg once per month
Infliximab	TNF inhibitor	IV	RA: 3 mg/kg at 0, 2, and 6 weeks followed by maintenance every 8 weeks thereafter; may increase to maximum of 10 mg/kg every 4 weeks AS: 5 mg/kg at 0, 2, and 6 weeks, followed by 5 mg/kg every 6 weeks thereafter Plaque psoriasis: 5 mg/kg at 0, 2, and 6 weeks, then every 8 weeks thereafter Ulcerative colitis: 5 mg/kg at 0, 2, and 6 weeks, followed by 5 mg/kg every 8 weeks thereafter Pediatric Crohn's disease: 5 mg/kg at 0, 2, and 6 weeks, followed by a maintenance dose of 5 mg/kg every 8 weeks; if no response by week 14, consider discontinuing therapy
Natalizumab	Alpha 4 integrin blocker	IV	Crohn's disease: 300 mg infused over 1 hour every 4 weeks
Rituximab	Anti-CD 20a	IV	RA: 1000 mg on days 1 and 15 in combination with methotrexate

Abbreviations: AS, ankylosing spondylitis; CTLA 4-Ig, cytotoxic T-lymphocyte antigen 4; TNF, tumor necrosis factor; IL-1, interleukin-1; CD, cluster of differentiation; IM, intramuscular; IV, intravenous; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SQ, subcutaneous.

as an abstract. Investigators resolved disagreements about inclusion or exclusion by consensus or by involving a third reviewer.

Data extraction and quality assessment

We used a structured data abstraction form into which trained reviewers abstracted data from each study and assigned an initial quality rating. Abstracted data included the baseline

characteristics of the included patients, health-related outcomes (such as quality of life, response, remission, pain, hospitalization and mortality), adverse events, and overall and differential attrition. A senior reviewer read each abstracted article, evaluated completeness of data abstraction, and confirmed the quality rating. Investigators resolved any disagreements by discussion and consensus or by consulting an independent party.

Table 2 Eligibility criteria

Population	Adult outpatients with rheumatoid arthritis
Intervention	Anakinra alone or in combination with other DMARDs or biologics
Comparison	Placebo or other biologic
Outcomes	Health-related outcomes (eg: quality of life, response) Harms (adverse events, discontinuation due to adverse events)
Study design and timing (efficacy)	Controlled trial, ≥ 12 weeks study duration, $N \geq 30$
Study design and timing (safety)	Observational study, >6 months, ≥ 100 participants

Abbreviation: DMARD, disease-modifying antirheumatic drug.

We assessed the internal validity (quality) of trials based on predefined criteria and applied ratings of good, fair, or poor.²¹ Primary elements of quality assessment for RCTs included randomization and allocation concealment, similarity of compared groups at baseline, blinding, use of intention-to-treat analysis, and overall and differential loss to follow-up. To assess observational studies we used criteria involving selection of cases or cohorts and controls, adjustment for confounders, methods of outcomes assessment, length of follow-up, and statistical analysis.²² Studies with a fatal flaw in one or more categories were rated “poor” quality.

To identify effectiveness studies, we used a tool that distinguishes efficacy trials from effectiveness studies based on certain elements of study design.²³ Such studies have a higher applicability of results than efficacy trials because they enroll less selected study populations, employ treatment modalities that mimic clinical practice, and assess health outcomes along with adverse events.

Data synthesis

Where data were insufficient to conduct meta-analyses (ie, too sparse or too heterogeneous), we synthesized the evidence on the majority of outcomes qualitatively. Where data from RCTs were sufficient, we conducted meta-analyses. The outcome of interest for efficacy was the number of patients achieving a response according to the ACR scoring system (American College of Rheumatology). We chose ACR50 as the primary outcome measure because a 50% improvement is likely to translate to a clinically significant improvement in health-related quality of life. For example, a patient with 12 swollen and 8 tender joints at baseline would need to have fewer than 6 swollen and 4 tender joints at the trial endpoint. This would be accompanied by at least a 50%

improvement in at least 3 of the following 5 measures: the patient’s assessment of pain, the patient’s assessment of global disease activity, the physician’s assessment of global disease activity, the Health Assessment Questionnaire (HAQ)-Disability Index, and either a C-reactive protein (CRP) or sedimentation rate (Westergren erythrocyte sedimentation rate [WESR]). In addition, we report the results for an ACR20 (20% improvement) and ACR70 (70% improvement).

For each meta-analysis, we conducted a test of heterogeneity (I^2 index) and applied both random and fixed effects models. We consider I^2 greater than 60% to be too high to compare data. We report the random effects results because the results from both models were very similar in all meta-analyses. We assessed publication bias using funnel plots and Kendall’s tests. All statistical analyses used StatsDirect Statistical Software program, version 2.6.6 (StatsDirect LTD, 2008).

Because only limited head-to-head evidence on biologics was available, we conducted adjusted indirect comparisons when data was sufficient and trials were of similar design, conducted in similar settings with a comparable patient population. However, because of limited data on individual biologics as active comparators, we assessed the comparative risk of anakinra relative to anti-TNF agents as a class. We based these analyses on the method proposed by Bucher et al.²⁴ Evidence suggests that adjusted indirect comparisons agree with head-to-head trials if component studies are similar and treatment effects are expected to be consistent in patients included in different trials.^{25,26} Nevertheless, findings must be interpreted cautiously.

Results

In the original DERP report on biologics, we identified 3451 citations from searches and reviews of reference lists. Of these, 236 articles met the inclusion criteria and were included. Some studies had multiple publications. Finally, for this report on anakinra, we included 4 RCTs for efficacy and 5 additional studies for safety. Figure 1 represents the results of the literature search and the disposition of the literature. We did not find any study that could be classified as an effectiveness trial. All trials reported on anakinra for the treatment of rheumatoid arthritis. We did not locate any publication that met our inclusion criteria for psoriatic arthritis, plaque psoriasis, ankylosing spondylitis, juvenile idiopathic arthritis, Crohn’s disease or ulcerative colitis (all other indications covered in the DERP report).

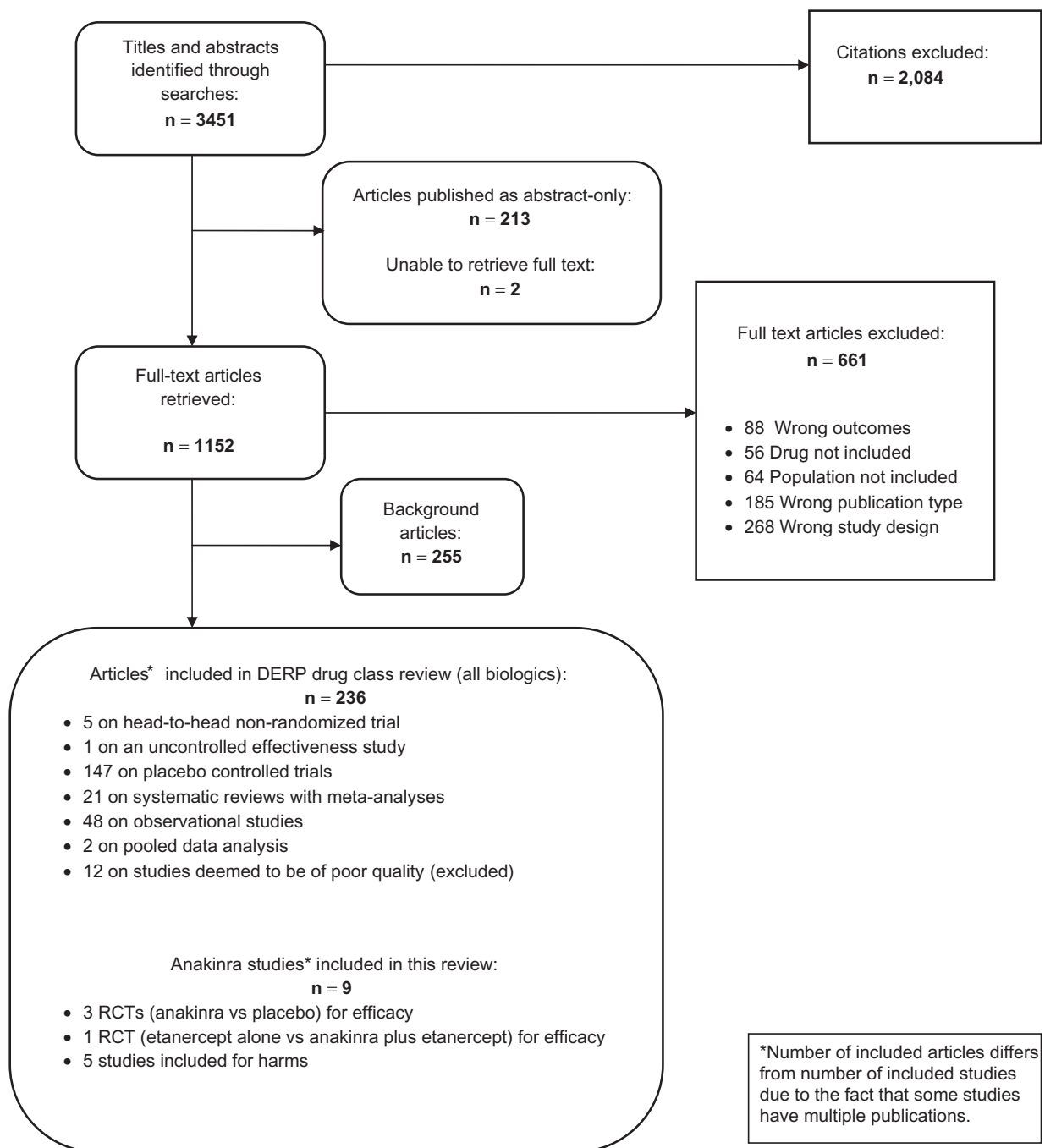


Figure 1 Disposition of the literature.

Abbreviation: DERP, oregon drug effectiveness review project.

Efficacy of anakinra

We located 5 publications that met our inclusion criteria for efficacy in patients with rheumatoid arthritis. Three RCTs reported on the efficacy of anakinra compared with placebo,²⁷⁻²⁹ and 1 RCT compared anakinra in combination with etanercept with etanercept alone.³⁰ We found additional information on ACR response rates for 1 RCT²⁷ in the CDER database.³¹ One RCT was published as an

abstract only.³² Table 3 presents a summary of the included studies.

Population and outcome measures

A total of 1625 patients were included in the trials. All patients suffered from active RA of at least 3 to 6 months duration. Mean disease duration varied between 6 and 10 years. Trials variably allowed concomitant treatment with a stable dose of

Table 3 Summary of anakinra (AKA) efficacy studies

Author	Study design, N, duration	Comparisons	Outcomes	Population	Results	Quality rating
Anakinra compared with placebo						
Bresnihan et al ²⁷	RCT 472 24 wks	AKA (30 mg, 70 mg, 150 mg/day) vs placebo	ACR20, Paulus crit., SJC, TJC, HAQ, Larsen score, pain (VAS), morning stiffness	>6 months active severe RA, NSAIDs, steroids < 10 mg/day allowed, no other DMARDs	Significant improvement in all ACR components (SJC, TJC, disease activity, pain ESR) in 150 mg/day group compared with placebo group	Fair
Cohen et al ²⁸	RCT 419 24 wks	AKA (0.04, 0.1, 0.4, 1.0, 2.0 mg/kg/day) vs placebo	ACR20, ACR50/70, HAQ, morning stiffness	6- to 8-year history of moderate-severe RA, stable dose MTX (15–25 mg/week)	More patients in AKA 1 mg/kg had ACR20 response (42%) than placebo group (23%). More patients in AKA 1 mg/kg and 2 mg/kg groups had an improvement on HAQ and pain	Fair
Cohen et al ³⁰	RCT 501 24 wks	AKA (100 mg/day) vs placebo	ACR20, ACR50/70, HAQ, TJC, SJC	>6-month history of active RA; stable MTX regimen 10–25 mg/wk; mean disease duration: 10.5 years	Significantly more patients in AKA group achieved a response (ACR20/50/70). Decrease in TJC greater in the AKA group	Fair
Anakinra in combination with another biologic						
Genovese et al ³⁰	RCT 242 24 wks	ETA (25 mg/week or 50 mg/week) plus AKA (100 mg/day) vs ETA alone	ACR50, ACR20/70, EULAR, DAS, SF-36	>6-month history of RA; > 16 weeks MTX and >8 weeks stable dose MTX of 10–25 mg/week; 50% also using steroids	Overall, no significant difference in efficacy between treatment groups	Fair

Abbreviations: ACR20/50/70, American College of Rheumatology (numbers refer to percentage improvement); AKA, anakinra; ASHI, arthritis-specific health index; DAS28, disease activity score; DMARD, disease-modifying antirheumatic drug; ETA, etanercept; EULAR, European League Against Rheumatism; HAQ, Health Assessment Questionnaire; Larsen score, radiographic evaluation; MA, meta-analysis; MTX, methotrexate; RA, rheumatoid arthritis; RCT, randomized controlled trial; SF-36, Medical Outcomes Study Short Form 36 Health Survey; SJC, swollen joint count; TJC, tender joint count; VAS, visual analogue score.

MTX and/or corticosteroids. Most patients used NSAIDs in addition to the study medication. The majority of patients in the trials had active disease despite therapy with at least one disease-modifying anti-rheumatic drug (DMARD). Patients with an autoimmune disease other than RA, a history of active listeriosis or mycobacterial infection, another infection or recent antibiotic treatment were generally excluded from studies. Between 70% and 80% of trial participants were female.

All trials assessed response rates after 24 weeks of therapy as defined by the ACR. One trial also reported the European League Against Rheumatism (EULAR) response rate.³⁰ In addition, three studies evaluated functional capacity with the HAQ.^{27–29}

All studies were funded by Amgen Inc., Thousand Oaks, California.^{28–30}

Anakinra compared with placebo

Three fair RCTs compared various doses of anakinra with placebo (between 0.04 mg/kg/day and 150 mg/day) for patients with moderate to severe RA that had not responded to DMARDs.^{27–29} Two studies allowed concomitant treatment with MTX.^{28,29} All three studies lasted 24 weeks. In total, 1392 patients were randomized to anakinra (N = 946) or placebo (N = 446). Based on the ACR criteria, significantly more patients receiving anakinra 100 mg/day, 150 mg/day, 1 mg/kg/day, or 2 mg/kg/day responded to treatment compared with placebo. Specifically, the pooled relative risk of an ACR50 response for the approved doses of anakinra compared with placebo is 2.28 (95% CI 1.41 to 3.67). The RR for an ACR20 response is 1.73 (95% CI 1.34 to 2.25) and for an ACR70 response 2.90 (95% CI 1.21 to 6.97) (see Figure 2).

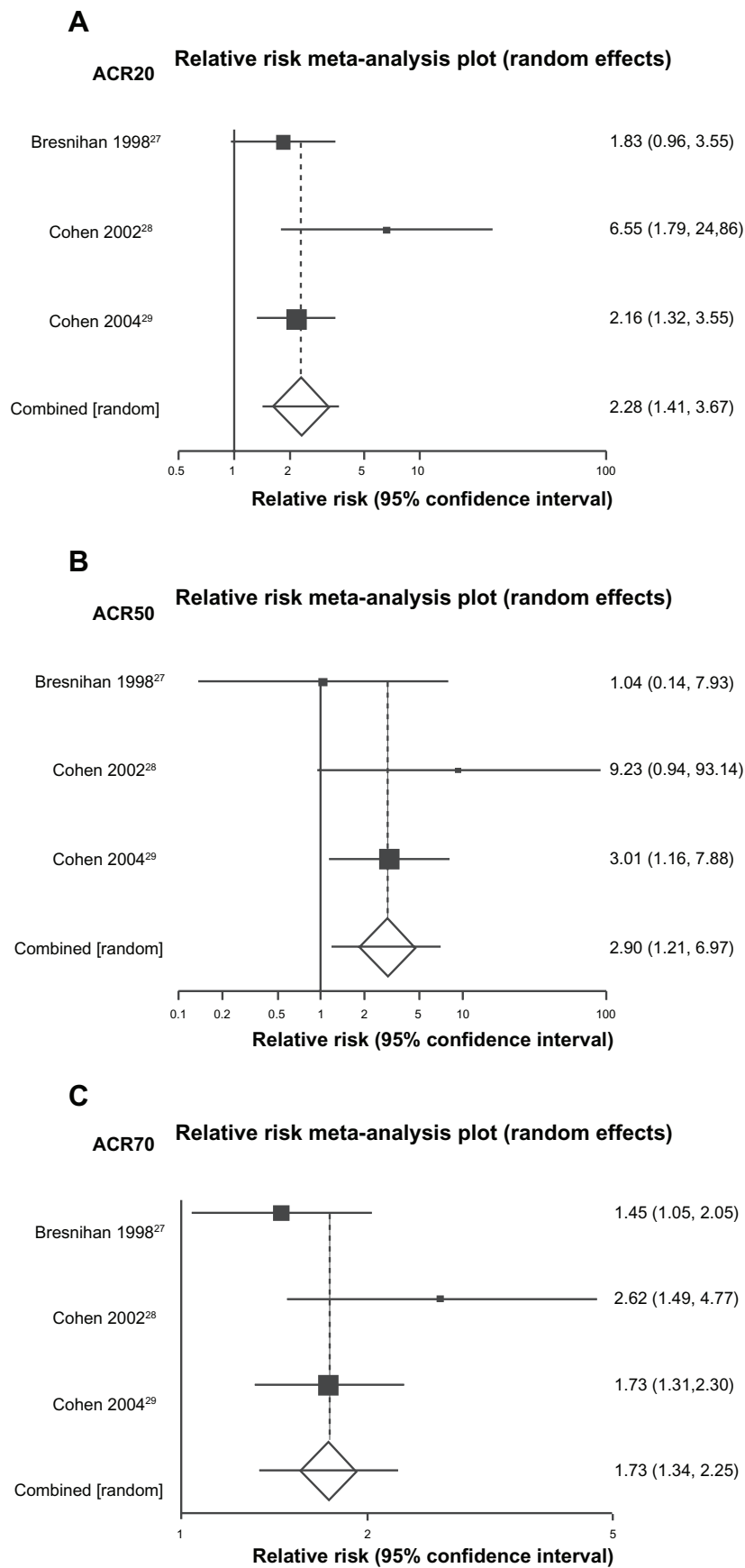


Figure 2 Meta-analysis of ACR20, ACR50 and ACR70 response (anakinra vs placebo).

In addition, in all three RCTs, patients receiving anakinra demonstrated a greater improvement in health assessment questionnaire (HAQ) than patients receiving placebo score (approximately 0.4 for anakinra compared to 0.2 for placebo; scale values 0 to 3). This result reached statistical significance for all doses except one (2 mg/kg/day).

Comparative efficacy

We did not locate any trials that directly compared anakinra to another biologic. Because of the lack of direct head-to-head evidence for anakinra compared with other biologics we conducted adjusted indirect comparisons based on meta-analyses of placebo-controlled trials to compare the treatment effects of individual biologics. We included data from published studies or from the CDER website. For all analyses we used only data derived from study arms at or near the recommended dosage. We did not perform indirect comparisons for biologics other than adalimumab, etanercept, and infliximab because the populations included in the trials were too heterogeneous compared with the anakinra trials and therefore performing indirect comparisons may lead to erroneous conclusions. Appendix 1 summarizes studies included for indirect comparisons.

For ACR50 response, point estimates of anakinra compared with the anti-TNF biologics consistently favored the comparator: adalimumab (RR 0.64, 95% CI 0.36 to 1.14); etanercept (RR 0.41, 95% CI 0.13 to 1.31); and infliximab (RR 0.69, 95%CI 0.41 to 1.18). Compared with anti-TNF

agents as a class, the RR of an ACR50 response is 0.67 (95% CI 0.38 to 1.17). That differences do not reach statistical significance is likely attributable to a lack of power. Despite this, the differences may be clinically relevant.

Figure 3 depicts results of adjusted indirect comparisons of anakinra with adalimumab, etanercept, infliximab, and anti-TNF drugs as a class. The evidence on abatacept, certolizumab, and rituximab was insufficient or too heterogeneous to be included for indirect comparisons.

General efficacy of anakinra for other indications

We did not locate any published studies of anakinra for psoriatic arthritis, plaque psoriasis, ankylosing spondylitis, juvenile idiopathic arthritis, Crohn's disease, or ulcerative colitis.

Safety of anakinra

General safety

For safety we included the three RCTs included for efficacy,²⁷⁻²⁹ 1 RCT of anakinra plus etanercept compared with etanercept alone,³⁰ and one 6-month RCT of anakinra versus placebo with a 3-year open treatment follow-up phase.^{4-6,33}

In addition, we located 1 RCT that reported the safety results of 3 doses of anakinra.¹⁹ (This study is an extension of Bresnihan et al. Patients who had received placebo in the initial 24 weeks were re-randomized to 30 mg/day, 75 mg/day, or 150 mg/day of anakinra and followed up for an additional 52 weeks). We also included safety data comparing patients taking anakinra and conventional DMARDs from

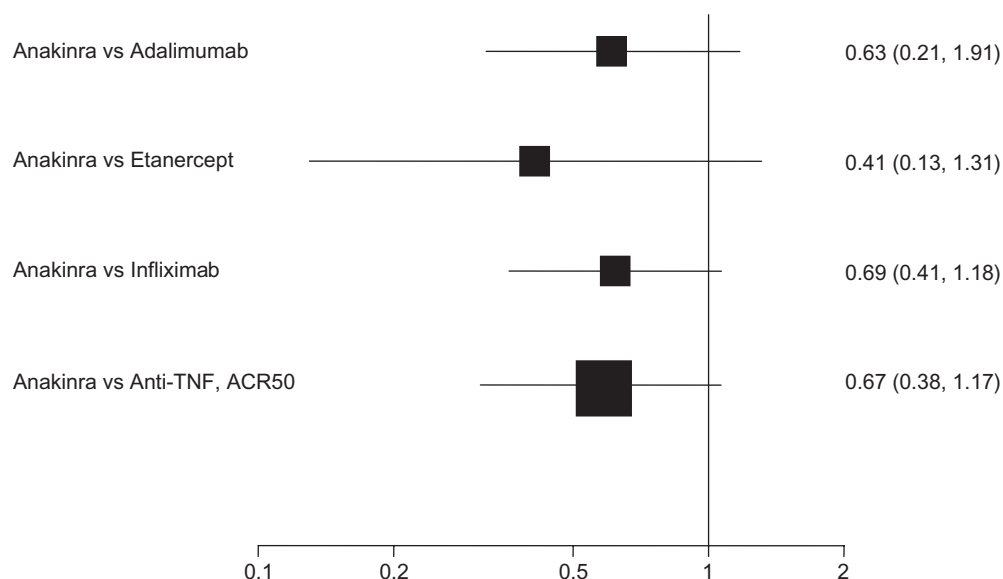


Figure 3 Adjusted indirect comparisons of anakinra with anti-TNF drugs for an ACR50 response.
Abbreviation: RR, relative risk.

the German RABBIT Registrar (RABBIT = Rheumatoid Arthritis – Observation of Biologic Therapy)^{34,35} and a case series of patients receiving anakinra.³⁶ Table 4 presents a summary of the studies included for safety.

Overall, between 6.5% and 30% of patients withdrew from anakinra therapy due to adverse events compared with 4% to 13% of patients on placebo. The most common adverse event was injection site reaction. The mean, crude incidence of injection site reactions was 67.2% (95% CI 38.7 to 95.7).¹¹

Infections occurred in 5% to 33% of patients taking anakinra compared with 12% to 26% of placebo-treated patients. Infections included influenza-like symptoms, respiratory infections, and urinary tract infections. We located 1 systematic review that reported on the safety of anakinra.³⁷ The authors included all 4 RCTs of anakinra versus placebo for rheumatoid arthritis that we also located.^{6,27–29} Thirty serious infections (1.4%) occurred in the anakinra groups compared with 4 in the placebo groups (0.5%). The meta-analysis of the studies demonstrated an odds ratio for serious infections of 2.75 (95% CI 0.91 to 8.35).³⁷

Two of the 24-week RCTs reported 2 malignancies each that were “not considered to be related to the study medication”.^{27,28} The 3-year open label study of anakinra³³ reported a higher than expected incidence of melanoma and lymphoma (incidence compared with data from the general population). The results submitted to the CDER by Amgen reported that “21 malignancies of various types were observed in 2531 rheumatoid arthritis patients treated with anakinra for up to 50 months”. We are unable to draw any conclusions regarding malignancy due to the overall small number of participants in the studies.

Comparative harms

We did not locate any studies that directly compared the incidence of adverse events between anakinra and other biologics. We calculated a higher crude incidence of injection site reactions for anakinra (67.2%, 95% CI 38.7 to 95.7) compared with adalimumab (17.5%, 95% CI 7.1 to 27.9) and etanercept (22.4%, 95% CI 8.5 to 36.3). This is consistent with numbers reported in the respective package inserts.^{38–40}

Combination strategies

Anakinra combined with etanercept compared with etanercept alone

One RCT compared anakinra 100 mg/day combined with 2 different doses of the anti-TNF agent etanercept (25 mg/once

a week or 25 mg/twice a week) with etanercept alone (25 mg/twice a week) in 242 patients with moderate rheumatoid arthritis.³⁰ After 24 weeks of therapy 41% of patients in the etanercept groups had an ACR50 response, compared with 39% of those receiving once weekly etanercept and anakinra, and 31% in the groups who received the combination of twice weekly etanercept and daily anakinra (results not statistically significant). The odds ratio for an ACR50 response for the etanercept plus anakinra groups versus the etanercept alone group was 0.64 (95% CI 0.37 to 1.09).

Furthermore, 15% of patients in the twice-weekly etanercept plus anakinra group experienced a serious adverse event, compared with 2.5% in the etanercept alone group and 5% in the once-weekly etanercept and anakinra group. Twenty-two percent of patients in the anakinra/etanercept once per week group and 20% of the patients randomized to anakinra and etanercept twice per week did not complete the study compared with 7% of patients receiving etanercept alone. Injection-site reactions were the common reason for adverse-event related withdrawal from the study. Injection site reactions occurred in 69% of patients receiving combination therapy compared with 40% of those receiving etanercept alone.

Subgroups

We did not locate any studies that provided results on the efficacy or safety of anakinra for subgroups.

Discussion

In this systematic review, we found 3 RCTs that confirmed the efficacy of anakinra compared with placebo for adult patients with RA. Our results are consistent with several other published systematic reviews of anakinra.^{20,41–43} In one RCT that used a combination of anakinra and etanercept the response rates were not better than etanercept alone, and the adverse events rates were significantly higher. There appears to be greater harm and no additional benefit in combining anakinra and the anti-TNF drugs.

No direct evidence comparing anakinra and other biologics exists, however our indirect comparison of anakinra and anti-TNF agents as a class revealed a non-significant RR of 0.67 (95% CI 0.38 to 1.17) that favors the anti-TNF drugs adalimumab, etanercept and infliximab. The authors of a meta-analysis with indirect comparisons calculated that anakinra is inferior to adalimumab, etanercept and infliximab.²⁰ This result was statistically significant. Our update, which includes several newer studies of the anti-TNF biologics, indicates a lesser degree of certainty.

Table 4 Summary of studies assessing adverse events

First author	Study design N Duration	Population comparison	Results	Quality rating
Bresnihan et al ²⁷	RCT 472 24 wks	>6 months active severe RA, NSAIDs, steroids <10 mg/day allowed, no other DMARDs Placebo	More patients with ISRs in AKA groups compared with placebo: 30 mg/day 50%; 70 mg/day 73%; 150 mg/day 81%; placebo 25% Infections resulting in antibiotic use in 12% placebo vs 15%–17% AKA; of the 6 patients hospitalized for infections 4 were in the AKA 150 mg/day group vs 1 each from placebo and 75 mg/day Two patients in AKA group developed a malignancy, neutropenia occurred in 3 AKA patients compared with no placebo patients	Fair
Nuki et al ¹⁹	Uncontrolled extension of RCT ²⁷ 309 76 weeks	Patients with RA randomized to 30 mg/day, 75 mg/day or 150 mg/day AKA	The most common AE was ISR. ISRs occurred in 72% of patients who received 75 mg/day and 80% of patients who received 150 mg/day over the 76 week study 30% AKA withdrew from study, 14% withdrew due to AEs	Fair
Cohen et al ²⁸	RCT 419 24 weeks	6- to 8-year history of moderate-severe RA, stable dose MTX (15–25 mg/week) placebo	ISRs reported more frequently in AKA 1 mg/kg and 2 mg/kg groups (64% and 63%) compared with placebo 28% Five patients in the AKA groups experienced leukopenia 13.6% (1 mg/kg/day) and 15.3% (2 mg/kg/day) withdrew due to AEs	Fair
Fleischmann et al ⁴ Schiff et al ⁶ Tesser et al ⁵ Fleischmann et al ³³	RCT with open-label follow-up 1399 RCT 6 months Open-label 3 years	>3 month active RA; stable NSAIDs, steroids, DMARDs dose placebo	Rate of ISRs significantly higher in AKA group compared with placebo (72.6% vs 32.9%) At 6 months, there were more serious infections in AKA group (2.1%) vs placebo (0.4%) not statistically significant; after 3 years the exposure adjusted event rates were AKA 5.4/100 patient-years vs placebo 1.6/100 patient-years The event rate for pneumonia occurred was 1.28 per 100 patient-years After 3 years of therapy, incidence rates for melanoma and lymphoma were higher than expected for the general population	Fair
Cohen et al ²⁹	RCT 501 24 weeks	>6 months history of active RA; stable MTX regimen; mean disease duration: 10.5 years. placebo	65% of patients in the AKA groups experienced ISR compared with 24% in the placebo group	Fair
Genovese et al ³⁰	RCT 242 24 weeks	>6-month history of RA; stable dose MTX; approx 50% also using steroids AKA combined with ETA vs ETA alone	More patients receiving AKA in addition to ETA experienced AEs, including ISR and serious infections, compared with ETA alone	Fair
Langer et al ³⁶	Case series efficacy –166 safety –454 up to 6 months	Patients with RA receiving AKA; population-based	Rate of adverse events was similar to those reported in efficacy trials 42.2% of patients experienced AEs: 20.7% had ISRs; 4.2% serious AEs; 5.1% infectious episodes.	Fair
Listing et al ³⁴	Prospective cohort study 1529 Up to 12 months	Infections in patients with RA treated with AKA, ETA, INF, DMARDs (German RABBIT cohort)	70 patients received open-label AKA. Those that received a biologic had more severe disease than the control patients receiving a DMARD Infections were observed in 13% of AKA patients compared to 6% of control patients AEs occurred at a rate of 17.5/100 patient-years for AKA Serious AEs occurred at 3.2/100 patient-years	Fair

(Continued)

Table 4 (Continued)

First author	Study design N Duration	Population comparison	Results	Quality rating
Zink et al ³⁵	Prospective cohort study 1523 12 months	Patients with RA treated with AKA, ETA, INF (German RABBIT cohort)	Of the 70 patients receiving AKA, 41% discontinued treatment within 12 months: 16.3% discontinued due to AEs; 29.6% discontinued due to lack of efficacy In comparison, 31.4% of patients receiving ETA and 34.6% of patients receiving INF discontinued therapy within 12 months	Fair

Abbreviations: ACR 20/50/70, American College of Rheumatology (numbers refer to percentage improvement); ADA, adalimumab; AE, adverse event; AKA, anakinra; ASHI, arthritis-specific health index; DAS28, disease activity score; DMARD, disease-modifying antirheumatic drug; ETA, etanercept; EULAR, European League Against Rheumatism; HAQ, Health Assessment Questionnaire; ISR, injections site reaction; MA, meta-analysis; MTX, methotrexate; RA, rheumatoid arthritis; RCT, randomized controlled trial; SF-36, Medical Outcomes Study Short Form 36 Health Survey; SJC, swollen joint count; TJC, tender joint count.

Patients receiving anakinra experienced more injection site reactions and serious infections than patients receiving placebo. The number of patients in the included trials was too small to reach any conclusions regarding malignancies.

Our review has limitations. We did not locate any direct comparisons of anakinra compared with other biologics. Like other authors, we have relied on indirect comparisons to report the comparative efficacy of anakinra with other biologics. Although evidence suggests that adjusted indirect comparisons agree with head-to-head trials if component studies are similar and treatment effects are expected to be consistent in patients included in different trials, results have to be interpreted cautiously. Many of the underlying assumptions of indirect comparisons are not verifiable and confidence intervals are often wide leading to indeterminate results. Nevertheless, in the absence of direct evidence indirect comparisons can provide valuable information about the comparative efficacy of drugs.

Secondly, publication bias is an issue for all systematic reviews. Selective availability of studies with positive results can seriously bias conclusions of systematic reviews, particularly when the focus is on placebo controlled trials which are generally conducted for regulatory approval by the manufacturer of a specific drug. All three placebo-controlled trials included in this review were funded by Amgen, Thousand Oaks, CA, US, the makers of anakinra.

Finally, all of the studies we included for efficacy were conducted in patients with moderate to severe rheumatoid arthritis with an average disease duration of 6 to 10 years who also took anti-inflammatory drugs, corticosteroids and in 3 trials also methotrexate. The applicability of their results to the average patient with rheumatoid arthritis might be limited.

Conclusion

Anakinra is certainly effective for treating moderate to severe RA that is resistant to traditional DMARDs in comparison

with placebo. Indirect comparisons with adalimumab, etanercept and infliximab, however, showed a trend towards greater efficacy for the anti-TNF drugs. Anakinra also seems to be associated with comparably high rates of injection site reactions. The frequency of administration (daily) might also disadvantage anakinra in comparison with these agents, although the subcutaneous route of administration may be preferable to intravenous. Our results and these factors should be taken into account when considering biologic therapy for patients with RA.

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Appendix I

Appendix I Anti-TNF biologic studies included for indirect comparisons with anakinra

Author	Study design	N	Duration	Comparisons	Primary outcome	Population
Furst et al ¹	RCT	636	24 weeks	ADA + Standard RA therapy/Placebo + Standard RA therapy	Safety	Active RA for at least 3 months; DMARD naïve/or on stable regimen; mean disease duration: 10.5 years.
Keystone et al ²	RCT	619	52 weeks	ADA + MTX/Placebo + MTX	Sharp, ACR 20, HAQ	Active RA; on stable MTX regimen; mean disease duration: 11 years.
Kim et al ³	RCT	128	24 weeks	ADA + MTX/MTX	ACR 20	Active RA; had failed at least 1 DMARD treatment; mean disease duration: 6.9 years.
Miyasaka et al ⁴	RCT	352	24 weeks	ADA/Placebo	ACR 20	Active RA; had failed at least 1 DMARD treatment; mean disease duration: 9.5 years.
Van de Putte et al ⁵	RCT	284	12 weeks	ADA/Placebo	ACR 20	Active RA; had failed at least 1 DMARD treatment; mean disease duration: 10 years.
Van de Putte et al ⁶	RCT	544	26 weeks	ADA/Placebo	ACR20	Active RA; had failed at least 1 DMARD treatment; mean disease duration: 11 years.
Weinblatt et al ⁷	RCT	271	24 weeks	ADA + MTX/MTX + Placebo	ACR20, HAQ	Active RA; stable MTX regimen; had failed at least 1 other DMARD; mean disease duration: 12 years.
Klareskog et al ⁸	RCT	682	52 weeks	ETA/MTX/MTX + ETA	Sharp	>6 months active RA; ACR functional class I–III; unsatisfactory response to at least 1 DMARD other than MTX; mean disease duration: 6.5 years.
Lan et al ⁹	RCT	58	12 weeks	ETA + MTX/Placebo + MTX	Number of swollen/tender joints	Active RA > 1 year; stable MTX for 4 weeks; mean disease duration: NR
Moreland et al ¹⁰	RCT	180	12 weeks	ETA/Placebo	Number of swollen/tender joints	Active RA; failed 1 to 4 DMARD treatments; mean disease duration: NR
Moreland et al ^{11,12}	RCT	234	12 weeks	ETA/Placebo	ACR 20/50	Active RA; failed 1 to 4 DMARD treatments other than MTX; mean disease duration: 12 years.
Weinblatt et al ¹³	RCT	89	24 weeks	ETA + MTX/Placebo + MTX	ACR 20	Active RA; >6 months MTX, stable > 1 month; mean disease duration: 13 years
Abe et al ¹⁴	RCT	147	14 weeks	INF + MTX/Placebo + MTX	ACR 20	>6 months history of active RA; mean disease duration 7.9 years.
Kavanaugh et al ¹⁵	RCT	28	12 weeks	INF + MTX/Placebo + MTX	ACR 20	RA < 15 years; MTX > 3 months; mean disease duration 4.9 to 7.5 years.
Maini et al ¹⁶	RCT	43	26 weeks	INF + MTX/Placebo + MTX	Paulus 20	MTX > 6 months; mean disease duration 7.6 to 11.3 years.
Maini et al ¹⁷	RCT	428	30 weeks	INF + MTX/Placebo + MTX	ACR 20	MTX stable >4 weeks; mean disease duration 7.2 to 9.0 years.
Westhovens et al ¹⁸	RCT	1084	22 weeks	INF + MTX/Placebo + MTX	ACR 20	Active RA despite MTX treatment; median disease duration: 15 years.
Zhang et al ¹⁹	RCT	173	18 weeks	INF + MTX/MTX	ACR 20/50/70	Adult outpatients with active RA and insufficient response to standard antirheumatic therapy.

Abbreviations: ACR20/50/70, American College of Rheumatology (numbers refer to percentage improvement); DMARD, disease-modifying antirheumatic drug; ETA, etanercept; HAQ, Health Assessment Questionnaire; MTX, methotrexate; N, number; NR, not reported; RA, rheumatoid arthritis; RCT, randomized controlled trial.

Appendix I: References

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