

Anakinra for Rheumatoid Arthritis: A Systematic Review

MARTY MERTENS and JASVINDER A. SINGH

ABSTRACT. Objective. To perform a systematic review of clinical effectiveness and safety of anakinra in rheumatoid arthritis (RA).

Methods. We searched Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, CINAHL, and the reference lists of included articles for randomized controlled trials comparing anakinra to placebo in adults with RA.

Results. Five trials involving 2846 patients, 781 randomized to placebo and 2065 to anakinra, were included. There was a significant improvement in the number of participants achieving American College of Rheumatology (ACR)20 (38% vs 23%) treated with anakinra 50–150 mg daily versus placebo after 24 weeks. ACR50 (18% vs 7%), ACR70 (7% vs 2%), Health Assessment Questionnaire, visual analog scale for pain, Larsen radiographic scores, and erythrocyte sedimentation rate all demonstrated significant improvement with anakinra versus placebo as well. There were no statistically significant differences noted in the number of withdrawals, deaths, adverse events (total and serious), and infections (total and serious). An increase in incidence of serious infections in anakinra versus the placebo group (1.8% vs 0.6%) was noted that may be clinically significant. Injection site reactions were significantly increased, occurring in 71% of anakinra versus 28% of placebo group.

Conclusion. Anakinra is a relatively safe and modestly efficacious biologic therapy for RA. More studies are needed to evaluate safety and efficacy, especially in comparison to other therapies, and adverse event data for the longterm use of anakinra have yet to be assessed. (First Release May 15 2009; J Rheumatol 2009;36:1118–25; doi:10.3899/jrheum.090074)

Key Indexing Terms:

ANAKINRA
BIOLOGIC

INTERLEUKIN 1

RHEUMATOID ARTHRITIS
SYSTEMATIC REVIEW

Rheumatoid arthritis (RA) is the most common systemic inflammatory arthritis in adults, affecting 0.5% to 1% of the population worldwide¹, leading to significant pain, stiffness, and functional limitation, reduced quality of life, and work

disability². The pathogenesis of RA is largely driven by the activation of T cells³ and macrophages⁴ and subsequent release of various chemokines, metalloproteinases, and inflammatory cytokines, including tumor necrosis factor (TNF), interleukin 1 (IL-1), and IL-6⁵. These cytokines initiate and maintain the synovial and systemic inflammatory process present in RA.

In the past decade, a novel class of therapies called the biologics, which target specific inflammatory cytokines such as TNF- α and IL-1, have greatly improved and expanded treatment for RA. Anakinra is an IL-1 receptor antagonist (IL-1ra) that is currently approved by the US Food and Drug Administration (FDA) for moderate-severe RA that has been unresponsive to initial disease modifying antirheumatic drug (DMARD) therapy. Animal models that develop an overproduction of IL-1 have demonstrated cartilage and joint histopathologic changes that are very similar to RA⁶. IL-1 has also been demonstrated to stimulate osteoclast precursor differentiation and osteoclast activity, likely indicating a further role in the osteopenia and joint destruction seen with RA⁷. Blockade of IL-1 was associated with prevention of bone and cartilage destruction in a murine collagen arthritis model⁸ and other inflammatory effects of IL-1 were blocked by IL-1 antagonist⁹.

From the Medicine Service and Rheumatology Section, VA Medical Center, and Division of Rheumatology, Department of Medicine, University of Minnesota, Minneapolis; and Department of Health Sciences and Orthopaedic Surgery, Mayo Clinic School of Medicine, Rochester, Minnesota, USA.

This is a version of a Cochrane Review, which is available in The Cochrane Library – Issue 1, 2009.

Supported by National Institutes of Health CTSA Award 1 KL2 RR024151-01 (Mayo Clinic Center for Clinical and Translational Research).

The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs.

M. Mertens, MD, Medicine Service and Rheumatology Section, VA Medical Center; J.A. Singh, MD, MPH, Medicine Service and Rheumatology Section, VA Medical Center and Division of Rheumatology, Department of Medicine, University of Minnesota, and Department of Health Sciences and Orthopaedic Surgery, Mayo Clinic School of Medicine.

Address reprint requests to Dr. J.A. Singh, Minneapolis VA Medical Center, Rheumatology (111R), One Veteran's Drive, Minneapolis, MN 55417. E-mail: Jasvinder.md@gmail.com

Accepted for publication January 30, 2009.

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2009. All rights reserved.

Anakinra (tradename: Kineret) is the recombinant form of a human IL-1ra, and is the first biologic agent designed specifically to modify the biological immune response of IL-1. It has been found in a number of studies to significantly improve clinical markers of RA and was approved by the FDA in 2001 for patients with moderate-severe RA who failed at least 1 DMARD therapy¹⁰. It is administered as a daily subcutaneous injection and adverse effects primarily include injection-site reactions, although infections and a possible risk of malignancy are also of concern^{10,11}. Our systematic review summarizes the previous randomized control trials (RCT) evaluating the clinical effectiveness and safety of anakinra for the treatment of RA.

MATERIALS AND METHODS

The following were the criteria for including studies for our review.

Study design. RCT comparing anakinra alone or in combination with other DMARD/biologics to placebo or other DMARD/biologics.

Types of participants. Adults 18 years of age and older meeting the American College of Rheumatology (ACR) 1987 revised criteria for RA¹².

Interventions. Anakinra alone or in combination with other drugs.

Outcome measures. Primary efficacy outcomes for our review include the number achieving an ACR20 response and improvement in Disease Activity Score (DAS)/DAS28. An ACR20 response is defined by a 20% improvement in tender and swollen joint counts and the same level of improvement in 3 of the 5 following variables: patient/physician global assessments, pain scores, Health Assessment Questionnaire (HAQ) score, and laboratory acute-phase reactants¹³. DAS scores are a composite index that includes the combination of tender and swollen joint counts, patient's global assessment of disease activity, and erythrocyte sedimentation rate (ESR)¹⁴. A DAS28 score is used when a 28-joint count is used as the index¹⁵.

Primary safety outcomes included in our review are the number of withdrawals, adverse events, injection site reactions, serious adverse events, infections (total and serious), and deaths.

Secondary efficacy outcomes include the following: (1) ACR50 and ACR70 responses; (2) number achieving a good European League Against Rheumatism (EULAR) response¹⁶ as defined by a decrease in the DAS or DAS28 of > 1.2 from baseline with a final DAS < 2.4 (or DAS28 < 3.2)^{16,17}; (3) number achieving low disease activity as defined by DAS < 2.4 or DAS < 3.2^{16,17}; (4) number achieving disease remission as defined by DAS < 1.6 or DAS < 2.6^{17,18}; (5) radiographic progression — as measured by the Sharp¹⁹, modified Sharp²⁰, or Larsen scores¹⁵; (6) change in health related quality of life as measured by change in mental and physical component scores (MCS and PCS) of the Medical Outcomes Study Short Form-36 (SF-36), proportion achieving minimal clinical important difference (MCID) in MCS/PCS scores (defined as change of 2.5–5 units)^{21–23}; (7) functional change as measured by changes in Stanford HAQ or modified HAQ^{24,25} scores, proportion achieving MCID (defined as $\Delta \geq 0.22$)²⁶ or population norm for HAQ (score = 0.25)²⁷; (8) change in visual analog scale (VAS) scores for pain; and (9) change in inflammatory markers — ESR and C-reactive protein (CRP).

Search methods for identification of studies. The following electronic bibliographic databases were searched up to February 2008: Cochrane Library and the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, CINAHL, and EMBASE. The reference lists of identified publications, including previous metaanalyses, were reviewed to identify any additional studies and/or citations. No language restrictions were applied and translations were obtained when necessary. Where information was missing, further information was sought from the authors or industry. Data from studies with multiple publications were extracted and reported as the original study.

Data collection and analysis. The 2 review authors independently applied inclusion/exclusion criteria to all potential studies, extracted efficacy and safety data using a standardized form, and assessed methodology quality. Any disagreements were resolved by discussion between the 2 reviewers, referring to a third party if necessary. Review authors were not blinded to any features of studies, since unblinding has minimal influence on selection bias²⁸. Figure 1 provides the details of search results and screening process.

Data extracted from each trial included study population and baseline characteristics of the intervention and control groups; details of the intervention — including dose, mode of administration, frequency of administration, duration of treatment, and coadministered medication; withdrawal rates; details of data lost to followup; individual outcomes as noted above — including ACR outcomes, DAS/DAS28 scores, pain scales, radiographic scores, and changes in quality of life or functional scores (e.g., SF-36, HAQ, mHAQ); and safety outcome data including adverse events (serious, total, injection site reactions), infections (serious, total), and number of deaths.

Results were extracted, where possible, for the intention to treat population, as raw numbers, plus any summary measures where standard deviations, confidence intervals (CI), or p values were given. For dichotomous outcomes, the absolute risk difference was calculated and presented and the number needed to treat (NNT) determined by 1/absolute risk difference value. For continuous outcomes the mean difference was calculated and presented. Relative percentage change from baseline was calculated as the absolute benefit divided by the baseline mean of the respective group. Ninety-five percent CI were defined for efficacy. In addition to reviewing forest plots, heterogeneity of the data was formally tested using the I² statistic, with a value greater than 50% indicating substantial heterogeneity²⁹. In the case of substantial heterogeneity, the data were explored further with subgroup analyses. In the absence of significant heterogeneity, a fixed-effects model was used. If significant heterogeneity existed, a random-effects model was used. A funnel plot was created to assess the possibility of publication bias.

The following subgroup analyses were planned to investigate possible differences: (1) variable anakinra dosage or duration of treatment; and (2) anakinra used in combination with methotrexate (MTX) or other specified DMARD therapy.

Quality assessment strategy. The validity of included studies was assessed by looking at the method of randomization, the concealment of allocation, the comparability of baseline characteristics between the different arms, blinding, number of withdrawals, and number of patients lost to followup. A quality of evidence was based upon the following scale: Platinum, Gold, Silver, or Bronze, as defined by the Cochrane Musculoskeletal Group and Tugwell, *et al*³⁰, as performed for other systematic reviews^{31,32}.

RESULTS

An overview of the included studies is provided in Table 1. Five trials^{33–37}, representing a total of 2846 patients (781 placebo, 2065 anakinra), were included in our review. Bresnihan 1998³³ and Fleischman 2003³⁴ compared anakinra with placebo. Cohen 2002³⁵ and Cohen 2004³⁶ compared anakinra + MTX with placebo + MTX. Genovese 2004³⁷ had the following comparisons: anakinra + etanercept biweekly, anakinra + etanercept weekly, and placebo + etanercept biweekly. For true placebo-controlled comparisons, only the anakinra + etanercept biweekly and placebo + etanercept biweekly data were used for our review.

Cohen 2004³⁶, Fleischman 2003³⁴, and Genovese 2004³⁷ used anakinra 100 mg subcutaneous daily dosing. Bresnihan 1998³³ used doses of 30 mg, 75 mg, and 150 mg subcutaneously daily of anakinra. Cohen 2002³⁵ used the following

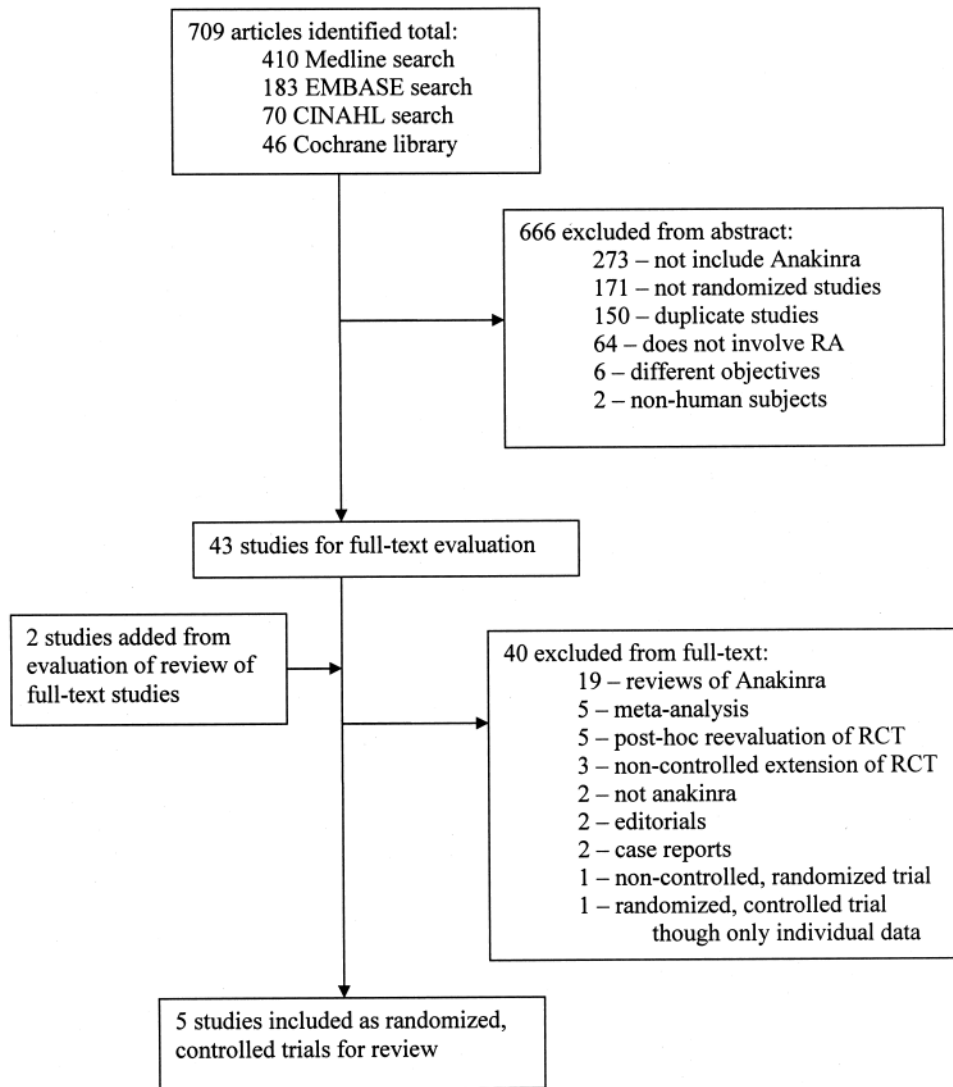


Figure 1. Collection of studies for the systematic review.

doses: 0.04 mg/kg, 0.1 mg/kg, 0.4 mg/kg, 1.0 mg/kg, and 2.0 mg/kg daily, which was computed to approximate doses of 3 mg, 7.5 mg, 30 mg, 75 mg, and 150 mg for our review given average adult weight of 75 kg. Due to the large variability in doses, 2 groups were created to help with data analysis based on the current standard dose of anakinra 100 mg daily being used in clinical practice: doses of < 50 mg/day of anakinra and doses of 50–150 mg/day of anakinra. For continuous data, data from the same study were analyzed separately to avoid double-counting of the placebo groups. The Cohen 2002 study³⁵ did not report standard deviations or errors when describing its continuous data results. Therefore, we were unable to use these data.

With inclusion of all 5 studies, there was noted significant heterogeneity for ACR20 (the primary outcome) with an I^2 statistic of 80.7%. This was thought to be secondary to the Genovese 2004 study³⁷, since it compared anakinra to

placebo in the setting of etanercept, a significant variation from the other studies and from standard clinical practice. After removal of the Genovese 2004 study, heterogeneity was noted to be 0% for the primary outcome and < 50% for the majority of secondary efficacy outcomes. Significant heterogeneity (> 50%) was present for HAQ scores, total infections, and total adverse events.

Subgroup analysis was performed between studies that compared anakinra to placebo^{19,22} and studies comparing anakinra + MTX to placebo + MTX^{20,21}.

Due to the small number of studies for the primary outcome, ACR20, a funnel plot for evaluation of publication bias was not interpretable.

Efficacy results. Primary outcomes: A significantly greater proportion of patients receiving anakinra 50–150 mg daily versus those receiving placebo achieved ACR20, 38% versus 23%, respectively [relative risk (RR) 1.61 (95% CI 1.32

Table 1. Studies included in this systematic review.

Study	No. of Participants	Duration	Interventions	Outcomes	Methodological Quality*	Notes
Bresnihan 1998 ³³	472	24 wks	Placebo (n = 119), 30 mg anakinra (n = 119), 75 mg anakinra (n = 115), 150 mg anakinra (n = 115)	ACR 20, HAQ, VAS (pain), ESR, CRP, Larsen scores, withdrawals, injection site reactions	Silver; no intention-to-treat analysis; method of randomization was not reported; 26.7% withdrawal rate	Excluded patient data from analysis if outcome data was missing
Cohen 2002 ³⁵	317	24 wks	Placebo (n = 48), 0.04 mg/kg (n = 63), 0.1 mg/kg (n = 46), 0.4 mg/kg (n = 55), 1.0 mg/kg (n = 59), 2.0 mg/kg (n = 46) daily. Methotrexate was required for inclusion in this study	ACR20/50/70, withdrawals, injection site reactions (continuous data not included as no SD/SE data provided)	Silver; method of randomization was not reported; blinding was only described for the patients; 21% withdrawal rate at 24 weeks	Originally designed as a 12 wk trial, expanded to 24 wks; only 3 patients reconsented to the 24 wk study
Cohen 2004 ³⁶	506	24 wks	Placebo (n = 251), anakinra 100 mg daily (n = 250)	ACR20/50/70, HAQ, ESR, injection site reactions, adverse events (total, serious), infections (total, serious),	Silver; no intention-to-treat analysis; method of randomization was not reported	Number of total withdrawals was not reported in this study
Fleischman 2003 ³⁴	1414	6 mo	Placebo (n = 283), anakinra 100 mg daily (n = 1116)	withdrawals, injection site reactions, deaths, adverse events (total, serious), infections (total, serious)	Silver; no intention-to-treat analysis; method of randomization was not reported; 21.9% withdrawal rate	
Genovese 2004 ³⁷	244	24 wks	Placebo + etanercept 25 mg biweekly (n = 80), anakinra 100 mg daily + etanercept 25 mg weekly (n = 81), anakinra 100 mg daily + etanercept 25 mg biweekly (n = 81). Methotrexate was required for inclusion in this study	ACR20/50/70, withdrawals, injection site reactions, adverse events (total, serious), infections (total, serious)	Silver; though full blinding was only reported for the patients; no intention-to-treat analysis; method of randomization was not reported; 17.4% withdrawal rate	The anakinra+ etanercept 25 mg weekly group did not have a placebo-controlled comparison

* Methodological quality was defined using the system described by Tugwell, *et al*³⁰ as follows: Platinum: A published systematic review that has at least 2 individual controlled trials each satisfying the following: Sample size of at least 50 per group — if these do not find a statistically significant difference, they are adequately powered for a 20% relative difference in the relevant outcome. Blinding of patients and assessors for outcomes. Handling of withdrawals > 80% followup [imputations based on methods such as last observation carried forward (LOCF) are acceptable]. Concealment of treatment allocation. Gold: At least 1 randomized clinical trial meeting all the following criteria for the major outcome(s) as reported: Sample sizes of at least 50 per group — if these do not find a statistically significant difference, they are adequately powered for a 20% relative difference in the relevant outcome. Blinding of patients and assessors for outcomes. Handling of withdrawals > 80% followup (imputations based on methods such as LOCF are acceptable). Concealment of treatment allocation. Silver: A randomized trial that does not meet the above criteria. Silver ranking would also include evidence from at least 1 study of non-randomized cohorts that did and did not receive the therapy, or evidence from at least one high quality case-control study. A randomized trial with a “head-to-head” comparison of agents would be considered silver level ranking unless a reference were provided to a comparison of one of the agents to placebo showing at least a 20% relative difference. Bronze: The bronze ranking is given to evidence if a least 1 high quality case series without controls (including simple before/after studies in which patients act as their own control) or if the conclusion is derived from expert opinion based on clinical experience without reference to any of the foregoing (for example, argument from physiology, bench research, or first principles). ACR: American College of Rheumatology; HAQ: Health Assessment Questionnaire; VAS: visual analog scale; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; SD/SE: standard deviation/error.

to 1.98)]. This resulted in an absolute treatment benefit of 15% with NNT of 6.7 after 24 weeks. The Genovese 2004 study³⁷ demonstrated no benefit with addition of anakinra to etanercept therapy compared to placebo for the proportion of patients achieving ACR20 at 24 weeks.

None of the included studies evaluated DAS or DAS28 as outcome data.

Secondary outcomes: There was significant improvement noted in the proportion achieving ACR50 and ACR70 outcomes with anakinra doses 50–150 mg/day compared to

placebo after 24 weeks as well. For ACR50, 18% of anakinra versus 7% placebo-treated patients achieved this outcome after 24 weeks [RR 2.51 (95% CI 1.56, 4.03)], with an absolute treatment benefit of 11%; the NNT was 9.1 (Table 2). For ACR70, 7% of anakinra versus 2% of placebo-treated patients achieved this outcome after 24 weeks [RR 3.71 (95% CI 1.44, 9.77)], with an absolute treatment benefit of 5% with NNT of 20. The Genovese 2004 study³⁷ did not find any treatment benefit with anakinra in addition to etanercept compared to placebo for ACR50 or ACR70 outcomes.

Table 2. Anakinra (50–150 mg/kg) vs placebo, ACR 20/50/70 at 24 wks.

Study (Reference)	ACR20			ACR50			ACR70		
	Anakinra n/N (%)	Placebo n/N (%)	NNT	Anakinra n/N (%)	Placebo n/N (%)	NNT	Anakinra n/N (%)	Placebo n/N (%)	NNT
Anakinra vs placebo									
Bresnihan 1998 ³³	88/230 (38)	32/119 (27)	9.1	No data	No data	No data	No data	No data	No data
Fleischman 2003 ³⁴	No data	No data	No data	No data	No data	No data	No data	No data	No data
Anakinra + Methotrexate vs Placebo + Methotrexate									
Cohen 2002 ³⁵	41/105 (39)	11/48 (23)	6.3	22/105 (21)	2/48 (4)	5.9	9/105 (9)	0/48 (0)	11.1
Cohen 2004 ³⁶	95/250 (38)	55/251 (22)	6.3	43/250 (17)	20/251 (8)	11.1	15/250 (6)	5/251 (2)	25
Totals (w/o Genovese)	224/585 (38)	98/418 (23)	6.7	65/355 (18)	22/299 (7)	9.1	24/355 (7)	5/299 (2)	20
Anakinra + Methotrexate + Etanercept vs Placebo + Methotrexate + Etanercept									
Genovese 2004 ³⁷	50/81 (62)	54/80 (68)	NA	25/81 (31)	33/80 (41)	NA	11/81 (14)	17/80 (21)	NA
Totals (w/Genovese)	274/666 (41)	152/498 (31)	10	90/436 (21)	55/379 (15)	16.7	35/436 (8)	22/379 (6)	50

NA: not available.

There were significant improvements with both pain VAS and HAQ scores with anakinra doses 50–150 mg/day at 24 weeks of treatment (Table 3). Only 1 study³³ utilized a standard radiographic scale — Larsen scores — for outcome data, and it found significant improvement with anakinra 50–150 mg/day doses after 24 weeks when compared to placebo. There were also significant improvements noted in change in ESR with anakinra doses 50–150 mg/day compared to placebo after 24 weeks of treatment. No significant difference was noted with change in CRP between anakinra and placebo.

Other secondary outcomes described above in the Methods section were not analyzed as outcome data in the included studies.

Safety outcomes. There was no difference in the number of withdrawals for anakinra 50–150 mg/day compared to placebo after 24 weeks, with both groups having 22% with-

drawal rates (Table 4). Only 1 study³⁴ presented mortality data after 24 weeks and found no significant difference in the anakinra 50–150 mg/day doses versus placebo groups, occurring in 0.3% of each group.

The total number of adverse events was not significantly increased in patients treated with anakinra 50–150 mg/day compared to placebo, occurring in 92% versus 87% of anakinra versus placebo-treated patients, after 24 weeks [RR 1.05 (95% CI 0.94, 1.17)]. However, in the anakinra + MTX subgroup, there was a significant increase in the total adverse events compared to placebo [RR 1.11 (95% CI 1.03, 1.20)] while no significant difference was found in the anakinra-alone subgroup compared to placebo [RR 1.00 (95% CI 0.96, 1.04)]. The majority of adverse events were injection-site reactions, which occurred significantly more often in the anakinra 50–150 mg/day group versus placebo group at rates of 71% versus 28%, respectively. There was

Table 3. Secondary outcome data for anakinra 50–150 mg compared to placebo[†].

	Mean at Baseline	Mean Difference (Confidence intervals)	Relative Change from Baseline*	Studies Providing Data
Change in HAQ	1.49	-0.19 (-0.30, -0.09)	0.13	Bresnihan 1998 ³³ Cohen 2004 ³⁶
Change in VAS (pain)	0.64	-0.10 (-0.15, -0.04)	0.16	Bresnihan 1998 ³³
Change in Larsen scores	13.5	-2.45 (-4.53, -0.36)	0.18	Bresnihan 1998 ³³
Change in ESR	45.97	-10.04 (-12.75, -7.33)	0.22	Bresnihan 1998 ³³ Cohen 2004 ³⁶
Change in CRP	4.1	-0.6 (-1.26, 0.06)	0.15	Bresnihan 1998 ³³

[†] Data exclude outcome data from Genovese 2004³⁷. * Relative change from baseline = mean difference/mean at baseline. HAQ: Health Assessment Questionnaire; VAS: visual analog scale; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

Table 4. Safety outcome data for anakinra 50–150 mg compared to placebo[†].

	Anakinra, n/N (%)	Placebo, n/N (%)	Absolute Risk Difference (%)	NNH*	Risk Ratio (Confidence intervals)	Studies
Withdrawals	331/1479 (22.4)	106/478 (22.2)	0.2	500	1.04 (0.86, 1.27)	Cohen 2002 ³⁵ Fleischman 2003 ³⁴ Bresnihan 1998 ³³ Fleischman 2003 ³⁴
Deaths	4/1116 (0.4)	1/283 (0.4)	0	α	1.01 (0.11, 9.04)	Fleischman 2003 ³⁴
Adverse events	1252/1366 (91.7)	464/534 (86.9)	4.8	20.8	1.05 (0.94, 1.17)	Fleischman 2003 ³⁴ Cohen 2004 ³⁶
Serious adverse events	96/1366 (7.0)	30/534 (5.6)	1.4	71	1.04 (0.70, 1.56)	Fleischman 2003 ³⁴ Cohen 2004 ³⁶
Injection site reactions	1235/1729 (71.4)	204/729 (28.0)	43.4	2.3	2.45 (2.17, 2.77)	Cohen 2002 ³⁵ Cohen 2004 ³⁶ Fleischman 2003 ³⁴ Bresnihan 1998 ³³
Total infections	543/1366 (39.8)	188/534 (35.2)	4.5	22	1.08 (0.80, 1.45)	Fleischman 2003 ³⁴ Cohen 2004 ³⁶
Serious infections	25/1366 (1.8)	3/534 (0.6)	1.2	83	3.15 (0.81, 12.20)	Fleischman 2003 ³⁴ Cohen 2004 ³⁶

[†] Data exclude safety data from Genovese 2004³⁷. * NNH (number needed to harm) = 1/absolute risk difference.

no significant difference in serious adverse events with anakinra 50–150 mg/day in comparison to placebo, occurring in 7% versus 6% of patients of each group. Malignancy data were reported in the Fleischman 2003 and Cohen 2002 studies; Fleischman³⁴ reported 4 malignancies (0.4%) in the anakinra group versus 4 malignancies (1.8%) in the placebo group, while Cohen³⁵ reported 1 malignancy each in the anakinra (0.8%) and placebo groups (1.4%).

The total rate of infections was not significantly increased in the anakinra 50–150 mg/day group compared to placebo after 24 weeks, occurring in 40% of the anakinra versus 35% of the placebo group [RR 1.08 (95% CI 0.80, 1.45)]. Similarly, no significant difference was noted in the rate of serious infections — 1.8% versus 0.6%, respectively [RR 3.15 (95% CI 0.81, 12.20)]. The specific types of serious infections were only reported in the Fleischman 2003 study³⁴. In this study, of the 24 serious infections reported, 23 occurred in the anakinra group (n = 1116) and 1 occurred in the placebo group (n = 283). The most common infections were pneumonia in 10 patients and cellulitis in 3 patients. Opportunistic infections were not reported in any of the included studies.

The Genovese 2004 study³⁷ reported a significant increase in the total number of withdrawals, serious adverse events, and injection-site reactions in patients treated with anakinra + etanercept compared to placebo + etanercept. No significant differences were seen in the number of infections (total or serious) between these 2 groups.

DISCUSSION

Our systematic review summarizes the data from 5 randomized controlled trials of anakinra totaling 2846 patients with

RA. There was a significant improvement in the proportion of patients achieving ACR20 with anakinra 50–150 mg daily compared to placebo after 24 weeks, with an absolute treatment benefit of 15% (38% vs 23%). Similar significantly greater improvements were noted in anakinra 50–150 mg daily compared to placebo for ACR50, ACR70, HAQ scores, and change in ESR and VAS pain scores.

When compared to other systematic reviews of etanercept and adalimumab for RA, the absolute differences in patients achieving ACR20, ACR50, and ACR70 was notably less for anakinra. In a systematic Cochrane review of etanercept 25 mg biweekly, there was a 49%, 39%, and 14% absolute treatment benefit over placebo in patients achieving ACR20, ACR50, and ACR70, respectively, after 6 months³¹. In a systematic Cochrane review of adalimumab 40 mg every other week, there were ranges of 18% to 53%, 18% to 47%, and 10% to 22% absolute treatment benefits over placebo for ACR20, ACR50, and ACR70, respectively, after 24 weeks (heterogeneity prevented pooling of RCT for adalimumab)³². In comparison, the absolute treatment benefits with anakinra 50–150 mg daily after 6 months were 15%, 11%, and 5% over placebo for ACR20, ACR50, and ACR70, each with a notably lower absolute treatment benefit than etanercept or adalimumab. This implies possible lower efficacy of anakinra versus other biologics. We are unaware of studies directly comparing treatment benefits between these biologic medications. Direct comparison studies of biologic therapies can more definitively answer this question.

There was no statistically significant difference between anakinra and placebo groups for the rate of withdrawals, deaths, adverse events (total and serious), and infections (total and serious). Injection-site reactions were significant-

ly increased in patients treated with anakinra (71%) versus placebo (28%). While serious infection rates between anakinra and placebo — 1.8% versus 0.6% — were not statistically significantly different, the 3-times higher rate for serious infections with anakinra seems clinically significant. A FDA warning related to this increased incidence of serious infections recommends discontinuation of anakinra in patients with active infections and/or if a patient develops serious infections¹⁰. The FDA also noted that the safety and efficacy of anakinra has not been evaluated in immunosuppressed patients and in those with chronic infections¹⁰. The risk of serious infections was even higher when anakinra was combined with etanercept without improvement in benefit noted with etanercept alone¹⁰. Larger registry-based post-marketing studies are needed to assess this potential increased risk and other rare events, such as opportunistic infections and malignancies.

Our review has several limitations. Significant variability in the sample sizes, reported outcomes, different anakinra doses, and lack of reporting of standard deviation in 1 study³⁵ limited the power of our systematic review. Fleischman 2003³⁴ included a much larger patient population (n = 1414) than other studies (n = 244 to 506), likely biasing the safety data. This may explain the significant heterogeneity found with the total number of adverse events and total infections following removal of the Genovese 2004 study. In addition, Fleischman 2003 included only safety outcomes, and Bresnihan 1998³³ did not include ACR50 or ACR70 data. Bresnihan 1998 and Cohen 2002³⁵ used varying ranges of doses of anakinra. We adjusted for this variability by pooling data to those utilizing < 50 mg/day and 50–150 mg/day of anakinra to allow for data analysis. Due to the limited number of studies, we were unable to examine for possible differences between different anakinra doses.

Our review is also limited by the same methodological deficits of the studies included. While the studies were RCT, the method of randomization was not reported in any study and a number of studies reported blinding without any details. Only the Cohen 2002 study³⁵ described a true intention to treat analysis; the other studies excluded patients from analysis if they did not receive at least 1 dose of a study drug (excluding a total of 30 patients). Bresnihan 1998³³ excluded 129 patients from the analysis for Larsen scores, citing missing data as the reason, introducing significant bias into the study, in particular resulting in the exclusion of 129 patients from their analysis of this outcome.

Anakinra is currently FDA-approved for the treatment of RA unresponsive to initial DMARD therapy. Our systematic review demonstrated significant improvement in the proportion of patients achieving an ACR20 response with anakinra versus placebo, as well as a significant improvement in a number of other efficacy outcomes including ACR50, ACR70, HAQ scores, VAS scores, and ESR. There was a significant increase in the number of injection-site

reactions, although no differences in infections (total or serious) or adverse events (total or serious) rates were noted. With the limitations of our review as described, the possible clinically significant increase in serious infections with anakinra, and the only modest absolute improvements in ACR outcomes compared to other biologic medications, the utility of anakinra for the treatment of RA is likely limited. The utility of anakinra may be better addressed through post-marketing surveillance studies to better inform patients and physicians about more rare or longterm safety outcomes, and studies comparing anakinra to other biologics to help clarify the relative efficacies of these agents for treatment of RA.

ACKNOWLEDGMENT

We thank Louise Falzon of the Cochrane Library for her support with electronic searches, and Rod MacDonald of the Minneapolis VA Medical center for assisting with this review.

REFERENCES

- Gabriel SE. The epidemiology of rheumatoid arthritis. *Rheum Dis Clin North Am* 2001;27:269-81.
- Yelin E. Work disability in rheumatic diseases. *Curr Opin Rheumatol* 2007;19:91-6.
- Cope AP. T cells in rheumatoid arthritis. *Arthritis Res Ther* 2008;10 Suppl 1:S1.
- Szekanecz Z, Koch AE. Macrophages and their products in rheumatoid arthritis. *Curr Opin Rheumatol* 2007;19:289-95.
- Choy EH, Panayi GS. Cytokine pathways and joint inflammation in rheumatoid arthritis. *N Engl J Med* 2001;344:907-16.
- Abramson SB, Amin A. Blocking the effects of IL-1 in rheumatoid arthritis protects bone and cartilage. *Rheumatology* 2002;41:972-80.
- Goldring SR, Gravalles EM. Pathogenesis of bone lesions in rheumatoid arthritis. *Curr Rheumatol Rep* 2002;4:226-31.
- Joosten LA, Helsen MM, Saxne T, van de Loo FA, Heinegard D, van den Berg WB. IL-1 alpha beta blockade prevents cartilage and bone destruction in murine type II collagen-induced arthritis, whereas TNF-alpha blockade only ameliorates joint inflammation. *J Immunol* 1999;163:5049-55.
- Dinarello CA. The role of the interleukin-1-receptor antagonist in blocking inflammation mediated by interleukin-1. *N Engl J Med* 2000;343:732-4.
- FDA. Kineret (anakinra) physician packet insert: Kineret (anakinra) prescribing information. Rockville, MD: U.S. Food and Drug Administration; 2001. [Internet. Accessed March 19, 2009.] Available from: <http://www.Fda.Gov/cder/foi/label/2001/anakamg111401lb.pdf>
- American College of Rheumatology subcommittee on rheumatoid arthritis guidelines. Guidelines for the management of rheumatoid arthritis: 2002 update. *Arthritis Rheum* 2002;46:328-46.
- Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988;31:315-24.
- Felson DT, Anderson JJ, Boers M, et al. American College of Rheumatology. Preliminary definition of improvement in rheumatoid arthritis. *Arthritis Rheum* 1995;38:727-35.
- Prevo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. *Arthritis Rheum* 1995;38:44-8.

15. Larsen A, Dale K, Eek M. Radiographic evaluation of rheumatoid arthritis and related conditions by standard reference films. *Acta Radiol Diagn (Stockh)* 1977;18:481-91.
16. van Gestel AM, Prevoo ML, van 't Hof MA, van Rijswijk MH, van de Putte LB, van Riel PL. Development and validation of the European League Against Rheumatism response criteria for rheumatoid arthritis. Comparison with the preliminary American College of Rheumatology and the World Health Organization/International League Against Rheumatism criteria. *Arthritis Rheum* 1996;39:34-40.
17. Fransen J, van Riel PL. The disease activity score and the EULAR response criteria. *Clin Exp Rheumatol* 2005;23:S93-9.
18. Prevoo ML, van Gestel AM, van 't Hof MA, van Rijswijk MH, van de Putte LB, van Riel PL. Remission in a prospective study of patients with rheumatoid arthritis. American Rheumatism Association preliminary remission criteria in relation to the disease activity score. *Br J Rheumatol* 1996;35:1101-5.
19. Sharp JT, Lidsky MD, Collins LC, Moreland J. Methods of scoring the progression of radiologic changes in rheumatoid arthritis. Correlation of radiologic, clinical and laboratory abnormalities. *Arthritis Rheum* 1971;14:706-20.
20. van der Heijde DM, van Riel PL, Nuver-Zwart IH, Gribnau FW, van de Putte LB. Effects of hydroxychloroquine and sulphasalazine on progression of joint damage in rheumatoid arthritis. *Lancet* 1989;1:1036-8.
21. Kosinski M, Zhao SZ, Dedhiya S, Osterhaus JT, Ware JE Jr. Determining minimally important changes in generic and disease-specific health-related quality of life questionnaires in clinical trials of rheumatoid arthritis. *Arthritis Rheum* 2000;43:1478-87.
22. Samsa G, Edelman D, Rothman ML, Williams GR, Lipscomb J, Matchar D. Determining clinically important differences in health status measures: A general approach with illustration to the Health Utilities Index mark II. *Pharmacoeconomics* 1999;15:141-55.
23. Tugwell P, Wells G, Strand V, et al. Clinical improvement as reflected in measures of function and health-related quality of life following treatment with leflunomide compared with methotrexate in patients with rheumatoid arthritis: Sensitivity and relative efficiency to detect a treatment effect in a twelve-month, placebo-controlled trial. *Leflunomide Rheumatoid Arthritis Investigators Group. Arthritis Rheum* 2000;43:506-14.
24. Fries JF, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. *Arthritis Rheum* 1980;23:137-45.
25. Pincus T, Summey JA, Soraci SA Jr, Wallston KA, Hummon NP. Assessment of patient satisfaction in activities of daily living using a modified Stanford Health Assessment Questionnaire. *Arthritis Rheum* 1983;26:1346-53.
26. Wells GA, Tugwell P, Kraag GR, Baker PR, Groh J, Redelmeier DA. Minimum important difference between patients with rheumatoid arthritis: The patient's perspective. *J Rheumatol* 1993;20:557-60.
27. Krishnan E, Sokka T, Hakkinen A, Hubert H, Hannonen P. Normative values for the Health Assessment Questionnaire Disability Index: Benchmarking disability in the general population. *Arthritis Rheum* 2004;50:953-60.
28. Berlin JA. Does blinding of readers affect the results of meta-analyses? University of Pennsylvania Meta-analysis Blinding Study Group. *Lancet* 1997;350:185-6.
29. Higgins JP, Thompson SG. Controlling the risk of spurious findings from meta-regression. *Stat Med* 2004;23:1663-82.
30. Tugwell P, Shea B, Boers M, Brooks P, Simon L, Strand V. Evidence-based rheumatology. London: Blackwell BMJ Books; 2003.
31. Blumenauer B, Judd M, Cranney A, et al. Etanercept for the treatment of rheumatoid arthritis. *Cochrane Database Syst Rev* 2003;CD004525.
32. Navarro-Sarabia F, Ariza-Ariza R, Hernandez-Cruz B, Villanueva I. Adalimumab for treating rheumatoid arthritis. *Cochrane Database Syst Rev* 2005;CD005113.
33. 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.
34. Fleischman 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.
35. 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.
36. 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.
37. 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.