

Anakinra for rheumatoid arthritis (Review)

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[Intervention Review]

Anakinra for rheumatoid arthritis

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Cochrane Database of Systematic Reviews, Issue 3, 2009 (Status in this issue: *Unchanged*)

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DOI: 10.1002/14651858.CD005121.pub3

This version first published online: 21 January 2009 in Issue 1, 2009.

Last assessed as up-to-date: 5 February 2008. (Help document - [Dates and Statuses](#) explained)

This record should be cited as: Mertens M, Singh JA. Anakinra for rheumatoid arthritis. *Cochrane Database of Systematic Reviews* 2009, Issue 1. Art. No.: CD005121. DOI: 10.1002/14651858.CD005121.pub3.

ABSTRACT

Background

In the past decade, a novel class of therapies directed against specific cytokines implicated in the disease process of rheumatoid arthritis (RA), called the 'Biologics' have greatly improved and expanded treatment for RA. Anakinra is an interleukin-1 receptor antagonist that is currently FDA-approved for moderate-severe RA that has been unresponsive to initial disease-modifying anti-rheumatic drugs (DMARD) therapy.

Objectives

To evaluate the clinical effectiveness and safety of anakinra in adult patients with rheumatoid arthritis.

Search strategy

We searched the following electronic databases: the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* Issue 1, 2008), MEDLINE (1950 to Week 4 2008), EMBASE (1980 to Week 5 2008), CINAHL (1982 to November 2007) and reference lists of articles.

Selection criteria

Randomized controlled trials comparing anakinra alone or in combination with DMARDs or biologics to placebo or other DMARDs or biologics in patients >18 years old with rheumatoid arthritis.

Data collection and analysis

Two review authors independently assessed trial quality and extracted data. We contacted study authors for additional information.

Main results

Five trials involving 2876 patients, 781 randomized to placebo and 2065 to anakinra, were included. There was a significant improvement in number of participants achieving ACR20 (38% versus 23%) who were treated with anakinra 50 to 150 mg daily versus placebo after 24 weeks. This 15% increase in patients achieving ACR20 with anakinra versus placebo is felt to be a clinically meaningful, though modest, outcome. Other efficacy data - including ACR50 (18% versus 7%), ACR70 (7% versus 2%), HAQ, visual analog score (VAS), Larsen radiographic scores, and change in erythrocyte sedimentation rate (ESR) - all demonstrated significant improvement with anakinra 50 to 150 mg daily versus placebo as well. There were no statistically significant differences noted in most safety outcomes with treatment with anakinra versus placebo - including number of withdrawals, deaths, adverse events (total and serious), and infections (total and serious). Injection site reactions were significantly increased, occurring in 1235/1729 (71%) versus 204/729 (28%) of patients

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treated with anakinra versus placebo, respectively. The incidence of serious infections was clinically higher, but not statistically different, in the anakinra (25/1366 patients, 1.8%) versus placebo group (3/534 patients, 0.6%).

Authors' conclusions

Anakinra is a relatively safe and modestly efficacious biologic therapy for rheumatoid arthritis. Although head to head comparison trials have not been carried out, the amount of improvement is notably less when compared to studies using other biologic therapies. More studies are needed to evaluate safety and efficacy, especially in comparison to other therapies, and adverse event data for the long-term use of Anakinra has yet to be assessed.

PLAIN LANGUAGE SUMMARY

Anakinra for Rheumatoid Arthritis

This summary of a Cochrane review presents what we know from research about the effect of Anakinra on rheumatoid arthritis (RA).

The review shows that in people with RA,

Taking Anakinra for 6 months may improve RA symptoms such as pain, function, and stiffness.

What are RA and Anakinra?

When you have rheumatoid arthritis, your immune system, which normally fights infection, attacks the lining of your joints. This makes your joints swollen, stiff and painful. The small joints of your hands and feet are usually affected first. There is no cure for RA at present, so the treatments aim to relieve pain and stiffness and improve your ability to move.

Anakinra is an interleukin-1 receptor antagonist which is a drug that blocks the inflammatory protein interleukin-1. The drug is used to slow the progression of moderate to severe active RA in patients over age 18 who have not responded to one or more of the disease-modifying anti-rheumatic drugs (DMARD). Anakinra can be used with other RA drugs.

Best estimate of what happens to people with RA who take Anakinra:

23 out of 100 people experienced improvement of RA symptoms such as pain, function, and stiffness when taking a placebo

38 out of 100 people experienced improvement of RA symptoms such as pain, function, and stiffness when taking Anakinra

15 more people out of 100 experienced improvement of RA symptoms after taking Anakinra for 6 months compared with taking a placebo.

BACKGROUND

Rheumatoid arthritis (RA) is the most common inflammatory arthritis in adults, affecting 0.5 to 1% of the population worldwide. It is a chronic systemic inflammatory disease with a particular predilection to the joint synovium. The clinical hallmark of RA is polyarticular synovial inflammation of peripheral joints - typically in the hands (MCP, PIPs), causing pain, stiffness, and - for many - some degree of irreversible joint damage and disability. In addition, there is also a significant systemic inflammatory state present that may lead to a number of other extra-articular effects, including coronary artery disease, pulmonary fibrosis, osteoporosis, and vasculitis (O'Dell 2004). RA is associated with a high degree of disability, leading to an estimated 50% of affected patients toward work disability within 10 years. In addition, there is an

estimated 2.5-fold increase in mortality rate, with life expectancy shortened by an average of three to seven years (Lipsky 2005).

The exact cause of RA remains unclear. It is likely a multi-factorial disease in which there are a number of genetic and environmental influences (Lipsky 2005). There is significant evidence that the activation of T-cells and macrophages with the consequent release of a number of inflammatory cytokines play a key role in the initiation and maintenance of both the systemic and local synovial inflammation present in RA (Lipsky 2005). In particular, tumor necrosis factor (TNF), interleukin-1 (IL-1), and IL-6 are considered the pivotal inflammatory mediators, though a large number of other cytokines are also likely contributing to its pathogenesis.

IL-1 has been demonstrated in a number of in vitro and animal models to play a role in the pathogenesis of the inflammation and joint destruction seen in rheumatoid arthritis. This includes direct stimulation of cartilage degradation processes and inhibition of cartilage matrix synthesis. Animal models that express overproduction of IL-1 have demonstrated cartilage and joint changes that are similar histopathologically to rheumatoid arthritis (Abramson 2002). IL-1 has also been demonstrated to be a stimulatory cytokine for both osteoclast precursor differentiation and osteoclast activity, likely indicating a further role in the osteopenia and joint destruction seen with rheumatoid arthritis (Gravallese 2002).

The American College of Rheumatology (ACR) guidelines for the effective management of patients with RA require a multidisciplinary approach coordinated with a rheumatologist. The objectives of treatment are to control joint inflammation and to reduce joint damage, minimize loss of function, improve quality of life and reduce pain, and treat extra-articular complications (ACR 2002). Medical therapy for RA falls into two categories: symptomatic therapy and disease-modifying anti-rheumatic drugs (DMARDs).

Symptomatic treatment for patients with RA may be achieved with the use of analgesics, most commonly non-steroidal anti-inflammatory drugs (NSAIDs). NSAIDs may reduce early morning stiffness and pain and improve quality of life, though have no effect on long-term outcomes of RA. Corticosteroids are also commonly used to acutely reduce inflammation with active disease. They are primarily used in short courses for flares or during the initiation of DMARD therapy and may be used for long-term therapy, though this may be associated with significant side effects. Local therapies - typically with corticosteroid injections to affected joints - have also been found to be beneficial. Other options for symptomatic improvement in RA may also include resting acutely inflamed joints, local application of heat/cold, and regular exercises to help strengthen muscles and improve range of motion in affected joints (ACR 2002).

Disease-modifying anti-rheumatic drugs (DMARDs) are the main-stay for therapy of rheumatoid arthritis. They are a group of medications designed to inhibit specific mediators of inflammation and have been found to significantly reduce and prevent damage to joints (radiographic and clinical) and improve/maintain function of joints in patients with RA. ACR guidelines recommend initiation of DMARD therapy within three months of the diagnosis of rheumatoid arthritis. Medications in this class include methotrexate, sulfasalazine, leflunamide, and azathioprine. In the last decade, a new class of DMARDs - called the 'biologics' has been developed for the treatment of rheumatoid arthritis. These medications act as selective inhibitors to specific cytokines - including TNF- α (etanercept, infliximab, adalimumab), CTLA-4 - a T-cell co-stimulator (abatacept), and IL-1 (anakinra). These medications have been found to further suppress inflammation and reduce joint damage in RA patients previously unresponsive to

standard DMARD therapy (ACR 2002).

Anakinra (tradename: kineret) is a recombinant form of a human interleukin-1 receptor antagonist (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 signs of RA and was FDA approved in 2001 for moderately-severe RA with at least one failed DMARD therapy (FDA 2003). It is administered as a daily subcutaneous injection and adverse effects primarily include injection-site reactions, recurrent infections - notably pulmonary infections with history of asthma/COPD - and possible risk of malignancy (ACR 2002).

OBJECTIVES

The aim of this review was to provide a systematic evaluation of the clinical effectiveness of Anakinra in adult patients (18 years and older) who have not responded to conventional DMARD treatments.

This review addressed the following questions:

1. What is the clinical effectiveness of Anakinra for the treatment of RA in terms of:
 - a. relieving symptoms?
 - b. delaying disease progression?
2. What are the risks (frequency and severity of adverse events) associated with Anakinra treatment in these patients?

METHODS

Criteria for considering studies for this review

Types of studies

All randomized controlled trials (RCTs) comparing anakinra alone or in combination with DMARDs or biologics to placebo or other DMARDs or biologics in patients with rheumatoid arthritis were considered.

Types of participants

Adults aged 18 years and above meeting the ACR 1987 revised criteria for rheumatoid arthritis (Arnett 1988).

Types of interventions

Anakinra alone or in combination with other drugs.

Types of outcome measures

Primary outcomes

Efficacy

a. An ACR20 response rate to treatment with anakinra as defined by the American College of Rheumatology (ACR) (Felson 1995). The variables included in this definition are:

- tender joint count;
- swollen joint count;
- patient's assessment of pain (VAS or Likert scale);
- patient and physician assessment of disease activity (VAS or Likert scale);
- patient assessment of functional ability (HAQ, AIMS, MACTAR);
- inflammatory markers, such as erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP).

An ACR20 response is defined as a 20 per cent improvement in tender and swollen joint counts and the same level of improvement in three of the five following variables: patient/physician global assessments, pain scores, HAQ score, and laboratory acute phase reactants.

b. Improvement in Disease Activity Score (DAS)/DAS28 score
The DAS is a composite index that includes a combination of the values of tender and swollen joint counts, patient's global assessment of disease activity, and ESR value (van der Heijde 1993). A DAS28 score is used when a 28 joint count is used as the index (Prevoo 1995).

Safety

- a. Adverse events, including allergic reactions, injection site reactions
- b. Serious adverse events, including serious infections, as defined by the individual studies
- c. Withdrawals due to lack of efficacy
- d. Withdrawals due to adverse events
- e. Total Withdrawals
- f. Number of Deaths

Secondary outcomes

1. An ACR50 and 70 response criteria: as defined by 50% and 70% improvements, respectively, in the criteria as outlined above under ACR20.
2. Proportion achieving the European League Against Rheumatism (EULAR) Response: EULAR criteria defines responses (good, moderate and none)

according to relative changes in the Disease Activity Score (DAS) (van Gestel 1996):

- A 'good' response is defined as a decrease in DAS or DAS 28 > 1.2 from baseline with a final DAS < 2.4 (or DAS 28 < 3.2) (Fransen 2005; van Gestel 1996)
- A 'none' response is defined as a decrease in DAS or DAS 28 < 0.6 or a decrease >0.6 and < 1.2 with a final DAS > 3.7 (or DAS 28 > 5.1) (Fransen 2005; van Gestel 1996)
- Any other scores are regarded as moderate response.

Low disease activity as defined by DAS score < 2.4 or DAS28 < 3.2 (Fransen 2005; van Gestel 1996)

Disease remission as defined by DAS < 1.6 or DAS28 < 2.6 (Fransen 2005; Prevoo 1996)

3. Radiographic progression, as measured by the Sharp, modified Sharp or Larsen methods (Larsen 1977; Sharp 1971; van der Heijde 1989)

4. Recently revised ACR criteria (Felson 2007):

e.g. Nominal measure of improvement such as ACR Step: 0 if ACR20 = 0, 1 if ACR20 but not ACR50, 2 if ACR50 but not ACR70, 3 if ACR70

5. Health-related quality of life (HRQoL) as measured by the Short Form (SF)-36 or other instruments: (Kosinski 2000; Tugwell 2000)

- Change in SF-36 Physical and Mental Component Summary (PCS and MCS) scores
- Change in SF-36 subscale scores
- Proportion achieving the population norms for PCS and MCS (Mean of 50)
- Proportion achieving the Minimal Clinical Important Change (MCID) in SF-36 PCS and MCS - defined as a change of 2.5 to 5 on each summary score (Kosinski 2000; Samsa 1999; Tugwell 2000)

6. Function Change, as measured by Composite Function scales: Stanford Health Assessment Questionnaire (HAQ), modified HAQ or others.

- HAQ is a self-report questionnaire aimed for assessment of effect of disease on 8 basic categories of functions (dressing, standing, eating, walking, toileting, reach, grip, and instrumental activities) (Fries 1980).

- mHAQ is the modified and simplified version of this scale utilizing the above categories (Pincus 1983).

- Proportion achieving a Minimal Clinical Important Change (MCID) in HAQ (defined as change ≥ 0.22) (Wells 1993) or in a similar functional assessment
- Proportion achieving HAQ of 0
- Proportion achieving the population norm for HAQ (0.25) (Krishnan 2004)

7. Pain Visual Analog Scale (VAS) scores

- pain VAS score is a validated measure of pain (0 to 10cm, 0 to 100mm or a similar scale).

8. Inflammatory Markers: Erythrocyte Sedimentation Rate (ESR) in mm/hr and C-reactive Protein (CRP) in mg/dl.

Search methods for identification of studies

See: Cochrane Musculoskeletal Group methods used in reviews.

We searched the following electronic bibliographic databases: Cochrane Central Register of Controlled Trials (CENTRAL (*The Cochrane Library* Issue 1, 2008) Appendix 1, MEDLINE (1950 to January Week 4 2008) Appendix 2 and EMBASE (1980 to 2008) Appendix 3 and CINAHL (1982 to November 2007) Appendix 4.

We also reviewed the reference lists of identified publications, including previous meta-analyses, to identify any additional studies or citations or both.

No language restrictions were applied and translations were obtained when necessary. If information was missing, further information was sought from the authors or industry. Data from studies with multiple publications were extracted and reported as a single study.

Data collection and analysis

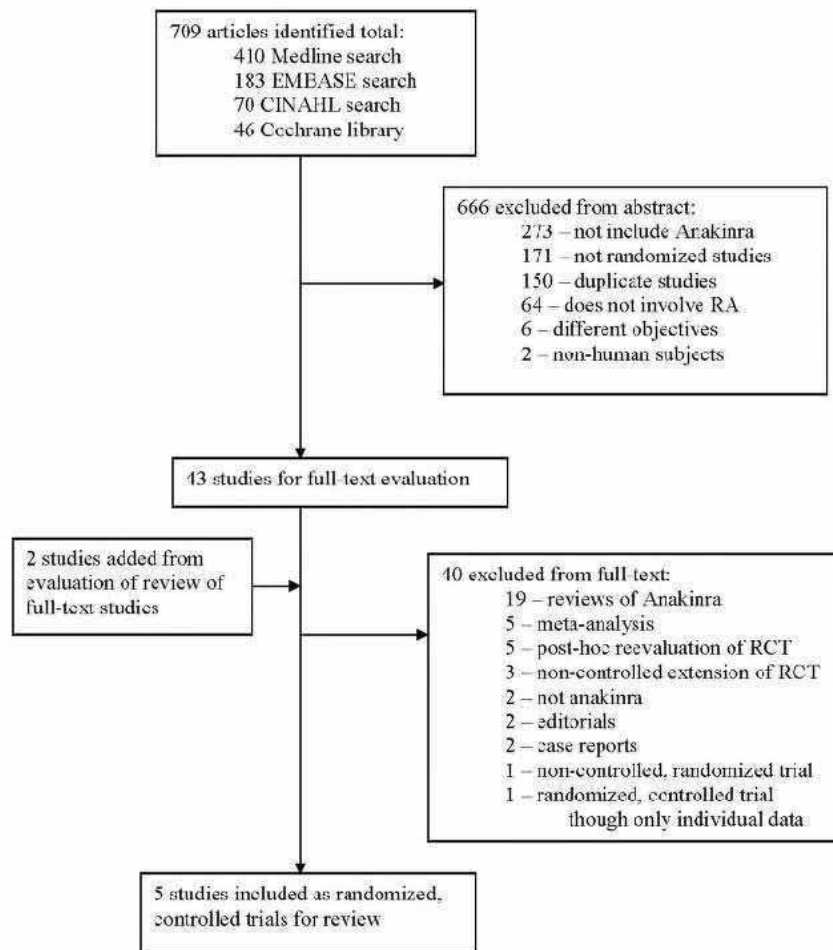
Selection of studies

Two review authors independently applied the following inclusion/exclusion criteria to all potential studies. Any disagreements were resolved by discussion; referring to a third party if necessary. Review authors were not blinded to any features of the report including authorship. However inclusion/exclusion decisions were made prior to detailed scrutiny of the results.

For details of screening process for articles identified from the above search, please refer to [Figure 1](#).

Figure 1. Article Screening Process for the Anakinra Cochrane Review

Anakinra Cochrane Review Screening Process
 = 2 independent evaluators with comparisons/discussion of differences per step



Data extraction strategy

Two review authors independently extracted data using a pre-designed data extraction form. Disagreements were resolved by discussion; consulting with a third party if there was still disagreement.

We extracted the following data.

1. Details of the study population and baseline characteristics of the intervention and control groups, with particular reference to disease characteristics and previous treatment history.
2. Details of the intervention, including dose, mode of administration, frequency of administration, duration of treatment, and co-administered medications.
3. Details of withdrawal rates across the groups, frequency of loss to follow-up.
4. Details of individual outcomes measured through tools as described above:
 - Changes in disease activity (e.g. ACR improvement criteria, DAS/DAS28 scores, pain scales, radiographic scores, inflammatory markers)
 - Changes in quality of life (e.g. HRQoL scores - SF-36)
 - Changes in function (e.g. HAQ or mHAQ scores)
 - Adverse events (serious, total, and injection site reactions)
 - Infections (serious and total)
 - Number of deaths

Results were extracted, where possible, for the intention-to-treat population, as raw numbers, plus any summary measures with standard deviations, confidence intervals and P values where given.

Quality assessment strategy

Two review authors independently undertook quality assessments using a structured form. Disagreements were resolved by discussion, with reference to a third party if there remained a disagreement. The information on quality assessment is presented in table form and summarized within the text of the report. 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, withdrawals and losses to follow-up for each patient. Each criteria was assessed and graded as 'yes', 'no', or 'unclear'.

Methods of analysis/synthesis

Clinical relevance tables

Clinical relevance tables were compiled under additional tables to improve the readability of the review. For dichotomous outcomes, the absolute risk difference was calculated between anakinra and control arms, using the risk difference (RD) statistic in RevMan. We calculated the numbers needed to treat to benefit (NNTB) for ACR20, ACR50 and ACR70 by taking the inverse of absolute risk difference i.e. $NNTB = 1/\text{absolute risk difference}$.

The tables summarizing continuous outcomes are also presented. The mean difference (MD) statistic in RevMan was calculated by weighting the absolute change by the group size, in cases where trials used the same scale. Relative per cent change from baseline was calculated as the absolute benefit divided by the baseline mean of the respective group.

Heterogeneity

In addition to reviewing forest plots, heterogeneity of the data was formally tested using the Chi-square with a P-value < 0.10 indicating significant heterogeneity. The I^2 statistic was also assessed (Higgins 2004). A value greater than 50% indicates substantial heterogeneity. In the case of substantial heterogeneity, we explored the data further. We performed sub-group analyses, in an attempt to explore the cause of the heterogeneity.

Data synthesis

In the absence of significant heterogeneity - defined by an I^2 statistic < 50%, a fixed-effect model was used. However, if significant heterogeneity was demonstrated, a random-effects model was used for analysis. Where available, the analyses were based on intention-to-treat data from the individual studies.

Publication bias

We constructed a funnel plot to assess the possibility of publication bias. A funnel plot is a scatter plot with sample size along the y-axis and the treatment effect along the x-axis. An asymmetric appearance of this plot in either x-axis likely indicates a level of publication bias in the literature.

Sub-group analysis

The following sub-group analyses were planned to explore possible effect size differences:

1. Intervention - variable dosage or duration of treatment
2. Characteristics of participants - severity of baseline disease; age; disease duration; sex; disease with or without peripheral joint involvement.
3. Patients in whom anakinra is being prescribed in combination with MTX (or other DMARDs)

Sensitivity analysis

The following sensitivity analyses were planned to explore effect size differences and the robustness of conclusions:

- Effect of study quality - defined as adequate allocation concealment and outcome assessor blinding.

Grading of the evidence

In addition, a further ranking based on the level of evidence was performed in the manner described by Tugwell and approved by the CMSG editorial team (Tugwell 2004). A simplified ranking scale was used to grade the strength of scientific evidence for the trial intervention. The scale is as follows, in decreasing order: Platinum: A published systematic review that has at least two individual controlled trials each satisfying the following:

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% follow-up (imputations based on methods such as Last Observation Carried Forward (LOCF) are acceptable).

Concealment of treatment allocation.

Gold: At least one randomized clinical trial meeting all of 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% follow-up (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 one 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 was 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 at least one 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).

RESULTS

Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#).

[Bresnihan 1998](#) was a randomized, double-blind, placebo-controlled trial involving 472 participants among 41 centers in 11 countries in Europe. It randomized participants into four groups: placebo (n = 119) and 30 mg (n = 119), 75 mg (n = 115), and 150 mg (n = 115) of recombinant IL-1 receptor antagonist. Four patients (two placebo, two anakinra) did not receive doses of the study drug and were not included in analysis. Doses were given as subcutaneous injections daily for 24 weeks. Patients included in the study had to meet all of the following criteria: (1) a diagnosis of rheumatoid arthritis based on the ACR Classification criteria with duration of > 6 months and < 8 years; (2) active disease - determined by presence of > 10 swollen joints and three of the

following four: > 10 tender joints, rheumatologists' grading of RA as severe-very severe, CRP > 1.5 mg/dl, or patient with severe-very severe RA. NSAIDs and oral steroids (< 10 mg prednisolone daily) were allowed, though any DMARD therapy had to be discontinued at least six weeks prior to study enrollment. Exclusion criteria included intraarticular or systemic corticosteroids within six weeks prior to the study or treatment failure (toxicity or lack of efficacy) with three or more DMARDs after at least 3 months of continuous administration. The study was sponsored by Amgen, Inc.

[Cohen 2002](#) was a randomized, double-blind, placebo-controlled trial involving 36 centers in the U.S, Canada and Australia that was originally designed as a 12-week trial involving 105 participants randomized to placebo and 0.1 mg/kg, 0.4 mg/kg, 2.0 mg/kg of anakinra given subcutaneous daily. An amendment was made to this original protocol so that the double-blind treatment was extended from 12 to 24 weeks and additional subcutaneous daily doses of 0.04 mg/kg and 1.0 mg/kg of anakinra were added in the study. An additional 314 participants were randomized into this 24 week treatment protocol. Three participants from the original 12 week study re-consented to remain blinded in their treatment group for the 24 week study. A total of 419 participants were evaluated at 12 weeks and 317 were evaluated at 24 weeks. For the 24 week analysis, the number of patients in each were as follows: 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).

Inclusion criteria for this study were as follows: (1) diagnosis of rheumatoid arthritis by ACR criteria for > 6 months and < 12 years; (2) active disease - defined as > 6 swollen joints and two of the following three criteria: > 9 tender joints, AM stiffness > 45 minutes, or CRP > 1.5 mg/dl; and (3) treatment with methotrexate for at least six consecutive months and on a stable dose for > 3 months prior to the study. NSAIDs and oral steroids (< 10 mg/day prednisone) were allowed and had to be stable for four weeks prior to the study. Exclusion criteria included the following: receiving systemic/intraarticular steroids within four weeks of the study, receiving penicillamine, oral or parenteral gold, azathioprine, or cyclosporine within 12 weeks of the study, receiving hydroxychloroquine or sulfasalazine within eight weeks of the study. The study was sponsored by Amgen, Inc.

[Cohen 2004](#) was a multi-center double-blind, placebo-controlled trial involving 506 participants who were randomized to placebo (n = 251) or anakinra 100 mg (n = 250) subcutaneous daily for 24 weeks. Five randomized patients (two placebo, three anakinra) did not receive any doses and were not included in analysis. Inclusion criteria were the following for this study: (1) diagnosis of rheumatoid arthritis by ACR criteria for > 24 weeks; (2) presence of radiographic erosions in hands, feet, or wrists; (3) active disease, defined by > 5 swollen joints, > 8 tender joints, and one of the following two criteria: CRP > 15 ml/L or ESR > 28 mm/hr. All patients were also required to be treated with a stable dose of methotrexate for at least 24 consecutive weeks, and were provided folic acid 1

mg daily. All other DMARD therapy was withdrawn for at least 60 days prior to study inclusion. NSAIDs and oral steroids (< 10 mg/day prednisone) were allowed and required to be stable for at least four weeks prior to the study. Exclusion criteria included the following: other autoimmune diseases, treatment with intraarticular/systemic steroids within four weeks of the study, treatment with other DMARDs within 60 days of the study, the use of narcotic analgesics for pain. The study was sponsored by Amgen, Inc. [Fleischman 2003](#) was a double-blind, placebo-controlled trial involving 169 centers in the U.S, Canada, Europe, and Australia involving 1414 participants randomized to placebo (n = 283) or anakinra 100 mg (n = 1116) subcutaneous daily for six months. Fifteen randomized patients (1 placebo, 14 anakinra) did not receive any study drug doses and were not included in analysis. Inclusion criteria were the following: (1) diagnosis of rheumatoid arthritis for > 3 months; (2) active disease: defined as > 3 swollen and > 3 tender joints or > 45 minutes of AM stiffness. NSAIDs and steroids were allowed as long as doses were stable for > 1 month. DMARDs were allowed as long as doses were stable for > 2 months. The use of TNF-inhibitors was not allowed during the study. Exclusion criteria included recent diagnosis of a malignancy (other than basal cell of skin and in situ cervical CA) in the last 5 years. The study was sponsored by Amgen, Inc.

[Genovese 2004](#) was a multi-center double-blind, placebo-controlled trial involving 41 centers in the U.S and 244 participants randomized into the following groups: placebo + etanercept 25 mg biweekly (n = 80), anakinra 100 mg daily + etanercept 25 mg weekly (with placebo for other biweekly etanercept dose) (n = 81), and anakinra 100 mg daily + etanercept 25 mg biweekly (n = 81). Two patients (both placebo) did not receive any study drug doses and were not included in analysis. Treatment duration was 24 weeks. Inclusion criteria were the following: (1) diagnosis of rheumatoid arthritis for > 6 months; (2) active disease, defined as following: > 5 swollen joints, > 8 tender joints, and two of the following 3: > 45 minutes of AM stiffness, CRP > 1.5 mg/dl, or ESR > 28 mm/hr.

All participants required treatment with methotrexate for at least >16 weeks prior to the study, with stable doses (10 to 25 mg/wk) for > 8 weeks. NSAIDs and corticosteroids were allowed as long as doses remained stable. Exclusion criteria included use of other DMARD therapy other than MTX in previous four weeks or intraarticular/systemic steroids within four weeks of the study. The study was sponsored by Amgen, Inc.

Please refer to the table [Characteristics of included studies](#) for overview of included studies above.

Risk of bias in included studies

[Bresnihan 1998](#) had blinding reported for both assessors and patients. Method of randomization was not reported. There was 73.3% follow-up through the entire study. The study did not have full intention-to-treat analysis, since safety analysis was done only

for those who received at least one dose of IL-1Ra. Missing data for efficacy outcomes was also excluded in their final analysis, resulting in four patients not included for ACR20 data, 129 patients not included for Larsen scores, 26 patients not included for ESR, and 12 patients not included for CRP outcomes.

[Cohen 2002](#) was reported as a double-blind study, though blinding was only described for the patients. Method of randomization was not reported. As stated above, the study was originally set as a 12 week study, though was amended to a 24 week study with the recruitment of additional patients. However, only three patients from the original 12 week study re-consented to the 24 week study and it was unclear about the methodology of maintaining blinding and randomization with the amended study. The small number of participants re-consenting for the longer study also poses a significant bias for the 24 week group. Full intention-to-treat analysis was performed on analysis of results. For the patients consenting to the 24 week trial, there was a 21.0% withdrawal rate. However, if the patients from the original 12 week trial who refused to consent for the full 24 week study extension were included, only 45.3% of the original study participants followed up for the full 24 weeks.

[Cohen 2004](#) had blinding reported for both patients and assessors. Method of randomization was not reported. The study did not have full intention-to-treat analysis as results were analyzed for only those who received at least one dose of the study drug (5 patients were not included in analysis because of this). Unfortunately, the number of total withdrawals was not reported in this study - with only reporting of withdrawals secondary to adverse events being reported.

[Fleischman 2003](#) had blinding reported for patients, health-care providers, and the sponsor. Method of randomization was not reported. The study did not have full intention-to-treat analysis with results analyzed for only those who received at least one dose of the study drug (15 patients not included because of this). There was 78.1% follow-up through the entire study.

[Genovese 2004](#) was reported as double-blinded study, though full blinding was only reported for the patients. For the assessors, blinding was described by having the patients wear clothing over potential injection-site reactions. Method of randomization was not reported. Treatment allocation was not reported in this study. The study did not have full intention-to-treat analysis as results were analyzed for only those who received at least one dose each of anakinra/placebo and etanercept/placebo (two patients not included because of this). There was 83.6% follow-up through the entire study.

Overall, this systematic review achieved a rating of Silver, based upon the CMSG rating described above. Only one study had < 20% withdrawals ([Genovese 2004](#)) though this study did not provide method of treatment allocation.

Excluded studies

Please refer to the table [Characteristics of excluded studies](#) for listing of studies excluded for not meeting inclusion criteria listed

above for this systematic review.

[Drevlow 1996](#) was a randomized, double-blinded placebo controlled trial that initially met inclusion criteria for the systematic review though was not included in the final review. It was a small trial including 23 participants randomized to placebo (n = 4), 125 mcg/m²/day (n = 3), 250 mcg/m²/day (n = 3), 500 mcg/m²/day (n = 3), 1000 mcg/m²/day (n = 8) of recombinant human IL-1 receptor-1 antagonist (rHuIL-1R1) given subcutaneous daily for 28 days. Unfortunately, data was only expressed as number of individuals achieving the primary outcome of > 40% improvement in # swollen joints. No numerical data for assessment was provided by this study.

Effects of interventions

Five trials ([Bresnihan 1998](#); [Cohen 2002](#); [Cohen 2004](#); [Fleischman 2003](#); [Genovese 2004](#)), representing a total of 3055 patients, were included in this review. [Bresnihan 1998](#), [Cohen 2004](#), and [Genovese 2004](#) followed patients for 24 weeks and [Fleischman 2003](#) followed patients for six months. [Cohen 2002](#) was initially a 12 week study though additional participants were recruited for an extension into a 24 week study. For correlation with the other studies in this review, only the 24 week data from the [Cohen 2002](#) study was utilized in the systematic review, excluding the 102 participants in the 12 week group. [Bresnihan 1998](#) and [Fleischman 2003](#) compared anakinra with placebo. [Cohen 2002](#) and [Cohen 2004](#) compared anakinra + MTX and placebo + MTX. [Genovese 2004](#) had the following comparisons: anakinra + etanercept biweekly + MTX, anakinra + etanercept once weekly + MTX, and placebo + etanercept biweekly + MTX. The 81 participants in the anakinra + etanercept once weekly + MTX were excluded in the systematic review as this group was not placebo controlled. Therefore, a total of 2872 participants - divided among 788 randomized to placebo and 2084 to anakinra - were included in this systematic review. Of these, data were not presented for 26 randomized patients (7 placebo, 19 anakinra) who did not receive any treatments in their respective studies, leaving us with 2846 patients for analysis in this systematic review - 2065 in anakinra and 781 in placebo.

The [Cohen 2002](#) study did not report standard deviations or errors when describing its continuous data results and was unable to be contacted by the time of this publication, therefore we were unable to utilize these data.

[Cohen 2004](#), [Fleischman 2003](#), and [Genovese 2004](#) used anakinra 100 mg daily dosing. [Bresnihan 1998](#) used doses of 30 mg, 75 mg, and 150 mg daily of anakinra. [Cohen 2002](#) used the following 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 correlated to approximate doses of 3 mg, 7.5 mg, 30 mg, 75 mg, and 150 mg for this review given average adult weight of 75 kg.

Due to the large variability in doses utilized by the trials, two groups were created to assist with analysis: data from doses < 50

mg/day of Anakinra and data from doses 50 to 150 mg/day of Anakinra. This was a clinical decision based upon the fact that the recommended daily dose for Anakinra is 100 mg daily. Given proximity of 24 weeks and 6 months, the data of [Fleischman 2003](#) was pooled with the other studies for analysis. For studies with multiple dosing arms of anakinra, dichotomous data were combined into the stated ranges (< 50 mg/day versus 50 to 150 mg/day) while continuous outcome data were analyzed separately to avoid double counting of the placebo groups, as recommended. With inclusion of all five studies, there was significant heterogeneity for ACR20 (the primary outcome) with an I² statistic of 80.7%. This was thought to be primarily secondary to the [Genovese 2004](#) study based upon its clinical design and our analysis of the collected data. [Genovese 2004](#) compared anakinra to placebo in the setting of etanercept, another biologic medication. This was a significant variation from the other studies included in this review and is not a standard therapy in current clinical practice. Therefore, this study was separated in our meta-analysis. After removal of the [Genovese 2004](#) study, heterogeneity was noted to be 0% for the primary outcome and < 50% for majority of the secondary efficacy outcomes.

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

Subgroup analysis was performed separating studies that utilized anakinra versus placebo ([Bresnihan 1998](#); [Fleischman 2003](#)) and studies that utilized anakinra versus placebo in the setting of methotrexate therapy ([Cohen 2002](#); [Cohen 2004](#)). The other subgroup analyses proposed in the methods section could not be performed due to lack of these group-level data in the included studies.

Efficacy Results

Primary Outcomes:

ACR20

There was a significantly greater improvement with anakinra doses 50 to 150 mg/day with 38% of anakinra versus 23% placebo treated patients achieving ACR20 at 24 weeks, (RR 1.61; 95% CI 1.32 to 1.98). The absolute treatment benefit for anakinra 50 to 150 mg/day was 15% with NNTB of 8 for ACR20 after 24 weeks. There was also a significantly greater improvement with anakinra doses < 50 mg/day with a RR of 1.38 (95% CI 1.01 to 1.89), 33% of anakinra versus 26% achieving ACR20 at 24 weeks. The [Genovese 2004](#) study demonstrated no benefit with addition of anakinra to etanercept therapy for the number achieving ACR20 at 24 weeks with a RR of 0.91 (95% CI 0.73 to 1.15). For anakinra 50 to 150 mg daily, there was also notable significant improvement in the sub-groups of anakinra versus placebo (without MTX) (RR 1.42; 95% CI 1.01 to 2.00) and anakinra + MTX versus placebo + MTX (RR 1.73; 95% CI 1.34 to 2.23) for achieving ACR 20 after 24 weeks at anakinra doses of 50 to 150 mg/day.

None of the studies reported data on DAS/DAS28 scores, a co-primary outcome for this review.

Secondary Outcomes:

ACR50

Significantly more improvement was noted with anakinra doses 50 to 150 mg/day with 18% of Anakinra versus 7% placebo treated patients achieving ACR50 after 24 weeks of therapy (RR 2.51; 95% CI 1.56 to 4.03). The absolute treatment benefit for anakinra 50 to 150 mg/day was 11% and NNTB was 9 for ACR50 after 24 weeks. Only one study (Cohen 2002) examined anakinra doses < 50 mg/day for ACR50 responses and there was no significant improvement noted (RR 3.37; 95% CI 0.82 to 13.77). The Genovese 2004 study demonstrated no additional benefit with addition of anakinra to etanercept therapy for the number achieving ACR50 after 24 weeks (RR 0.75; 95% CI 0.49 to 1.14). The two studies that evaluated anakinra + MTX versus placebo + MTX were the only studies that provided ACR50 data (Cohen 2002; Cohen 2004), so no sub-group analysis could be performed.

ACR70

There was a significantly greater improvement with anakinra doses 50 to 150 mg/day for achieving ACR70 at 24 weeks (RR 3.71; 95% CI 1.44 to 9.57), achieved by 7% of anakinra versus 2% of placebo treated patients. The absolute treatment benefit for anakinra 50 to 150 mg/day was 5% and NNTB was 22 for ACR70 after 24 weeks. Only one study (Cohen 2002) evaluated anakinra doses < 50 mg/day for ACR70 and there was no significant improvement noted at 24 weeks compared to placebo (RR 4.45; 95% CI 0.26 to 76.62). The Genovese 2004 study also demonstrated no additional improvement with addition of anakinra to etanercept therapy for achieving ACR70 after 24 weeks (RR 0.64; 95% CI 0.32 to 1.28). The two studies that evaluated anakinra + MTX versus placebo + MTX were the only studies that provided ACR70 data, so no sub-group analysis could be performed.

Clinical Relevance Table detailing ACR20, ACR50 and ACR70 is provided in Table 1.

Table 1. Clinical Relevance table: ACR outcome data for Anakinra 50-150 mg daily versus placebo after six months

Outcome	# patients (# trials)†	Control event rate	Anakinra event rate	Wt absolute RD (95% CI)	Wt Rel % change (95% CI)	NNTB (95% CI)	statistical significance	quality of evidence
ACR20	1003 (3)	23.4% 23 out of 100	38.3% 38 out of 100	15% (9,20) 15 more out of 100	61% improvement (32%, 98%)	8 (5, 14)	statistically significant	silver

Table 1. Clinical Relevance table: ACR outcome data for Anakinra 50-150 mg daily versus placebo after six months (Continued)

ACR50	654 (2)	7.4% 7 out of 100	18.3% 18 out of 100	11% (6, 16) 11 more out of 100	151% im- provement (56%, 303%)	9 (5, 25)	statistically significant	silver
ACR70	654 (2)	1.7% 2 out of 100	6.8% 7 out of 100	5% (2, 8) 5 more out of 100	271% im- provement (44%, 857%)	22 (7, 134)	statistically significant	silver

Wt = weighted

RD = risk difference

CI = confidence interval

NNTB = number needed to treat to benefit

† Note: data excludes outcome data from [Genovese 2004](#)

Data from individual studies for ACR20, ACR50, and ACR70 outcome data is provided in [Table 2](#).

Table 2. Summary of ACR outcome data for Anakinra 50-150 mg daily versus placebo after six months

	ACR 20		ARD (%), NNTB	ACR 50		ARD (%), NNTB	ACR70		ARD (%), NNTB
	Anakinra	Placebo		Anakinra	Placebo		Anakinra	Placebo	
Study	n/N (%)	n/N (%)		n/N	n/N		n/N	n/N	
Bresnihan 1998	88/230 (38)	32/119 (27)	11, 9.1	no data	no data	no data	no data	no data	no data
Cohen 2002	41/105 (39)	11/48 (23)	16, 6.3	22/105 (21)	2/48 (4)	17, 5.9	9/105 (9)	0/48 (0)	9, 11.1
Cohen 2004	95/250 (38)	55/251 (22)	16, 6.3	43/250 (17)	20/251 (8)	9, 11.1	15/250 (6)	5/251 (2)	4, 25
Fleischman 2003	no data	no data	no data	no data	no data	no data	no data	no data	no data
Genovese 2004	50/81 (62)	54/80 (68)	-4, NA	25/81 (31)	33/80 (41)	-7, NA	11/81 (14)	17/80 (21)	-7, NA

Table 2. Summary of ACR outcome data for Anakinra 50-150 mg daily versus placebo after six months (Continued)

Totals (excluding Genovese)	224/585 (38)	98/418 (23)	15, 8	65/355 (18)	22/299 (7)	11, 9	24/355 (7)	5/299 (2)	5, 22
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NNTB: number needed to treat to benefit

ARD: absolute risk difference [n/N (Anakinra) - n/N (placebo)]

Functional Scales (HAQ, pain VAS)

There was significant improvement noted with both VAS and HAQ scores with anakinra doses 50 to 150 mg/day at 24 weeks of treatment. HAQ scores were significantly better with anakinra with a MD of -0.19 (95% CI -0.30 to -0.09). Only one study (Bresnihan 1998) measured pain VAS scores as outcome data and this noted a significant improvement with a WMD of -0.10 (95% CI -0.15 to -0.04) for anakinra 50 to 150 mg/day after 24 weeks. Bresnihan 1998 was the only study to evaluate both HAQ and VAS scores for anakinra doses < 50 mg/day. This study found a significant improvement in HAQ scores (WMD -0.20; 95% CI -0.33 to -0.07) but no significant improvement in VAS scores (WMD -0.08; 95% CI -0.16 to 0).

Radiographic scales (Larsen scores)

Only one study utilized standard radiographic scales for outcome data (Bresnihan 1998) and there was significant improvement noted in Larsen radiographic scores with both anakinra 50 to 150 mg/day doses (WMD -2.45; 95% CI -4.53 to -0.36) and anakinra < 50 mg/day (WMD -2.8; 95% CI -5.47 to -0.13), compared to placebo.

Inflammatory markers

There was significant improvement in change in ESR (WMD -10.04; 95% CI -12.75 to -7.33) with anakinra doses 50 to 150 mg/day after 24 weeks of treatment, compared to placebo. Only one study (Bresnihan 1998) evaluated change in CRP and there was no significant improvement noted with anakinra doses 50 to 150 mg/day after 24 weeks of treatment (WMD -0.60; 95% CI -1.26 to 0.06). Bresnihan 1998 was also the only study to evaluate change in ESR and CRP levels for anakinra doses < 50 mg/day and significant improvement was noted for both change in ESR [WMD -10.0 (95% CI -15.67 to -4.33)] and change in CRP levels (WMD -0.90; 95% CI -1.64 to -0.16) after 24 weeks as compared to placebo.

The following secondary efficacy outcomes listed in the methods section were not reported in the included studies: low disease activity or remission as defined by DAS/DAS28 scores, radiographic Sharp/modified Sharp scores, HRQoL/SF-36 scores for PCS/MCS, or % achieving MCID for PCS/MCS or population

norms, and % achieving MCID, population norm, or a score of 0 on mHAQ/HAQ. None of the studies described new revised ACR response criteria, since most studies preceded the description of these revised response criteria.

Safety Results

Withdrawals

There was no difference in the total number of withdrawals for anakinra 50 to 150 mg/day versus placebo. After 24 weeks, there were 22% withdrawals in the anakinra 50 to 150 mg/day group versus 22% withdrawals in the placebo group (RR 1.04; 95% CI 0.86 to 1.27). In the anakinra versus placebo (without MTX) subgroup, there was no significant difference in the total number of withdrawals (RR 1.01; 95% CI 0.82 to 1.25). In the anakinra + MTX versus placebo + MTX subgroup, there was also no significant difference in the total number of withdrawals [RR 1.29 (95% CI 0.74 to 2.26)]. For anakinra < 50 mg/day versus placebo, there was also no difference in the total number of withdrawals after 24 weeks (RR 0.85; 95% CI 0.62 to 1.18). However, Genovese 2004 reported a significant increase in the total number of withdrawals in the anakinra group versus control (RR 2.96; 95% CI 1.13 to 7.77).

Deaths

Mortality was only presented by one study, Fleischman 2003, and there was no significant difference in the number of deaths - 0.3% each for the anakinra 50 to 150 mg/day and placebo groups [RR 1.01 (95% CI 0.11 to 9.04)].

Adverse Events

Adverse events were presented by the studies, Cohen 2004 and Fleischman 2003, though specific definitions for adverse events were not provided in either study. Total number of adverse events was not significantly increased in anakinra 50 to 150 mg/day treated patients, occurring in 92% versus 87% of anakinra versus placebo treated patients, after 24 weeks (RR 1.05; 95% CI 0.94 to 1.17). In the anakinra versus placebo (without MTX) subgroup, there was no significant difference in total adverse events (RR 1.00;

95% CI 0.96 to 1.04). However, in the anakinra + MTX versus placebo + MTX subgroup, there was a significant difference in the total adverse events (RR 1.11; 95% CI 1.03 to 1.20). Injection site reactions occurred significantly higher in the anakinra 50 to 150 mg/day (71%) versus placebo (28%) groups (RR 2.45; 95% CI 2.17 to 2.77) and were significantly higher in both subgroups. Serious adverse events were presented in the [Fleischman 2003](#) and [Cohen 2004](#) studies. Definition for serious adverse events were not provided by [Fleischman 2003](#) though [Cohen 2004](#) defined these as adverse events that required hospitalization, resulted in persistent disability, or were life-threatening in nature. In the analysis of serious adverse events, there was no significant difference between anakinra 50 to 150 mg/day versus placebo groups (7% versus 6%, RR 1.04; 95% CI 0.70 to 1.56). Malignancy data was reported in the [Fleischman 2003](#) study - noting five malignancies (1.8%) in the placebo group versus four malignancies (0.4%) in the anakinra group. The [Cohen 2002](#) study reported one malignancy each in anakinra (0.8%; 1/131) and placebo group (1.4%; 1/74). The [Genovese 2004](#) study demonstrated no difference in the total number of adverse events (RR 1.04; 95% CI 0.95 to 1.14) though there was a significant increase in the number of serious adverse events (RR 5.93; 95% CI 1.37 to 25.64) when anakinra was compared to control. Only one malignancy was reported in the anakinra + etanercept group (1.3%) in this study, versus none in the etanercept + placebo group (0%). There was a significant increase in injection site reactions with anakinra versus control (RR 1.76; 95% CI 1.30 to 2.38).

Infections

The total number of infections was not significantly different between anakinra 50 to 150 mg/day and placebo treated patients after 24 weeks, occurring in 40% and 35% patients respectively (RR 1.08; 95% CI 0.80 to 1.45). Data on the number of serious infections were provided in the studies by [Cohen 2004](#) and [Fleischman 2003](#). Definitions for serious infections were not specified by either study. There was no significant difference between patients receiving anakinra 50 to 150 mg/day versus placebo, occurring in 1.8% versus 0.6% of patients (RR 3.15; 95% CI 0.81 to 12.20). The types of serious infections were not presented in the [Cohen 2004](#) study. In the [Fleischman 2003](#) study, of the 24 'serious' infections reported, 23 occurred in anakinra group (n = 1116) and 1 in placebo (n = 283). The most common were pneumonia in 10 patients and cellulitis in three patients. There was no difference in the total number of infections or serious infections within each subgroup of anakinra + placebo (without MTX) and anakinra + MTX versus placebo + MTX.

The [Genovese 2004](#) study demonstrated no significant difference in either total infections (RR 1.17; 95% CI 0.82 to 1.67) or serious infections (RR 12.84; 95% CI 0.74 to 224.23) after 24 weeks of therapy as well. There were six serious infections in the anakinra + etanercept group, of which they were clarified to two with serious pneumonia and two with serious cellulitis. No opportunistic

infections were reported in this study.

Other

None of the included studies reported opportunistic infections (including tuberculosis etc.), congestive heart failure or demyelinating syndromes.

DISCUSSION

This review had several limitations. Foremost, there was a significant variability among the included studies with the specific outcomes measured, limiting the power of our systematic review. For example, [Fleischman 2003](#) only included safety outcomes in its study and [Bresnihan 1998](#) did not include ACR50 or ACR70 data. Also, there was significant variability in the doses of anakinra used in [Bresnihan 1998](#) and [Cohen 2002](#) from the current standard dose of 100 mg daily. We divided the pooled data to those utilizing < 50 mg/day and 50 to 150 mg/day of anakinra based on clinical relevance to allow for data analysis. However, we were unable to examine for possible differences between individual doses of anakinra due to the limited number of studies. The lack of reporting of standard deviation/error data in the [Cohen 2002](#) study prevented inclusion in analysis of continuous outcomes, further limiting the power of these outcomes in our systematic review.

With the removal of the [Genovese 2004](#) study, significant heterogeneity remained with change in HAQ score, the total number of adverse events, and total number of infections. Explanations likely include the small number of studies involved as well as possible differing definitions for adverse events and infections within each of these studies. Only [Genovese 2004](#) specified a specific definition for adverse events of the included studies. Another explanation may be that one of the included studies, [Fleischman 2003](#), had a sample size much larger than other studies, thus likely impacting the overall outcomes far greater than other smaller studies.

While the studies were adequate as randomized controlled trials, the method of randomization was not reported in any study and a number did not report full blinding. None of the studies except for [Cohen 2002](#) described a true intention-to-treat analysis. All studies except for [Cohen 2002](#) excluded patients from analysis if they did not receive at least one dose of a study drug (excluding a total of 30 patients). [Bresnihan 1998](#) did not include patients with missing data for respective outcomes. This introduces significant bias, especially for Larsen scores, since 129 patients were excluded from the analysis.

This review systematically analyzed the efficacy and safety data from five randomized-controlled trials of anakinra, involving 2876 participants, divided among 781 randomized to placebo and 2065 to anakinra. At 24 weeks of therapy, there was a significant improvement in the number of participants achieving ACR20 (the

primary outcome for this review) who were treated with anakinra 50 to 150 mg daily versus placebo (38% versus 23%). The absolute treatment benefit was 15% with a NNTB of 8 for treatment with anakinra versus placebo. Other efficacy data - including ACR50, ACR70, HAQ, VAS, Larsen radiographic scores, and change in ESR - all demonstrated significant improvement with anakinra 50 to 150 mg daily versus placebo as well. In subgroup analysis, improvement was noted for both studies comparing anakinra/placebo and anakinra/placebo + MTX in ACR20 outcomes as well. The two studies that utilized doses < 50 mg/day demonstrated significant improvements in ACR20, HAQ, Larsen score, and inflammatory markers in anakinra versus placebo. The [Genovese 2004](#) study demonstrated no significant improvement in any outcome data (ACR20, ACR50, or ACR70) in its evaluation of anakinra + etanercept + MTX versus placebo + etanercept + MTX.

When compared to other Cochrane reviews of biologic therapies for rheumatoid arthritis - specifically etanercept, infliximab, and adalimumab, the absolute benefit of treatment versus placebo for the proportion achieving ACR20, ACR50, and ACR70 was notably lower. With etanercept 25 mg biweekly, there was a 49%, 39%, and 14% absolute treatment benefit over placebo for ACR20, ACR50, and ACR70, respectively, after six months ([Blumenauer 2003](#)). With 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 after 24 weeks (heterogeneity prevented pooling of RCTs for adalimumab) ([Navarro-Sarabia 2005](#)). With infliximab 3 mg/kg IV every eight weeks, there was a 33%, 21%, and 8% absolute treatment benefit over placebo for ACR20, ACR50, and ACR70, respectively, after six months ([Blumenauer 2002](#)). In comparison, the absolute treatment benefits with anakinra 50 to 150 mg daily after 6 months were 15%, 11%, and 5% over placebo for ACR20, ACR50, and ACR70 respectively. For each of these outcomes, there was a notably lower level of improvement than the above biologics.

The analysis of safety data for anakinra revealed no statistically significant differences between anakinra versus placebo groups for the total number of withdrawals, deaths, adverse events (total and serious), and infections (total and serious). While the difference between serious infection rates between anakinra and placebo - 1.8% versus 0.6% - was not statistically significantly different, the relative difference of 3.15 may be clinically significant. This may be secondary to the lack of power of the included studies where larger populations may demonstrate statistical significance. Larger registry-based post-marketing study would likely be helpful to clarify this risk as well. Opportunistic infections were not reported in any of the included studies. Injection site reactions were noted to be significantly increased in patients treated with anakinra versus placebo - occurring in 71% versus 28% of patients respectively, with a number needed to harm of 2.3.

On subgroup analysis, the total number of adverse events was significantly increased with the anakinra/placebo + MTX group, raising some clinical concern for the use of these medications together. Malignancy rates were generally rare and without notable difference between anakinra and placebo groups of the included studies. However, post-marketing analysis would likely be more helpful to evaluate the risk of malignancy or other rare serious adverse events that may be associated with anakinra.

The [Genovese 2004](#) study did demonstrate significant increases in the number of withdrawals, injection site reactions, and serious adverse events, likely indicating the poor tolerability and increased risks associated with combining biologic therapies. With the observation of a lack of significant improvement in clinical outcomes noted in this study, we conclude that the use of a combination of biologic medications with anakinra should be avoided in treatment of rheumatoid arthritis.

AUTHORS' CONCLUSIONS

Implications for practice

Anakinra is currently FDA approved for the treatment of rheumatoid arthritis that is unresponsive to initial DMARD therapy. This review demonstrated significant improvement in the primary outcome of ACR20, as well as a number of other efficacy outcomes - including ACR50, ACR70, HAQ scores, VAS scores, and ESR - in those treated with anakinra versus placebo. When compared to other biologics for RA - specifically adalimumab, infliximab, and etanercept - the absolute treatment benefit seen versus placebo in ACR20, ACR50, ACR70 was notably larger than the treatment benefit with anakinra. There was no statistically significant increase in the number of adverse events (total or serious) or infections (total or serious) with anakinra versus placebo. Injection site reactions were significantly more common with anakinra versus placebo. The relative increase in serious infections was statistically insignificant, but may be clinically significant. There was no significant difference in number of withdrawals between anakinra versus placebo.

Implications for research

Limited data are available for safety of anakinra and post-marketing surveillance studies are needed to better inform patients and physicians. Studies comparing anakinra to other traditional DMARDs or other biologics may also be helpful to inform physicians about relative efficacies of these agents for treatment of RA.

ACKNOWLEDGEMENTS

We thank Louise Falzon for her support with electronic searches.

We thank Rod MacDonald for his efforts in assisting with this review.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Bresnihan 1998

Methods	A randomized, placebo-controlled, double blinded trial comparing anakinra to placebo.
Participants	472 patients with rheumatoid arthritis with active disease where all DMARDs were discontinued 6 weeks prior, allowing only NSAIDs and/or steroids
Interventions	placebo (n = 119) and IL-1 receptor antagonist 30 mg daily (n = 119), 75 mg daily (n = 115), 150 mg daily (n = 115) for 24 weeks. 4 excluded from analysis after not receiving any doses of study drug.
Outcomes	Outcome Data: ACR20, change in HAQ, change in CRP, change in ESR, change in Larsen score, change in pain VAS scale; Safety Data: withdrawals, injection site reactions
Notes	excluded missing data; only partial intention-to-treat analysis

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Cohen 2002

Methods	A randomized, double blinded, placebo-controlled trial comparing anakinra to placebo in the setting of methotrexate therapy; Originally set up as a 12 week trial with 105 participants, though extended as a 24 week trial involving 317 participants (314 new participants and 3 recruited from original 12 week trial).
Participants	419 patients with active rheumatoid arthritis and on methotrexate for at least 6 months while off other DMARDs for at least 2 months
Interventions	placebo (n = 48) and anakinra 0.04 mg/kg/day (n = 63), 0.1 mg/kg/day (n = 46), 0.4 mg/kg/day (n = 55), 1.0 mg/kg/day (n = 59), and 2.0 mg/kg/day (n = 46) for 24 weeks.
Outcomes	Outcome data: ACR20, ACR50, ACR70. Change in HAQ score, change in CRP, and change in ESR data was also collected, though no standard deviations were given with these continuous data. Safety data: withdrawals, injection site reactions
Notes	Only 3 reconsented from original 12 week trial for full, extended 24 week trial. Results were missing standard deviation data from all continuous data. Data analyzed with full intention-to-treat analysis

Risk of bias

Cohen 2002 (Continued)

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Cohen 2004

Methods	A randomized, double-blinded, placebo-controlled trial comparing anakinra to placebo in the setting of methotrexate therapy.	
Participants	506 patients with active rheumatoid arthritis, including erosive disease on X-ray, and on methotrexate for at least 24 weeks and other DMARDs discontinued at least 60 days prior to the study.	
Interventions	placebo + methotrexate + folic acid (n = 251) vs. anakinra 100 mg daily + methotrexate + folic acid (n = 250). 5 excluded from analysis after not receiving any doses of study drug.	
Outcomes	Outcome Data: ACR20, ACR50, ACR70, change in HAQ, change in ESR; Safety Data: infections, serious infections, adverse events, serious adverse events, injection site reactions	
Notes	no withdrawal data provided; only partial intention-to-treat analysis	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Fleischman 2003

Methods	A randomized, double-blinded, placebo-controlled trial comparing anakinra to placebo.	
Participants	1414 patients with active rheumatoid arthritis and any DMARD therapy except for TNF-inhibitors that had been stable for 2 months.	
Interventions	Anakinra 100 mg daily (n = 1116) vs. placebo (n = 283) for 6 months. 15 excluded from analysis after not receiving any doses of study drug.	
Outcomes	Outcome Data: none; Safety Data: withdrawals, infections, serious infections, adverse effects, serious adverse events, deaths, injection site reactions	
Notes	no outcome data reported; only partial intention-to-treat analysis	

Risk of bias

Fleischman 2003 (Continued)

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Genovese 2004

Methods	A randomized, double blinded, placebo-controlled trial comparing anakinra to placebo in the setting of treatment with etanercept and methotrexate.	
Participants	244 patients with active RA and on methotrexate for at least 16 weeks though other DMARD therapy discontinued at least 4 weeks prior to the study.	
Interventions	Etanercept 25 mg 2 doses/week + placebo + methotrexate (n = 80) vs. etanercept 25 mg 1 dose/week + anakinra 100 mg daily + methotrexate (n = 81) vs. etanercept 25 mg 2 doses/week + anakinra 100 mg daily + methotrexate (n = 81). 2 excluded from analysis after not receiving any doses of study drug.	
Outcomes	Outcome Data: ACR20, ACR50, ACR70, change in HAQ, change in ESR, change in CRP; Safety Data: withdrawals, infections, serious infections, adverse events, serious adverse effects, injection site reactions	
Notes	Etanercept 25 mg 1 dose/week group without control arm; full intention-to-treat analysis	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

CRP: C-reactive protein

DMARD: Disease-modifying anti-rheumatic drugs

ESR: Erythrocyte sedimentation rate

HAQ:

NSAID: Non steroidal anti-inflammatory drugs

RA: Rheumatoid arthritis

TNF: Tumor necrosing factor

vs: versus

Characteristics of excluded studies *[ordered by study ID]*

AMGEN FDA 2001	FDA document review
Bresnihan 2001	Review, anakinra studies
Bresnihan 2002	Review, anakinra studies
Bresnihan 2002b	Review, anakinra studies
Bresnihan 2004	Extension of Bresnihan 1998 trial (24wk); no placebo/control arm; same as Nuki
Burls 2004	Editorial, of Genovese, 2004
Calabrese 2002	Case report
Campion 1996	No placebo/control arm to study, randomized
Choy 2005	Meta-analysis, DMARD combination and safety
Cohen 2003	Reevaluation of Cohen, 2002 study with emphasis on functional outcomes
Cohen 2004b	Meta-analysis, Bresnihan 1998, Cohen 2001, Cohen 2002
De La Mata 2007	Review - anakinra studies in RA
Dinarelli 2005	Editorial, IL-1 overview
Dougados 1992	Not anakinra (IX 207-887 = organic compound)
Drevlow 1996	Randomized, double blinded; though only individual data with 28 days on 12 patients
Fleischmann 2002	Review, safety of anakinra from Fleischmann 2003 study
Fleischmann 2006	36 month extension of Fleischmann, 2003; open label study
Garces 2001	Review - anakinra studies
Garrood 2001	Review of DMARDs
Genant 2001	Review of post-hoc analysis/validation of Genant radiograph evaluation from Bresnihan, 1998
Haraoui 2003	Review
Jiang 2000	Reevaluation of Bresnihan, 1998 (with Genant radiograph validation and analysis)

(Continued)

Jones 2003	Meta-analysis, radiographic changes in RA
Loft 2003	Review, anakinra studies
National Horizon 2001	Review
Nixon 2007	Meta-analysis
Nuki 2002	Extension (24 wk) of Bresnihan, 1998 trial: no placebo/control arm; same as Bresnihan, 2004
Paget 2002	Review
Rau 1998	Same study as Bresnihan 1998
Rau 2003	Case report
Riente 2004	Review, anakinra studies
Schiff 2004	Reevaluation of Fleischmann, 2003; emphasis on evaluation of comorbid conditions
Schwetz 2002	Not anakinra (xigris)
Strand 2002	Review, radiographic analysis following RA treatments
Strand 2004	Review of DMARD therapy on radiographic changes
Tesser 2004	Reevaluation of Fleischmann, 2003 study, with emphasis on concomitant medications used
Tomoo 2005	Review
Watt 2001	Re-evaluation of Bresnihan, 1998 study with emphasis on radiographic changes
Zundorf 2003	Review of Biologics for RA

DATA AND ANALYSES

Comparison 1. Anakinra (0 to 50 mg/day)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ACR20	2	450	Risk Ratio (M-H, Fixed, 95% CI)	1.38 [1.01, 1.89]
1.1 Anakinra	1	238	Risk Ratio (M-H, Fixed, 95% CI)	1.47 [1.01, 2.13]
1.2 Anakinra + Methotrexate	1	212	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [0.69, 2.17]
2 ACR50	1	212	Risk Ratio (M-H, Fixed, 95% CI)	3.37 [0.82, 13.77]
2.1 Anakinra + Methotrexate	1	212	Risk Ratio (M-H, Fixed, 95% CI)	3.37 [0.82, 13.77]
3 ACR70	1	212	Risk Ratio (M-H, Fixed, 95% CI)	4.45 [0.26, 76.62]
3.1 Anakinra + Methotrexate	1	212	Risk Ratio (M-H, Fixed, 95% CI)	4.45 [0.26, 76.62]
4 Withdrawals	2	528	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.62, 1.18]
4.1 Anakinra	1	240	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.50, 1.14]
4.2 Anakinra + Methotrexate	1	288	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.60, 1.79]
5 change in pain VAS score	1	238	Mean Difference (IV, Fixed, 95% CI)	-0.08 [-0.16, 0.00]
5.1 Anakinra	1	238	Mean Difference (IV, Fixed, 95% CI)	-0.08 [-0.16, 0.00]
6 change in HAQ score	1	230	Mean Difference (IV, Fixed, 95% CI)	-0.2 [-0.33, -0.07]
6.1 Anakinra	1	230	Mean Difference (IV, Fixed, 95% CI)	-0.2 [-0.33, -0.07]
7 change in ESR	1	228	Mean Difference (IV, Fixed, 95% CI)	-10.0 [-15.67, -4.33]
7.1 Anakinra	1	228	Mean Difference (IV, Fixed, 95% CI)	-10.0 [-15.67, -4.33]
8 change in CRP	1	237	Mean Difference (IV, Fixed, 95% CI)	-0.9 [-1.64, -0.16]
8.1 Anakinra	1	237	Mean Difference (IV, Fixed, 95% CI)	-0.9 [-1.64, -0.16]
9 change in Larsen score	1	172	Mean Difference (IV, Fixed, 95% CI)	-2.80 [-5.47, -0.13]
9.1 Anakinra	1	172	Mean Difference (IV, Fixed, 95% CI)	-2.80 [-5.47, -0.13]

Comparison 2. Anakinra (51 to 150 mg/day)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ACR20	3	1003	Risk Ratio (M-H, Fixed, 95% CI)	1.61 [1.32, 1.98]
1.1 Anakinra	1	349	Risk Ratio (M-H, Fixed, 95% CI)	1.42 [1.01, 2.00]
1.2 Anakinra + Methotrexate	2	654	Risk Ratio (M-H, Fixed, 95% CI)	1.73 [1.34, 2.23]
2 ACR50	2	654	Risk Ratio (M-H, Fixed, 95% CI)	2.51 [1.56, 4.03]
2.1 Anakinra + Methotrexate	2	654	Risk Ratio (M-H, Fixed, 95% CI)	2.51 [1.56, 4.03]
3 ACR70	2	654	Risk Ratio (M-H, Fixed, 95% CI)	3.71 [1.44, 9.57]
3.1 Anakinra + Methotrexate	2	654	Risk Ratio (M-H, Fixed, 95% CI)	3.71 [1.44, 9.57]
4 Withdrawals	3	1957	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.86, 1.27]
4.1 Anakinra	2	1752	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.82, 1.25]
4.2 Anakinra + Methotrexate	1	205	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [0.74, 2.26]
5 Infections	2	1900	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.80, 1.45]
5.1 Anakinra	1	1399	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.82, 1.10]
5.2 Anakinra + Methotrexate	1	501	Risk Ratio (M-H, Random, 95% CI)	1.28 [0.98, 1.69]
6 Serious Infections	2	1900	Risk Ratio (M-H, Fixed, 95% CI)	3.15 [0.81, 12.20]
6.1 Anakinra	1	1399	Risk Ratio (M-H, Fixed, 95% CI)	5.83 [0.79, 43.00]

6.2 Anakinra + Methotrexate	1	501	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.14, 7.07]
7 Adverse Events	2	1900	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.94, 1.17]
7.1 Anakinra	1	1399	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.96, 1.04]
7.2 Anakinra + Methotrexate	1	501	Risk Ratio (M-H, Random, 95% CI)	1.11 [1.03, 1.20]
8 Serious Adverse Events	2	1900	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.70, 1.56]
8.1 Anakinra	1	1399	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.63, 1.55]
8.2 Anakinra + Methotrexate	1	501	Risk Ratio (M-H, Fixed, 95% CI)	1.26 [0.50, 3.13]
9 Injection site reactions	4	2458	Risk Ratio (M-H, Fixed, 95% CI)	2.45 [2.17, 2.77]
9.1 Anakinra	2	1752	Risk Ratio (M-H, Fixed, 95% CI)	2.40 [2.06, 2.79]
9.2 Anakinra + Methotrexate	2	706	Risk Ratio (M-H, Fixed, 95% CI)	2.57 [2.10, 3.15]
10 Deaths	1	1399	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.11, 9.04]
10.1 Anakinra	1	1399	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.11, 9.04]
11 change in pain VAS score	1	468	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.15, -0.04]
11.1 Anakinra 75	1	234	Mean Difference (IV, Fixed, 95% CI)	-0.07 [-0.15, 0.01]
11.2 Anakinra 150	1	234	Mean Difference (IV, Fixed, 95% CI)	-0.12 [-0.20, -0.04]
12 change in HAQ score	2	951	Mean Difference (IV, Random, 95% CI)	-0.19 [-0.30, -0.09]
12.1 Anakinra 75	1	226	Mean Difference (IV, Random, 95% CI)	-0.2 [-0.31, -0.09]
12.2 Anakinra 150	1	224	Mean Difference (IV, Random, 95% CI)	-0.3 [-0.44, -0.16]
12.3 Anakinra + Methotrexate	1	501	Mean Difference (IV, Random, 95% CI)	-0.11 [-0.19, -0.03]
13 change in ESR	2	949	Mean Difference (IV, Fixed, 95% CI)	-10.04 [-12.75, -7.33]
13.1 Anakinra 75	1	224	Mean Difference (IV, Fixed, 95% CI)	-8.8 [-14.45, -3.15]
13.2 Anakinra 150	1	224	Mean Difference (IV, Fixed, 95% CI)	-11.20 [-17.95, -4.45]
13.3 Anakinra + Methotrexate	1	501	Mean Difference (IV, Fixed, 95% CI)	-10.2 [-13.67, -6.73]
14 change in CRP	1	463	Mean Difference (IV, Fixed, 95% CI)	-0.6 [-1.26, 0.06]
14.1 Anakinra 75	1	233	Mean Difference (IV, Fixed, 95% CI)	-0.6 [-1.42, 0.22]
14.2 Anakinra 150	1	230	Mean Difference (IV, Fixed, 95% CI)	-0.6 [-1.71, 0.51]
15 change in Larsen score	1	341	Mean Difference (IV, Fixed, 95% CI)	-2.45 [-4.53, -0.36]
15.1 Anakinra 75	1	172	Mean Difference (IV, Fixed, 95% CI)	-2.5 [-5.56, 0.56]
15.2 Anakinra 150	1	169	Mean Difference (IV, Fixed, 95% CI)	-2.40 [-5.25, 0.45]
16 ACR20 (Genovese 2004)	1	161	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.73, 1.15]
16.1 Anakinra + Etanercept BW	1	161	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.73, 1.15]
17 ACR50 (Genovese 2004)	1	161	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.49, 1.14]
17.1 Anakinra + etanercept BW	1	161	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.49, 1.14]
18 ACR 70 (Genovese 2004)	1	161	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.32, 1.28]
18.1 Anakinra + etanercept BW	1	161	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.32, 1.28]
19 Withdrawals (Genovese 2004)	1	161	Risk Ratio (M-H, Fixed, 95% CI)	2.96 [1.13, 7.77]
19.1 Anakinra + etanercept BW	1	161	Risk Ratio (M-H, Fixed, 95% CI)	2.96 [1.13, 7.77]
20 Infections (Genovese 2004)	1	161	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.82, 1.67]
20.1 Anakinra + etanercept BW	1	161	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.82, 1.67]
21 Serious Infections (Genovese 2004)	1	161	Risk Ratio (M-H, Fixed, 95% CI)	12.84 [0.74, 224.23]
21.1 Anakinra + etanercept BW	1	161	Risk Ratio (M-H, Fixed, 95% CI)	12.84 [0.74, 224.23]
22 Adverse Events (Genovese 2004)	1	161	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.95, 1.14]

22.1 Anakinra + etanercept BW	1	161	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.95, 1.14]
23 Serious Adverse Events (Genovese 2004)	1	161	Risk Ratio (M-H, Fixed, 95% CI)	5.93 [1.37, 25.64]
23.1 Anakinra + etanercept BW	1	161	Risk Ratio (M-H, Fixed, 95% CI)	5.93 [1.37, 25.64]
24 Injection Site Reactions (Genovese 2004)	1	161	Risk Ratio (M-H, Fixed, 95% CI)	1.76 [1.30, 2.38]
24.1 Anakinra + etanercept BW	1	161	Risk Ratio (M-H, Fixed, 95% CI)	1.76 [1.30, 2.38]
25 ACR20 (including Genovese 2004)	4	1164	Risk Ratio (M-H, Random, 95% CI)	1.37 [0.94, 1.98]
25.1 Anakinra	1	349	Risk Ratio (M-H, Random, 95% CI)	1.42 [1.01, 2.00]
25.2 Anakinra + Methotrexate	2	654	Risk Ratio (M-H, Random, 95% CI)	1.73 [1.34, 2.23]
25.3 Anakinra + Etanercept BW	1	161	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.73, 1.15]
26 Injection site reactions	2	528	Risk Ratio (M-H, Fixed, 95% CI)	1.69 [1.30, 2.21]
26.1 Anakinra	1	240	Risk Ratio (M-H, Fixed, 95% CI)	2.03 [1.42, 2.91]
26.2 Anakinra + Methotrexate	1	288	Risk Ratio (M-H, Fixed, 95% CI)	1.37 [0.92, 2.04]

WHAT'S NEW

Last assessed as up-to-date: 5 February 2008.

18 October 2008	Amended	Converted to new review format. CMSG ID: C107-R
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HISTORY

Protocol first published: Issue 1, 2005

Review first published: Issue 1, 2009

CONTRIBUTIONS OF AUTHORS

All review authors contributed to the review.

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

- Minneapolis VA Medical Center, USA.
- NIH CTSA Award 1 KL2 RR024151-01 (Mayo Clinic Center for Clinical and Translational Research), USA.
- National Institute of Health, USA.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Antirheumatic Agents [*therapeutic use]; Arthritis, Rheumatoid [*drug therapy]; Interleukin 1 Receptor Antagonist Protein [*therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Humans