

Etanercept for the treatment of rheumatoid arthritis (Review)

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[Intervention Review]

Etanercept for the treatment of rheumatoid arthritis

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ABSTRACT

Background

Etanercept is a soluble tumour necrosis factor alpha-receptor DMARD for the treatment of rheumatoid arthritis (RA).

Objectives

To assess the efficacy and safety of etanercept for the treatment of RA.

Search strategy

Five electronic databases were searched from 1966 to February 2003 with no language restriction.

Selection criteria

All randomized controlled trials (minimum 6 month duration) comparing three possible combinations 1) etanercept (10 mg or 25 mg twice weekly) with methotrexate (MTX) to MTX alone 2) etanercept to MTX, or 3) etanercept to placebo were eligible.

Data collection and analysis

Two reviewers extracted data and assessed the methodological quality of the trials. The American College of Rheumatology (ACR) core set of disease activity measures for RA clinical trials, radiographic, withdrawals and toxicity outcomes were analyzed.

Main results

Three trials were included in this review. Two trials compared an experimental group who were started on etanercept compared to a control group; both groups had the same ongoing background therapy of nonsteroidals in both trials plus in one trial one group was on stable methotrexate.

In these two trials the ACR 20, ACR 50 and ACR 70 response rates at 6 months were statistically significantly and clinically important with etanercept 25 mg subcutaneous injections (SC) twice weekly. Sixty-four percent of people receiving etanercept achieved an ACR 20 response compared to 15% of controls and the number needed to treat (NNT) with etanercept is 2 people. Thirty-nine percent of those receiving etanercept achieved an ACR 50 response compared to 4% of taking control treatment and the NNT is three.

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Fifteen percent of people taking etanercept achieved an ACR 70 compared to 1% of controls with a NNT of 7 people.

In the third trial of starting etanercept compared to starting methotrexate the number of participants who achieved an ACR 20, 50 or response at 6 and 12 months were not statistically significant for either etanercept dose.

Etanercept treatment showed a statistically significantly and clinically important affect on joint damage as measured by the Sharp erosion score. Among participants who received etanercept 72% had no increase in their erosion score compared to 60% of participants in the methotrexate group. Withdrawal and toxicity results were acceptable.

Authors' conclusions

Etanercept 25 mg SC twice weekly was more efficacious than control treatment for ACR 20, 50 and 70 at 6 months, and over 12 months it slowed joint damage.

PLAIN LANGUAGE SUMMARY

Etanercept for the treatment of rheumatoid arthritis

HOW WELL DOES ETANERCEPT (ENBREL) WORK TO TREAT RHEUMATOID ARTHRITIS AND HOW SAFE IS IT?

To answer this question, scientists analysed 3 high quality studies. The studies tested over 900 people who had rheumatoid arthritis. People had either injections of etanercept at 10 mg to 25 mg two times a week, methotrexate (MTX) (pills or injections) or placebo injections. This Cochrane Review provides the best evidence we have today.

What is etanercept (Enbrel) and why is it prescribed?

Rheumatoid arthritis is a disease in which the body's immune system attacks its own healthy tissues. The attack happens mostly in the joints of the feet and hands and causes redness, pain, swelling and heat around the joint. Etanercept (Enbrel) is a "biologic" that is prescribed to decrease pain and swelling and slow the progress of rheumatoid arthritis. It is usually prescribed when other DMARDs (disease modifying antirheumatic drugs) do not work well, but can be expensive.

How well does it work?

After 6 months of treatment, a 50% improvement in symptoms occurred in 4 out of 100 people taking MTX or a placebo compared to 39 out of 100 people taking etanercept with or without MTX. This occurred in people with long standing rheumatoid arthritis in whom DMARDs (disease modifying anti-rheumatic drugs) were not working.

After 12 months of treatment, about the same number of people with newly diagnosed rheumatoid arthritis improved with etanercept injections or MTX pills. But etanercept slowed joint damage more than MTX: joint damage slowed in 72 out of 100 people taking etanercept compared to 60 out of 100 people taking MTX.

How safe is it?

Side effects such as headache, common colds, nausea, dizziness, weakness, stomach upset, mouth ulcers and reactions at the site of the injection may occur. But the number of people who stopped taking etanercept due to side effects was the same or less than the number who stopped taking MTX or the placebo. Long term side effects, such as infections like tuberculosis, and cancer still need to be studied.

What is the bottom line?

There is "Gold" level evidence that in people with long standing rheumatoid arthritis in whom DMARDs (disease modifying anti-rheumatic drugs) are not working, injections of etanercept at 25 mg two times a week for 6 months with or without methotrexate decreases pain and swelling better than metotrexate alone or no DMARDs.

In people newly diagnosed with rheumatoid arthritis, injections of etanercept at 25 mg two times a week for 12 months works just as well as methotrexate pills and slows damage to the joints more than methotrexate.

Etanercept is safe and side effects are well-tolerated. Rare and long-term side effects are not yet known.

BACKGROUND

Rheumatoid arthritis (RA) is chronic progressive inflammatory arthritis associated with significant morbidity, mortality, joint deformity and impaired quality of life. Disease modifying anti-rheumatic drugs (DMARDs) are drugs that have been shown to reduce disease activity, slow down joint damage and improve quality of life. DMARDs are the mainstay of treatment of RA. However, patients often fail or are unable to tolerate traditional DMARDs.

Newer biological drugs have been introduced and approved for the treatment of RA over the last few years. Etanercept is one biological agent (a soluble TNF alpha receptor) that inhibits the action of tumour necrosis factor (TNF), thus suppressing inflammation. It is usually prescribed when other DMARDs do not work well.

This review summarizes the current data available on etanercept's efficacy and safety for the treatment of RA. This information will enable clinicians to choose appropriate treatment for their RA patients using the best medical evidence available.

OBJECTIVES

To assess the efficacy and safety of etanercept for the treatment of RA.

METHODS

Criteria for considering studies for this review

Types of studies

All randomized controlled (RCTs) or controlled clinical trials (CCTs) comparing etanercept to placebo, etanercept to methotrexate, or etanercept plus methotrexate to methotrexate alone that were at least six months long were eligible for inclusion. Patients could be on other DMARDs, non steroidal anti-inflammatories or corticosteroids provided they were on stable doses and were randomly allocated to treatment with or without etanercept.

Types of participants

Patients 16 years of age or older meeting the ACR 1987 revised criteria (Arnett 1988) for RA. Patients had to have evidence of active disease as demonstrated by at least two of:

1. Tender joint count
2. Swollen joint count
3. Duration of early morning stiffness >30 minutes
4. Acute phase reactants such as Westergren erythrocyte sedimentation rate (ESR) or C reactive protein (CRP)

Types of interventions

Treatment trials with etanercept versus placebo, etanercept and methotrexate versus methotrexate, and etanercept versus MTX

were eligible for inclusion. Doses of etanercept eligible for inclusion were 10 mg or 25 mg Subcutaneous injections (SC) twice weekly, with a minimum trial duration of 6 months. SC are given by a needle injection into the fatty layer of tissue just below the skin because there is little blood flow to fatty tissue so the injected medication is absorbed slowly.

Types of outcome measures

The primary efficacy outcomes included in this review were the response of rheumatoid arthritis (RA) to treatment with etanercept by the World Health Organization (WHO), the International League of Associations for Rheumatology (ILAR) core set of disease activity measures and the American College of Rheumatology outcome measures for RA clinical trials (OMERACT 1993, Boers 1994, Felson 1993).

EFFICACY OUTCOMES

1. Tender joint count
2. Swollen Joint Count
3. Patients' assessment of pain using 10 cm visual analogue scale or Likert scale
4. Patient global assessment of disease activity
5. Physician global assessment of disease activity using 10 cm visual analogue scale or Likert scale
6. Patient assessment of functional ability as measured by a validated scale such as the Health Assessment Questionnaire (HAQ), which is a standardized, validated scale used in arthritis patients.
7. Acute phase reactants such as ESR or CRP.
8. Radiographic bone changes are accepted as part of the core set of disease activity measures in studies of a minimum of 12 months duration. Radiographic progression as measured by Sharp score or Larsen scale was included as a primary outcome measure of studies with a minimum duration of 12 months.

Definition of Improvement:

Statistical versus clinical significance is relevant to clinical care. Based on the set of efficacy measures outlined above, a definition of clinical improvement has been established (Felson 1995, Pincus 1999). An ACR 20 response represents a 20% improvement in tender and swollen joint counts plus a 20% improvement in 3 of the 5 following remaining core measures: patient and physical global assessments, pain, functional status and an acute phase reactant. Results have been calculated to provide an indication of the number needed to treat (NTT) for each dichotomous outcome. The NTT reflects the effort required (or number of patients one would need to treat) to obtain a beneficial outcome with an intervention.

Secondary outcome measures included health related quality of life (HrQoL) such as the HAQ and SF-36 when available.

SAFETY OUTCOMES

Safety outcomes presented include adverse event outcomes and withdrawals (total, due to lack of efficacy, and due to toxicity).

Search methods for identification of studies

Electronic databases including Biological Abstracts, Current Contents, Dissertation Abstracts, EBM Reviews and all Cochrane electronic databases were searched from 1966 to February 2003. Rheumatoid arthritis was searched as an exploded MESH heading. Etanercept was searched as a text word as it is not currently indexed. The search was not limited by language, year or publication or type of publication. The search strategy used is in Appendix 1. The proceedings of major rheumatology conferences including the American College of Rheumatology (ACR 1990-2003) the European League of Rheumatology (1990-2002) and the Canadian Rheumatology Association were hand searched. The reference lists from standard rheumatology textbooks, comprehensive reviews, and identified clinical trials were searched. Content experts and the pharmaceutical companies that manufacture etanercept were contacted. Additional unpublished data was sought through the FDA web site. The only unpublished data used in this review was additional information from published trials from manufacturers.

Data collection and analysis

STUDY SELECTION

Each study was independently reviewed by two reviewers (BB, MJ) to determine if the study met the inclusion criteria outlined in the a priori protocol developed for the review. Case reports or case series were not eligible. Disagreements on study eligibility were resolved by discussion. The reason(s) for exclusion of any study were noted.

QUALITY ASSESSMENT

Two independent reviewers (BB, AC) assessed methodological quality of each study on the basis of randomization, adequate concealment of randomization, degree of blinding, use of intention to treat analysis and description of dropouts and withdrawals. The validated Jadad ([Jadad 1996](#)) instrument was used to score each study's quality.

DATA ABSTRACTION

Data was abstracted by one reviewer (BB) and the extraction forms were then double-checked independently by another individual against the original data source. Any discrepancies were resolved through consensus by both reviewers returning to the original data source to confirm which value was correct.

DATA SYNTHESIS AND ANALYSIS

The data was analyzed using an intention to treat model. Continuous data was analyzed as a weighted mean difference (WMD). Dichotomous data were reported as a relative risk (RR). Chi square test using $n-1$ degrees of freedom and a p value of less than 0.05 was performed to test homogeneity of the data. A fixed effects model was used to calculate a pooled estimate of effect. The mean and standard deviation (sd) were used when available. When only the median and interquartile ranges were reported, the median was used as the mean, and one half of the difference between the

1st and 3rd quartile range was used as the sd. When only the baseline sd was available, it was used as the end of study sd as well. Outcome variables that were reported only graphically were not included in the study.

GRADING THE STRENGTH OF THE EVIDENCE

The common system of grading the strength of scientific evidence for a therapeutic agent that is described in the CMSG module scope and in the Evidence-based Rheumatology BMJ book ([Tugwell 2003](#)) was used to rank the evidence included in this systematic review. Four categories are used to rank the evidence from research studies: Platinum, Gold, Silver, and Bronze. The ranking is included in the synopsis of this review.

SENSITIVITY AND SUBGROUP ANALYSIS

Sensitivity and subgroup analysis were planned to determine the effects of disease duration, previous DMARD treatment, corticosteroid dose and disease severity on the response to etanercept.

RESULTS

Description of studies

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

[Weinblatt 1999](#) was a 24 week randomized double blind trial comparing etanercept 25 mg SC twice weekly plus stable doses of MTX (15 to 25 mg once weekly, or as low as 10 mg if patient unable to tolerate higher doses) was compared to etanercept placebo plus MTX. All drugs were administered for a 24-week period. All patients received either folic acid or folinic acid. Patients had to have had an incomplete response to at least six months of MTX at a stable dose for at least four weeks prior to randomization. Patients had to be at least 18 years of age, and meet 1987 American Rheumatology Association criteria for rheumatoid arthritis (RA), be in functional class I, II, III according to the revised criteria of the American College of Rheumatology (ACR) and have active disease with at least six tender and six swollen joints. Sulphasalazine and plaquenil were discontinued two weeks prior to starting study drug and all other DMARDs (except MTX) were discontinued four weeks prior. Prednisone at 10 mg daily or less and NSAIDs were permitted as long as the dose had been stable for at least four weeks prior to the study, and remained stable throughout the study.

[Moreland 1999](#) was a 6 month double blind randomized study with 3 arms: etanercept 25 mg SC twice weekly, etanercept 10 mg SC twice weekly and injectable placebo twice weekly. Patients had to have had an inadequate response to 1 to 4 DMARDs, with an inadequate response being defined as discontinuation of the drug due to lack of efficacy. DMARDs had to be washed out at least one month prior to starting study drug and no DMARDs aside from

etanercept were permitted during the trial. Patients had to have evidence of active disease at enrolment, with at least 12 tender joints, at least 10 swollen joints and one of: an ESR of at least 28, CRP of at least 20 mg/L or EMS of at least 45 minutes. Intra-articular steroids were not allowed during the study, or within four weeks of enrolment. 8 placebo patients from an earlier 3-month study were enrolled in this trial. Stable doses of steroids at prednisone 10 mg daily or less and stable doses of NSAIDs that didn't exceed the manufacturer's recommended doses were allowed. Ninety percent of patients had used MTX previously, and 22% were on MTX prior to the DMARD washout period.

[Bathon 2000](#) was a 12 month randomized study with 3 treatment arms: etanercept 10 mg SC twice weekly, etanercept 25 mg SC twice weekly, escalating weekly MTX (7.5 mg at week 0, 15 mg at week 4 and 20 mg at week 8.) One milligram dose reduction allowed for preset laboratory abnormalities. The etanercept/placebo dose was not adjusted. All patients received one mg of folic acid daily. Patients were at least 18 years old with RA for 3 years or less and no other significant concurrent illnesses. Patients had never received methotrexate. Patients had to be either rheumatoid factor positive, or have 3 bony erosions visible on x-rays of the hands, wrists or feet. Patients also had to have at least 10 swollen joints, at least 12 tender joints. Patients also had to have one of either an ESR of at least 28 mm/hour, a CRP of at least mg/d or a minimum of 45 minutes of EMS. DMARDs were discontinued at least 4 weeks before starting the study. Stable dose of NSAIDs and prednisone (10 mg daily or less) were allowed.

Risk of bias in included studies

The [Weinblatt 1999](#) paper did not describe the method of randomization or the method of double-blinding. The [Bathon 2000](#) paper did not describe the study as being a double blind study. It did not describe the method of randomization use or the method of double-blinding (if indeed the study was double blinded). [Moreland 1999](#) received an allocation concealment rating of A as randomization of subjects was blinded. Bathon and Weinblatt received an allocation concealment rating of B, as the methods of randomization were unclear.

Effects of interventions

Three trials ([Weinblatt 1999](#), [Moreland 1999](#), [Bathon 2000](#)), representing a total of 955 participants, met the inclusion criteria. Seven studies were excluded ([ACP 2001](#); [Garnero 2002](#); [Lukina 2001](#); [Moreland 1997](#); [Moreland 2001](#); [Genovese 2002](#); [Paleolog 1998](#)) as they did not meet the inclusion criteria, specific reasons for exclusion are provided in the table of excluded studies in this review.

[Weinblatt 1999](#) and [Moreland 1999](#) followed participants for six months. [Bathon 2000](#) followed patients for 12 months at which

point the study was unblinded. [Weinblatt 1999](#) and [Moreland 1999](#) were pooled to obtain 6-month results for ACR response rates. [Bathon 2000](#) six month results are presented separately. Moreland, Weinblatt and Bathon were pooled to obtain the end of study withdrawal rates and toxicity results. [Bathon 2000](#) was used to calculate ACR response rates at 12 months. Therefore the six month results are from 1) etanercept versus placebo or etanercept plus MTX versus MTX and placebo and 2) etanercept (at two different doses) compared to MTX while the twelve month results represent etanercept (at two different doses) compared to MTX.

All results have been reported using a fixed effects model unless significant heterogeneity existed, at which point a random effects model was used. Efficacy outcomes are reported as weighted mean differences with 95% confidence intervals (CI) for continuous data and as relative risk with 95 % CI for dichotomous outcomes. A priori sensitivity and subgroup analysis were planned to determine the effects of disease duration, previous DMARD treatment, corticosteroid dose and disease severity on the response to etanercept but were not performed due to the small number of studies identified for inclusion in this review.

[Moreland 1999](#) and [Weinblatt 1999](#) studies included participants with long-standing rheumatoid arthritis (RA) (11 to 13 years), whereas the Bathon study included participants who had only had RA for three years or less. We hypothesized that the different disease durations could affect the results when all three study trials were combined together. Therefore, the data was analyzed individually, with all three trials together, and with the two duration trials combined together. The results did not significantly vary with the different study combinations, so it was felt that it was appropriate to combine the data from the differing disease durations (presented in the table of comparisons under "all three studies"). One study compared etanercept to placebo, another to MTX while a third compared etanercept and MTX to MTX alone. Differing drug regimes could affect results and feasibility of pooling. For example, if etanercept and MTX were synergistic a greater response in the etanercept and MTX group could be seen. Comparing etanercept to MTX could diminish the effect of etanercept as compared to placebo since it isn't inactive. The trials were analyzed individually, together, and in pairs to assess the drug regime effect, and no significant difference was found.

A. EFFICACY (see "definition of improvement" in methods section for description of measures presented below)

EFFICACY AT 6 MONTHS: Etanercept vs control (control = either MTX alone or placebo)

ACR 20

ACR 20 response rates were significantly improved with both etanercept doses compared to the control groups. For etanercept 10 mg SC twice weekly compared to control the RR of achieving an ACR 20 was 4.6 (2.4, 8.8), 51% achieved an ACR 20 response (compared to 11% of controls), with an absolute treatment benefit of 40% and a number needed to treat (NNT)

of 3 people. For etanercept 25 mg SC twice weekly compared to control the RR of achieving an ACR 20 was 3.8 (2.5,6.0), 64% achieved an ACR 20 response (compared to 15% of controls), with an absolute treatment benefit (ATB) of 49% and a number needed to treat (NNT) of 2 people.

ACR 50

ACR 50 was significantly improved with both etanercept doses. For etanercept 10 mg SC twice weekly compared to control the RR of achieving an ACR 50 was 4.74 (1.68, 13.36), 24% achieved an ACR 50 response (compared to 5% of controls), with an absolute treatment benefit of 19% and a NNT of 5 people. For etanercept 25 mg SC twice weekly compared to control the RR of achieving an ACR 50 was 8.89 (3.61, 21.89); 39% achieved an ACR 50 response (compared to 4% of controls) with an ATB of 35% and a NNT of 3 people.

ACR 70

ACR 70 was significantly improved with etanercept 25 mg SC twice weekly, but not with etanercept 10 mg SC twice weekly. The relative risk of achieving an ACR 70 with etanercept 10 mg SC twice weekly was 7.37 (0.93, 58.49) which does not reach statistical significance. For etanercept 25 mg SC twice weekly, the relative risk was 11.31 (2.19, 58.30), 15% achieved an ACR 70 (compared to 1% of controls) with an ATB of 14% and a NNT of 7 people.

EFFICACY AT 6 MONTHS: Etanercept vs MTX

There was no statistically difference in ACR 20, 50 or 70 response rates between those who received etanercept compared to those who received MTX after six months.

EFFICACY AT 12 MONTHS: Etanercept vs methotrexate (MTX)

ACR 20

The ACR 20 response at 12 months was not statistically significant at either etanercept 10 mg SC or 25 mg SC twice weekly with a RR of 0.93 (0.79,1.10) and 1.12 (0.96,1.29) respectively.

ACR 50

The ACR 50 just reached statistical significance with etanercept 10 mg SC twice weekly with a RR of 0.75 (0.58,0.98) and p-value of 0.04 but was not significantly improved with etanercept 25 mg SC twice weekly (RR of 1.17(0.93,1.46).

ACR 70

The ACR 70 was not statistically significant for etanercept 10 or 25 mg SC twice weekly with RR of 0.74(0.49,1.12) and 1.16(0.81,1.67) respectively.

Total Sharp Score

The total Sharp Score was significantly reduced with etanercept 25 mg SC twice weekly, but not etanercept 10 mg SC twice weekly. The WMD for etanercept 10 mg SC twice weekly was -1.70 (-4.42,1.02), which is not statistically significant. The WMD for etanercept 25 mg SC twice weekly was -10.50 (-13.33, -7.67), which was significant.

Erosion Sharp Score

The erosion Sharp Score was not significantly reduced for either

dose of etanercept with a WMD of -1.40(-3.13,0.33) for etanercept 10 mg SC twice weekly and WMD of -1.10(-2.83,0.63) for etanercept 25 mg SC twice weekly.

Joint Space Narrowing

Joint Space Narrowing was not significantly reduced with either dose of etanercept with a WMD of -0.40 (-1.72,0.92) for etanercept 10 mg SC twice weekly and WMD of 0.60 (-0.78,1.98) for etanercept 25 mg SC twice weekly.

B. SAFETY

END OF STUDY WITHDRAWALS

Withdrawals are reported three ways in this meta-analysis. First, withdrawals at 6 months are reported from the control comparison trials by [Moreland 1999](#) and [Weinblatt 1999](#).

Withdrawals for [Bathon 2000](#) were reported for 12 months only. End of study withdrawals for all three trials are also reported by combining the 12 month data from Bathon with the six month results from [Moreland 1999](#) and [Weinblatt 1999](#) to calculate the end of study withdrawal outcomes for the pooled data (represented in the metaview graphs and labelled as "all three trials combined").

1. Total Withdrawals

AT 6 MONTHS: Etanercept vs control

Significantly more people withdrew from the control group than from the etanercept (RR was 0.34 (0.22, 0.50), 55% of those taking the control withdrew compared to 15% of those taking etanercept.

AT 12 MONTHS: Etanercept vs methotrexate (MTX)

There was no significant difference in the number of withdrawals between the etanercept and control groups (RR was 0.78 (0.6, 1.03) at 12 months.

All three trials combined

Total withdrawals were analyzed with a random effects model as significant heterogeneity was present. Total withdrawals were reduced in the etanercept 25 mg SC twice weekly group, but not the 10 mg SC twice weekly group. For etanercept 10 mg SC twice weekly, the RR of withdrawal was 0.65 (0.34,1.26), which does not achieve statistical significance. For etanercept 25 mg SC twice weekly, 15% withdrew (compared to 33% of controls) giving an RR of withdrawal of 0.43 (0.24,0.77).

2. Lack of Efficacy

AT 6 MONTHS: Etanercept vs control

Withdrawals were reduced in the etanercept 25 mg SC twice weekly group compared to the control group. The RR was 0.34 (0.22, 0.55), 15% withdrew from the treatment group compared to 54% from the control group.

AT 12 MONTHS: Etanercept vs methotrexate (MTX)

There was no statistically significant difference in the number of withdrawals between the etanercept and control groups.

All three trials combined

When all three studies were combined to examine the number of withdrawals due to lack of efficacy there was significant heterogeneity in the results (p= 0.009 for 25 mg dose). This was because there was no difference in the number of withdrawals between the

two groups in the Bathon study (which was a head to head comparison). In the MTX group (10 out of 207 or 4.8%) withdrew and in the etanercept group (8 out of 217 or 3.7%).

3. Adverse Effects

AT 6 MONTHS: Etanercept vs control

There was no statistically significant difference in the number of adverse events between the etanercept and control groups (RR 0.6 (0.16,2.19)).

AT 12 MONTHS: Etanercept vs methotrexate (MTX)

There were significantly fewer withdrawals due to adverse events in the etanercept group compared to the control group for both 10 mg and 25 mg doses of etanercept (RR 0.43(0.20,0.91 and 0.48(0.23,0.98) respectively.

All three trials combined

There was no difference in withdrawals for adverse effects in the etanercept 10 mg SC twice weekly group compared to controls with a RR of 0.59 (0.31,1.10). The withdrawal rate for adverse events in the etanercept 25 mg SC twice weekly was 4% (compared to 8% in controls) with an ARR of 4% and a RR of 0.50 (0.27,0.94).

END OF STUDY TOXICITY

Injection Site Reaction

AT 6 MONTHS: Etanercept vs control

More people receiving etanercept developed injection site reactions than those taking MTX. The RR 4.42 (2.48,7.87), 46% of those taking etanercept experienced reactions compared to 11% of those taking MTX.

AT 12 MONTHS: Etanercept vs methotrexate (MTX)

More people receiving etanercept developed injection site reactions than those taking MTX. The RR 5.04 (3.05, 8.35), 37% of those taking etanercept experienced reactions compared to 7% of those taking MTX.

END OF STUDY: All three trials combined

There was a statistically significant increase in injection site reactions at both doses of etanercept compared to controls. For etanercept 10 mg SC twice weekly, the RR of having an injection site reaction was 3.86 (2.59,5.77) with 34% of patients having reactions (compared to 9% of controls). This is absolute risk increase of 25% and yields a number needed to harm (NNH) of 4 patients. For etanercept 25 mg SC twice weekly the RR of having an injection site reaction was 4.77(3.26,6.97) with 41% of patients having reactions (compared to 9% of controls). This is absolute risk increase of 32% and yields a number needed to harm (NNH) of 3.1 patients.

Headache

AT 6 MONTHS: Etanercept vs control

There was no statistically significant difference between the etanercept and control groups. 17% of those taking etanercept 25 mg SC twice weekly experienced headaches compared to 11% in the control group.

AT 12 MONTHS: Etanercept vs methotrexate (MTX)

There was no statistically significant difference between the etan-

cept and control groups.

END OF STUDY: All three trials combined

There was not statistically significant difference in the occurrence of headache in either dose of etanercept with a RR of having headache of 1.04 (0.78,1.40) in the etanercept 10 mg SC twice-weekly group and 0.92 (0.68,1.24) in the etanercept 25 mg SC twice-weekly group compared to controls.

Rhinitis (inflammation and fluid production that occurs in the eyes, nose and throat when airborne irritants trigger the release of histamine)

AT 6 MONTHS: Etanercept vs control

There was no statistically significant difference between the etanercept and control groups. 12% of those taking etanercept 25 mg SC twice weekly experienced headaches compared to 10% in the control group.

AT 12 MONTHS: Etanercept vs methotrexate (MTX)

There was no statistically significant difference between the etanercept and MTX group.

END OF STUDY: All three trials combined

There was not statistically significant difference in the occurrence of rhinitis in either dose of etanercept with a RR of 1.21 (0.81,1.79) in the etanercept 10 mg SC twice-weekly group and 1.14 (0.77,1.71) in the etanercept 25 mg SC twice-weekly group compared to controls.

Diarrhoea

AT 6 MONTHS: Etanercept vs control

There was not statistically significant difference between the etanercept and control groups. 8% of those taking etanercept 25 mg SC twice weekly experienced headaches compared to 10% in the control group.

AT 12 MONTHS: Etanercept vs methotrexate (MTX)

There was no statistically significant difference between the etanercept and MTX group.

END OF STUDY: All three trials combined

There was no statistically significant difference in the occurrence of diarrhoea in either dose of etanercept with a RR of 1.11 (0.71,1.75) in the etanercept 10 mg SC twice-weekly group and 1.01 (0.67,1.51) in the etanercept 25 mg SC twice-weekly group compared to controls.

The following adverse reports were only reported in the 6 month studies (not reported at 12 months):

Sinusitis (sinuses are infected or inflamed)

There was not a statistically significant difference in the occurrence of sinusitis in either dose of etanercept with a RR of 0.84 (0.56,1.26) in the etanercept 10 mg SC twice-weekly group and 0.67(0.43,1.04) in the etanercept 25 mg SC twice-weekly group compared to controls.

URTI

There was not a statistically significant difference in the incidence of upper respiratory tract infections (URTI) in either dose of etan-

cept compared to controls. A random effects model was used. For Etanercept 10 mg SC the relative risk of having a URTI was 1.08 (0.44,2.66) and for etanercept 25 mg SC twice weekly the RR was 1.30 (0.58,2.92).

Nausea

Nausea was reported for only the 25 mg dose of etanercept. The RR of having nausea was 0.57(0.40,0.81) with 15% of patients having nausea (compared to 28% of controls) with an absolute risk decrease of 13%.

Dizziness

Dizziness was reported only for etanercept 25 mg twice weekly. There was not a statistically significant difference in dizziness between the etanercept and control group with a RR of having dizziness of 1.03 (0.63,1.68).

Asthenia (lack of energy and strength)

Asthenia was reported only for the etanercept 25 mg SC twice weekly dose. There was not a statistically significant difference in the occurrence of asthenia with a RR of 1.12 (0.69,1.82) in the etanercept group compared to controls.

Abdominal pain

Abdominal pain was reported only for etanercept 25 mg SC twice weekly. There was not a statistically significant difference in abdominal pain in etanercept compared to controls with a RR of 0.99 (0.57,1.72).

Dyspepsia (a disorder of digestive function characterized by discomfort or heartburn or nausea)

Dyspepsia was reported only for the etanercept 25 mg SC twice weekly group. There was no statistically significant difference in dyspepsia in the etanercept group compared to controls as evidenced by a RR of 1.26 (0.74,2.15).

Mouth ulcers

Mouth ulcers were reported only for the etanercept 25 mg SC twice weekly dose. The risk of mouth ulcers was significantly reduced in the etanercept group (5% versus 13% in the control group) with a ARR of 8%.

DISCUSSION

Rheumatoid arthritis (RA) is a common systemic inflammatory arthritis associated with significant morbidity, mortality, joint deformity and impaired quality of life. Drugs called disease modifying anti-rheumatic drugs (DMARDs) have been shown to reduce disease activity, slow down joint damage and improve quality of life. While DMARDs are the mainstay of treatment of RA, many patients fail or are unable to tolerate traditional DMARDs. Newer biological drugs have been introduced and approved for the treatment of RA. Etanercept is one biological agent (a soluble TNF alpha receptor) that inhibits the action of tumour necrosis factor (TNF). Infliximab (another anti TNF alpha inhibitor) has been summarized in a separate Cochrane Review (Blumenauer 2003).

At six months, the ACR 20 and 50 response rates were improved with both etanercept 10 and 25 mg SC twice weekly, whereas the ACR70 response rate was significantly improved only with etanercept 25 mg SC twice weekly when compared to control treatment. When etanercept was compared to MTX in the Bathon 2000 trial there were no statistically significant differences in ACR response rates between the groups after six or twelve months. However, the participants in the Bathon 2000 study were different than those in the other two included studies (Moreland 1999; Weinblatt 1999). This may have influenced the result that etanercept was less efficacious in the Bathon study (which compared etanercept to MTX) than in the etanercept versus control comparison. Participants in the Bathon study were more recently diagnosed with RA (average length since diagnosis was one year) while participants in the other two studies had RA for an average of 12 years. Also, participants in the Bathon study had never received MTX before. In contrast non-responders to MTX were included in the Weinblatt study and those who had failed to respond to one of four DMARDs were included in the Moreland trial. The Bathon trial compared two different doses of etanercept to MTX therefore the lack of improvement at 12 months should be interpreted with caution.

When withdrawals were analyzed as end of study withdrawals (six months for Moreland 1999 and Weinblatt 1999, 12 months for Bathon 2000) the total withdrawals were reduced in the etanercept 25 mg SC twice weekly group, but not the 10 mg SC twice-weekly group, as compared to controls. There was no significant difference in withdrawals due to lack of efficacy for either etanercept 10 mg or 25 mg SC twice weekly compared to controls. There was no difference in withdrawals for adverse effects in the etanercept 10 mg SC twice weekly group compared to controls, although the withdrawals due to adverse events was reduced in the etanercept 25 mg SC twice weekly group compared to controls.

Toxicity was analyzed as end of study toxicity as that was how it was reported (six months for Moreland 1999 and Weinblatt 1999, 12 months for Bathon 2000). There was a statistically significant increase in injection site reactions at both doses of etanercept compared to controls. There was not a statistically significant difference in the incidence of upper respiratory tract infections, headache, sinusitis, rhinitis or diarrhoea in either etanercept 10 mg or 25 mg SC twice weekly compared to controls. The incidence of nausea, dizziness, asthenia, abdominal pain, dyspepsia and mouth ulcers was reported only for the etanercept 25 mg twice weekly and control groups. Nausea was reduced in the etanercept 25 mg SC twice weekly group compared to controls. There was not a statistically significant difference in dizziness, asthenia, abdominal pain, and dyspepsia between the etanercept 25 mg SC twice weekly group and control group. The risk of mouth ulcers was significantly reduced in the etanercept group compared to controls.

Radiographic data was reported for the Bathon study at the 12-month mark. The total Sharp Score was significantly improved for etanercept 25 mg SC (but not 10 mg SC) twice weekly com-

pared to controls. Neither the Erosion Sharp Score nor the Joint Space Narrowing were significantly improved with either dose of etanercept compared to controls.

AUTHORS' CONCLUSIONS

Implications for practice

Etanercept is approved for the treatment of rheumatoid arthritis (RA) at a dose of 25 mg SC twice weekly. While some outcome variables were significantly improved with etanercept 10 mg SC twice weekly, etanercept 25 mg SC twice weekly was a more efficacious treatment than 10 mg SC twice weekly compared to controls.

ACR 20, 50 and 70 response rates were significantly improved at 6 months, but not at 12 months. This may be due to the different treatments compared at six and twelve months. Six month significant results reflect etanercept plus MTX vs control or etanercept versus placebo comparisons. Six month nonsignificant results were found when etanercept (at two different doses) was compared to MTX. Non significant 12 month results represent only etanercept (at two different doses) compared to MTX and therefore the lack of improvement at 12 months should be interpreted with caution.

Twelve month radiographic data showed improvement in total Sharp Scores and erosion score, but not joint space narrowing. The question is whether longer term treatment would maintain radiographic improvement, or whether the effects are reduced with on-going treatment. Although radiographic data from the original Bathon study are available for beyond the 12-month mark, the study was unblinded after 12 months, and the results were therefore not included in the meta-analysis.

There was little difference in withdrawals, and toxicity was either the same or less in the etanercept as compared with the control groups. This suggests etanercept is well tolerated and safe. The most common side effect was a site reaction to the needle and ceased after a few injections. However, there are concerns with increased incidence of infections (particularly tuberculosis) and possibly increased malignancy risks, so the long-term efficacy and safety need to be further evaluated.

The availability of etanercept varies within and between countries. In most countries the cost of etanercept is significantly more than that of other DMARDS.

Implications for research

Further long-term studies are required to assess the efficacy of both clinical and radiographic outcome variables beyond 12 months. Long term monitoring of adverse events is required to determine the long-term safety of etanercept. Since etanercept may be most beneficial in the first six months, studies where etanercept is used as induction therapy and the patients are then switched to more traditional DMARDS are needed. This would determine not only efficacy but also the cost-effectiveness of etanercept for the treatment of RA. Finally, head-to-head comparison with the other licensed biological agents (anakinra and infliximab) would be useful to allow physicians to select the best treatment for each patient. Information on which group of patients are most likely to benefit from biological treatment would be helpful so patients most likely to benefit could be offered this expensive treatment.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Bathon 2000

Methods	Randomized study	
Participants	632 pts. At least 18 y.o. ; RA max 3 years;no other illnesses	
Interventions	E 10mg SC vs 25 mg SC vs MTX po 7.5mg	
Outcomes	ACR 20,50,70 Radiographic	
Notes	Early RA; MTX naive; Most erosions and RF+;12 month	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Moreland 1999

Methods	Randomized, double-blind	
Participants	234 pts Active RA. 99% of patients had used MTX previously	
Interventions	E10 vs E25 vs PBO twice weekly SC	
Outcomes	ACR 20,50,70 Radiographic TJC;SJC; HAQ;	
Notes		
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Weinblatt 1999

Methods	Double-blinded study	
Participants	83 pts at least 18 y.o., 1987 ARA RA ;fx class I,II,III	
Interventions	E 25 mg SC twice weekly + MTX vs E PBO + MTX	
Outcomes	TJC;SJC; HAQ; ACR 20,50,70; ESR;CRP;pt & MD global;	
Notes		
Risk of bias		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Characteristics of excluded studies [ordered by study ID]

ACP 2001	Summary of Bathon 2000 with no new information provided.
Garnero 2002	Patient subset from published studies looking at collagen markers and joint destruction. The relationship of collagen markers to joint destruction was not an outcome of interest.
Genovese 2002	Study was an extension of the Bathon study at 24 months. Patients were given etanercept 10 mg, 25 mg, or MTX in an open-label manner.
Lukina 2001	Compared TNF alpha (?drug) to interferon gamma to placebo. Drugs given IM daily for 5 days with outcome determination at days 7 and 28. Even if etanercept used, study duration too short to meet inclusion criteria.
Moreland 1997	3 month study only so does not meet inclusion criteria
Moreland 2001	Examined all patients who had recieved at least 1 dose of etanercept in controlled or open label trials for efficacy and safety at a date removed from trial. doesn't meet inclusion criteria.
Paleolog 1998	Looked at synovial cells from patients treated with anti-TNF alpha.

DATA AND ANALYSES

Comparison 1. Efficacy at 6 months: Etanercept vs control (Weinblatt and Moreland)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ACR 20	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Etanercept 10 mg SC twice weekly	1	156	Risk Ratio (M-H, Fixed, 95% CI)	4.56 [2.37, 8.77]
1.2 Etanercept 25 mg SC twice weekly	2	247	Risk Ratio (M-H, Fixed, 95% CI)	3.84 [2.47, 5.98]
2 ACR 50	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Etanercept 10 mg SC twice weekly	1	156	Risk Ratio (M-H, Fixed, 95% CI)	4.74 [1.68, 13.36]
2.2 Etanercept 25 mg SC twice weekly	2	247	Risk Ratio (M-H, Fixed, 95% CI)	8.89 [3.61, 21.89]
3 ACR 70	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Etanercept 10 mg SC twice weekly	1	156	Risk Ratio (M-H, Fixed, 95% CI)	7.37 [0.93, 58.49]
3.2 Etanercept 25 mg SC twice weekly	2	247	Risk Ratio (M-H, Fixed, 95% CI)	11.31 [2.19, 58.30]

Comparison 2. Efficacy at 6 months: Etanercept vs MTX (Bathon)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ACR 20	1	424	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.84, 1.18]
2 ACR 50	1	424	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.75, 1.33]
3 ACR 70	1	424	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.59, 1.60]

Comparison 3. Efficacy at 12 Months: Etanercept vs MTX (Bathon)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ACR 20	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Etanercept 10 mg SC twice weekly	1	424	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.79, 1.10]
1.2 Etanercept 25 mg SC twice weekly	1	425	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.96, 1.29]
2 ACR 50	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

2.1 Etanercept 10 mg SC twice weekly	1	424	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.58, 0.98]
2.2 Etanercept 25 mg SC twice weekly	1	425	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.93, 1.46]
3 ACR 70	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Etanercept 10 mg SC twice weekly	1	424	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.49, 1.12]
3.2 Etanercept 25 mg SC twice weekly	1	425	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.81, 1.67]
4 Radiographic: Total Sharp Score (0 to 398)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 Etanercept 10 mg SC twice weekly	1	425	Mean Difference (IV, Fixed, 95% CI)	-1.70 [-4.42, 1.02]
4.2 Etanercept 25 mg SC twice weekly	1	424	Mean Difference (IV, Fixed, 95% CI)	-10.5 [-13.33, -7.67]
5 Erosion Sharp Score (0 to 230)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.1 Etanercept 10 mg SC twice weekly	1	425	Mean Difference (IV, Fixed, 95% CI)	-1.40 [-3.13, 0.33]
5.2 Etanercept 25 mg SC twice weekly	1	424	Mean Difference (IV, Fixed, 95% CI)	-1.10 [-2.83, 0.63]
6 Joint-Space Narrowing (0 to 168)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
6.1 Etanercept 10 mg SC twice weekly	1	425	Mean Difference (IV, Fixed, 95% CI)	-0.40 [-1.72, 0.92]
6.2 Etanercept 25 mg SC twice weekly	1	424	Mean Difference (IV, Fixed, 95% CI)	0.60 [-0.78, 1.98]

Comparison 4. End of Study Withdrawals 6 mos: Etanercept vs control (Weinblatt & Moreland)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Etanercept 25 mg SC twice weekly	2	247	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.22, 0.50]
2 Lack of Efficacy	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Etanercept 25 mg SC twice weekly	2	247	Risk Ratio (M-H, Fixed, 95% CI)	0.26 [0.15, 0.45]
3 Adverse Event	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Etanercept 25 mg SC twice weekly	2	247	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.16, 2.19]
4 Death	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Comparison 5. End of Study Toxicity 6 mos: Etanercept vs control (Weinblatt & Moreland)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Injection Site Reaction	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Etanercept 25 mg SC twice weekly	2	247	Risk Ratio (M-H, Fixed, 95% CI)	4.42 [2.48, 7.87]
2 URTI Not Applicable	0		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3 Headache	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Etanercept 25 mg SC twice weekly	2	247	Risk Ratio (M-H, Fixed, 95% CI)	1.32 [0.70, 2.50]
4 Sinusitis- Not Applicable	0		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5 Rhinitis	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Etanercept 25 mg SC twice weekly	2	247	Risk Ratio (M-H, Fixed, 95% CI)	1.32 [0.59, 2.94]
6 Diarrhea	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Etanercept 25 mg SC twice weekly	2	247	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.31, 1.49]
7 Nausea - Not Applicable	0		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8 Dizziness - Not Applicable	0		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9 Asthenia - Not Applicable	0		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10 Abdominal Pain - Not Applicable	0		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
11 Dyspepsia - Not Applicable	0		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
12 Mouth Ulcers - Not Applicable	0		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

Comparison 6. End of Study Withdrawals 12 mos: Etanercept vs MTX (Bathon)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total	1	849	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.60, 1.03]
1.1 10 mg	1	425	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.63, 1.32]
1.2 25 mg	1	424	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.43, 0.99]
2 Lack of Efficacy	1	849	Risk Ratio (M-H, Fixed, 95% CI)	1.63 [0.89, 3.02]
2.1 10 mg	1	425	Risk Ratio (M-H, Fixed, 95% CI)	1.96 [0.85, 4.52]
2.2 25 mg	1	424	Risk Ratio (M-H, Fixed, 95% CI)	1.31 [0.53, 3.26]
3 Adverse event	1	849	Risk Ratio (M-H, Fixed, 95% CI)	0.45 [0.27, 0.76]
3.1 10 mg	1	425	Risk Ratio (M-H, Fixed, 95% CI)	0.43 [0.20, 0.91]
3.2 25 mg	1	424	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.23, 0.98]
4 Death	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Comparison 7. End of Study Toxicity 12 mos: Etanercept vs MTX (Bathon)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 injection site reaction	1	424	Risk Ratio (M-H, Fixed, 95% CI)	5.04 [3.05, 8.35]
1.1 25 mg	1	424	Risk Ratio (M-H, Fixed, 95% CI)	5.04 [3.05, 8.35]
2 URTI	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3 Headache	1	424	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.58, 1.14]
3.1 25 mg	1	424	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.58, 1.14]
4 Sinusitis	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5 Rhinitis	1	424	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.68, 1.72]
5.1 25 mg	1	424	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.68, 1.72]
6 Diarrhea	1	424	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.72, 1.89]
6.1 25 mg	1	424	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.72, 1.89]
7 Nausea	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
8 Dizziness	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
9 Asthenia	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
10 Abdominal pain	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
11 Dyspepsia	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
12 Mouth ulcers	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Comparison 8. Efficacy at 6 Months (all 3 studies)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ACR 20	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Etanercept 10 mg SC twice weekly	2	580	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [1.05, 1.47]
1.2 Etanercept 25 mg SC twice weekly	3	672	Risk Ratio (M-H, Fixed, 95% CI)	1.51 [1.29, 1.76]
2 ACR 50	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Etanercept 10 mg SC twice weekly	2	580	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.92, 1.59]
2.2 Etanercept 25 mg SC twice weekly	3	672	Risk Ratio (M-H, Fixed, 95% CI)	1.80 [1.40, 2.31]
3 ACR 70	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Etanercept 10 mg SC twice weekly	2	580	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.75, 1.91]
3.2 Etanercept 25 mg SC twice weekly	3	672	Risk Ratio (M-H, Fixed, 95% CI)	2.12 [1.40, 3.21]

Comparison 9. End of Study Toxicity (all 3 studies)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 injection site reaction	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 etanercept 10 mg SC twice weekly	2	581	Risk Ratio (M-H, Fixed, 95% CI)	3.86 [2.59, 5.77]
1.2 etanercept 25 mg SC twice weekly	3	671	Risk Ratio (M-H, Fixed, 95% CI)	4.77 [3.26, 6.97]
2 URTI	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Etanercept 10 mg SC twice weekly	2	581	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.66, 1.09]
2.2 Etanercept 24 mg SC twice weekly	2	582	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.84, 1.33]
3 Headache	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 etanercept 10 mg SC twice weekly	2	581	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.78, 1.40]
3.2 Etanercept 25 mg SC twice weekly	3	671	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.68, 1.24]
4 Sinusitis	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Etanercept 10 mg SC twice weekly	2	581	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.56, 1.26]
4.2 Etanercept 25 mg SC twice weekly	2	582	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.43, 1.04]
5 Rhinitis	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Etanercept 10 mg SC twice weekly	2	581	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.81, 1.79]
5.2 Etanercept 25 mg SC twice weekly	3	671	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.77, 1.71]
6 diarrhea	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Etanercept 10 mg SC twice weekly	2	581	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.71, 1.75]
6.2 Etanercept 25 mg SC twice weekly	3	671	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.67, 1.51]
7 nausea	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 Etanercept 25 mg SC twice weekly	2	513	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.40, 0.81]
8 dizziness	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 Etanercept 25 mg SC twice weekly	2	513	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.63, 1.68]
9 asthenia	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.1 Etanercept 25 mg SC twice weekly	2	513	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.69, 1.82]
10 abdominal pain	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1 Etanercept 25 mg SC twice weekly	2	513	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.57, 1.72]
11 dyspepsia	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
11.1 etanercept 25 mg SC twice weekly	2	513	Risk Ratio (M-H, Fixed, 95% CI)	1.26 [0.74, 2.15]

12 mouth ulcers	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
12.1 Etanercept 25 mg SC twice weekly	2	513	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.19, 0.69]

Comparison 10. End of Study Withdrawals (all 3 studies)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Etanercept 10 mg SC twice weekly	2	581	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.34, 1.26]
1.2 Etanercept 25 mg SC twice weekly	3	671	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.24, 0.77]
2 Lack of Efficacy	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Etanercept 10 mg SC twice weekly	2	581	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.44, 0.97]
2.2 Etanercept 25 mg SC twice weekly	3	671	Risk Ratio (M-H, Fixed, 95% CI)	0.41 [0.27, 0.64]
3 Adverse Event	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Etanercept 10 mg SC twice weekly (Bathon lumps AE and LTF)	2	581	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.31, 1.10]
3.2 Etanercept 25 mg SC twice weekly (Bathon lumps AE and LTF)	3	671	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.27, 0.94]
4 Death	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Etanercept 10 mg SC twice weekly	2	4	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4.2 Etanercept 25 mg SC twice weekly	3	6	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Comparison 11. Efficacy at 6 Months (Bathon and Moreland)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ACR 20	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Etanercept 10 mg SC twice weekly	2	580	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [1.05, 1.47]
1.2 Etanercept 25 mg SC twice weekly	2	583	Risk Ratio (M-H, Fixed, 95% CI)	1.41 [1.20, 1.65]
2 ACR 50	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Etanercept 10 mg SC twice weekly	2	580	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.92, 1.59]

2.2 Etanercept 25 mg SC twice weekly	2	583	Risk Ratio (M-H, Fixed, 95% CI)	1.61 [1.25, 2.07]
3 ACR 70	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Etanercept 10 mg SC twice weekly	2	580	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.75, 1.91]
3.2 Etanercept 25 mg SC twice weekly	2	583	Risk Ratio (M-H, Fixed, 95% CI)	1.94 [1.27, 2.95]

Comparison 12. Efficacy at 6 Months (Weinblatt and Bathon)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ACR 20	2	514	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [1.07, 1.46]
1.1 Etanercept 25 mg SC twice weekly	2	514	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [1.07, 1.46]
2 ACR 50	2	514	Risk Ratio (M-H, Fixed, 95% CI)	1.44 [1.10, 1.87]
2.1 Etanercept 25 mg SC twice weekly	2	514	Risk Ratio (M-H, Fixed, 95% CI)	1.44 [1.10, 1.87]
3 ACR 70	2	514	Risk Ratio (M-H, Fixed, 95% CI)	1.76 [1.14, 2.71]
3.1 Etanercept 25 mg SC twice weekly	2	514	Risk Ratio (M-H, Fixed, 95% CI)	1.76 [1.14, 2.71]

Comparison 13. End of Study Toxicity (Bathon & Moreland)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Injection Site Reaction	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Etanercept 10 mg SC twice weekly	2	581	Risk Ratio (M-H, Fixed, 95% CI)	3.86 [2.59, 5.77]
1.2 Etanercept 25 mg SC twice weekly	2	582	Risk Ratio (M-H, Fixed, 95% CI)	4.60 [3.11, 6.81]
2 URTI	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Etanercept 10 mg SC twice weekly	2	581	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.66, 1.09]
2.2 Etanercept 25 mg SC twice weekly	2	582	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.84, 1.33]
3 Headache	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Etanercept 10 mg SC twice weekly	2	581	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.78, 1.40]
3.2 Etanercept 25 mg SC twice weekly	2	582	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.65, 1.21]
4 Sinusitis	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Etanercept 10 mg SC twice weekly	2	581	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.56, 1.26]

4.2 Etanercept 25 mg SC twice weekly	2	582	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.43, 1.04]
5 Rhinitis	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Etanercept 10 mg SC twice weekly	2	581	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.81, 1.79]
5.2 Etanercept 25 mg SC twice weekly	2	582	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.69, 1.58]
6 Diarrhea	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Etanercept 10 mg SC twice weekly	2	581	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.71, 1.75]
6.2 Etanercept 25 mg SC twice weekly	2	582	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.71, 1.74]
7 Nausea - Not Applicable	0		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8 Dizziness - Not Applicable	0		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9 Asthenia - Not Applicable	0		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10 Abdominal Pain - Not Applicable	0		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
11 Dyspepsia - Not Applicable	0		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
12 Mouth Ulcers - Not Applicable	0		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

Comparison 14. End of Study Toxicity (Weinblatt & Bathon)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Injection Site Reaction	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Etanercept 25 mg SC twice weekly	2	513	Risk Ratio (M-H, Fixed, 95% CI)	5.24 [3.25, 8.43]
2 URTI - Not Applicable	0		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3 Headache	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Etanercept 25 mg SC twice weekly	2	513	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.63, 1.18]
4 Sinusitis - Not Applicable	0		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5 Rhinitis	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Etanercept 25 mg SC twice weekly	2	513	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.77, 1.90]
6 Diarrhea	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Etanercept 25 mg SC twice weekly	2	513	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.67, 1.59]
7 Nausea - Not Applicable	0		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8 Dizziness - Not Applicable	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
9 Asthenia - Not Applicable	0	0	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
10 Abdominal Pain - Not Applicable	0		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
11 Dyspepsia - Not Applicable	0		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
12 Mouth Ulcers - Not Applicable	0		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

Comparison 15. End of Study Withdrawals (Bathon & Moreland)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Etanercept 10 mg SC twice weekly	2	581	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.52, 0.88]
1.2 Etanercept 25 mg SC twice weekly	2	582	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.37, 0.67]
2 Lack of Efficacy	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Etanercept 10 mg SC twice weekly	2	581	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.44, 0.97]
2.2 Etanercept 25 mg SC twice weekly	2	582	Risk Ratio (M-H, Fixed, 95% CI)	0.45 [0.29, 0.71]
3 Adverse Event	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Etanercept 10 mg SC twice weekly	2	581	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.31, 1.10]
3.2 Etanercept 25 mg SC twice weekly	2	582	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.26, 0.98]

Comparison 16. End of Study Withdrawals (Weinblatt & Bathon)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Etanercept 25 mg SC twice weekly	2	513	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.39, 0.87]
2 Lack of Efficacy	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Etanercept 25 mg SC twice weekly	2	513	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.36, 1.64]
3 Adverse Event	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Etanercept 25 mg SC twice weekly	2	513	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.24, 0.94]

WHAT'S NEW

Last assessed as up-to-date: 10 March 2003.

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CONTRIBUTIONS OF AUTHORS

BB and AC extracted and analyzed the data and selected trials of the initial review and preparation of the initial manuscript.

AB and MH contributed data, updated of the selection of the reference list, updated the analyses and updated the interpretation of results.

BB and MJ wrote the manuscript, contributed data extraction, updated the analyses and interpretation of results.

AC, DC, GW and PT contributed methodological expertise and commented on drafts.

DECLARATIONS OF INTEREST

None known

INDEX TERMS

Medical Subject Headings (MeSH)

Antirheumatic Agents [administration & dosage; *therapeutic use]; Arthritis, Rheumatoid [*drug therapy]; Immunoglobulin G [administration & dosage; *therapeutic use]; Methotrexate [therapeutic use]; Randomized Controlled Trials as Topic; Receptors, Tumor Necrosis Factor [administration & dosage; *therapeutic use]

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