A systematic review and meta-analysis of the efficacy and safety of etanercept for treating rheumatoid arthritis

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CRD summary
This review concluded that compared to controls, etanercept demonstrated greater efficacy for management of rheumatoid arthritis, no difference in adverse events and fewer withdrawals due to lack of efficacy. Although the review process was well conducted, concerns with the analysis mean the results should be treated with some caution.

Authors' objectives
To evaluate the efficacy and safety of etanercept for treating rheumatoid arthritis.

Searching
MEDLINE, EMBASE, The Cochrane Library, SCIELO, LILACS and International Pharmaceutical Abstracts were searched without language or date restrictions (date were not reported); search terms were reported. Studies available only as abstracts were excluded.

Study selection
Randomised controlled trials (RCTs) that compared etanercept (25mg twice weekly or 50mg weekly in subcutaneous injections) with placebo or etanercept plus methotrexate to methotrexate alone in adults with rheumatoid arthritis were eligible for inclusion. Patients who received additional disease-modifying antirheumatic drugs (DMARDs) were not excluded. Studies had to report clinical outcomes; studies that reported only laboratory measures were excluded. The primary outcome was American College of Rheumatology outcome measures ACR20, ACR50 and ACR70. Safety and reasons for withdrawals were investigated.

Where reported, across the arms of trials, mean age of participants ranged from 47.5 to 54 years and mean disease duration was from one to 13 years, mean number of swollen and/or tender joints ranged from 13% to 35%. The proportion of patients who took concomitant medication ranged from 39% to 81% for steroids and 67% to 88% for non-steroidal anti-inflammatory drugs; all patients had tried between one and four other DMARDs.

Two independent reviewers selected studies for inclusion; differences were resolved by consensus

Assessment of study quality
Two independent reviewers assessed study quality using the Jadad criteria (maximum score 5). Trials that scored 3 or more were considered moderate to high quality and included in the review. Differences were resolved by consensus.

Data extraction
Two independent reviewers extracted the number of patients who responded to treatment as measured with ACR20, ACR50 and ACR70. From these, risk ratio (RR) and 95% confidence intervals (CI) were calculated. Differences were resolved by consensus.

Methods of synthesis
Pooled risk ratios and 95% CI were calculated using a random-effects model. Heterogeneity was assessed using the I² statistic; heterogeneity was considered present when I² was over 50%. Sensitivity analyses were conducted to investigate the impact of missing data (withdrawals from the experimental group were considered failures and withdrawals from the control group successes).

Results of the review
Eight trials met the inclusion criteria (n=2,385; range 26 to 682). Follow-up ranged from eight weeks to three years. Trials scored 3, 4 or 5 on the Jadad scale.
Efficacy up to six months (four trials): With etanercept, more people achieved an ACR20 response (55% versus 19%, RR 2.94, 95% CI 2.27 to 3.81), ACR50 (26% versus 6%, RR 5.28, 95% CI 3.12 to 8.92) and ACR70 (7% versus 1%, RR 4.83, 95% CI 1.74 to 13.47). No significant heterogeneity was observed.

Efficacy at one year (five trials): With etanercept, more people achieved an ACR20 response (77% versus 67%, RR 1.14, 95% CI 1.07 to 1.23), ACR50 (59% versus 43%, RR 1.36, 95% CI 1.21 to 1.53) and ACR70 (34% versus 21%, RR 1.56, 95% CI 1.30 to 1.88). Statistical heterogeneity was observed for all these analyses ($I^2=59\%$ to 66%).

Safety and withdrawals: There was no statistically significant increase in the number of serious adverse events (four trials), serious infections (three trials), malignancy (four trials), death (four trials) and withdrawal due to adverse event (eight trials). Withdrawal due to lack of efficacy was lower in the etanercept groups (5% versus 10%, RR 0.48, 95% CI 0.30 to 0.78).

Authors' conclusions
Compared to controls, etanercept demonstrated greater efficacy for the management of rheumatoid arthritis, no statistically significant difference in adverse events and fewer withdrawals due to lack of efficacy.

CRD commentary
The authors addressed a clear research questions with appropriate inclusion criteria. Several relevant sources were searched without language restrictions for published studies. There was no specific search for unpublished studies, so publication bias could not be ruled out. All stages of the review were conducted in duplicate, which reduced potential for error and bias. Study quality was assessed using appropriate criteria. All the analyses of results at one year showed statistically significant heterogeneity. Where trials with multiple comparison groups shared a control group, no adjustment was made for statistical dependency; this could have led to narrowing of the confidence intervals. Therefore, although the direction of effect was the same in all trials, the magnitude of the effect and the uncertainty around it was uncertain. Although the review process was generally well conducted, most of the analysis were informed by four or five studies. Given the concerns with the analysis, the results and conclusions should be treated with some caution.

Implications of the review for practice and research
The authors did not report implications for practice or research.

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