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

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CRD summary

This generally well-conducted review concluded that adalimumab was more effective than placebo for patients with rheumatoid arthritis, but that adverse events need careful attention. The authors' conclusions appear appropriate, but the longer term results were based on only two trials, one of which had a markedly different patient group, so this analysis may be less reliable.

Authors' objectives

To evaluate the efficacy and safety of adalimumab for the treatment of rheumatoid arthritis.

Searching

MEDLINE, EMBASE, the Cochrane Library, SCIELO, LILACS and International Pharmaceutical Abstracts were searched. Search terms were reported. There were no restrictions by language or by dates of study publication.

Study selection

To be eligible for the review, studies needed to be randomised controlled trials (RCTs) that compared adalimumab versus placebo (with or without methotrexate) in adult patients with rheumatoid arthritis. Eligible doses were 20mg weekly or 40mg every other week through subcutaneous injections. Trials that evaluated different doses of adalimumab or different routes of administration were excluded. Patients could be receiving other disease-modifying antirheumatic drugs (DMARDs). Eligible trials had to provide clinical results and needed to be of moderate or high quality (3 or more points on the Jadad scale). Articles only available as abstracts were excluded.

The primary outcome of interest was the efficacy of response of rheumatoid arthritis to treatment with adalimumab using the American College of Rheumatology (ACR) outcome measures ACR20, 50 and 70; these included a count of tender and swollen joints, patient assessment of global pain, physician assessment of disease activity, a health assessment questionnaire (HAQ) and laboratory parameters. Secondary outcomes were safety (serious adverse events, serious infections, malignancy and deaths) and withdrawal from treatment due to lack of efficacy or adverse events.

Mean age across the included trials varied from 48.5 to 57 years. Almost all of the included trials were in patients with mean disease duration of longer than one year (range 6.8 to 12 years) and with active disease according to ACR criteria. Over half of the trials included patients with failure to at least one treatment with DMARD. In most trials, outcome measurement was at 12 to 24 weeks post-treatment; the other trials evaluated outcomes after 24 and 52 weeks.

Two independent reviewers assessed the articles for inclusion, with any discrepancies resolved by consensus.

Assessment of study quality

Trials were assessed using the Jadad scale (0 to 5 points), awarding points for randomisation, blinding and drop-outs.

Two independent reviewers assessed validity, with any discrepancies resolved by consensus.

Data extraction

Two independent reviewers extracted trial data, with any discrepancies resolved by consensus.

Methods of synthesis

Risk ratios (RR) and associated 95% confidence intervals (CI) were combined using the inverse variance method. I^2 was used to measure between trial heterogeneity. Sensitivity analyses were conducted, substituting a range of values for missing data. Data were analysed using both fixed-effect and random-effects models.

Results of the review

Eight trials were included in the review (n=2,692 participants). Three trials compared adalimumab versus placebo without concomitant methotrexate. In four trials, both treatment groups received methotrexate. In one trial, 83% of patients used at least one disease-modifying antirheumatic drug (DMARD) during the comparison between adalimumab and placebo.

Within six months of treatment, adalimumab was associated with a significantly higher rate of ACR20 response (RR 2.26, 95% CI 1.82 to 2.81), ACR50 response (RR 3.50, 95% CI 2.75 to 4.44) and ACR 70 response (RR 5.36, 95% CI 3.76 to 7.64) compared with placebo. Heterogeneity was observed for ACR20 results (I^2=69%).

Based on two trials that also used methotrexate, after 52 weeks adalimumab was associated with a significantly higher rate of ACR20 response (RR 1.85, 95% CI 1.07 to 3.19), ACR50 response (RR 2.80, 95% CI 1.16 to 6.77) and ACR70 response (RR=3.23, 95%CI 1.37 to 7.61) compared with placebo. A high level of heterogeneity was observed for all three ACR outcomes (I^2 from 87% to 95%), which was attributed to one trial where patients had less than three years mean disease duration.

There were no statistically significant differences between groups for serious adverse events, serious infections, malignancy and deaths.

There were more withdrawals due to adverse events in the adalimumab group (RR 1.56, 95%CI 1.04 to 2.35) and more withdrawals due to lack of efficacy in the control group (RR 0.29, 95% CI 0.20 to 0.42).

Authors' conclusions

Adalimumab was more effective in treating rheumatoid arthritis than placebo, but there were more patient withdrawals due to adverse events.

CRD commentary

This review was based on defined inclusion criteria for patients, interventions, outcomes and study designs. Searching encompassed a range of databases and studies in languages other than English were eligible, which minimised the possibility of language bias. Unpublished studies appeared not to be eligible, which raised the possibility of publication bias. Procedures to minimise errors and bias in the processes of study selection, data extraction and quality assessment were used throughout the review

Trial quality was assessed and used as inclusion criteria for the review, but the results of the assessment were not reported in full. Trials were pooled statistically and some potential sources of heterogeneity were explored. However, there was no adjustment for the use of a common control group in trials with multiple adalimumab treatment arms.

The review was generally well conducted and the conclusions appeared to be supported by the evidence. However, longer term results were based on only two trials, one of which had a markedly different patient group, so this analysis may be less reliable.

Implications of the review for practice and research

The authors did not state any implications for practice or research.

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Bibliographic details

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Other publications of related interest
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