Comparison of the efficacy of the tumour necrosis factor alpha blocking agents adalimumab, etanercept, and infliximab when added to methotrexate in patients with active rheumatoid arthritis

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CRD summary

This review compared adalimumab, etanercept and infliximab when added to methotrexate in patients with active rheumatoid arthritis. The authors concluded that the three agents have similar efficacy when combined with methotrexate. Overall, the methods of analysis may mean that the trials were not powered to detect any true treatment effect differences. Head-to-head comparisons between the three drugs are therefore warranted.

Authors' objectives

To investigate potential differences in the efficacy of tumour necrosis factor alpha (TNFalpha)-blocking agents in patients with rheumatoid arthritis with an incomplete response to methotrexate.

Searching

This report is an update of a previous systematic review (see Other Publications of Related Interest). In the previous review, MEDLINE was searched from July 1997 to December 2000 (the search terms were documented in the paper), the references of retrieved articles were checked, abstracts of presentations from meetings of the ACR (1998 to 2000) were consulted, and authors working in the field were contacted. The update extended the MEDLINE search to the end of December 2002 and referred to abstracts from the 2001 and 2002 meetings of the ACR and the European League Against Rheumatism. The Humira (adalimumab) briefing package submission to the Food and Drug Administration Arthritis Advisory Committee in February 2003 was also examined. It was unclear whether foreign language studies were eligible for inclusion.

Study selection

Study designs of evaluations included in the review

Randomised, controlled double-blind trials were eligible for inclusion. The trials needed to have a placebo control group and to be of at least 24 weeks' duration.

Specific interventions included in the review

Included in this review were three approved TNFalpha-blocking agents when combined with methotrexate: adalimumab, etanercept and infliximab. All of the patients in the included trials received stable doses of methotrexate; the mean or median weekly doses ranged from 16 to 19 mg.

Participants included in the review

Participants with rheumatoid arthritis with an incomplete response to methotrexate were included. The mean or median age of the patients in the included trials was between 50 and 56 years. The patients were predominantly white women who were rheumatoid factor positive, with a disease duration of approximately 10 years.

Outcomes assessed in the review

The primary outcome measures were the American College of Rheumatology (ACR) 20, 50 and 70 responses. These represented at least 20%, 50% and 70% improvements, respectively, in a core set of measures. Only data on ACR20 and ACR50 outcomes were presented in the report as ACR70 responses could not be determined.

How were decisions on the relevance of primary studies made?

The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
Although the previous review had used a published quality scale, this updated report did not discuss issues of study quality.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. Data on a range of both patient and treatment characteristics were extracted. Outcome measures were extracted for either the end of the trial, or for 24 to 30 weeks' duration if the trial lasted for 52 weeks.

The rate ratio and its 95% confidence interval (CI) for patients achieving an ACR20 or ACR50 response for the active treatment group compared with placebo were calculated for each of the three treatments. Where there was more than one placebo-controlled trial for an agent, the data were combined across the trials using the Mantel-Cochrane-Haenszel technique.

Methods of synthesis
How were the studies combined?
The three TNFalpha-blocking agents were compared using a published method of adjusted indirect comparison. The relative risk (RR) and CI were presented for ACR20 and ACR50 responses.

How were differences between studies investigated?
Differences between the studies, in terms of demographic and disease characteristics and intervention delivery, were explored within the report. Differences in response rates in the placebo groups across the trials were also assessed for homogeneity.

Results of the review
Four randomised controlled trials (RCTs) with 1,053 patients were included in this review.

The indirect comparisons did not show a statistically significant difference between the treatments. When etanercept was compared with adalimumab, the RR was 1.10 (95% CI: 0.57, 2.12) for an ACR20 response and 2.60 (95% CI: 0.35, 19.0) for an ACR50 response. When infliximab was compared with adalimumab, the RRs were 1.07 (95% CI: 0.66, 1.73) and 1.35 (95% CI: 0.47, 3.85) for ACR20 and ACR50 responses, respectively. When etanercept was compared with infliximab, the RRs were 1.03 (95% CI: 0.49, 2.18) and 1.92 (0.22, 17.0), respectively.

Authors' conclusions
The three TNFalpha-blocking agents etanercept, adalimumab and infliximab had similar efficacy when added to methotrexate in patients with rheumatoid arthritis with active disease.

CRD commentary
The review had a clear objective with defined inclusion criteria for the participants, interventions, study designs and outcomes. The literature search was based on just one electronic database, although it did include other information sources such as conference abstracts, thus reducing the potential for missing studies. Attempts were made to find unpublished material. The quality of the studies does not appear to have been formally assessed, thus making it difficult to assess the potential effect on the validity of the indirect comparison. Aspects of the review methodology, such as the study selection and data extraction processes, were not described in full. It is, therefore, difficult to assess any potential bias in the review process.

In the absence of direct comparisons between these agents, this review provided some evidence of similar effectiveness. There was a suggestion at the ACR50 response level that etanercept might be more effective than the other agents, although this was not statistically significant. However, owing to the differences in sample size between the studies, and the increased variance that is encountered when using adjusted indirect comparisons, it is likely that this comparison

was powered to detect any true differences in treatment effect. This issue would therefore need to be assessed in any future direct head-to-head comparisons, alongside any relevant safety data.

Implications of the review for practice and research

Practice: The authors stated that their findings provided strong evidence for the provision of several alternatives for the patient who has had an inadequate response to treatment with methotrexate.

Research: The authors stated that any future trials directly comparing TNFalpha-blocking agents should use the ACR50 or 70 responder index to increase sensitivity. They further stated that long-term observational studies using registries were needed to examine the long-term effectiveness and safety of the treatments.

Bibliographic details

Hochberg M C, Tracy J K, Hawkins-Holt M, Flores R H. Comparison of the efficacy of the tumour necrosis factor alpha blocking agents adalimumab, etanercept, and infliximab when added to methotrexate in patients with active rheumatoid arthritis. Annals of the Rheumatic Diseases 2003; 62(Supplement 2): 13-16

Original Paper URL

http://ard.bmjjournals.com/cgi/content/full/62/suppl_ 2/ii13

Other publications of related interest

Hochberg MC, Tracy JK, Flores RH. "Stepping-up" from methotrexate: a systematic review of randomised placebo controlled trials in patients with rheumatoid arthritis with an incomplete response to methotrexate. Ann Rheum Dis 2001;60 Suppl 3:51-4.

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.