A systematic review of infliximab in the treatment of early rheumatoid arthritis

Du Pan S M, Gabay C, Finckh A

CRD summary
This review assessed the efficacy and safety of the treatment of early rheumatoid arthritis with infliximab. The authors concluded that infliximab in combination with methotrexate was more efficacious than methotrexate alone. Due to shortcomings in the review, this conclusion may not be reliable.

Authors' objectives
To assess the efficacy and safety of early rheumatoid arthritis treatment with infliximab.

Searching
MEDLINE (from 1966), EMBASE (from 1974) and the Cochrane Central Register of Controlled Trials were searched to May 2006. Conference abstracts from the American College of Rheumatology and the European League Against Rheumatism were reviewed from 2004 to 2005. The manufacturers were contacted for unpublished data. Bibliographies of included studies were also searched. Search terms were reported. There was no search restriction based on language.

Study selection
Randomised controlled trials (RCTs) of subjects diagnosed with rheumatoid arthritis (using American College of Rheumatology criteria) comparing methotrexate-infliximab and methotrexate-placebo were eligible for inclusion. Patients in the included trials had to have disease duration of less than three years (early rheumatoid arthritis).

In the included trials, infliximab doses ranged from 3 to 6 mg/kg. Disease duration in included patients ranged from less than one year to less than three years. A range of outcomes of interest were identified, relating to efficacy and safety. Various criteria and scales were used to assess efficacy. The meta-analysis centred on the change in van der Heijde-Sharp score rating disease progression.

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

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
The authors did not state how the data were extracted for the review or how many reviewers performed the data extraction.

Using the van der Heijde-Sharp score (where a lower number represented less bone erosion), the mean difference in change scores between the two treatment groups was calculated. The standard deviation of change score was computed by assuming unpaired data.

Methods of synthesis
Mean differences were combined in a fixed-effects meta-analysis.

Results of the review
Eight RCTs met inclusion criteria (n=3,699 patients). Three trials were excluded from the meta-analysis, as two trials used the same data and a third used data from a previous trial.

Four RCTs (n=1,647) assessed structural joint destruction based on van der Heijde-Sharp scores. These found a significant reduction in radiographic damage progression in favour of methotrexate-infliximab compared with methotrexate-placebo (standard deviation -4.1, 95% CI: 3.5 to 4.6).
The results of the RCTs comparing methotrexate-infliximab with methotrexate alone revealed modest improvements on measures of disease activity (Disease Activity Score, American College of Rheumatology response criteria). Three of the trials exhibited a benefit of methotrexate-infliximab on Health Assessment score. Patients improved their scores by 58% to 80% after one year of follow-up on methotrexate-infliximab combination and between 18% and 50% on methotrexate-placebo. Three trials reported treatment side-effects.

**Cost information**
The authors found no studies addressing cost-effectiveness analyses of infliximab in early rheumatoid arthritis. Cost-effectiveness analyses in advanced/chronic rheumatoid arthritis have found benefits of methotrexate-infliximab but these studies focused upon historical comparator groups and used different definitions of costs.

**Authors' conclusions**
For patients with early rheumatoid arthritis, infliximab in combination with methotrexate was more effective than methotrexate alone. Infliximab should be restricted to early rheumatoid arthritis patients, with clinical and biological indications of aggressive disease.

**CRD commentary**
The review question was clear and was supported by appropriate inclusion criteria. A thorough search for studies was undertaken, with no restrictions based on language. Attempts were made to identify unpublished data. The methods used for study selection and data extraction were not reported, so it is unclear whether methods were used to reduce error and bias. There was no assessment of the methodological quality of the included studies. Also, the authors did not report any formal assessment of between study heterogeneity. Although the authors' conclusions were supported by the evidence presented, they may not be reliable due to the poor reporting of a number of aspects of the review, the potential study heterogeneity and the lack of validity assessment.

**Implications of the review for practice and research**
Practice: Infliximab should be restricted to early rheumatoid arthritis patients with clinical and biological indications of aggressive disease.

Research: The effect of anti-tumour necrosis factor agents on survival should be addressed in long-term follow-up studies. Cost-effectiveness analyses comparing methotrexate-infliximab with intensive disease-modifying antirheumatic drug therapy in early rheumatoid arthritis, including both direct and indirect costs, are needed.

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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.