Infliximab and methotrexate in the treatment of rheumatoid arthritis: a systematic review and meta-analysis of dosage regimens

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CRD summary
This review concluded that infliximab at 10 mg/kg in combination with methotrexate was more effective for the treatment of active rheumatoid arthritis than methotrexate alone or in combined therapy with infliximab at 3 mg/kg, without increased adverse events. This conclusion closely reflected the results of the review but its reliability may be limited by the relative narrowness of the search.

Authors' objectives
To assess the efficacy and tolerability of infliximab plus methotrexate compared with methotrexate alone for the treatment of active rheumatoid arthritis; to identify subgroups of patients who benefit most from infliximab plus methotrexate treatment.

Searching
MEDLINE and the Cochrane Database of Systematic Reviews were searched from inception to November 2006 for English language studies. Search terms were reported. References of retrieved studies and rheumatology textbooks were checked.

Study selection
Randomised controlled trials (RCTs) that compared infliximab plus methotrexate with methotrexate alone in patients diagnosed with active rheumatoid arthritis, based on American College of Rheumatology (ACR) criteria, were eligible for inclusion. Trials were required to report efficacy outcomes of scores on the ACR20, ACR50 or ACR 70 instruments. Trials also had to provide sufficient data to permit the calculation of odds ratios with 95% confidence intervals (CI). Trials which enrolled patients with juvenile arthritis, Crohn’s disease, psoriatic arthritis and other spondyloarthropathies were excluded. Also excluded were trials in which patients received other disease modifying antirheumatic drugs.

In the majority of the included trials infliximab was given at 3 mg/kg or 10 mg/kg every four or eight weeks. Mean doses of methotrexate ranged from 7.1 to 19 mg. The proportion of female participants ranged from 66.6% to 100%. The mean ages of patients ranged from 44.6 to 56 years.

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

Assessment of study quality
Two reviewers independently assessed the studies for validity using blinding, allocation concealment and use of an intention-to-treat analysis.

Data extraction
Two reviewers independently performed the data extraction in a blinded fashion. Discrepancies were resolved through consensus with a third reviewer.

Methods of synthesis
Pooled odds ratios with 95% confidence intervals (CIs) were calculated using both fixed-effect and random-effects model meta-analyses. Statistical heterogeneity was assessed using the Q statistic. Odds ratios of subgroups were compared using a z test for interaction. Subgroup analyses assessed the use of low dose (3 mg/kg every four or eight weeks) versus high dose (10 mg/kg every four or eight weeks), disease severity, completion of study (drop-out rate of 20% or lower), concomitant steroid use, previous disease modifying antirheumatic drug treatment, methotrexate naïveté, disease duration (up to three years versus longer than three years), and trial duration (up to 54 weeks versus longer than 54 weeks).
Results of the review

Twelve RCTs (n = 4,899) were included in the review; 3,919 patients received infliximab plus methotrexate and 980 methotrexate alone. Nine RCTs used double-blinding, seven reported adequate allocation concealment and six used an intention-to-treat analysis.

Infliximab at 3 mg/kg plus methotrexate was significantly more effective than methotrexate alone on all American College of Rheumatology (ACR) efficacy measures (ACR 20 odds ratio 3.52, 95% CI: 2.14, 5.79; ACR 50 odds ratio 2.87, 95% CI: 2.28, 3.61; ACR 70 odds ratio 2.42, 95% CI: 1.87, 3.13).

Infliximab at 10 mg/kg plus methotrexate was also significantly more effective than methotrexate alone on all American College of Rheumatology (ACR) efficacy measures (ACR 20 odds ratio 5.06, 95% CI: 3.88, 6.59; ACR 50 odds ratio 5.72, 95% CI: 4.05, 8.08; ACR 70 odds ratio 7.32, 95% CI: 2.28, 23.50).

Regimes using higher doses of infliximab were significantly more effective on the outcome of ACR 50 than lower doses (p=0.001).

Subgroup results were also reported separately for treatments administered at 4 and 8 week intervals. There was some evidence of increased efficacy with 4 weekly compared to 8 weekly administration for 3 mg/kg infliximab (ACR 20 p=0.03; ACR 50 p>0.05; ACR 70 p=0.02) but no such effect for 10 mg/kg treatments (p>0.05 in all cases).

Incidence of adverse effects was not significantly different between the groups either for infliximab 3 mg/kg plus methotrexate versus methotrexate alone every eight weeks or for infliximab 10 mg/kg plus methotrexate versus methotrexate alone every eight weeks. There was no statistically significant difference between groups treated with lower or higher doses of infliximab given every four versus every eight weeks.

Further results of subgroup analyses were extensively reported, including findings of increased efficacy for high doses in patients with severe disease activity, in patients with concomitant steroid use and in trials lasting longer than 54 weeks.

Authors' conclusions

Higher dose (10 mg/kg) infliximab therapy in combination with methotrexate was more effective than standard (3 mg/kg) therapy, particularly for patients with severe disease activity. Treatment benefits accrued over time and higher doses were not linked to increased adverse effect incidence. Efficacy was significantly increased by concomitant use of oral low dose steroids.

CRD commentary

The inclusion criteria were clear. The authors searched two relevant databases and some other sources, but the restriction of the review to studies reported in English may have increased the chance of language bias and the omission of some relevant studies. The probability of publication bias was acknowledged by the authors, although not formally assessed. The authors reported using methods designed to reduce reviewer bias and error in the extraction of data and the assessment of validity, but not in the selection of studies. Validity was assessed and the influence of some aspects on results was examined. The use of meta-analysis and the assessment of heterogeneity appeared appropriate. While the conclusions closely reflected the results of the review, the relatively limited search may affect their reliability.

Implications of the review for practice and research

Practice: The authors did not state any implications for practice.

Research: The authors stated that observations on the differential effectiveness of infliximab plus methotrexate in different subgroups of active rheumatoid arthritis patients should be used for hypothesis generation and the design of further RCTs.

Funding

Not stated.
Bibliographic details

PubMedID
19108784

DOI
10.1016/j.clinthera.2008.11.007

Other publications of related interest

Indexing Status
Subject indexing assigned by NLM

MeSH
Administration, Oral; Adult; Age Factors; Antibodies, Monoclonal /administration & dosage /adverse effects /therapeutic use; Anti-rheumatic Agents /administration & dosage /adverse effects /therapeutic use; Arthritis, Rheumatoid /drug therapy; Dose-Response Relationship, Drug; Drug Therapy, Combination; Female; Humans; Infliximab; Male; Methotrexate /administration & dosage /adverse effects /therapeutic use; Middle Aged; Randomized Controlled Trials as Topic; Time Factors; Treatment Outcome

AccessionNumber
12009102167

Date bibliographic record published
31/03/2009

Date abstract record published
01/07/2009

Record Status
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.