The number needed to treat for adalimumab, etanercept, and infliximab based on ACR50 response in three randomized controlled trials on established rheumatoid arthritis: a systematic literature review
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CRD summary
This review compared tumour necrosis factor-alpha blocking drugs for rheumatoid arthritis and concluded that adalimumab, etanercept and infliximab had similar efficacy, but infliximab may need higher doses for a similar effect. Given that this was based on an indirect comparison of only one trial of each drug and the authors highlighted a cautious interpretation, this conclusion may be overstated.

Authors' objectives
To compare the efficacy of the tumour necrosis factor-alpha blocking drugs adalimumab, etanercept and infliximab in rheumatoid arthritis patients taking methotrexate, by comparing the number needed to treat (NNT).

Searching
The Cochrane Musculoskeletal Group register of controlled trials was searched as well as systematic reviews performed by this group. The Cochrane Library, MEDLINE and EMBASE were also searched from inception to June 2006. Search terms were reported and only published articles in English were included.

Study selection
Double-blind randomised controlled trials (RCTs) with a minimum of two arms that compared adalimumab, etanercept or infliximab plus methotrexate to methotrexate and placebo with at least 12 months of follow up were eligible. Studies had to evaluate patients with rheumatoid arthritis with an average disease duration of at least five years and report ACR50 response at 12 months (American College of Rheumatology criteria for achieving at least 50% reduction in symptoms).

Included studies evaluated infliximab 3mg for four and for eight weeks and evaluated etanercept 50mg/week and adalimumab 40mg for two weeks. Across treatment groups, the proportion of women ranged from 73% to 81%, mean disease duration from 6.8 to 11 years, mean age from 51 to 56 years and the proportion of patients who were rheumatoid factor positive ranged from 71% to 90%.

Studies were screened by two review groups (from Denmark and Sweden) independently following a predefined protocol.

Assessment of study quality
The authors did not assess study validity, but only double-blind RCTs were included in the review.

Data extraction
Baseline patient and disease characteristics, ACR50 response and number of withdrawals were extracted. If a study had more than one treatment arm, the arm with the recommended drug dose was used. Data were extracted on an intention to treat and a per-protocol basis. The per-protocol population was patients who completed the full intervention. Number needed to treat was calculated using the standard method (inverse of the risk difference) and, for the intention to treat population only, from the odds ratio using the control group risk as the baseline risk. Data were extracted by the two review groups independently.

Methods of synthesis
Results were presented descriptively in tables and the text. Clinical heterogeneity was discussed.

Results of the review
Three trials were included in the review (n=1,126), one for each of the three drugs.
Adherence to treatment ranged from 73.3% to 83.5% for the intervention arms and 50% to 70% for placebo. Adherence was better for etanercept (83.5%) than adalimumab (76.8%) and infliximab (73.3% double dose and 76.7% standard dose). The number needed to treat was 4 for the intention to treat populations for adalimumab, etanercept and single-dose infliximab (the widest 95% CI was 3 to 7). The number needed to treat for double-dose infliximab was larger at 8 (95% CI: 5 to 38). The results for the per-protocol population were similar, and so were the number needed to treat when calculated using adjustment for the baseline event rate.

Authors' conclusions
This review indicated that adalimumab, etanercept and infliximab in combination with methotrexate had equal efficacy for ACR50 response in patients with rheumatoid arthritis. Infliximab may need an increased dose to reach an efficacy level comparable to adalimumab and etanercept.

CRD commentary
This review had clear inclusion and exclusion criteria. The search used a specialist Cochrane group database, as well as other relevant databases. The only limitation of the search was the inclusion of only published material in English, which may have increased the risk of language bias. The risk of error and bias in the review methods was minimised by having two separate review groups independently perform the study selection and data extraction.

No formal validity assessment was performed, but the inclusion criteria was limited to only double-blind RCTs. The main aim was to calculate and compare the number needed to treat (number of patients needed to treat to gain one additional ACR50 response). The authors presented 95% confidence intervals for the number needed to treat, which was good as it indicated the possible range of the true value. The authors also presented additional results for the per-protocol population and used a different calculation method to try and account for differences in baseline risk between patients. However, the conclusion of equal efficacy was based on an indirect comparison with only one trial of each drug.

This was a generally well-conducted review, but the conclusion may be overstated given that the authors noted that the results should be interpreted with caution.

Implications of the review for practice and research
Practice: Infliximab may need more than the standard dose to achieve comparable efficacy, therefore, increasing the cost of treatment.

Research: The authors did not state any recommendations for research.

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