A mixed treatment comparison of the short-term efficacy of biologic disease modifying anti-rheumatic drugs in established rheumatoid arthritis

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CRD summary
The review concluded that treatment with anakinra appeared to be inferior to other biological disease modifying antirheumatic drugs and that etanercept and certolizumab may be more effective in the treatment of established rheumatoid arthritis. Although there were limitations and it was possible that relevant trials may have been missed, the authors' cautious conclusions seem appropriate.

Authors' objectives
To compare the short-term efficacy of nine biological disease modifying anti-rheumatic drugs (DMARDs) for the treatment of established moderate to severe rheumatoid arthritis.

Searching
MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials were searched from 1998 to October 2010; the search was limited studies in English. Search terms were reported. The Cochrane Library was also searched for systematic reviews and meta-analyses of the target biological DMARDs. References of systematic reviews and identified relevant articles were manually searched for any additional trials.

Study selection
Double-blind randomised controlled trials (RCTs) that compared biological DMARDs (abatacept, adalimumab, anakinra, certolizumab, etanercept, golimumab, infliximab, rituximab and tocilizumab) with control (placebo and/or a DMARD) in patients with active established rheumatoid arthritis were eligible for inclusion. Trials were required to be of at least six months duration and report efficacy data. Trials without a recommended dose, open-label trials, and trials set in non-western countries were excluded.

In included trials, dose, frequency and delivery varied. Patients in the golimumab trials who did not have a minimal response at 12 or 14 weeks received a dose increase. All but one trial required treatment failure of previous DMARDs. Mean disease duration ranged from 4.5 to 13.1 years. Mean swollen joint count ranged from 12 to 25. Mean tender joint count ranged from 21 to 35.5. Mean baseline Health Assessment Questionnaire score ranged from 1.3 to 2.0. Mean C-reactive protein levels ranged from 8 to 57.0mg/L.

The authors did not state how many reviewers were involved in the trial selection.

Assessment of study quality
One reviewer assessed each trial for bias in randomisation and blinding during intervention and analysis and checked by a second reviewer.

Data extraction
One reviewer extracted data which was then checked by a second reviewer. Three clinical response measures were used, as defined by the American College of Rheumatology (ACR); 20%, 50% or 70% improvement in tender or swollen joint counts plus equivalent improvement in three of five other criteria (ACR20, ACR50 and ACR70).

Methods of synthesis
Mixed treatment comparisons were performed using methods adopted from Nixon et al (2007), to give an estimate of the efficacy of each drug against placebo or methotrexate, as well as each drug compared with each other.

Mixed treatment comparison regression analyses were performed using the Markov chain Monte Carlo simulation techniques for model estimations. Covariates included: C-reactive protein, duration of disease, baseline Health Assessment Questionnaire score, swollen joint count, and tender joint count.
Results of the review

Twenty-seven RCTs (11,049 patients) were included in the review. The number of patients receiving biological DMARDs were: 847 for abatacept (three RCTs), 1,027 for adalimumab (four RCTs), 250 for anakinra (one RCT), 750 for certolizumab (three RCTs), 795 for etanercept (four RCTs), 277 for golimumab (three RCTs), 611 for infliximab (three RCTs), 473 for rituximab (three RCTs), and 1,473 for tocilizumab (four RCTs). In all trials were randomised, no important differences in baseline characteristics were observed, and patients, providers and outcome assessors were blinded.

All drugs except anakinra and golimumab demonstrated a significant advantage compared with control for ACR20 (American College of Rheumatology 20% response). All drugs except anakinra demonstrated a significant advantage over placebo for ACR50 and ACR70. Preliminary analyses indicated that swollen joint count and disease duration were statistically significant covariates, so the analyses were performed with these as covariates. The results suggested that the mean effectiveness of drugs compared with placebo decreased as swollen joint count increased, and the relative effectiveness of biological DMARDs improved for those with a longer duration since diagnosis. No other covariate was found to be statistically significant.

Between drug comparisons demonstrated a significant advantage for certolizumab compared with all other individual drugs for ACR20 and ACR50, and for etanercept versus anakinra and adalimumab for ACR50 and ACR70. A sensitivity analysis excluding one trial (that did not require treatment failure of previous DMARDs) did not change the outcomes of the meta-analyses.

Authors' conclusions

The results suggested that treatment with anakinra was inferior to other biological DMARDs, and that etanercept and certolizumab may be more effective than other biological DMARDs.

CRD commentary

The review question was supported by defined inclusion and exclusion criteria. The literature search included a number of relevant sources, but this search was restricted by language, so some trials may have been missed. Steps were taken to minimise the likelihood of error and bias in the extraction of data and assessment of validity (although not carried out in duplicate); it is not clear whether a similar procedure was used in the selection of trials.

Trial quality was assessed based on some relevant criteria, although allocation concealment was not included in this assessment. The quantitative analyses performed seemed appropriate. However, as highlighted by the authors, there were a number of limitations in the analyses, including assumptions about the mixed treatment comparison analyses and variations in trial design. It should also be noted that only short-term outcomes were assessed and that safety profiles were not considered.

Although there were limitations and it was possible that relevant trials may have been missed, the authors' cautious conclusions seem appropriate.

Implications of the review for practice and research

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

Research: The authors suggested that, whilst it was unlikely that more head-to-head randomised trials comparing two or more current biological DMARDs will become available in the future, direct head-to-head trials might provide superior evidence. They also stated that there was a lack of long term efficacy data.

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Bibliographic details

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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.