Similar effects of disease-modifying antirheumatic drugs, glucocorticoids, and biologic agents on radiographic progression in rheumatoid arthritis: meta-analysis of 70 randomized placebo-controlled or drug-controlled studies, including 112 comparisons

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CRD summary
This review concluded that treatment with disease-modifying antirheumatic drugs, glucocorticoids, biological agents and combination agents significantly reduced radiographic progression in patients with rheumatoid arthritis at one year, with a relative effect of 48 to 84%. Although there were several methodological limitations, the authors' conclusions adequately reflect the data presented.

Authors' objectives
To assess the effects of single compared with combination disease-modifying antirheumatic drugs (DMARDs) on the progression of joint destruction in patients with rheumatoid arthritis.

Searching
The Cochrane Library, PubMed, EMBASE and ClinicalTrials.gov were searched up to December 2009 for full-length studies published in peer-reviewed journals in any language. Search terms were reported. Reference lists of identified studies and relevant meta-analyses were handsearched.

Study selection
Randomised controlled trials (RCTs) of any size with patients with rheumatoid arthritis, diagnosed according to criteria of the American College of Rheumatology, were eligible for inclusion. Eligible trials had to score joint radiographs as the primary or secondary outcome at two separate time points (at least three months apart). The eligible interventions were grouped into the following comparisons: disease-modifying antirheumatic drug (DMARD) versus DMARD; DMARD versus placebo or analogue; combination DMARDs versus single DMARD; DMARD with or without glucocorticoids versus placebo or analogue with or without DMARD; and a combination biological agent plus methotrexate versus methotrexate or other DMARDs with or without glucocorticoids. Full details of the five groups were reported in the paper.

In included trials across the five comparisons, the mean disease duration ranged from 1.5 to 4.1 years; the initial R-score (% of maximum) ranged from 5.0 to 11.8; radiographic estimation time was 12 months. Baseline patient characteristic were given in a separate online appendix (see URL for Additional Data).

Two reviewers independently selected studies and disagreements were resolved by consensus.

Assessment of study quality
Methodological quality of the included trials was assessed using sequence generation, allocation concealment, blinding, and incomplete outcome data at the individual study level using the Cochrane risk of bias tool. Additionally, blinding of outcomes was evaluated.

The number of reviewers that assessed study quality was unclear.

Data extraction
The difference in the percentage of the annual radiographic progression rate (PARPR) was calculated (formulae reported in paper). Data to calculate mean difference (MD) and 95% confidence intervals (CIs) were independently extracted by two reviewers. Medians were substituted where means were unavailable; standard deviations were calculated if not reported in the primary paper. Authors of primary papers were contacted for additional information if necessary.
Methods of synthesis
Mean differences and 95% confidence intervals were pooled in meta-analyses. A fixed-effects model was used when trials were homogeneous; where heterogeneity was substantial, a random-effects model was used. Heterogeneity was quantified using $I^2$.

Subgroup analyses were performed for different radiographic scoring methods, and for trials in which the second radiographic reading was performed at 12 months.

Funnel plots were used to assess publication bias.

Results of the review
Seventy RCTs were included in the review (n=18,846; 112 comparisons). The five comparisons that were meta-analysed were similar in the frequency of reporting sequence generation. However, trials with biological agents reported allocation concealment less frequently.

Placebo was associated with a statistically significantly larger percentage of the annual radiographic progression rate than single disease-modifying antirheumatic drug (DMARD; MD -0.65, 95% CI -1.05 to -0.25; n=762 patients) and glucocorticoid treatment (MD -0.54, 95% CI -0.71 to -0.38; n=1,141 patients). Single DMARD was associated with a significantly larger percentage of the annual radiographic progression rate than combination DMARDs (MD -0.62, 95% CI -1.00 to -0.24; n=1,384 patients) and biological agent plus methotrexate (MD -0.61, 95% CI -0.72 to 0.51; n=4,965 patients). The difference in percentage of the annual radiographic progression rate between two DMARDs combined plus step-down glucocorticoids was not statistically significantly different from biological agents plus methotrexate. The analyses for single DMARD versus placebo ($I^2=93\%$) and combination DMARDs versus single DMARD ($I^2$ not reported) were associated with substantial heterogeneity.

Subgroup analyses showed similar results.

The funnel plots were asymmetric for the comparison single DMARD versus placebo, suggesting that publication bias may be present.

Authors' conclusions
Treatment with disease-modifying antirheumatic drugs, glucocorticoids, biological agents and combination agents significantly reduced radiographic progression at one year, with a relative effect of 48 to 84%. A direct comparison between biological agent plus methotrexate and two disease-modifying antirheumatic drugs combined plus initial corticosteroids revealed no difference.

CRD commentary
The research question was supported by defined inclusion criteria. A range of relevant databases were searched for studies in any language, which reduced the possibility of language bias. However, only published studies were included; a funnel plot suggested the presence of publication bias in one of the analyses. Study selection and data extraction was performed by two reviewers, which reduced the possibility of reviewer error and bias. It was unclear whether similar steps were taken for quality assessment.

Trial quality was assessed using appropriate criteria and taken into account in the analysis to some extent. Heterogeneity was investigated (where present); the authors acknowledged that the presence of clinical heterogeneity precluded the ranking of the effectiveness of individual agents.

Although there were several methodological limitations in this review, the authors' conclusions adequately reflect the data presented.

Implications of the review for practice and research
Practice: The authors stated that biological agents should continue to be reserved for patients in which rheumatoid arthritis is not sufficiently responsive to treatment with a combination of DMARDs. They also noted this contrasted...
with the European League Against Rheumatism recommendations that in patients whose rheumatoid arthritis is not sufficiently responsive to therapy with a single DMARD, biological agents should be initiated without first trying therapy with a combination of DMARDs.

**Research:** The authors stated that future trials should compare biological agents with combination treatments involving DMARDs and glucocorticoids in patients with rheumatoid arthritis.

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