A meta-analysis of the efficacy and toxicity of combining disease-modifying anti-rheumatic drugs in rheumatoid arthritis based on patient withdrawal

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CRD summary
The review assessed treatment with two or more disease-modifying anti-rheumatic drugs (DMARDs) compared with a single DMARD for rheumatoid arthritis. The authors concluded that the balance of beneficial and adverse effects is most favourable with methotrexate plus either sulphasalazine and/or antimalarial drugs, or tumour necrosis factor inhibitors. The evidence presented is not sufficient to support definitive conclusions favouring particular treatments.

Authors' objectives
To determine the efficacy and toxicity of disease-modifying anti-rheumatic drug (DMARD) combinations for treating rheumatoid arthritis (RA).

Searching
EMBASE, MEDLINE and PubMed were searched from 1975 to 2004. The search terms reported were the MeSH terms ‘arthritis, rheumatoid’ and ‘drug therapy, combination’ and the publication type ‘randomized controlled trial’. Reference lists in relevant trial articles and reviews were checked to identify additional studies. Only publications in the English language were eligible for inclusion.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) and quasi-randomised trials were eligible for inclusion. It was also reported that trials were only included if they had adequate allocation concealment, double-blinding and low loss to follow-up, although this appeared to contradict the inclusion criteria with regard to quasi-randomised trials, which have inadequate allocation concealment.

Specific interventions included in the review
Studies that compared combination therapy of two or more DMARDs, or one DMARD and one biological therapy with DMARD monotherapy, were eligible for inclusion. The DMARD and biological therapies had to be among those used in routine clinical practice. Studies of experimental or non-licensed treatments were excluded. The DMARDs used in the included studies were methotrexate, sulphasalazine, azathioprine, gold, hydroxychloroquine/chloroquine, cyclosporin A, leflunomide, auranofin, anakinra, D-penicillamine and bucillamine. The biological therapies were tumour necrosis factor (TNF) inhibitors (infliximab, adalimumab, etanercept) and corticosteroids (prednisolone, methylprednisolone). Two-drug DMARD therapy was used in most (83%) of the studies; 17% used triple therapy.

Participants included in the review
Studies of patients with RA as defined by the American College of Rheumatology (ACR) or the American Rheumatism Association diagnostic criteria (or judged by the authors to have RA in the absence of reported criteria) were eligible for inclusion. The participants in 75% of the included studies had established RA; the other 25% enrolled patients with early RA (duration less than 3 years).

Outcomes assessed in the review
The eligible outcomes were the number of patients withdrawn due to lack of efficacy, the number of withdrawals due to adverse events, the number of patients who achieved an ACR20 response, and the number who achieved a major clinical response defined as either an ACR70 response or as having entered remission (no specific criteria were used to define remission). Withdrawals due to lack of efficacy and due to adverse events were the primary outcomes in the review.

How were decisions on the relevance of primary studies made?
Three reviewers applied the inclusion criteria independently.

### Assessment of study quality
A quality score was assigned to each study using the instrument developed by Jadad et al. The criteria assessed were the description of randomisation, double-blinding, and withdrawals or drop-outs. The maximum attainable score was 5. Two reviewers assessed study quality independently.

### Data extraction
Two reviewers extracted the data independently using a standard form. The number of participants, the number of events for each outcome, and the number lost to follow-up in the treatment and control group in each trial appear to have been extracted.

### Methods of synthesis
**How were the studies combined?**

Meta-analysis was used to calculate pooled estimates of relative risk (RR) with 95% confidence intervals (CIs) for combination therapy compared with monotherapy. The authors reported using a random-effects model although the actual measure of effect calculated appeared to be the Peto odds ratio (OR). Meta-analysis was also conducted using the secondary outcome measures ACR20 and major clinical response. It was unclear how trials with more than two treatment arms were included in the meta-analysis, or if the analysis was conducted by intention-to-treat.

**How were differences between studies investigated?**

A chi-squared test and I-squared ($I^2$) test were applied to the meta-analysis of the primary outcomes in order to investigate statistical heterogeneity.

A sensitivity analysis was conducted by repeating the meta-analysis of the primary efficacy outcome excluding studies with a quality score of 2 or less, and excluding studies that used a combination of three therapies. The meta-analysis was also repeated in subgroups of studies according to disease duration (early RA, established RA, established RA excluding TNF inhibitors), study design (parallel, step-down, step-up, step-up excluding TNF inhibitors), treatment combinations (methotrexate plus TNF inhibitors, methotrexate plus sulphasalazine and/or antimalarials), and use of corticosteroids (corticosteroids added to one DMARD as bridging therapy, DMARD combinations excluding corticosteroids as bridging therapy). It was unclear if the subgroup analyses were pre-specified.

### Results of the review
Thirty-six studies were included. A total of 5,289 participants were included in the analysis of the review's primary outcomes. Sixteen trials used a parallel study design, 13 used a step-up design and 7 used a step-down design.

**Efficacy.**

The meta-analysis of all trials showed fewer withdrawals due to lack of efficacy with combination therapy compared with monotherapy and the difference was statistically significant (RR 0.35, 95% CI: 0.28, 0.45, p=0.00001). There was moderate heterogeneity between the trials (p=0.05, I² 32.9%).

The combination of methotrexate with TNF inhibitors was more effective than methotrexate monotherapy (6 trials, 1,530 participants; RR 0.22, 95% CI: 0.14, 0.32, p=0.00001). Methotrexate plus sulphasalazine and/or antimalarials was more effective than methotrexate monotherapy (8 trials, 946 participants; RR 0.41, 95% CI: 0.24, 0.70, p=0.00001). There was no significant difference between corticosteroids added to one DMARD as bridging therapy and DMARD alone (7 trials, 289 participants).

Combination therapy was significantly better than monotherapy in early RA (9 trials, 1,031 participants, p=0.02), established RA (22 trials, 4,258 participants, p=0.00001) and established RA excluding TNF inhibitors (21 trials, 2,728 participants, p=0.00001).
Study design and quality score and the exclusion of studies of triple therapy did not affect the findings.

The meta-analysis of ACR20 response reported in 18 trials showed a significant difference in favour of combination therapy (RR 1.53, 95% CI: 1.26, 1.86, p=0.00001), as did the meta-analysis of ACR70 response or remission reported in 14 trials (RR 2.06, 95% CI: 1.55, 2.74, p=0.00001).

Toxicity.

The meta-analysis of all trials showed a statistically significant difference in withdrawals due to toxicity in favour of monotherapy (RR 1.37, 95% CI: 1.16, 1.62, p=0.0003). The difference between methotrexate plus sulphasalazine and/or antimalarials and monotherapy was not statistically significant. No other analyses were reported.

Authors’ conclusions
DMARD combination therapies vary regarding the ratio of efficacy to toxicity. Methotrexate plus sulphalazine and/or antimalarials, and methotrexate plus TNF inhibitors, have particularly favourable benefit-to-risk ratios.

CRD commentary
The review addressed a clear question apart from some ambiguity concerning randomisation in the study design. A limited number of sources were searched for relevant trials and there was insufficient detail to judge the thoroughness of the search strategy. Steps were taken to minimise reviewer bias in the selection of studies for inclusion. As only two trials were excluded on the basis of language, the restriction to English was unlikely to have affected the findings. However, the potential for publication bias, which tends to overestimate treatment effects, was real and not explored.

The quality of the included trials was assessed systematically but not well reported, which precluded independent judgment of the potential for bias in the included studies (particularly important given the uncertainty regarding randomisation). Methods were used to minimise reviewer errors in the data extraction, but poor reporting left uncertainty about the data analysis regarding trials with more than two comparator groups and patients lost to follow-up.

The primary outcomes assessed in the review were not the primary outcomes in the trials, and there was insufficient information to assess the reliability of the collection or reporting of those data in the trial reports.

The use of an OR to estimate the RR was probably appropriate given the low event rates, but the CIs reported might be too narrow if the intention was to use a random-effects model. It was unclear whether the subgroup analyses were pre-specified and the potential for reporting bias in the review is unknown. The evidence presented does not lend robust support to the conclusion of more favourable benefit-to-risk ratios with specific therapies because the review analysed combination therapy versus monotherapy, treatment subgroup analyses of adverse events were not reported in full, and the statistical significance of differences between treatment subgroups was not tested.

Implications of the review for practice and research
Practice: The authors stated that the analysis supported the use of DMARD combination therapy in patients with established RA. Furthermore, combinations of methotrexate with TNF inhibitors, and methotrexate with sulphalazine and/or antimalarials, are most effective. (It should be noted that direct comparisons of alternative combination therapies were not analysed in this review.) There were too few trials to determine the benefit of triple therapy. The authors stated that the analysis also argued strongly for the use of DMARD combination therapy in most patients with early RA.

Research: The authors stated that a large RCT is needed to establish whether combination therapy is as effective as biological therapy. More research is also needed on combinations involving corticosteroids.

Funding
American College of Rheumatology

Bibliographic details

PubMedID
16030080

DOI
10.1093/rheumatology/kei031

Indexing Status
Subject indexing assigned by NLM

MeSH
Antirheumatic Agents /adverse effects /therapeutic use; Arthritis, Rheumatoid /drug therapy; Drug Therapy, Combination; Humans; Patient Dropouts; Randomized Controlled Trials as Topic; Treatment Outcome

AccessionNumber
12005002084

Date bibliographic record published
31/05/2007

Date abstract record published
31/05/2007

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.