Combination therapy in rheumatoid arthritis: updated systematic review

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Authors' objectives
To undertake a second update of a systematic review of combination therapy in rheumatoid arthritis (see Other Publications of Related Interest nos.1-2).

Searching
MEDLINE was searched from August 1992 (the closing date for the last review) to July 1997 using the MeSH terms 'arthritis, rheumatoid' and 'drug therapy, combination'. The bibliographies of all the retrieved studies were scrutinised, and the first authors of studies published only in abstract form were contacted; such studies were only eligible for inclusion if a full manuscript was available. Relevant articles published in English, French, German or Dutch were retrieved. Studies from the previous review that were rated as providing moderately strong or strong evidence were also included.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were included. The follow-up periods were reported to be 3 to 12 months in the table of study characteristics, but results for a 2-year follow-up were reported in the text.

Specific interventions included in the review
The types of intervention strategies included:

'step-up', defined as trials in which patients with insufficient benefit from one second-line agent continued the use of this drug and had another (or placebo) added to this;

'parallel', defined as starting a combination of new drugs; and

'step-down' defined as sequential withdrawal of simultaneously started drugs.

Step-up studies included the following comparisons: cyclosporin with prednisolone as anchor; monoclonal anti-CD4 antibody with methotrexate as anchor; cyclosporin with methotrexate as anchor; and each of cyclosporin, bucillamine and hydroxychloroquine with gold as anchor.

Parallel studies included the following comparisons: hydroxychloroquine with gold as anchor; sulphasalazine plus hydroxychloroquine versus each drug alone; D-penicillamine plus chloroquine versus each drug alone; dapsone plus hydroxychloroquine versus each drug alone; hydroxychloroquine plus methotrexate versus hydroxychloroquine; methotrexate plus chloroquine versus methotrexate; methotrexate plus sulphasalazine plus hydroxychloroquine versus sulphasalazine plus hydroxychloroquine versus methotrexate; methotrexate plus auranofin versus each drug alone; methotrexate plus azathioprine versus each drug alone; and methotrexate plus sulphasalazine versus each drug alone.

Step-down studies included the following: sulphasalazine plus methotrexate plus prednisolone versus sulphasalazine; gold plus prednisolone versus gold; gold plus methylprednisolone pulses versus gold; and sulphasalazine plus methylprednisolone versus sulphasalazine.

Participants included in the review
The participants were patients with rheumatoid arthritis, who had had the disease from less than one year to 11 years.

Outcomes assessed in the review
Efficacy was assessed using the core set measures of the World Health Organization and International League of Associations for Rheumatology. When less than 4 of these measures were assessed, first grip strength and second
morning stiffness were selected as well.

How were decisions on the relevance of primary studies made?
The titles and abstracts (when available) were screened by one of the authors.

Assessment of study quality
The validity of the studies was scored on a 3-point scale on the basis of randomisation and blinding. Strong evidence was considered to be provided by randomised double-blind studies, whilst moderately strong evidence came from open or partially blinded randomised trials. The following criteria derived from Sackett et al. (see Other Publications of Related Interest no.4) were also applied: adequate outcome assessment; adequate description of study patients; adequate description of intervention; and complete accounting for study patients in the results. The authors do not state how the papers were assessed for validity, or how many of the authors performed the validity assessment.

Data extraction
The following data were extracted: baseline patient characteristics; study and concomitant treatment; outcome measures; details on toxicity; the number of withdrawals; and eligibility criteria for disease activity.

Methods of synthesis
How were the studies combined?
The studies were combined in a narrative review.

How were differences between studies investigated?
Differences between the studies, in terms of the combinations, strategies and patient material, were acknowledged.

Results of the review
Twenty RCTs (1,956 patients) were included: 6 step-up RCTs (N=447), 10 parallel RCTs (N=1,217) and 4 step-down RCTs (N=292).

There were problems with the review methodology of the studies. These included a lack of data, small patient numbers in the primary studies, and many untested combinations. All trials used a fairly strict criterion to verify the presence of active disease.

Mixed results for the efficacy and toxicity of combinations of drugs versus single drugs were reported. The authors reported that, with the exception of corticosteroids, there appeared to be no particular trend for an overall beneficial effect of a particular drug in a combination.

Authors' conclusions
In early rheumatoid arthritis patients, step-down bridge therapy that includes corticosteroids led to enhanced efficacy at acceptable or low toxicity. In late patients, cyclosporin improved a suboptimal clinical response to methotrexate, and the triple combination of methotrexate, sulphasalazine and hydroxychloroquine appeared to be clinically better than the components. Other combinations were either untested, tested at low sample size or showed negative interaction. In view of the low volume of evidence, most studies should be repeated to confirm the results.

CRD commentary
Studies published in four languages were included. The method used to select the primary studies was described. A narrative review was appropriate given the diversity of the drug regimens used. The validity of the studies was assessed using two sets of criteria.

By restricting the literature search to one database some relevant studies may have been omitted. The inclusion criteria
for the primary studies were not specified. Although two sets of validity criteria were defined, the results were only reported according to the strength of the evidence based on the degree of blinding. More comprehensive details of the included studies would have been helpful. It was unclear whether the results quoted were from an intention to treat analysis. No two studies used similar drug regimens and study designs; this limited the results from the review.

There was insufficient evidence to support the authors’ conclusion.

**Implications of the review for practice and research**
The authors consider that the results from most studies need to be confirmed by repeating the studies.

**Bibliographic details**

**PubMedID**
9667614

**Other publications of related interest**

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Antirheumatic Agents /therapeutic use; Arthritis, Rheumatoid /drug therapy; Drug Therapy, Combination; Female; Humans; Male; Randomized Controlled Trials as Topic; Treatment Outcome

**AccessionNumber**
11998001091

**Date bibliographic record published**
30/11/1999

**Date abstract record published**
30/11/1999

**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.