A systematic comparison of combination DMARD therapy and tumour necrosis inhibitor therapy with methotrexate in patients with early rheumatoid arthritis

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CRD summary
This review concluded that there was strong evidence in support of disease-modifying antirheumatic drug therapies and tumour necrosis factor inhibitors plus methotrexate compared with methotrexate monotherapy in patients with early rheumatoid arthritis. Although the data appeared to support these findings, concerns over the review methodology and variation between studies suggest that the conclusions should be interpreted with caution.

Authors' objectives
To assess the effects of disease-modifying antirheumatic drugs (DMARD) therapies and tumour necrosis factor inhibitors plus methotrexate on clinical and radiological outcomes compared with methotrexate monotherapy, in patients with early rheumatoid arthritis.

Searching
MEDLINE and EMBASE were searched for reports written in English from 1980 to 2008. Search terms were reported.

Study selection
Randomised controlled trials (RCTs) that compared combination disease-modifying antirheumatic drugs (DMARDs) and/or tumour necrosis factor inhibitors/methotrexate combination therapy versus methotrexate monotherapy were eligible for inclusion in the review. Eligible patients had to be diagnosed with rheumatoid arthritis (using American College of Rheumatology classification) for less than three years. Eligible interventions appeared to be infliximab, adalimumab or etanercept with methotrexate.

Eligible outcomes were the number of patients meeting different American College of Rheumatology response criteria, patient withdrawals (due to inefficacy and toxicity), patient disability score (assessed on the Health Assessment Questionnaire) and X-ray assessment of progression.

Most of the included trials assessed infliximab in combination with methotrexate; other treatments combined with methotrexate included adalimumab, bucillamine, cyclosporine, doxycycline and sulfasalazine. Maximum disease duration ranged from 0.5 to three years. In included combination DMARD trials, the proportion of females in the treatment arms ranged from 64 to 93%; in included tumour necrosis factor inhibitors/methotrexate trials the proportion was 66 to 79%. Mean age of participants ranged from 46 to 57 years for trials of combination DMARDS, and 50 to 54 years for trials of tumour necrosis factor inhibitors/methotrexate. A range of disease activity scores (DAS) were reported including DAS28, DAS, DAS44 and DAS28-CRP. The mean baseline DAS28 ranged from 5.2 to 6.7 (where reported); all DAS scores were high.

Titles and abstracts of the retrieved studies were screened for relevance by two reviewers; further details of the selection process were not reported.

Assessment of study quality
The quality of each included trial was assessed using the Jadad criteria (randomisation, blinding and follow-up/withdrawals). A score up to 5 points was awarded for each trial.

The authors did not state how many reviewers performed the assessment.

Data extraction
Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for dichotomous outcomes. Mean changes were extracted for X-ray (assessment of progression) scores and disability scores (Health Assessment Questionnaire); these were divided by the duration of follow-up. Scores were standardised as percent maximal change. The number needed to
Methods of synthesis

Odds ratios and weighted mean differences (WMD), with 95% confidence intervals, were pooled using a random-effects model. Statistical heterogeneity was assessed using the Cochran's $\chi^2$ test and the $I^2$ statistic. For trials with multiple intervention arms, the arm reporting the greatest effect was used in the analysis.

Sensitivity analyses were performed to examine the effects of excluding trials using different trial designs (i.e. step-down and tight-control designs).

Results of the review

Fifteen RCTs were included in the review (n=4,200 patients); thirteen RCTs used a parallel design, one RCT used a step-up design, and one RCT used a tight-control design. Sample sizes ranged from 20 to 1,049. The mean Jadad score was 3.9 points. Four RCTs scored the maximum number of points; two RCTS were described as low quality (2 out of 5 points). Follow-up periods ranged from one to two years.

Significant beneficial effects in favour of disease-modifying antirheumatic drugs (DMARD) combinations compared with methotrexate monotherapy were reported for American College of Rheumatology (ARC) 20-70 responses (ACR20, OR 2.02, 95% CI 1.27 to 3.20, six RCTs; ACR50, OR 1.64, 95% CI 1.15 to 2.34, five RCTs; ACR70, OR 1.84, 95% CI 1.31 to 2.57, five RCTs), withdrawals due to inefficacy (OR 0.52, 95% CI 0.33 to 0.82; eight RCTs), disability measured on the Health Assessment Questionnaire (WMD -0.17, 95% CI -0.33 to -0.01; two RCTs), and annual X-ray progression (WMD -1.20%, 95% CI -1.36 to -1.04; five RCTs). However, DMARD combinations were associated with increased withdrawals for toxicity (OR 2.69, 95% CI 1.49 to 4.83; eight RCTs);

Significant beneficial effects in favour of tumour necrosis factor inhibitors/methotrexate compared with methotrexate monotherapy were reported for ACR20-70 responses (ACR 20, OR 2.03, 95% CI 1.63 to 2.54, six RCTs; ACR50, OR 2.17, 95% CI 1.78 to 2.64, five RCTs; ACR70, OR 2.30, 95% CI 1.89 to 2.79, five RCTs), withdrawals due to inefficacy (OR 0.29, 95% CI 19 to 0.44; seven RCTs), disability measured on the Health Assessment Questionnaire (WMD -0.16, 95% CI -0.26 to -0.04; two RCTs), and annual X-ray progression (WMD -0.84%, 95% CI -1.23 to -0.45; four RCTs). There was no difference for withdrawals due to toxicity.

There was little evidence of significant statistical heterogeneity.

Further sensitivity analyses, numbers needed to treat and numbers needed to harm were reported in the review and showed similar findings.

All forest plots and some of the tables were only available as supplementary online material (see URL for Additional Data).

Authors' conclusions

There was strong evidence in support of combination disease-modifying antirheumatic drugs (DMARDs) and/or tumour necrosis factor inhibitors/methotrexate combination therapy for early rheumatoid arthritis, but there was uncertainty about the preferred regimen.

CRD commentary

The review assessed a clearly defined research using a broad range of study designs. Searches for relevant data were performed in two major databases, but relevant studies may have been missed as only studies published in English were eligible for inclusion. Consequently, the review may be at risk from publication and/or language bias. Although attempts were made to reduce the risk of reviewer error and bias when selecting studies for inclusion, but it was unclear whether similar measures were applied throughout the rest of the review.

The quality of the included trials was assessed using relevant criteria; although scores were not reported in detail for each criterion, overall scores suggested that only a small number of trials were of low quality. Trials were summarised using a meta-analysis. Some attempt was made to investigate potential sources of heterogeneity, which appeared to be
present, especially in the included trial populations, interventions and outcomes. The authors acknowledged a number of limitations which may have affected their data and highlighted the need for further head-to-head trials.

Overall, the data appeared to support the review findings, but concerns over the review methodology and the variation between included trials, suggest that the findings should be interpreted with caution.

**Implications of the review for practice and research**

Practice: The authors stated that their findings supported guidance from the National Institute for Health and Clinical Excellence (NICE) that early rheumatoid arthritis should initially be treated using combination DMARDs.

Research: The authors stated that further head-to-head studies comparing different combination DMARD regimens and tumour necrosis factor/methotrexate combinations are required.

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