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

E. H. S. Choy, C. Smith, C. J. Dore\textsuperscript{1} and D. L. Scott

Introduction. Combinations of disease-modifying anti-rheumatic drugs (DMARDs) are increasingly used to treat rheumatoid arthritis (RA). Early trials showed their toxicity while recent trials suggest superior efficacy. Trials of DMARD combinations have enrolled different types of patient (early or established RA), used different designs (step-up, parallel or step-down) and utilized a range of outcome measures. We undertook a systematic review of combination DMARD therapy for RA and carried out a meta-analysis to evaluate the evidence for efficacy and toxicity.

Method. Medline, PubMed and EmBase were searched using MESH headlines ‘arthritis, rheumatoid’, ‘drug therapy, combination’ and ‘randomized controlled trial’ (RCT) for papers published from 1975 to April 2004. References from published articles were also searched. Three independent assessors evaluated abstracts and selected trials for detailed examination. Trials were excluded if their quality was poor, were not published in English or studied DMARDs not licensed to treat RA. Two independent assessors extracted data. Efficacy was assessed by the numbers of patients withdrawn due to lack of efficacy. Toxicity was assessed by the numbers of patients withdrawn due to adverse events. Risk ratios (RR) with 95% confidence intervals (CI) were calculated and meta-analysis was carried out based on a random effects model. Sensitivity analyses evaluated different treatment combinations, trial designs, study populations and outcome measures.

Results. Fifty-three potentially relevant RCTs were identified. Twelve were excluded due to: using unlicensed DMARDs (n = 3); reporting in journal supplements of RCTs already included (n = 2); follow-up of an earlier RCT; report of biological outcomes or pharmacokinetics (n = 5); and non-English language publications (n = 2). Forty-one RCTs were evaluated in detail and another five excluded (three open-labelled studies and two with high patient attrition); 36 studies were included in the meta-analysis. These comprised 13 step-up, 16 parallel and 7 step-down trials. Nine assessed early RA and 27 established RA. Seven added steroids to DMARD monotherapy and one study added steroids to DMARD combinations. Six assessed methotrexate (MTX) plus tumour necrosis factor (TNF) inhibitors. Overall, combination DMARD therapy was more effective than monotherapy (RR 0.35; 95% CI 0.28, 0.45) although the risk of toxicity was also slightly higher (RR 1.37; 95% CI 1.16, 1.62). Combinations of MTX with TNF inhibitors and MTX with sulphasalazine or anti-malarials showed good efficacy/toxicity ratios.

Conclusions. DMARD combinations vary in their efficacy/toxicity ratio. MTX plus sulphasalazine and/or anti-malarials and MTX plus TNF inhibitors have particularly favourable benefit/risk ratios.

Key words: Rheumatoid arthritis, Treatment, Randomized controlled trial, Combination therapy, DMARD, Anti-rheumatic drugs, Meta-analysis.

The treatment of rheumatoid arthritis (RA) is based on disease-modifying anti-rheumatic drugs (DMARDs), which reduce inflammatory synovitis, improve function and prevent structural damage. The results of DMARD therapy have been improved by their early introduction [1] and by the predominant use of methotrexate (MTX) [2]. However, DMARD monotherapy often fails to control RA. Patients who fail to respond to DMARD monotherapy often require tumour necrosis factor (TNF) antagonists, although combining conventional DMARDs may be a reasonable alternative.

Combination DMARD therapy has been advocated for several decades with many randomized controlled trials (RCTs). Although most recent reviews are positive about the value of combination therapy [3–9], many RCTs have been equivocal or negative and it is questionable whether improved outcomes from combining DMARDs outweigh increased toxicity. As small improvements from combination DMARDs may be beneficial, a meta-analysis of existing trials can help resolve the value of such treatment.

Clinical trial methodologies in RA have developed substantially since combination DMARD therapy was first evaluated. In particular, recent trials have used summated indices like the American College of Rheumatology (ACR) response criteria [10], which cannot be applied retrospectively to earlier trials. Consequently we based our meta-analysis on the simplest criterion of benefit—whether treatment is stopped for inefficacy or adverse effects. These outcome measures are now routinely reported in clinical trials as stipulated by the CONSORT guidelines [11]. They have face validity and are used to assess effectiveness in clinical

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practice although their responsiveness is unknown. This simplistic approach will be relevant in other chronic diseases.

Methods

Criteria for considering studies for this review

Using a predefined protocol we selected studies for evaluation using the following criteria:

(i) They were randomized or quasi-randomized controlled trials.
(ii) They enrolled patients who fulfilled the ACR or American Rheumatism Association (ARA) diagnostic criteria for RA and if no diagnostic criteria were cited the assessors had to judge from the evidence available that patients enrolled had definite RA.
(iii) One treatment arm involved combination therapy with two or more DMARDs or one DMARD and one biological therapy.
(iv) The DMARDs or biologicals were those currently used in routine clinical practice and trials involving experimental and non-licensed treatments were excluded.
(v) The publication was in English.

Quality of trials

We used the Jadad score [12] to assess the quality of the trials.

Types of outcome measures

The primary endpoint for efficacy was the number of patients withdrawn because of lack of efficacy. Secondary endpoints for efficacy were the number of patients who achieved ACR20 responses [10] and the number of patients who achieved a major clinical response, shown by either an ACR70 response or being recorded as having entered remission; no specific criteria were applied to this latter term but we assumed remission would be at least equivalent to an ACR70 response. The primary endpoint for toxicity was the number of patients withdrawn due to adverse events.

Search strategy

We searched the Medline, PubMed and EmBase databases from 1975 to April 2004 for articles with the headline ‘arthritis, rheumatoid’, ‘drug therapy, combination’ and ‘randomized controlled trial’. A manual search was also used based on references from these articles as well as review articles (i.e. we searched trial bibliographies). Three reviewers (EC, DLS and CD) independently selected the trials to be included in the review. Trials were only included if they had adequate allocation concealment (studies were excluded if an open allocation schedule or unsealed or open envelopes were used), double-blinded assessment and trial design (step-up, parallel or step-down) and Jadad score. The validity of patient withdrawal due to lack of efficacy as an outcome measure was evaluated by comparing it with ACR20 and ACR70 responses or remission in studies in which both were available.

Results

Description of studies

A preliminary search identified 53 potentially relevant RCTs. Twelve studies were excluded [13–24] for the following reasons: three because they used experimental treatments that are not relevant for routine clinical practice; five because they reported data that had already been published as an original RCT elsewhere; two because they were articles in journal supplements and the key clinical data had been reported elsewhere; and two because they were not written in English (subsequent review indicated these were not high-quality trials). The 41 remaining articles were reviewed in detail and another five excluded; three because they were open label studies [25–27] and two because of high patient attrition [28, 29]. The remaining 36 studies that fulfilled the criteria for inclusion in this review [30–65] are listed in Table 1.

Study characteristics

Most studies recruited patients with established RA; only nine involved early RA (disease duration less than 3 yr). Fourteen studies used step-up designs, 16 used parallel designs and seven used step-down designs. In seven corticosteroids were added to one DMARD as bridging therapy. One added corticosteroids to two DMARDs. In six studies TNF inhibitors were given to patients who had partial response to MTX using step-up designs in established RA. The average Jadad score was 3; 24 studies (66%) had Jadad scores of 4.

Efficacy

Combination therapy was more effective than monotherapy (RR = 0.35; 95% CI 0.28, 0.45; P = 0.00001; Fig. 1). The trials showed a moderate degree of heterogeneity (χ² = 41.73; P = 0.05); the combination of DMARDs involved was the main contributor to heterogeneity. Combining MTX with anti-TNF inhibitors was more effective than MTX monotherapy (RR = 0.22; 95% CI 0.14, 0.32; P = 0.00001). MTX plus sulphasalazine and/or anti-malarials was a common combination (Table 2); in eight studies it showed more efficacy than monotherapy (RR = 0.41; 95% CI 0.24, 0.7; P = 0.00001). In seven studies corticosteroids were added to a single DMARD as bridging therapy (Table 2); the benefits were small and not significant (RR = 0.48; 95% CI 0.2, 1.14; P = 0.1). Other non-biological DMARD combinations were effective (RR = 0.37; 95% CI 0.27, 0.51; P = 0.00001) with insufficient trials of specific combinations for further sub-analyses.

Sensitivity analyses based on patient populations and trial designs (Table 2) show that combination therapy is more effective in established RA (RR = 0.31; 95% CI 0.24, 0.4; P = 0.00001); the benefit remained after excluding studies involving TNF inhibitors (RR = 0.4; 95% CI 0.28, 0.56; P = 0.00001). In nine studies of early RA combination therapy was better than monotherapy (RR = 0.56; 95% CI 0.35, 0.91; P = 0.02). Combination therapy was superior in parallel (RR = 0.45; 95% CI 0.32, 0.62; P = 0.00001), step-up (RR = 0.28; 95% CI 0.2, 0.4; P = 0.00001) designed trials and step-down (RR = 0.32; 95% CI 0.16, 0.62; P = 0.001) trials. Excluding studies with a Jadad score of 2 or less also had little impact on our results (RR = 0.31, 95% CI 0.24, 0.41).

Since triple therapy may be more effective than combining only two DMARDs, we undertook an additional analysis that excluded...
all triple therapy studies; this analysis showed that studies that compare monotherapy with a combination of two therapies still showed a highly significant effect in favour of combination therapy (RR = 1.37, 95% CI 1.16, 1.62; P = 0.0001) (Fig. 2). Combining MTX with sulphasalazine or anti-malarials or both appeared less toxic than monotherapy, although the difference was not significant (RR = 0.81; 95% CI 0.52, 1.27; P = 0.66).

**Toxicity of combination therapy**

Combination therapy resulted in more withdrawals for toxicity than monotherapy (RR = 1.37; 95% CI 1.16, 1.62; P = 0.0001) (Fig. 2). Combining MTX with sulphasalazine or anti-malarials or both appeared less toxic than monotherapy, although the difference was not significant (RR = 0.81; 95% CI 0.52, 1.27; P = 0.66).

**Combined withdrawals for lack of efficacy or toxicity**

Fewer patients withdrew from combination therapy than from monotherapy. Overall, 513 (19%) out of 2637 patients given combination therapy withdrew from treatment compared with 850 (22%) out of 2652 controls (RR = 0.89; 95% CI 0.80, 0.99; P = 0.033).

**Discussion**

Our meta-analysis supports the use of combination DMARD therapy in some RA patients. Using patient withdrawals from lack of efficacy and adverse events as primary outcome measures circumvented the complexities resulting from disparate outcome measures in these trials. Finding comparable results using ACR response criteria confirmed its validity.
FIG. 1. Overall efficacy.

### Table 2. Sensitivity analyses for efficacy based on choice of DMARD, patient population studied and trial design

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>No. of studies</th>
<th>No. of patients</th>
<th>Risk ratio [95% CI]</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Established RA [31–38, 42–50, 52–54, 56, 57, 59–63]</td>
<td>22</td>
<td>4258</td>
<td>0.31 [0.24, 0.4]</td>
<td>0.00001</td>
</tr>
<tr>
<td>Established RA after excluding TNF-α inhibitors [31–34, 42–50, 52, 56, 57, 59, 60, 63]</td>
<td>21</td>
<td>2728</td>
<td>0.4 [0.28, 0.56]</td>
<td>0.00001</td>
</tr>
<tr>
<td>Early RA [30, 39–41, 51, 55, 58, 64, 65]</td>
<td>9</td>
<td>1031</td>
<td>0.6 [0.35, 0.91]</td>
<td>0.02</td>
</tr>
<tr>
<td>Step-up [30–38, 56–61, 63]</td>
<td>14</td>
<td>2259</td>
<td>0.28 [0.2, 0.4]</td>
<td>0.0001</td>
</tr>
<tr>
<td>Step-up after excluding TNF-α inhibitors [30–34, 59, 60, 63]</td>
<td>8</td>
<td>1411</td>
<td>0.51 [0.31, 0.82]</td>
<td>0.006</td>
</tr>
<tr>
<td>Parallel [39–50, 58, 62, 64, 65]</td>
<td>16</td>
<td>2648</td>
<td>0.45 [0.32, 0.62]</td>
<td>0.00001</td>
</tr>
<tr>
<td>Methotrexate + TNF-α inhibitors [35–38, 61, 62]</td>
<td>7</td>
<td>382</td>
<td>0.32 [0.16, 0.62]</td>
<td>0.0009</td>
</tr>
<tr>
<td>Methotrexate + sulphasalazine ± anti-malarials [40–42, 44, 45, 48, 50, 55]</td>
<td>5</td>
<td>1530</td>
<td>0.22 [0.14, 0.32]</td>
<td>0.0001</td>
</tr>
<tr>
<td>Corticosteroids as bridging therapy to one DMARD [39, 51–54, 56, 57]</td>
<td>7</td>
<td>289</td>
<td>0.48 [0.2, 1.14]</td>
<td>0.1</td>
</tr>
<tr>
<td>DMARD combinations excluding corticosteroids as bridging therapy [12, 31–38, 40–50, 55, 58–65]</td>
<td>30</td>
<td>4516</td>
<td>0.35 [0.27, 0.44]</td>
<td>0.0001</td>
</tr>
<tr>
<td>Excluding studies with Jadad score of ≤2 [30–37, 39–46, 48, 49, 51, 54, 55, 57–65]</td>
<td>30</td>
<td>4516</td>
<td>0.35 [0.27, 0.44]</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Total events: 136 (Combination DMARD), 260 (Monotherapy)  
Test for heterogeneity: Chi² = 41.75, df = 28 (P = 0.05), I² = 32.9%  
Test for overall effect: Z = 0.92 (P < 0.00001)

### Table 3. Sensitivity analysis using alternative outcome measures for meta-analysis

<table>
<thead>
<tr>
<th>Outcome measures</th>
<th>ACR20 (n = 18)</th>
<th>Major clinical response (ACR70 or remission) (n = 14)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ACR20</td>
<td>Patient withdrawal</td>
</tr>
<tr>
<td>Risk ratio</td>
<td>1.53</td>
<td>0.36</td>
</tr>
<tr>
<td>95% CI</td>
<td>1.26, 1.86</td>
<td>0.27, 0.48</td>
</tr>
<tr>
<td>P value</td>
<td>0.00001</td>
<td>0.00001</td>
</tr>
</tbody>
</table>
Combination DMARD therapy has a reduced risk of withdrawals (75%) due to inefficacy compared with monotherapy both overall and in step-up, parallel and step-down studies. This is balanced by an increased risk of withdrawals (37%) due to adverse events. The benefits of combination therapy are evident in early and established RA considered separately and together; this is relevant as patients with early and late RA entered into RCTs of DMARDs may not be directly comparable. Combinations of MTX with TNF inhibitors and MTX with sulphasalazine and/or anti-malarials are most effective. As there are few trials comparing combinations of two DMARDs with combinations of three DMARDs the overall benefit of triple therapy (MTX, sulphasalazine and anti-malarials) cannot be established in our meta-analysis. There was no evidence of benefit with combinations involving corticosteroids, reflecting Saag’s negative analysis of steroids [66]. However, as there are few trials involving steroids, the negative may reflect insufficient statistical power. As steroids are widely used in RA more primary research is needed on steroid–DMARD combinations.

Many researchers have expressed concerns over trials using a step-up design. By selecting patients with inadequate response to a DMARD who have active disease it is relatively easy to show that combination DMARD is more beneficial. Our data showed that trials using step-up design (RR = 0.28) indeed showed much greater effect size than parallel (RR = 0.45) or step-down trials (RR = 0.32).

Additional sensitivity analyses showed that our conclusions remain unchanged when different criteria were used to select studies or analyse data, including studies that were not blinded. We also found identical positive results using tender joint counts; this alternative analysis was only applicable to the minority of RCTs reporting tender joint counts, and we therefore did not pursue comparisons involving such individual clinical measures in all studies. Attempts were made to analyse the outcome of radiological assessment but this proved impossible because only a minority of studies included X-ray scores and these used different methods of assessment, which is a significant obstacle to pooled analysis of radiological outcome in RA. Since radiological outcome is often considered fundamental to the claim of disease modification in RA, international consensus is needed on the assessment and reporting of radiological outcomes in clinical trials.

Clinical practice surveys show growing use of DMARD combinations [67, 68]. We have identified five modern systematic reviews of combination DMARD therapies [69–73]. Two early systematic reviews were inconclusive or negative [69, 70]. In contrast the three more recent systematic reviews [71–73], together with our own meta-analysis, reported positive evidence for combination DMARDs, and all reported strong evidence for combining MTX with sulphasalazine and/or hydroxychloroquine in established RA, although this is not included in the current UK guidelines [74]. This meta-analysis also suggests that combining DMARDs is superior to monotherapy in early RA and argues strongly that increasingly combination DMARDs should be used in most patients early in the disease process. One of the crucial questions in RA is whether combination therapy is as effective as biological therapy. Only a large-scale randomized control trial comparing these directly will answer the question.
We conclude that combination DMARD therapy is effective in RA. The evidence is strongest in established RA for combinations of MTX with anti-TNF and sulphasalazine–hydroxychloroquine given to patients who have partially responded to DMARD monotherapy. There is good evidence for its widespread clinical use.

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