Efficacy and toxicity of methotrexate (MTX) monotherapy versus MTX combination therapy with non-biological disease-modifying antirheumatic drugs in rheumatoid arthritis: a systematic review and meta-analysis

Katchamart W, Trudeau J, Phumethum V, Bombardier C

CRD summary
The review evaluated the efficacy and toxicity of methotrexate monotherapy compared to methotrexate in combination with other non-biological disease-modifying anti-rheumatic drugs (DMARDs) in adults with rheumatoid arthritis and concluded that in DMARD-naïve patients the balance of efficacy/toxicity favoured methotrexate monotherapy. In DMARD nonresponders the evidence was inconclusive. The limitations of the included studies make the reliability of the conclusions unclear.

Authors’ objectives
To evaluate the efficacy and toxicity of methotrexate monotherapy compared to methotrexate in combination with non-biological disease-modifying anti-rheumatic drugs in adults with rheumatoid arthritis.

Searching
MEDLINE (1950 to June 2007), EMBASE (1980 to 2007) and Cochrane Central Register of Controlled Trials (CENTRAL) (2nd quarter 2007) were searched for publications in any language. Abstracts of the meetings of the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) were also searched from 2005 to 2007. Bibliographies of relevant studies, review articles and letters were handsearched. Search terms were reported.

Study selection
Randomised controlled trials (RCTs) of methotrexate monotherapy versus methotrexate combined with other non-biological disease-modifying anti-rheumatic drugs (DMARDs) were eligible for inclusion. Included trials needed to be at least 12 weeks duration in patients with rheumatoid arthritis who were at least 18 years old. To be eligible for inclusion studies had to make data available on specified outcomes (ACR 20, 50 or 70 responses; ACR remission; Disease Activity Score (DAS); EULAR response; withdrawal due to lack of efficacy or adverse events; and number of total or individual adverse events. Only commonly reported individual adverse events were reported. The primary outcomes were withdrawals for adverse events or lack of efficacy.

Studies with open-label extensions were excluded, as were studies that compared DMARDs that were no longer in use. Methotrexate was administered orally in all of the included studies. The range of dosage of methotrexate used varied from 5mg/week to 18mg/week. Study duration ranged from six to 60 months. A variety of DMARDs was used in combination with methotrexate. Details of the dosage and frequency of the specific drugs used were given in the review. Patients in the included studies were either DMARD-naïve patients (DMARD-N), methotrexate inadequate response patients (MTX-IR) or non-methotrexate DMARDs inadequate response patients (non-MTX-IR); for one study this was not clear.

Two reviewers independently performed the literature search and the selection of papers for the review.

Assessment of study quality
Study quality was assessed by two reviewers independently with van Tulder’s scale. Eleven criteria were used for the quality scale. These included: randomisation; blinding (patients, provider and outcome assessor); concealment of treatment allocation; similarity of the important baseline characteristics; co-intervention; timing of the outcome assessment; compliance; withdrawals; and intention-to-treat analysis. Each criteria was rated as yes=1 or no/do not know=0 up to a maximum score of 11.

Data extraction
The numbers of events for each outcome were extracted in order to calculate weighted mean differences and relative
risk (RR) and 95% confidence intervals (95% CI). Two independent reviewers performed the data extraction.

**Methods of synthesis**
Efficacy analysis was stratified into three groups based on previous DMARD use. Toxicity analysis was stratified by DMARD combination and pooled across trials for each combination. For continuous measures of efficacy, either end of trial data or changes from baseline were pooled as weighted mean differences using a random-effects model. For categorical measures of efficacy, end of trial results were pooled using a random-effects model giving a pooled relative risk and 95% CI. The prespecified primary analysis was based on total withdrawal rates for efficacy or toxicity. A pooled analysis was performed, which combined withdrawal due to adverse effects and toxicity. Statistical heterogeneity was determined using $\chi^2$ and $I^2$ tests.

**Results of the review**
Nineteen RCTs (n=2,025, range 37 to 263) were identified. The quality score ranged from 3 to 10; only three RCTs scored lower than 7. Ten studies had appropriate randomisation and adequate blinding for both patients and care providers. For the remaining studies, the method of randomisation was either not explicitly described or was unclear.

**Efficacy:**
In DMARD-N patients there was no significant difference in patient withdrawal due to lack of efficacy of methotrexate combination versus monotherapy (five studies). Patient withdrawal due to toxicity was significantly increased with methotrexate combination therapy (RR 1.72, 95% CI 1.04 to 2.83). Data for ACR response was available for three RCTs with combination arms that used ciclosporin (two RCTs) or doxycycline (one RCT). The only significant result was for ACR 70 response in one of the ciclosporin trials (RR 2.41, 95% CI 1.07 to 5.44), which favoured the methotrexate combination arm. The outcomes for EULAR response or remission were not significant (two RCTs).

In MTX-IR patients, significantly fewer patients withdrew in the methotrexate combination group compared with the monotherapy group due to lack of efficacy (RR 0.42, 95% CI 0.21 to 0.84; three studies). Patient withdrawal due to toxicity was significantly increased with methotrexate combination therapy (RR 1.89, 95% CI 1.05 to 3.41).

Combination therapy was significantly more effective than methotrexate monotherapy for ACR response (four studies): RR 2.51 (95% CI 1.92 to 3.28) for ACR 20; RR 4.54 (95% CI 2.51 to 8.20) for ACR 50; and RR 5.59 (95% CI 2.08 to 15.01) for ACR 70 response. There were no data for ACR remission or EULAR response.

In non-MTX-IR patients there was a significant benefit for patient withdrawal due to lack of efficacy of methotrexate combination versus monotherapy (RR 0.37, 95% CI 0.16 to 0.87; five studies). Data for ACR response were available for two RCTs, where combination therapy was only significantly more effective than methotrexate monotherapy for ACR 20 response (RR 1.85, 95% CI 1.21 to 2.83). The outcome for EULAR response was not significant (one RCT). There were no data on ACR remission.

**Withdrawal:**
In 17 of the 19 RCTs, combination therapy had higher withdrawal due to adverse reactions than monotherapy. The differences were significant only for ciclosporin (RR 1.88, 95% CI 1.02 to 3.50) and azathioprine (RR 5.18, CI 95% 1.58 to 16.96).

Combined withdrawal due to lack of efficacy:
There was no significant difference in withdrawals for both efficacy and safety for DMARD-N patients, MTX-IR patients or non-MTX-IR patients (13 trials). There was significant heterogeneity for non-MTX-IR patients ($I^2=57.4\%$), with one important outlier. The outlier RCT of non-MTX-IR patients with a combination of methotrexate with sulfasalazine and hydroxychloroquine gave a better efficacy/toxicity ratio than methotrexate alone (RR 0.30, 95% CI 0.14 to 0.65).

Results for toxicity were also reported in the paper.
Authors’ conclusions
In DMARD-naïve patients the balance of efficacy/toxicity favoured methotrexate monotherapy. In both methotrexate nonresponders and nonresponders to other DMARDs, the evidence was inconclusive.

CRD commentary
The review addressed a well-defined question in terms of participants, interventions, study design and relevant outcomes. Relevant databases were searched for studies in any language and unpublished studies were considered. Publication bias was not assessed. Study quality was assessed using suitable criteria. Efforts were made in the review process to reduce error and bias, but it was not clear how conflicts between reviewers were resolved. Relevant study details were reported, but no details of the sex or age of patients was provided. Statistical heterogeneity was assessed and there was evidence for heterogeneity with some outcomes. The statistical method used for the meta-analysis of the RCTs seemed appropriate and was used to derive relative risks. A sensitivity analysis was not performed. The authors pointed out that the doses of methotrexate used in the studies of MTX-IR patients (7mg/week to 15mg/week) were lower than those used currently. Some other studies also had design faults. The authors identified other study limitations: some relatively small studies and half of the DMARDs used in the studies were not commonly used in practice. In view of the limitations of the included studies, the reliability of the conclusions is unclear.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors identified a need for further studies that compared the currently used doses of methotrexate with combination therapies.

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