Withdrawal of disease-modifying antirheumatic drugs in patients with rheumatoid arthritis: a systematic review and meta-analysis

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CRD summary
The authors concluded that withdrawal of disease-modifying antirheumatic drugs (DMARDs) in patients with established rheumatoid arthritis increased the risk of flare-up or deterioration. Patients with established rheumatoid arthritis, but adequate symptom control with DMARDs, should normally continue to receive treatment. Although the authors’ conclusions reflected the evidence, the limited evidence available means that they should be interpreted with some caution.

Authors’ objectives
To assess whether withdrawal of disease-modifying antirheumatic drugs (DMARDs) is feasible and appropriate in patients with established rheumatoid arthritis receiving stable, effective long-term DMARD treatment.

Searching
MEDLINE, EMBASE, CINAHL, and the Cochrane Library were searched from inception to June 2008 for English language papers. Search terms were reported (in supplementary online material). Reference lists of retrieved articles were manually searched. Experts in the field were contacted.

Study selection
High quality studies that assessed the effects of withdrawal or titration/reduction of the dose of disease-modifying antirheumatic drugs (DMARDs) in adults with established (disease of over two years duration) rheumatoid arthritis were eligible for inclusion. Studies of non-UK relevant populations were excluded.

The outcome of interest was the total number of patients at the end of the study who experienced disease flares or deleterious effects (clinical deterioration, exacerbation of symptoms).

The included studies were of patients with a disease duration that ranged from 40 months to 16 years (where reported). At baseline, between 60 and 80% of patients were reported to be rheumatoid factor positive (where reported). The mean disease duration ranged from 7.4 to 16 years. Randomised controlled trials compared the effects of withdrawal or dose reduction of azathioprine, penicillamine, methotrexate, intramuscular gold or different DMARDs versus placebo (patients remaining on treatment), or compared varying doses of D-penicillamine. Case series tapered or withdrew infliximab with methotrexate, prednisolone, or methotrexate alone. Study duration ranged from one to 24 months (where reported). The outcomes measured were rheumatoid arthritis flare, clinical deterioration, treatment failure, and changed joint counts.

One reviewer screened studies for inclusion; their appropriateness for addressing the objectives were considered by a clinician.

Assessment of study quality
The quality of randomised controlled trials (RCTs) was assessed according to the National Institute of Health and Clinical Excellence quality assessment criteria, including items on randomisation, allocation concealment, blinding, intention-to-treat analysis, and drop-outs/withdrawals. RCTs demonstrating two or more of the main sources of bias were excluded from the review. It appeared that two reviewers assessed the quality of the trials.

Data extraction
Three reviewers independently extracted outcome data at baseline and follow-up to calculate relative risks (RRs) and 95% confidence intervals (CIs).

Methods of synthesis
Outcome data from RCTs were pooled using a fixed-effect model, or a random-effects model where there was evidence of statistical heterogeneity. Heterogeneity was assessed using $X^2$ and $I^2$. Sensitivity analyses were undertaken to investigate sources of heterogeneity, including follow-up duration (under one year versus over one year), trial design (tapered dose reduction or total DMARD withdrawal), and sample size (under 30 patients versus over 30 patients).

Data from observational studies were presented as a narrative synthesis.

Publication bias was not formally assessed.

**Results of the review**

Six RCTs ($n=503$ patients, range 10 to 285) and three case series ($n=263$ patients, range 15 to 210) were included in the review. One RCT was rated as good quality, with the remaining RCTs rated as moderate quality.

Patients withdrawing from disease-modifying antirheumatic drug (DMARD) treatment showed significantly higher risk of flare or deterioration in rheumatoid arthritis compared with patients remaining on treatment ($RR\ 0.31,\ 95\%\ CI\ 0.16$ to 0.57; six RCTs; $I^2=54\%$). Sensitivity analyses did not significantly alter the findings (data not presented).

Findings from individual case series were inconsistent (as reported in the review).

**Authors' conclusions**

Withdrawal of disease-modifying antirheumatic drug (DMARD) treatment in patients with established rheumatoid arthritis increased the risk of flare-up or deterioration, regardless of the DMARD used. Patients with established rheumatoid arthritis who have adequate control of their symptoms with DMARDs should normally continue to receive treatment.

**CRD commentary**

The review question and supporting inclusion criteria were clearly defined. The literature search was adequate. However, as language restrictions were applied, language bias may have been introduced. Publication bias was not formally assessed, so potentially relevant data may have been missed. Attempts were made to reduce the potential for reviewer error and bias, with each stage of the review in performed duplicate. Details of the review methodology (inclusion criteria, search strategy, data extraction, data analysis and quality assessment) were only available as supplementary online material (see URL for Additional Data).

The quality of the RCTs was assessed. Only higher quality trials were included in the meta-analysis, although only one RCT was rated as high quality. The authors acknowledged the limitations of observational studies and that conclusions could not be drawn about cause and effect relationships. The authors acknowledged the presence of heterogeneity among trials, which suggested that pooling of the RCTs may not have been appropriate. Only a small number of RCTs with small sample sizes were included in the meta-analysis.

Although the authors' conclusions seemed to reflect the evidence, the potential for some bias in the review and the limited evidence available mean that they should be interpreted with some caution.

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

**Practice:** The authors stated that dose reduction or withdrawal from treatment should be performed cautiously and patients' disease activity should be monitored carefully so that they can re-start previous disease-controlling DMARD treatment in the event of disease flare or symptom deterioration.

**Research:** The authors stated that further primary research is needed to assess the risks and benefits of tapering or withdrawing biological drugs.

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