Long-term impact of early treatment on radiographic progression in rheumatoid arthritis: a meta-analysis

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CRD summary
The authors concluded that starting disease-modifying antirheumatic drugs early in the course of rheumatoid arthritis may reduce long-term joint damage. Overall, this was a well-conducted review and the authors’ cautious conclusion appears to reflect the evidence from studies of limited quality.

Authors' objectives
To evaluate the long-term effects of early treatment with disease-modifying antirheumatic drugs (DMARDs) on radiographic progression in patients in the early stages of rheumatoid arthritis.

Searching
MEDLINE, EMBASE and the Cochrane Controlled Trials Register were searched from inception to September 2004; the search terms were reported. No language restrictions were applied. In addition, reference lists and abstracts from the American College of Rheumatology and the European League Against Rheumatism from between 2002 and 2004 were screened and consultants were contacted. Published and unpublished studies were sought.

Study selection
Study designs of evaluations included in the review
Cohort studies that reported the time delay between disease onset and the start of DMARDs, and follow-up studies of randomised controlled trials (RCTs) with follow-up of at least 1 year after the end of the RCT, were eligible for inclusion. Amongst the included studies, the duration of follow-up (after the RCT ended) ranged from 1 to 5.6 years (median 3).

Specific interventions included in the review
Studies that compared early and delayed DMARDs were eligible for inclusion. Studies had to have a delay of between 3 and 24 months between the early and delayed DMARD groups, and had to use DMARDs of comparable efficacy in the treatment arms. The included studies evaluated level 1 (hydroxychloroquine, oral gold or penicillamine), level 2 (methotrexate, sulphasalazine or parenteral gold) and level 3 (combination treatments) DMARDs. In the included studies, the treatment delay ranged from 5 to 14 months (average 9).

Participants included in the review
Studies of patients with rheumatoid arthritis (defined according to American College of Rheumatology criteria) for less than 2 years were eligible for inclusion. The mean age of the participants in the included studies ranged from 44 to 57 years.

Outcomes assessed in the review
Studies that evaluated radiographic progression were eligible for inclusion. Most of the included studies assessed radiological progression using the Sharp or Larsen scoring methods.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
Two reviewers independently assessed validity based on the comparability of patients in the treatment groups, the comparability of DMARD regimens and radiographic joint progression data (longitudinal or cross-sectional data). The maximum possible score was 6 points. Any disagreements were resolved through discussion with a third reviewer.

Data extraction
Two reviewers independently extracted the data. Any disagreements were resolved through discussion with a third reviewer. Authors were contacted where required for missing data. Annual rates of radiographic progression with standard deviations were estimated from reported or obtainable data or statistics, and standardised mean differences (SMDs) with 95% confidence intervals (CIs) were calculated.

**Methods of synthesis**

How were the studies combined?
Pooled SMDs with 95% CIs were calculated using random-effects models. Separate analyses were conducted for cohort and follow-up studies and then, since no significant differences were found between the study designs, the studies were combined. The percentage reduction in disease progression was also calculated, along with the 95% CI. Publication bias was assessed using a funnel plot and Begg and Mazumdar’s test.

How were differences between studies investigated?
Statistical heterogeneity was assessed using the Mantel-Haenszel method. Sensitivity analyses were used to examine the influence of the radiographic progression scoring method (Larsen versus Sharp), study quality, annual progression rate at baseline, disease duration at baseline and delay before the start of DMARD. The analysis was repeated including all possible studies to assess the review’s exclusion criteria.

**Results of the review**

Twelve studies (n=1,188 in the tables; n=1,133 in the text) were included: 6 follow-up studies of RCTs (n=630) and 6 cohort studies (n=558).

The quality scores ranged from 2 to 5 out of 6 points.

There were no significant differences between early and delayed DMARD treatment in either the follow-up of RCTs (SMD -0.18, 95% CI: -0.39, 0.02) or cohort studies (SMD -0.21, 95% CI: -0.48, 0.06). There was no statistically significant difference in the results between study designs (p=0.89).

For all studies combined, early DMARD treatment was associated with a significant reduction in long-term radiographic progression compared with delayed treatment (SMD -0.19, 95% CI: -0.34, -0.04). Some heterogeneity was found (p=0.16). The exclusion of one study removed the heterogeneity without significantly affecting the pooled results.

There was no evidence of publication bias from the funnel plot or Begg’s test (p=0.27).

The benefits of early DMARD therapy appeared to be greater in patients with more aggressive disease (higher estimated rates of progression at baseline, p=0.04).

**Authors’ conclusions**

Starting DMARDs early in the course of rheumatoid arthritis may reduce long-term joint damage.

**CRD commentary**

The review addressed a clear question that was defined in terms of the participants, intervention, outcomes and study design. Several relevant sources were searched and attempts were made to minimise publication and language bias. In addition, the potential for publication bias was assessed and no evidence of it was found. Appropriate methods were used to minimise reviewer error and bias in the assessment of validity and extraction of data, but it is not clear whether similar steps were taken at the study selection stage. Validity was assessed using specified criteria but only the composite score was presented, making it difficult to independently comment on the reliability of the evidence presented. In addition, the assessment was limited. Statistical heterogeneity was assessed, the studies were appropriately combined in a meta-analysis, and the influence of various factors was examined. Overall, this was a well-conducted review and the authors’ cautious conclusion appears to reflect the evidence from studies of limited quality.

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

Practice: The authors stated that physicians and patients should be aware that it is important to start treatment with
DMARDs early in aggressive rheumatoid arthritis in order to minimise the period between the onset of rheumatoid arthritis and the start of treatment.

Research: The authors stated that further research is necessary given the limitations in quality of the available data.

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