Commentary

# Evidence for early disease-modifying drugs in rheumatoid arthritis

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Received: 6 Oct 2003 Accepted: 6 Nov 2003 Published: 16 Dec 2003

*Arthritis Res Ther* 2004, **6**:15-18 (DOI 10.1186/ar1030)


## Abstract

Some research evidence supports early aggressive treatment of rheumatoid arthritis (RA) using combination therapy with two or more disease modifying anti-rheumatic drugs (DMARDs) plus steroids, or even DMARDs plus an anti-TNF. By contrast, conservatively delayed DMARD monotherapy, given after non-steroidal anti-inflammatory drugs have failed, has been criticised. However, recent long-term studies highlight the complexities in evaluating whether to abandon pyramidal treatment in favour of early DMARDs. Although patients given early DMARD therapy show short-term benefits, longer-term results show no prolonged clinical advantages from early DMARDs. By 5 years patients receiving early DMARDs had similar disease activity and comparable health assessment questionnaire scores to patients who received DMARDs later in their disease course. X-ray progression was persistent and virtually identical in both groups. These negative findings do not invalidate the case for early DMARD therapy, as it is gives sustained reductions in disease activity in the early years of treatment without excessive risks from adverse effects. However, early DMARDs alone do not adequately control RA in the longer term. This may require starting with very aggressive therapy or treating patients more aggressively after early DMARD therapy has been initiated.

## Introduction

The optimal treatment for early rheumatoid arthritis (RA) remains the subject of intense debate. There are many options. There is some support for aggressive treatment by immediately starting combination therapy with two or more disease-modifying antirheumatic drugs (DMARDs) plus steroids, or even with DMARDs plus antitumour necrosis factor (anti-TNF). The most conservative alternative involves initially using nonsteroidal anti-inflammatory drugs (NSAIDs), only starting DMARD monotherapy if this proves insufficient. The value of this latter therapeutic pyramid has been questioned for many years [1]. Current opinion favours early DMARD therapy [2]. A recent report by Verstappen and colleagues [3] focused attention on the complexities in evaluating whether to abandon the pyramidal approach to treatment and to focus on starting DMARDs early.

Observational studies provide an opportunity to explore the benefits of early DMARDs. The Norfolk Arthritis Register, a large observational study in early arthritis, enrols cases of early polyarthritis from one area of England. A recent report from the register evaluated DMARD therapy in 353 consecutive RA patients followed for 5 years [4]. As patients with mild arthritis inevitably have good outcomes without DMARDs, statistical adjustment was essential to control for disease severity. Although patients who received DMARDs had more radiographic progression, this was related to their high initial disease severity. After adjusting for baseline severity, early DMARD therapy in severe RA gave the most beneficial outcomes at 5 years.

Evidence from randomised controlled trials (RCTs) supports these observational findings. Early treatment with

anti-TNF = antitumour necrosis factor; ASPIRE = Active Controlled Study of Patients Receiving Infliximab for Treatment of Rheumatoid Arthritis of Early Onset; COBRA = Combinatietherapie Bij Reumatoide Artritis; DMARD = disease modifying antirheumatic drug; FIN-RACo = Finnish Rheumatoid Arthritis Combination; NSAID = nonsteroidal anti-inflammatory drug; RA = rheumatoid arthritis; RCT = randomised controlled trial.

sulphasalazine reduces disease activity and X-ray progression over 12 months compared with persisting with NSAIDs alone [5]. As a relatively potent DMARD, sulphasalazine is also more effective than a 'weaker' DMARD such as hydroxychloroquine in limiting the X-ray progression in early RA [6]. Benefits from early DMARD therapy extend over 5 years. Borg and colleagues [7] compared early treatment with a weak DMARD (auranofin) against a wait-and-see policy in 137 patients with early RA. After 2 years there was convincing evidence favouring early DMARD therapy. A subsequent review of 75 of these patients after 5 years [8] showed continuing benefits from early DMARD therapy on clinical and radiological outcomes. A comparable study [9] evaluated 104 of 119 patients who had participated in a 9-month RCT of hydroxychloroquine versus placebo in early RA. Three years after the study ended, early DMARD therapy still resulted in less pain and disability.

The report by Verstappen and colleagues [3] shows that the situation is very complex. The report outlined 5-year follow-up results from an earlier trial involving 238 patients with recently diagnosed RA. The minority of cases had been randomised to pyramid treatment, receiving NSAIDs for at least 12 months and waiting an average of 14 months before starting DMARDs. The majority were randomised to receive early DMARDs. Five-year results in 44 patients given pyramid treatment and in 145 patients given early DMARDs, however, showed no prolonged clinical advantages from early DMARDs. In the first 12 months there had been many advantages from early DMARDs; most clinical variables showed better responses. These benefits were reported in an initial paper [10], which provided strong support for early DMARD therapy. Nevertheless, the benefits of early DMARDs became less obvious with time. By 5 years patients receiving early DMARDs had similar disease activity and comparable health assessment questionnaire scores with patients who received DMARDs later in their disease course. X-ray progression was persistent and virtually identical in both groups.

Such negative results do not weaken the case for early DMARD therapy. Patients receiving early DMARDs benefited from sustained reductions in disease activity in the early years of treatment without excessive risks from adverse effects. However, early DMARDs alone do not adequately control RA in the longer term. Two alternative strategies may be needed. First, starting with more aggressive therapy and, second, treating patients more aggressively after early DMARD therapy has been initiated.

More aggressive initial therapy may involve adding low-dose steroids, using combination DMARDs and the early use of biologics. The early use of low-dose steroids is very controversial. Two RCTs have addressed this question. The Arthritis Research Council steroid study [11] showed that adding low-dose steroids to DMARDs reduced the subsequent X-ray progression. van Everdingen and colleagues [12] enrolled 81 patients with early active RA who had not been treated with DMARDs. Patients received 10 mg/day oral prednisone or placebo. After 6 months sulphasalazine could be prescribed as rescue medication. Radiological scores after 6 months showed significantly less progression with prednisone compared with placebo without major side effects from steroids.

Although such benefits from low-dose steroids meant that some experts believe they should become standard treatment [13], other experts disagree [14]. The issue is made more complex by the potential role of high-dose step-down steroid therapy used in combination studies (discussed later). Interestingly, an analysis of the cost-effectiveness of low-dose steroids in RA concluded that their use was economically favourable [15].

The next question is whether to use one DMARD or several DMARDs in early RA. The COBRA (Combinatietherapie Bij Reumatoide Artritis) study [16] compared sulphasalazine monotherapy with the combination of sulphasalazine, methotrexate and prednisolone (tapered from 60 mg/day to 7.5 mg/day over 9 months and then stopped) in 155 patients with early RA. By 6 months 72% of patients on combination therapy had ACR-20 responses compared with 49% of patients on monotherapy, and median X-ray damage had increased by 1 Sharp unit with combined therapy and by 4 Sharp units with monotherapy. Five years later the benefits of combination therapy on joint damage persisted [17]. After adjusting for treatment and disease activity during follow-up, the between-group difference in radiological progression (3.7 points/year) still favoured combination therapy. Economic analysis also showed that the COBRA study was cost-effective [18].

Another RCT, the FIN-RACo (Finnish Rheumatoid Arthritis Combination) trial, also favoured combination therapy in early RA [19]. It compared combination therapy (sulphasalazine, methotrexate, hydroxychloroquine and prednisolone) with DMARD monotherapy (with or without prednisolone) in 199 patients over 2 years. At 12 months, 24 of 97 patients achieved remission with combination therapy but only 11 of 98 patients achieved remission with monotherapy. Remission remained more frequent with combination therapy at 2 years. Subsequent analyses found that delaying DMARD therapy by only a few months decreased the ability of the monotherapy to induce remission [20]. The benefits of combination therapy were unaffected by delay.

Not all trials of early combination DMARDs are positive. Haagsma and colleagues [21] found that combination therapy was no more effective than monotherapy with sul-

phasalazine or methotrexate in 105 patients with early RA. Dougados and colleagues [22] also found no benefit from combining methotrexate and sulphasalazine in 205 patients with active RA. A 5-year review of these cases also showed no benefits from combination DMARDs [23]. RCTs with cyclosporin as part of a DMARD combination in early RA have also given equivocal [24] or negative [25] results, although these latter studies were relatively small.

The final approach to early aggressive treatment is to use biologics. The only published evidence for biologics is from the early RA trial of etanercept, which showed that this biologic is more effective than methotrexate over 2 years in reducing X-ray progression and in controlling symptoms [26]. More impressive results are likely from combining anti-TNF therapy with methotrexate. Unpublished data from a RCT combining infliximab with methotrexate, presented at the European League Against Rheumatism congress (the ASPIRE [Active Controlled Study of Patients Receiving Infliximab for Treatment of Rheumatoid Arthritis of Early Onset] trial), strongly suggests this will be the case. Preliminary data from the ASPIRE trial indicate that patients treated with infliximab plus methotrexate had no X-ray progression and had markedly less disability than patients receiving methotrexate monotherapy.

There is similar unpublished data with other anti-TNF drugs. The implication is that excellent short-term outcomes can be achieved by treating all early RA patients with a combination of methotrexate and anti-TNF. However, before introducing such a policy in routine practice, several questions need to be addressed. The short-term benefits of combination therapy with biologics may not last and, as with the report from Verstappen and colleagues [3], initial good results may not give long-term benefits. Another problem is that many patients with early RA may not need aggressive treatment. Observational studies and RCTs in early RA invariably identify cohorts of patients with mild disease that respond well to NSAIDs alone. The blanket use of DMARD/biologic combinations would expose such mild cases to prolonged courses of highly active drugs. An added difficulty is the high cost of biologics, which may mean that their widespread use cannot be economically justified.

An alternative assessment of the results reported by Verstappen and colleagues [3] is that early DMARDs are useful in the short term, but that in the medium term more aggressive treatment is needed in some patients. There is a relative dearth of information on this issue, although one RCT (Tight Control of Rheumatoid Arthritis, C Grigor and colleagues) presented at The British Society for Rheumatology meeting, 2003, and not yet published suggests that adding DMARDs sequentially to obtain tight control of RA is practical and effective. It seems most logical to treat some patients with early RA with NSAIDs alone, to treat some patients with DMARD monotherapy, to treat some patients with DMARD combination therapy and to treat some patients with DMARDs and biologics. Although treating all patients with DMARDs and biologics may seem better than other choices over 12–24 months, the gradual addition of drugs in an organised manner over 5 years may be equally clinically effective and will be substantially more cost-effective. Providing answers to such complex questions will take many years, and it is likely to remain an area of research endeavour for the foreseeable future.

## Competing interests

None declared.

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