Effective treatment of early rheumatoid arthritis with a combination of methotrexate, prednisolone and cyclosporin

SIR, In active rheumatoid arthritis (RA) the greatest increase in joint destruction is found in the first and second years of the disease course [1]. Therefore, it has become a primary goal to suppress and even stop inflammation in RA as early as possible [2]. Methotrexate (MTX) is currently regarded as the disease-modifying anti-rheumatic drug (DMARD) with the best efficacy in relation to its toxicity. However, in about half of all RA patients MTX does not suppress inflammation sufficiently. In these patients, combinations of different DMARDs and combinations of DMARDs with glucocorticoids are used increasingly and successfully [3–5]. The aim of our study was to assess the efficacy of adding cyclosporin A (Cs) to the treatment of early RA patients without previous DMARD or steroid treatment who did not respond sufficiently to a high dose of parenteral MTX combined with a moderate dose of glucocorticoids given for 8 weeks.

Twenty-six patients (17 females, nine males; mean age 46 yr, range 41–74 yr; 58% were positive for rheumatoid factor) fulfilling the American College of Rheumatology criteria for RA [6] with a disease duration of less than 2 yr (median disease duration 11 months, range 3–23 months) were treated daily for 8 weeks with MTX 15 mg intramuscularly and oral prednisolone (Pred) 20 mg initially, the dose being tapered to 5 mg over the 8-week period. The modified disease activity score (DAS) (28-joint count) was used to monitor disease activity [7]. All patients had active disease at study entry, as indicated by a DAS >4 [mean (s.d.) DAS 6.21 (0.81)].

Thirteen of the 26 patients (50%) responded to 15 mg MTX in combination with steroid treatment after 8 weeks. In these 13 patients, the DAS declined significantly from a pretreatment value [mean (s.d.)] of 6.17 (0.88) to 2.48 (0.80) \((P < 0.001; \text{Mann–Whitney } U\text{-test})\) 6 months after the start of the study (Fig. 1A). No significant improvement was found in the placebo group [DAS before treatment 5.6 (0.9), after treatment 5.1 (1.3)] (Fig. 1B). When the differences before and after treatment were compared between the two groups, the Cs group showed a significantly greater change (decrease of 2.2 in DAS) than the placebo group (decrease of 0.5) \((P < 0.05; t\text{-test})\).

![Fig. 1. DAS before and after 3 months of treatment with additional Cs (A) or (B) placebo in individual patients not responding to MTX/Pred treatment alone.](attachment:image1.png)
The most important result of this study was that about 85% of the patients with early active RA showed an acceptable response to treatment in the first 4–6 months if they were treated aggressively enough. Half of the patients responded to a combination of a relatively high parenteral dose of MTX plus Pred and about a further 25% of patients showed a response to additional Cs if MTX/Pred alone failed.

There are few reports on the aggressive treatment of RA patients with early disease [8–10]. To control disease activity effectively, combination therapy has been used both as a step-up [3] and a step-down [8] treatment. In our study, we started with a high dose of MTX and used it in combination with a steroid; steroids have an immediate effect and are regarded as bridging therapy. Disease activity was reduced in about 50% of our patients with early RA, from DAS 6.17 to 2.48, which comes close to remission. Thus, 50% of the patients would have been overtreated if they had been started with a step-down protocol.

To avoid delay in the suppression of inflammation, Cs was added after 8 weeks in patients in whom treatment had failed. Cs has been used in previous combination treatment studies only in patients with long-standing RA [3]. Our study investigated for the first time the application of Cs in a step-up protocol for patients with early RA. Although the two groups who failed to respond to MTX/Pred alone contained only small numbers of patients, our data indicate that such an approach can be used and is effective. The main side-effects of Cs treatment are arterial hypertension and deterioration of renal function. In our study only one patient had to stop Cs treatment because of hypertension. No other side-effects were observed.

Recently, it has been demonstrated that the new biologicals that inhibit TNF-α can stop the progression of disease nearly completely [11]. However, the general use of such treatments is hampered both by their high cost and by lack of knowledge about long-term side-effects. Therefore other, cheaper treatments have to be used as the first-line therapy, and only if they fail does the use of anti-TNF-α seem to be justified at present. The treatment protocol investigated in this study is one option.


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