

## CONCISE REPORTS

## Methotrexate treatment of rheumatoid arthritis: is a fortnightly maintenance schedule enough?

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### Abstract

In 15 patients with rheumatoid arthritis who were in clinical remission the weekly regimen of methotrexate treatment was changed to fortnightly without a change in dose. A total of 13 patients completed a 12 month trial. No change in clinical or laboratory parameters occurred. There was no change in the use of analgesics or non-steroidal anti-inflammatory drugs and the patients remained in remission. Two patients had to be withdrawn after two and four months respectively because of a flare in disease activity. It is suggested that in most patients with rheumatoid arthritis who are treated with methotrexate and whose disease activity is stable a fortnightly regimen can be permitted without affecting drug efficacy.

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Low dose pulse methotrexate has been established in the last decade as an effective drug in the treatment of rheumatoid arthritis (RA). Long term studies have demonstrated both its sustained efficacy and its acceptable toxicity profile.<sup>1-4</sup> The drug is usually given weekly and previous experience has shown that when methotrexate is discontinued, even after prolonged treatment, a flare of arthritis activity occurs.<sup>5</sup> The purpose of this study was to determine whether patients with RA who are treated with methotrexate and who are in remission could be changed from a weekly to a fortnightly treatment regimen similar to the schedule used in gold injections.<sup>6</sup>

### Patients and methods

#### PATIENTS

The study group comprised 15 patients with RA, all fulfilling the criteria of the American College of Rheumatology, who were treated with methotrexate. These patients are among the cohort of patients prospectively followed up by the authors to determine the efficacy and toxicity of methotrexate in patients with RA and who were the subjects of a previous report.<sup>7</sup> Patients chosen for this study were those in whom the disease was stable for the six months before the start of the trial (a stable methotrexate weekly dosage, up to four tender joints, no non-steroidal anti-inflammatory drugs (NSAIDs) or steroid adjunct treatment). All

patients had radiographic erosions but none had any signs of extra-articular disease. Table 1 summarizes the clinical characteristics of the patients.

#### STUDY DESIGN

Patients were evaluated by the same doctor before changing the methotrexate schedule and during the study period. The dose of methotrexate was kept unchanged but the schedule was changed from a weekly oral pulse to a fortnightly one. All patients gave informed consent before entering the study. All patients were seen every four to six weeks for evaluation of toxicity, and laboratory and clinical assessment. Clinical evaluation recorded at the baseline visit and every 3 months thereafter consisted of the duration of morning stiffness, the Ritchie index, mean grip strength, and the doctor's and patient's global assessment of pain and disease activity, which were graded as 1 (severe), 2 (moderate), 3 (mild), and 4 (asymptomatic).

Laboratory tests performed included complete blood counts, serum creatinine, alkaline phosphatase, albumin and transaminase levels, erythrocyte sedimentation rate and C reactive protein levels. The use of NSAIDs and analgesics was carefully monitored at each visit. A precondition for restoring the previous once a week schedule after change of the methotrexate regimen was arthritis flare.

#### STATISTICAL ANALYSIS

Differences between means were determined using a *t* test for paired differences; *p* values of less than 0.05 were considered to be significant.

### Results

Thirteen of the 15 patients completed the 12

Table 1 Clinical characteristics of patients treated with fortnightly methotrexate. Values for age, disease duration, and duration of methotrexate treatment are means (SD)

Age (years)	57.3 (6.8)
Male/female ratio	3/12
Disease duration (years)	7.4 (2.1)
Duration of methotrexate treatment before changing schedule (months)	36.4 (8.2)
Methotrexate weekly dosage (mg)	7.7 (2.3)
Seropositive	12/15
Use of other remittive agents before methotrexate	
Gold	13/15
Sulphasalazine	6/15
Penicillamine	7/15

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Table 2 Clinical and laboratory parameters of 13 patients taking methotrexate fortnightly. Values are means (SD)

	Before methotrexate treatment	Biweekly methotrexate schedule			
		Baseline	Three months	Six months	12 months
Erythrocyte sedimentation rate (mm/h)	65.2 (15.7)	27.3 (5.7)	26.1 (4.2)	24.3 (6.1)	25.2 (7.2)
Haemoglobin (g/l)	108 (8)	118 (5)	121 (4)	120 (5)	119 (4)
Ritchie index	35 (8)	2.1 (0.5)	1.8 (0.4)	2.3 (0.6)	2.2 (0.5)
Grip strength (mmHg)	65 (15)	115 (37)	121 (40)	117 (41)	123 (38)
Patients' global assessment	1.7 (0.6)	3.4 (0.3)	3.3 (0.3)	3.5 (0.2)	3.4 (0.3)
Doctor's global assessment	1.8 (0.5)	3.4 (0.2)	3.5 (0.3)	3.4 (0.3)	3.5 (0.3)

Significance level for all parameters before treatment versus baseline is  $p < 0.05$ . All parameters from baseline to 12 months are non-significant.

month trial. In two patients a flare of arthritis activity, consisting of joint pain and a rise in the erythrocyte sedimentation rate, occurred at two and four months respectively after changing the methotrexate schedule to a fortnightly dose. Reinstitution of weekly methotrexate treatment resulted in control of disease activity. In the 13 patients who were followed up for 12 months there was no deterioration in the beneficial effect of methotrexate after changing the schedule of the drug. Table 2 presents the clinical and laboratory findings. No differences in laboratory and clinical parameters were noted 12 months after changing methotrexate to a fortnightly schedule. There was no increase in the use of analgesics or NSAIDs during the study period and all 13 patients sustained a stable disease course.

### Discussion

Among the disease modifying drugs currently used for the treatment of RA, methotrexate appears to have one of the most favourable combinations of efficacy and safety. In the 1960s, it was used in a daily regimen of 2.5 mg, to treat patients with psoriasis and polyarthritis. The potential complications revealed in this schedule encouraged several prospective studies, which noted that a weekly low dose pulse of methotrexate was markedly less toxic and caused less hepatotoxicity in patients with psoriasis.<sup>8</sup> This regimen was later accepted by rheumatologists and was used to treat severe RA that was unresponsive to other disease modifying drugs.<sup>1-4</sup> An attempt to discontinue methotrexate after more than 40 months of treatment resulted in a rapid flare of disease in all patients within one month after stopping treatment.<sup>5</sup> By contrast, gold injections are given weekly at a dose of up to 1 g and are continued as 'maintenance' treatment every two, three and four weeks thereafter.<sup>6</sup> Bearing this regimen in mind, we studied the application of a similar schedule of methotrexate treatment in patients with RA in whom the disease was in clinical remission. In 13 of the 15 patients, pulse methotrexate was continued biweekly without any change in the clinical and laboratory

parameters, reflecting no change in disease activity. This was achieved with the same dose of methotrexate that had been used weekly by these patients and without changes in their consumption of NSAIDs or analgesics. Only two patients had a flare of their disease activity and resumption of the weekly schedule of methotrexate suppressed the inflammatory signs.

Our preliminary results suggest that in most patients treated with methotrexate in whom disease activity is well controlled it is possible to change the drug schedule. The advantage of using a fortnightly regimen without affecting methotrexate efficacy is double. Besides the cost effectiveness and the convenience for the patient, there is the possibility of reducing late side effects. Several studies have shown that the cumulative dose of methotrexate correlates with liver fibrosis.<sup>9,10</sup> Further controlled studies with a larger group of patients followed up for a longer period are needed to confirm this observation.

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