

Reappraisal of the Effectiveness of Methotrexate in Psoriatic Arthritis: Results from a Longitudinal Observational Cohort

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ABSTRACT. *Objective.* In a previous study in our clinic, methotrexate (MTX) conferred no advantage with respect to clinical response or progression of damage after 24 months in patients with psoriatic arthritis (PsA). Our aim was to determine if MTX is being used earlier in the course of PsA and in a higher dose and whether that has led to improved outcomes.

Methods. All patients treated with MTX for at least 24 months in our clinic, between 1994 and 2004, were included in the study. The outcome measures were the progression of radiographic peripheral joint damage score and a $\geq 40\%$ reduction in the number of actively inflamed joints. The data from our study were compared to those obtained from our previous study.

Results. Fifty-nine patients (36 men) treated with MTX for 24 months were identified. The mean age was 46 years, PsA duration 8 years, and active joint count 12.1 (4.6 swollen). The mean increase in radiographic damage score was 1.5. Sixty-eight percent of patients demonstrated improvement at 24 months. When compared to our previous study, there was a trend for MTX to be used earlier, at a higher dose, with greater clinical improvement and less progression of damage.

Conclusion. Our study suggests that treatment with MTX has changed in the past decade to include patients with shorter disease duration and less damage, at increased dose, and that there may be better response with less progression of damage. (First Release Dec 15 2007; J Rheumatol 2008;35:469–71)

Key Indexing Terms:

PSORIASIS

ANTIRHEUMATIC AGENTS

METHOTREXATE

Psoriatic arthritis (PsA) is an inflammatory arthritis associated with psoriasis, usually seronegative for rheumatoid factor¹. Methotrexate (MTX) is the most widely used disease modifying antirheumatic drug (DMARD) in PsA. There are only 2 randomized controlled trials comparing MTX to placebo in PsA^{2,3}. A controlled study done in our clinic more than a decade ago suggested that compared to other regimens, MTX conferred no advantage with respect to clinical response or longterm damage even after 24 months of therapy⁴. However, patients had long disease duration and high baseline radiographic damage score. The dose of MTX used (10.6 mg/wk)

was low by current standards⁴. Since then we have tended to use MTX earlier and at a higher dose. We therefore decided to reappraise the effectiveness of MTX use in our clinic, to determine whether we have indeed been using MTX earlier and at a higher dosage than previously, and if so, whether it has led to improved radiological and clinical outcomes.

MATERIALS AND METHODS

Our study was conducted at the University of Toronto PsA Clinic. Patients are evaluated using a standard protocol every 6–12 months. A detailed description of the protocol has been reported⁵. Methods used in the clinic have been found to be reliable^{6,7}. All patients treated with MTX (either orally or by subcutaneous injection) for at least 2 years between January 1994 and December 2004 were identified from the database. Patients treated prior to 1994 and those treated with MTX prior to clinic entry were excluded. The data were censored when the patient was treated with a biologic agent. The maximum dose of MTX used was recorded. Concomitant DMARD were allowed. The primary outcome measure was increase in radiographic damage score as assessed by the modified Steinbrocker method previously validated in our clinic⁷. Briefly, each joint is scored 1 = normal (with possible soft tissue swelling); 2 = surface or pocket erosions; 3 = erosion and joint space narrowing; or 4 = disorganization (including ankylosis, pencil-in-cup change, or total joint destruction) or as having required surgery. This method has proven reliable in our clinic in terms of both inter- and intraobserver agreement (< 2% variation) and sensitivity to change over time⁷. Actively inflamed joints were defined by the presence of joint effusion and/or joint line tenderness and/or stress pain. As in our previous study, a $\geq 40\%$ reduction in the number of actively inflamed joints (American College of Rheumatology 68/66 tender/swollen) was used as the outcome measure for joint inflammation⁴. Clinical damage was defined as any joint with limited movement > 20% of its

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normal range, not due to effusion (including subluxation and flexion contractures), joint ankylosis, flail joint, or surgery. Psoriasis was assessed by the Psoriasis Area and Severity Index (PASI)⁸. Descriptive statistics was used to describe the study patients. The response to MTX was determined using paired t-test and chi-squared test. The results were compared to those obtained from our previous study⁴.

RESULTS

Fifty-nine patients fulfilled the study criteria. Their mean [\pm standard deviation (SD)] age was 46 (11.6) years, mean duration of psoriasis was 13 (10) years, and mean duration of PsA was 8 (7.9) years. At baseline, they had a mean actively inflamed joint count of 12.1 (8.2), swollen joint count of 4.6 (4.1), clinically damaged joint count of 3.4 (8.8), radiographic damage score of 5.1 (7.7), and mean PASI score of 7.5 (10.2). The mean dose of MTX used was 16.2 mg/week. MTX was used in combination with other drugs in 18 patients (9 with sulfasalazine, 8 with chloroquine, and 1 with gold). Concomitant prednisone was given to 2 patients. At 24 months the mean (\pm SD) progression in radiographic damage score was 1.5 (1.8). Sixty-eight percent of patients had a $\geq 40\%$ decrease in actively inflamed joint count and 66% of patients had a $\geq 40\%$ decrease in swollen joint count. Fifty-seven percent of patients had a PASI50 response. The mean (\pm SD) reductions in actively inflamed joint count and swollen joint count were 7.1 (7.7) and 2.8 (3.0), respectively ($p < 0.001$ compared to baseline). The mean (\pm SD) increase in clinically damaged joint count was 1.9 (3.3). Among the responders, 65% had achieved the response criteria by 6 months and 84% by 12 months. Among the nonresponders, only 18% had at least 20% reduction in actively inflamed joint count at any timepoint. There was no statistically significant difference in the highest dose of MTX used, use of concomitant DMARD, swollen joint count, clinically damaged joint count, or PASI score between the responders and nonresponders at baseline, although responders had higher actively inflamed joint counts (13.5 vs 7.5; $p = 0.0018$). Comparison with our previous study showed no statistically significant difference between the 2 time periods. However, in the period 1994-2004, MTX was used earlier in the disease course (less disease duration, less radiographic damage), with a higher average weekly dose, leading to better clinical response and slower radiographic progression (Table 1).

DISCUSSION

Previous studies have documented the beneficial effects of MTX in PsA^{2,3,9-11}. However, a controlled study done in our clinic earlier suggested that compared to other regimens, MTX conferred no advantage with respect to clinical response or longterm damage even after 24 months of therapy⁴. The current study was done to reappraise the effectiveness of MTX in our clinic. Our results indicate that regular use of MTX for at least 24 months leads to significant decline in the actively inflamed joint count compared to baseline, with $\geq 40\%$ reduction in actively inflamed joint count in 68% of

Table 1. Comparison between the results of our study and that conducted between 1978 and 1993.

Characteristics	1978–1993	1994–2004
No. of patients	19	59
Mean disease duration, yrs	11.5 \pm 11.6	8.0 \pm 7.9
Methotrexate dose, mg/wk	10.8	16.2
Baseline		
Actively inflamed joint count	13.7 \pm 9.1	12.1 \pm 8.2
Radiographic damage	8.0 \pm 12.2	5.1 \pm 7.7
At 24 months		
$\geq 40\%$ reduction in joint counts, %	47	68
Radiographic progression	2.3 \pm 1.2	1.5 \pm 1.8

patients, and significant decline in the psoriasis compared to baseline, with 57% achieving a PASI50 response. In the responders, the response was achieved in the majority within 6 months, and this was sustained at 12 and 24 months. Only 18% of nonresponders achieved at least 20% reduction in actively inflamed joint count. However, there still was progression in clinical and radiographic damage. In the past decade, we have used a higher average weekly dose of MTX earlier in the disease course, and the rate of radiographic progression was lower. Statistical significance could not be demonstrated primarily because of the low numbers of patients in the previous study⁴.

The strength of our study is that the response to a prolonged course of MTX was demonstrated in a “real life” scenario and radiographic progression was evaluated by a validated method. However, it has some limitations. There is no control group, because no group with active disease not treated with DMARD could be identified from the database. Standard outcome measures like ACR20¹², EULAR response criteria¹³, or Psoriatic Arthritis Response Criteria (PsARC)¹⁴ were not used to assess clinical response to MTX. Complete data to assess such response were not available at each timepoint. We used a $\geq 40\%$ decrease in joint counts as an outcome measure so that the results could be compared with those obtained in our previous study⁴. Since only those patients who continued treatment with MTX for 24 months were analyzed, we excluded patients who stopped treatment before 24 months due to side effects or lack of efficacy. Thus the results are biased towards a better response to MTX. However, since the primary outcome considered was radiological progression in patients taking MTX for 24 months, results of our study remain valid.

Interestingly, we show that 32% of patients continued to be treated with MTX for at least 2 years in spite of not achieving $\geq 40\%$ decrease in joint counts. Indeed, only 18% of patients in this group achieved at least 20% reduction in actively inflamed joint count. Moreover, 43% of patients did not achieve a PASI50 response. Why these patients were continued on MTX for 24 months with no objective evidence of improvement is not clear. Perhaps the patient and the physician felt that there was some benefit, but what that benefit

was, is not clear from data available. The patients may have improved subjectively, which was not determined in our study, since patient-reported outcomes were not studied. Lack of other more effective treatment options may have been one of the reasons, since the study largely involved patients treated in the pre-biologic era.

Our study demonstrates that in the past 10 years, we have been using MTX earlier in the disease course with a higher dose and this has led to better outcomes. There is now a need to reevaluate the proper role of MTX in PsA with regard to newer biologic agents, especially in early disease.

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