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METHOTREXATE IN RHEUMATOID ARTHRITIS

A Five-Year Prospective Multicenter Study

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Objective. **To evaluate the efficacy and tolerability of oral methotrexate (MTX) in rheumatoid arthritis (RA) in a long-term prospective trial.**

Methods. **One hundred twenty-three patients with RA who completed a 9-month multicenter randomized trial comparing MTX and auranofin enrolled in this 5-year prospective study of MTX.**

Results. **Significant ($P = 0.0001$) improvement compared with baseline was noted in all clinical disease variables, functional status, and the Westergren erythrocyte sedimentation rate (ESR). "Marked improvement" occurred in 87 (71%) and 85 (69%) of the patients, respectively, in the joint pain/tenderness index and the joint swelling index at the last evaluable visit. Forty-four patients (36%) withdrew during the study. Eight (7%) withdrew due to lack of efficacy, and 8 (7%) due to adverse experiences, including 1 patient with cirrhosis. At 5 years, 64% of patients were still taking MTX and completed the study.**

Conclusion. **This large prospective study of long-term MTX treatment demonstrates sustained clinical response and improvement in the Westergren ESR and functional assessment scores, with an acceptable toxicity profile.**

Small long-term prospective studies of low-dose methotrexate (MTX) have demonstrated sustained clinical response in patients with active rheumatoid arthritis (RA) (1,2). The patients in these studies had had either lack of response to, or intolerable side effects with, standard second-line therapies including gold salts. Reported herein are the findings of a 5-year prospective study of MTX treatment in 123 patients who had not received prior gold salt therapy.

PATIENTS AND METHODS

One hundred twenty-three patients with RA who had successfully completed a 9-month multicenter randomized trial comparing MTX and auranofin (3) enrolled in a 5-year open study of MTX. Patients were not eligible to enroll in the initial randomized trial (3) if they had ever received therapy with gold salts, D-penicillamine, MTX, or azathioprine. Patients were allowed to continue, if needed, treatment with aspirin or another nonsteroidal antiinflammatory drug and/or prednisone at a dosage not to exceed 10 mg/day. MTX tablets (2.5 mg) were ingested once a week. During the open study, adjustments in the MTX dosage were allowed; the maximum dosage was 20 mg/week. Clinical evaluations were performed every 12 weeks and included determinations of the number of painful joints, number of swollen joints, joint tenderness/pain index, joint swelling index, duration of morning stiffness, and patient and physician global assessments (3). A modified Stanford Health Assessment Questionnaire (MHAQ) (4) was completed at baseline, yearly, and at the last study visit.

Overall response to treatment was designated using the following arbitrary criteria: 1) Therapeutic remission, defined by the preliminary criteria of the American College

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Table 1. Demographic and clinical characteristics of the 123 rheumatoid arthritis patients studied

No. from MTX group/no. from AUR group*	89/34
Age, years	
Mean ± SEM	51.6 ± 1.0
Range	26–81
Disease duration, months	
Mean ± SEM	76 ± 9.7
Median	30
Range	6–612
No. (%) receiving prednisone (≤10 mg/day)	27 (22)
No. (%) rheumatoid factor positive	95 (77)

* Patients had previously been enrolled in a 36-week randomized trial comparing methotrexate (MTX) and auranofin (AUR) (ref. 3).

of Rheumatology (ACR; formerly, the American Rheumatism Association) (5); 2) Marked improvement in the joint swelling index and the joint tenderness/pain index, defined as a decrease of >50% in the values determined in the open study compared with values at baseline; 3) Improvement in physician and patient assessments of disease activity representing changes of at least 2 integers in the 0–4 scale, or from mild to asymptomatic; and 4) Paulus criteria for response, defined as improvement in 4 of 6 selected parameters (6) (improvement defined as ≥20% improvement in morning stiffness, joint pain/tenderness index, joint swelling index, and Westergren erythrocyte sedimentation rate [ESR] and ≥2-grade improvement in physician global and patient assessments).

Every 4 weeks for the first 12 months of the study, and every 6 weeks thereafter, a complete blood cell count

Table 2. Changes in clinical and laboratory parameters over the 60 months of the study*

Parameter, visit (month)	n	Mean value at baseline visit	Mean value	Mean ± SEM change	P†	95% CI
No. of painful joints						
12	120	22.03	8.63	13.40 ± 1.11	0.0001	10.61–16.19
24	109	21.90	6.06	15.84 ± 1.19	0.0001	13.24–18.44
36	98	21.41	6.78	14.63 ± 1.12	0.0001	11.85–17.41
48	88	21.23	5.90	15.33 ± 1.29	0.0001	12.50–18.15
60	70	21.44	7.87	13.57 ± 1.51	0.0001	10.22–16.91
No. of swollen joints						
12	120	18.61	6.67	11.93 ± 0.99	0.0001	9.52–14.34
24	109	18.14	5.37	12.77 ± 1.07	0.0001	10.42–15.12
36	98	17.59	5.05	12.54 ± 1.02	0.0001	10.13–14.95
48	88	17.93	5.48	12.45 ± 1.08	0.0001	10.04–14.87
60	70	18.23	6.56	11.67 ± 1.19	0.0001	9.05–14.28
Physician global assessment						
12	121	2.12	1.16	0.96 ± 0.06	0.0001	0.81–1.10
24	109	2.13	1.15	0.98 ± 0.08	0.0001	0.81–1.14
36	98	2.11	1.22	0.89 ± 0.08	0.0001	0.72–1.05
48	88	2.07	1.15	0.92 ± 0.08	0.0001	0.74–1.09
60	71	2.13	1.28	0.85 ± 0.09	0.0001	0.66–1.02
Patient global assessment						
12	121	2.27	1.19	1.08 ± 0.09	0.0001	0.89–1.27
24	109	2.27	1.29	0.97 ± 0.10	0.0001	0.76–1.18
36	98	2.22	1.35	0.88 ± 0.09	0.0001	0.67–1.08
48	88	2.17	1.30	0.88 ± 0.10	0.0001	0.65–1.10
60	71	2.21	1.44	0.77 ± 0.12	0.0001	0.53–1.02
ESR (mm/hour)						
6	119	41.91	26.36	15.55 ± 2.13	0.0001	11.37–19.72
12	119	42.01	27.34	14.67 ± 2.32	0.0001	8.26–21.08
24	109	42.83	24.58	18.25 ± 2.53	0.0001	11.91–24.58
36	99	41.60	23.77	17.83 ± 3.03	0.0001	10.77–24.87
48	87	40.60	24.43	16.17 ± 3.10	0.0001	9.06–23.28
60	66	41.83	21.98	19.85 ± 3.00	0.0001	12.10–27.59

* No. of painful joints is the number with tenderness on pressure and/or pain on passive motion of a possible 68. No. of swollen joints is the number of diarthroidial joints with swelling, of a possible 66. Physician and patient assessment of diasease activity is rated on a scale of 0–4, where 0 = asymptomatic, 1 = mild, 2 = moderate, 3 = severe, and 4 = very severe. ESR = erythrocyte sedimentation rate.

† Unadjusted for multiple tests. After correction for multiple tests (Bonferroni adjustment), $P = 0.0001$ becomes $P < 0.001$. CI = confidence interval.

was performed. Every 12 weeks, serum alkaline phosphatase, serum aspartate and alanine aminotransferase, total bilirubin, and serum albumin and creatinine levels and Westergren ESR were measured.

MTX was temporarily discontinued if the white blood cell (WBC) count decreased to <3,300/mm, the platelet count decreased to $<1.5 \times 10^5$/mm, the hepatic enzyme values increased to greater than twice the upper limit of normal, or a significant clinical adverse experience occurred. Abnormal findings that persisted longer than 3 weeks following discontinuation of MTX led to withdrawal from the study. Patients were also withdrawn from the study if the WBC count fell to <1,500/mm, the platelet count fell to $<1.0 \times 10^5$/mm, the serum creatinine level increased to >1.5 mg/dl, the hemoglobin and hematocrit values showed a progressive decline, or a serious adverse effect occurred.

Radiographs of the hands and wrists were obtained at baseline and after 18 months and 36 months of MTX therapy. A standardized protocol for obtaining and scoring these radiographs was used in this study (7), and radiographs were evaluated by 4 radiologists who were blinded with regard to their sequence.

A completer analysis was performed, in which disease variables were analyzed, by Student's 2-tailed *t*-test, for the significance of the difference in group means between the final study visit and the baseline visit for all patients who completed the study. The 4 primary disease variables were defined as the number of painful joints, number of swollen joints, and patient and physician global assessments. The baseline visit was defined as the visit immediately prior to initiation of MTX treatment. For those patients who received MTX in the randomized trial (3) and subsequently enrolled in the open study, the baseline visit was the initial visit in the randomized trial. For the patients who received auranofin in the randomized trial and subsequently enrolled in the open study of MTX, the baseline visit was the last visit in the auranofin study. We computed *P* values for the intermediate visits to indicate when changes were first apparent; however, these were considered to be of secondary importance. Efficacy parameters were also analyzed using an end-point analysis according to the intent-to-treat principle. The end point was defined as the 60-month visit in patients who completed the study and as the last visit in the study for patients who withdrew prior to study completion. Comparison between groups was done by chi-square analysis.

RESULTS

One hundred twenty-three patients (36 men, 87 women) enrolled in this long-term study. The characteristics of the study population are described in Table 1. Seventy-nine patients (64%) successfully completed the 60-month study. Among the patients who received 60 months of MTX therapy, there was a significant ($P = 0.0001$) improvement compared with baseline in the number of painful/tender joints, number of swollen joints, patient and physician global assessments, and Westergren ESR (Table 2). A significant improvement

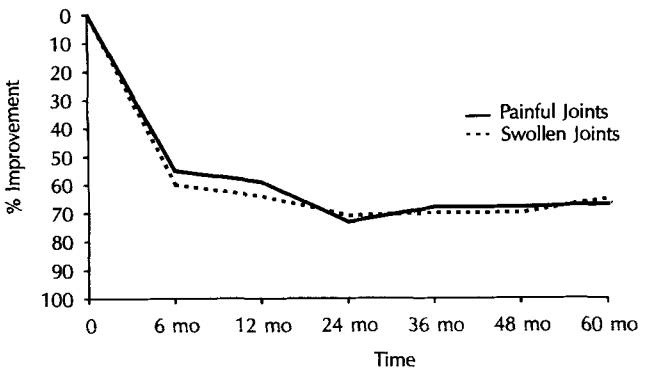

Figure 1. Mean percent change from baseline in the number of painful joints and the number of swollen joints, in rheumatoid arthritis patients treated with methotrexate. The number of patients at each visit was as follows: 120 patients at 12 months, 109 patients at 24 months, 98 patients at 36 months, 88 patients at 48 months, and 70 patients at 60 months.

was also noted in the joint pain/tenderness index, joint swelling index, and duration of morning stiffness (data not shown but available on request).

A significant improvement in these disease variables was observed at each visit over the entire course of the study. At the last visit at 60 months, there was a mean ± SEM improvement of 13.6 ± 1.5 in the number of painful joints, an improvement of 11.7 ± 1.2 in the number of swollen joints, a 0.85 ± 0.1–grade improvement in the physician global assessment, and a 0.77 ± 0.1–grade improvement in the patient global assessment. The mean number of painful joints and swollen joints had decreased by 64% at month 60 (Figure 1); there was no significant difference noted between the improvement at month 6 and that at month 60. Of the 79 patients who finished the study, the MHAQ was completed by 64. A significant improvement ($P < 0.001$) was observed between the mean ± SEM baseline score of 0.71 ± 0.05 and the 60-month score of 0.46 ± 0.05. MHAQ data from the last study visit (end-point analysis) were available for 95 of the 123 patients who enrolled in the study, and similar improvement was observed (0.57 ± 0.05 at the last visit, compared with 0.79 ± 0.05 at baseline; $P < 0.001$).

A significant improvement in disease variables was also noted in the end-point analysis (Table 3). All 123 patients returned for at least 1 followup visit and thus were included in this analysis.

A categorical assessment of marked improvement, determined as described in Patients and Methods, was performed for each patient at the last evalu-

Table 3. Changes in disease parameters: intent-to-treat analysis*

Parameter	n	Baseline visit	Last study visit	Mean change	*P*	95% CI
No. of painful joints	123	21.93 ± 1.07	8.79 ± 1.0	13.15 ± 1.20	0.001	10.3–16.0
No. of swollen joints	123	18.57 ± 0.99	7.36 ± 0.6	11.21 ± 1.04	0.001	8.8–13.6
Physician global assessment	123	2.10 ± 0.05	1.23 ± 0.1	0.85 ± 0.07	0.001	0.69–1.01
Patient global assessment	123	2.27 ± 0.07	1.37 ± 0.1	0.89 ± 0.10	0.001	0.69–1.09
ESR	123	42.13 ± 2.62	27.8 ± 2.2	14.38 ± 2.8	0.001	7.7–21.0

* Values are the mean ± SEM. See Table 2 for explanations and abbreviations.

able visit (mean 48 months). Marked improvement in the joint pain/tenderness index and the joint swelling index occurred in 87 (71%) and 85 (69%) of the patients, respectively. Marked improvement in the physician and patient assessments of disease activity occurred in 25 (20%) and 35 (28%) of the patients, respectively. Seventy-six patients (62%) met the Paulus criteria for response (6). Three patients (2%) met ACR criteria for remission during MTX therapy.

Seventy-eight patients had an elevated ESR (>28 mm/hour) at baseline. The ESR returned to normal levels during MTX therapy in 40 (51%) of these patients ($P < 0.007$).

Thirty-seven patients received prednisone during the study; 27 were taking prednisone at study entry and 10 began the therapy during the study. Eleven of the 37 patients discontinued prednisone; 9 of these patients were receiving prednisone at study entry. In 2 of the 37 patients, the prednisone dosage was increased during the study. Overall, there was a reduction in prednisone dosage from a mean ± SEM initial dosage of 6.7 ± 0.4 mg/day to a final dosage of 3.7 ± 0.5 mg/day ($P < 0.01$). The mean weekly dosage of MTX was 10.1 mg (range 7.5–20 mg) at month 12, 10.4 mg (range 2.5–20 mg) at month 24, 11.3 mg (range 5–20 mg) at month 36, 11.3 mg (range 5–20 mg) at month 48, and 11.3 mg (range 2.5–20 mg) at month 60.

Radiographs were available on 36 patients who received MTX in the initial 9-month randomized study and also completed the 60-month open study. The mean ± SEM erosion score was 13.89 ± 13.6 at baseline, 15.78 ± 13.2 at month 18, and 17.21 ± 15.1 at month 36. The change in erosion score between baseline and month 18 (1.89 ± 6.5) was not significantly different ($P = 0.80$) from the change between month 18 and month 36 (1.44 ± 5.4). The joint space narrowing score was 6.2 ± 7.5 at baseline, 7.9 ± 8.8 at month 18, and 8.7 ± 9.7 at month 36. The change in narrowing score between baseline and month 18 was not significantly different from the change between month 18 and month 36 (1.6 ± 5.1 versus 0.7 ± 3.5; $P = 0.40$).

Forty-four patients (36%) withdrew during the open study. Eight (7%) withdrew due to a lack of drug efficacy, 8 (7%) due to adverse experiences, 10 (8%) due to intercurrent illness, and 18 (15%) for administrative reasons including visit noncompliance and relocation. All 8 of the patients who withdrew due to lack of drug efficacy had received at least 9 months of MTX therapy at doses that ranged from 15 mg/week to 20 mg/week.

Adverse events occurred frequently during the study. Figure 2 shows the frequency of drug- and non–drug-related adverse occurrences throughout the study period. Within the first 6 months of therapy, 74% of the patients had 1 or more adverse reactions, whereas between months 48 and 60, 46% of the patients had an adverse experience. Adverse experiences that were considered by the investigator to be related to MTX were less frequent. Between months 0 and 6, 52% of the patients had an adverse event attributed to MTX, and between months 48 and 60, 16% of the patients had an adverse experience attrib-

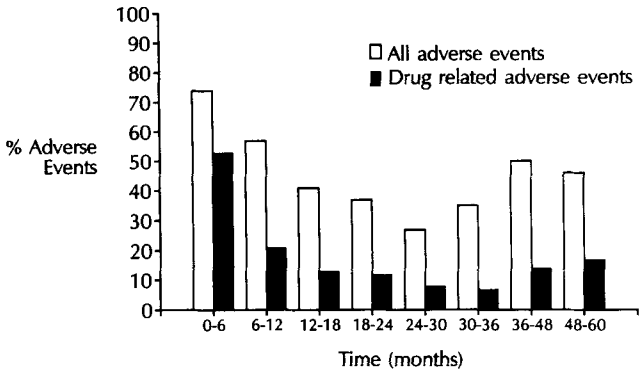

Figure 2. Frequency of adverse experiences, including methotrexate-related and non–drug-related experiences, over the course of the study.

uted to MTX. The adverse events included gastrointestinal toxicity (nausea, vomiting, diarrhea, anorexia, and stomatitis), headaches, rash, alopecia, and fatigue. Gastrointestinal intolerance occurred most frequently and occurred irrespective of the duration of therapy. Neither folic acid nor folinic acid was administered prophylactically in this study. During the course of the study, however, 15 patients received folic acid (1–2 mg/day) for a variety of adverse events ascribed to MTX, including stomatitis, anemia, alopecia, and an elevated mean corpuscular volume.

Eight patients withdrew from the study due to adverse experiences, including headache (1 patient), nausea (1 patient), hematologic toxicity (3 patients), and hepatic toxicity (3 patients). Three patients withdrew due to laboratory abnormalities (leukopenia in 2 and leukopenia with thrombocytopenia in 1), which resolved with drug discontinuation.

Three patients withdrew due to hepatic toxicity. One of these patients withdrew after 3 years of therapy due to recurrent elevations (2–4 times normal) in serum transaminase levels. A liver biopsy was recommended but the patient refused. The second patient developed persistent elevations in serum transaminase levels (3 times normal) and a low serum albumin level after 3 years of MTX. A liver biopsy showed moderate to severe hepatic necrosis. This patient denied alcohol intake, and results of hepatitis B and C serologic studies were negative. The third patient, a 52-year-old man, developed ascites after 4 years of therapy. Liver biopsy results were interpreted as indicative of cirrhosis. There was a history of moderate alcohol ingestion prior to MTX therapy, but the patient denied alcohol ingestion after initiation of MTX. Results of hepatitis B and C serologic studies were negative. MTX was withdrawn and the patient was treated with mild diuretics, with improvement in the ascites. A retrospective review of the records identified that the patient had had recurrent elevations in serum transaminase levels (1–2 times normal) and a low serum albumin level (2.8–3.4 gm/dl) for the 10 months prior to the development of ascites. Two years after discontinuation of MTX, the ascites had resolved with spironolactone treatment. Blood tests continued to show a low serum albumin level at 2.9 gm/dl, with elevations above the upper limit of normal in the serum transaminase levels.

Intercurrent medical problems led to withdrawal in 10 patients. These included malignancy (lung, esophagus, and pelvis) in 3 patients, and pericarditis, peripheral vascular disease, corneal ulcers, asthma, hilar adenopathy, pyoderma, and cerebral vascular accident in 1 patient each. There were no cases of MTX-associated pulmonary toxicity over the 60 months of study.

DISCUSSION

This long-term open study was an extension of our previous study comparing MTX and auranofin, in which MTX was found to be not only more effective, but also less toxic than auranofin over a 36-week period (3). Following completion of the randomized trial, 123 patients were enrolled in this 5-year open extension study of MTX. The present report is an update of our earlier publication on the trial status after a mean of 26 months of treatment (8). With the conclusion of the 60-month prospective study of MTX, this is the final report. A sustained improvement in the standard parameters of RA activity was noted over the 60 months of therapy. Only 36% of the patients withdrew from the study, and only 8 (7%) withdrew due to lack of efficacy. Individual patient responses were highly favorable, with 71% and 69% of patients achieving at least a 50% reduction in the painful and swollen joint indexes, respectively. An improvement in functional status as assessed by a standardized health assessment questionnaire (the MHAQ) was observed. A significant improvement in the Westergren ESR was also achieved, with normalization of previously elevated levels occurring in 51% of the patients.

Efficacy conclusions from open prospective studies must be viewed with some caution due to the lack of a control group, the continued investigator–patient interaction, and the various incentives for patients to be maintained on the treatment regimen. Irrespective of this, the clinical response appears to be quite favorable with MTX in this group of patients.

This large long-term study confirms the observations of several other long-term prospective studies of MTX treatment (1,2,9–11). In those studies the mean duration of disease activity was in excess of 10 years and patients had been treated unsuccessfully (lack of response and/or toxicity) with gold salts or D-penicillamine. The majority of these patients had received 2 or more second-line therapies prior to the institution of MTX. The patients enrolled in the present study were a group with less chronic and refractory disease. The mean duration of disease was 76 months, and patients were not eligible for the study if they had received any prior second-line therapy other than hydroxychloroquine. In this large study,

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