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LONG-TERM PROSPECTIVE STUDY OF METHOTREXATE IN THE TREATMENT OF RHEUMATOID ARTHRITIS

84-Month Update

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Objective. **To determine the long-term efficacy and safety of low-dose methotrexate (MTX) in rheumatoid arthritis (RA).**

Methods. **Eighty-four–month open prospective trial at a single academic rheumatology center.**

Results. **Twenty-six patients were enrolled in a prospective study of the long-term efficacy of MTX in RA; a significant improvement had been demonstrated after 36 months of therapy. Twelve patients remained in the study at the 84-month visit; the mean weekly dosage of MTX was 10.2 mg. A significant improvement was still noted at 84 months in the number of painful joints, number of swollen joints, joint pain index, joint swelling index, and physician and patient global assessments. A 50% improvement in the joint pain index and joint swelling index was observed in more than 80% of the 12 patients still enrolled. A significant reduction in prednisone dosage was achieved; of 14 patients taking prednisone at entry, 7 had discontinued prednisone completely. Fourteen patients withdrew from the study: 10 between 0 and 36 months, and 4 between 36 and 84 months. Toxicity in 3 patients and visit noncompliance in 1 patient were the reasons for withdrawal between 36 and 84 months. At 84 months, 46% of the patients remained in the study; 11.5% had discontinued due to MTX toxicity.**

Conclusion. **The effectiveness of MTX in the treatment of RA continues to be demonstrated in this prospective study, after 84 months of treatment.**

Methotrexate (MTX) has become an established treatment in patients with active rheumatoid arthritis (RA). The efficacy of this drug has been demonstrated in short-term placebo-controlled studies (1–4), comparative trials (5–8), and open prospective studies (9–12). We have previously reported the results of a 36-month prospective study of low-dose weekly MTX in patients with severe RA (10). This study, which began in 1984, now comprises 84 months of treatment observation. A sustained clinical response with an acceptable toxicity profile has been observed in the cohort of study patients, who have received MTX treatment for more than 7 years.

PATIENTS AND METHODS

Patients. Twenty-six patients with classic or definite RA (13) who completed a 24-week randomized crossover

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trial comparing MTX with placebo (1) enrolled in a long-term open study of MTX. Each patient remained under the care of his or her personal rheumatologist during the study, and each continued to take aspirin or another nonsteroidal antiinflammatory drug (NSAID), if needed. All patients were advised to abstain from alcohol consumption. In patients who were taking prednisone at entry into the randomized trial, this treatment was maintained at a dosage not exceeding 10 mg/day; adjustment in the prednisone dosage was allowed during the open study.

Methotrexate tablets (2.5 mg) were ingested at 8 AM, 8 PM, and 8 AM once a week, always beginning on the same day. Adjustments in the dosage were allowed during the open study, but the maximum weekly dosage of MTX allowed in this study was 15 mg. Informed consent was obtained every 12 months during the open study.

Clinical assessments. Clinical evaluations were performed by the same physician-investigator every 2 months for the first 2 years of the study and every 6 months thereafter. The clinical disease variables determined at each visit were as follows: 1) of 66 diarthrodial joints, the number with swelling; 2) Of 68 joints, the number with tenderness on pressure and/or pain on passive motion; 3) A joint swelling index, expressed as a sum, where each joint was graded for swelling on a scale of 0 = none, 1 = mild, 2 = moderate, and 3 = severe; 4) A joint tenderness/pain index, expressed as a sum, where each joint was graded according to the above scale; 5) Duration of morning stiffness; 6) Physician assessment of disease activity, on a scale of 0 = asymptomatic, 1 = mild, 2 = moderate, 3 = severe, and 4 = very severe; 7) Patient assessment of disease activity, using the same scale as described for physician assessment.

Overall response to treatment was derived using the following arbitrary designations: 1) Therapeutic remission as defined by the preliminary criteria of the American College of Rheumatology (ACR; formerly, the American Rheumatism Association) (14); or 2) Marked improvement in the joint swelling index and in the joint tenderness/pain index, defined as a >50% decrease in the values determined in the open study compared with values at entry into the randomized trial, and improvement in physician and patient assessment of disease activity representing changes of at least 2 integers in the 5-point scale, or from mild to asymptomatic. Patients who had achieved a "marked improvement" in the joint swelling index, the joint tenderness/pain index, and the physician and patient assessments of disease activity at their last visit were termed "substantial" responders.

Laboratory assessments. Every 4 weeks for the initial 60 months of the study and every 8 weeks thereafter, a complete blood cell count and measurements of serum creatinine, serum aspartate aminotransferase, serum alanine aminotransferase, alkaline phosphatase, bilirubin, and albumin were obtained. MTX was temporarily discontinued if the white blood cell count decreased to $<3{,}500/mm^3$, the polymorphonuclear leukocyte count decreased to $<1{,}200/mm^3$, the platelet count decreased to $<1.5 \times 10^5/mm^3$, the liver enzyme values increased to greater than twice the upper limits of normal, or the serum creatinine level became abnormal. Patients with abnormal laboratory values persisting for longer than 3 weeks were withdrawn from the study.

Liver biopsy. After 24, 48, and 72 months of MTX therapy, a percutaneous liver biopsy was performed at an outpatient surgical unit. The same hepatologist performed all biopsies on all patients. The histologic sections were prepared with hematoxylin and eosin, trichrome, and reticulum stains. The findings were interpreted by the same pathologist and hepatologist in all cases, using the classifications described by Roenigk et al (15): class I = normal: mild fatty infiltration, mild nuclear variability, mild portal inflammation; class II = moderate to severe fatty infiltration, moderate to severe nuclear variability, portal tract inflammation, and moderate to severe portal tract expansion; class IIIA = mild fibrosis; class IIIB = moderate to severe fibrosis; class IV = cirrhosis. A score of IIIB or IV prompted discontinuation of the drug.

Radiographic assessments. Standard posteroanterior and oblique radiographs of the hands and wrists were obtained at the baseline visit in the randomized trial, and after a minimum of 28 months and 70 months of therapy. Radiographs were evaluated by an experienced bone radiologist, for the number and size of erosions, healing of erosions, and joint space narrowing.

Statistical analysis. Disease variables were analyzed as the difference in group means between the entry (baseline) visit in the randomized trial and the open study visit, by Student's 2-tailed *t*-test. An intent-to-treat analysis was performed for the patients who discontinued the trial. Group means for other parameters were compared by Student's 2-tailed *t*-test.

RESULTS

Patient course in the study. Of the 28 patients who had completed the randomized trial (1), 26 enrolled in the long-term extension study. Their average age at entry into the randomized trial was 59 years, with a mean duration of disease activity of 106 months (range 21–320 months). Twenty-five of the 26 patients were seropositive (rheumatoid factor titer ≥1:160), and 14 were receiving prednisone (≤10 mg/day) at study entry.

Ten patients withdrew from the study within the first 36 months (10). Since that time, an additional 4 patients withdrew from the study. Three of these 4 patients withdrew due to an adverse reaction and 1 withdrew due to visit noncompliance. Twelve patients remain in the open study and have received MTX therapy for at least 84 months.

Disease effects. For the patients who remained in the study, significant ($P \leq 0.002$) improvement was noted at all study visits during months 36–84, compared with baseline, in the mean number of painful joints, number of swollen joints, physician global assessment, patient global assessment, joint pain index, and joint swelling index. Significant improvement

Table 1. Changes in rheumatoid arthritis disease parameters, months 36–84 of methotrexate study versus baseline*

Variable	No. of patients	Value at baseline	Value during therapy	Difference	*P*
No. of painful joints					
36 months	16	34.4 ± 2.8	7.9 ± 3.7	26.5 ± 4.2	0.0001
48 months	16	34.4 ± 2.8	11.1 ± 4.5	23.3 ± 4.6	0.0001
60 months	15	35.4 ± 2.9	9.7 ± 4.4	25.7 ± 4.6	0.0001
72 months	13	37.5 ± 2.1	11.5 ± 5.0	25.9 ± 5.1	0.0003
84 months	12	38.1 ± 2.4	12.5 ± 6.6	25.6 ± 6.6	0.0003
No. of swollen joints					
36 months	16	32.0 ± 1.9	8.9 ± 1.9	23.1 ± 1.6	0.0001
48 months	16	32.0 ± 1.9	12.6 ± 2.4	19.4 ± 2.2	0.0001
60 months	15	32.4 ± 2.0	11.3 ± 2.0	21.1 ± 1.7	0.0001
72 months	13	32.5 ± 2.1	11.4 ± 2.4	21.1 ± 2.1	0.0001
84 months	12	32.0 ± 2.8	13.7 ± 1.9	18.3 ± 2.1	0.0001
Joint pain index					
36 months	16	52.6 ± 4.8	8.5 ± 4.0	44.1 ± 4.8	0.0001
48 months	16	52.5 ± 4.8	12.0 ± 4.9	40.6 ± 5.2	0.0001
60 months	15	54.1 ± 4.9	10.5 ± 4.7	43.6 ± 5.1	0.0001
72 months	13	57.6 ± 4.1	12.5 ± 5.4	45.1 ± 5.4	0.0001
84 months	12	58.9 ± 4.9	13.3 ± 5.7	45.6 ± 7.0	0.0001
Joint swelling index					
36 months	16	46.9 ± 3.7	9.9 ± 2.4	37.0 ± 3.4	0.0001
48 months	16	46.9 ± 3.7	13.8 ± 2.6	33.2 ± 4.2	0.0001
60 months	15	47.9 ± 3.9	12.5 ± 2.2	35.5 ± 3.9	0.0001
72 months	13	48.2 ± 4.5	13.4 ± 2.7	34.8 ± 4.1	0.0001
84 months	12	49.5 ± 5.7	16.4 ± 2.3	33.1 ± 5.2	0.0001
Morning stiffness (minutes)					
36 months	16	167.0 ± 56.1	24.0 ± 9.0	143.4 ± 56.0	0.02
48 months	16	167.0 ± 56.1	32.8 ± 11.1	135.0 ± 57.7	0.03
60 months	15	164.0 ± 59.9	23.7 ± 10.6	141.0 ± 61.0	0.04
72 months	13	155.0 ± 68.5	20.7 ± 10.3	134.6 ± 68.8	0.07
84 months	12	178.0 ± 88.4	14.7 ± 5.9	163.3 ± 82.6	0.07
MD global assessment†					
36 months	15	2.7 ± 0.2	0.9 ± 0.2	1.7 ± 0.3	0.0001
48 months	16	2.6 ± 0.2	0.9 ± 0.2	1.7 ± 0.2	0.0001
60 months	15	2.5 ± 0.2	0.9 ± 0.2	1.6 ± 0.2	0.0001
72 months	13	2.5 ± 0.2	0.8 ± 0.2	1.7 ± 0.3	0.0001
84 months	12	2.6 ± 0.2	1.0 ± 0.3	1.6 ± 0.3	0.001
Patient global assessment†					
36 months	15	2.7 ± 0.2	1.0 ± 0.2	1.7 ± 0.3	0.0001
48 months	16	2.7 ± 0.2	1.0 ± 0.3	1.7 ± 0.3	0.0002
60 months	15	2.6 ± 0.2	0.9 ± 0.2	1.7 ± 0.3	0.0003
72 months	13	2.5 ± 0.2	0.7 ± 0.2	1.8 ± 0.3	0.0001
84 months	12	2.6 ± 0.2	0.9 ± 0.3	1.7 ± 0.4	0.002
Erythrocyte sedimentation rate (mm/hour)					
36 months	13	84.3 ± 9.6	52.7 ± 6.7	28.9 ± 9.8	0.01
48 months	16	78.9 ± 8.7	47.9 ± 8.2	31.0 ± 12.3	0.02
60 months	13	72.8 ± 9.7	48.2 ± 6.8	24.5 ± 10.5	0.03
72 months	11	79.4 ± 10.5	47.8 ± 6.4	26.5 ± 11.0	0.03
84 months	10	72.4 ± 11.6	58.5 ± 8.8	13.9 ± 13.1	0.3

* Values are the mean ± SEM. Baseline data are the measurements obtained at the initial visit of the randomized trial. Difference represents the degree of change at the study visit versus baseline, for those patients evaluated.
† Scored on a scale of 0–4, where 0 = none and 4 = very severe. See Patients and Methods for details.

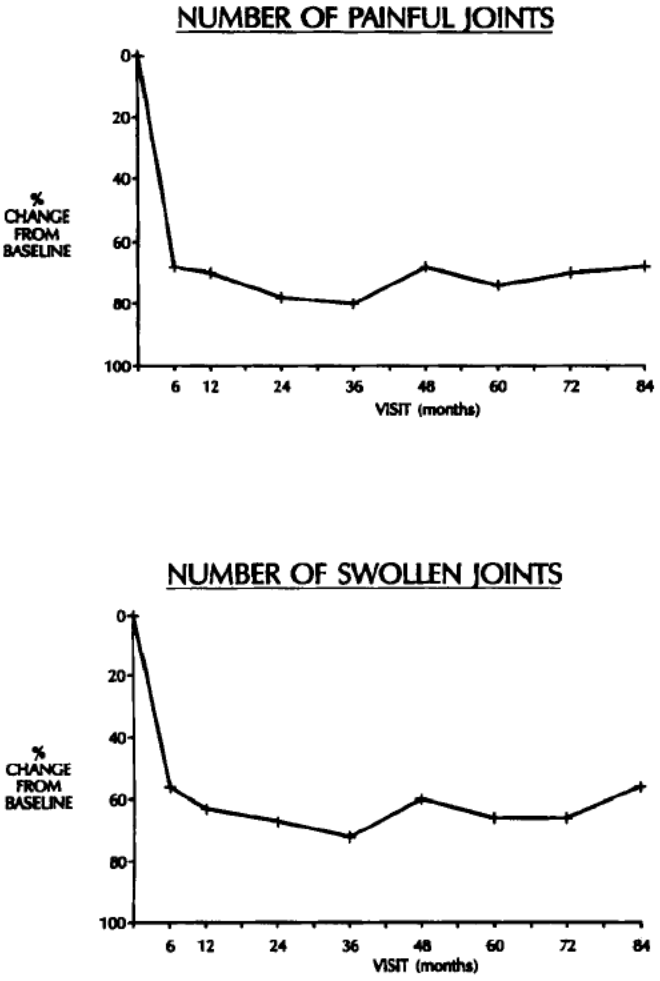

Figure 1. Mean change from baseline in number of painful joints and number of swollen joints. The number of patients at each visit was as follows: 12 months, 19 patients; 24 months, 18 patients; 36 months, 16 patients; 48 months, 16 patients; 60 months, 15 patients; 72 months, 13 patients; 84 months, 12 patients.

also occurred in the duration of morning stiffness from month 36 to month 60 ($P \leq 0.04$). An improvement from baseline in the mean erythrocyte sedimentation rate was observed and was statistically significant ($P \leq 0.03$) at the assessments between month 36 and month 72 (Table 1).

A similar degree of improvement was observed in the patients who discontinued the study. Significant ($P < 0.005$) improvement was noted at the last visit, compared with baseline, in the number of painful joints (mean ± SEM 40.7 ± 4.2 at baseline versus 19.8 ± 4.6), number of swollen joints (33.1 ± 3.3 at baseline versus 17.1 ± 3.7), physician global assessment (2.9 ± 0.2 at baseline versus 1.7 ± 0.3), and patient global assessment (3.0 ± 0.2 at baseline versus 1.5 ± 0.3), in patients who withdrew from the study. There was no significant difference in the response between the patients who remained in the study and those who withdrew.

There was a sustained clinical response in the disease parameters throughout the study. There was no significant difference in the degree of improvement noted at 12 months versus improvement at 84 months. The number of painful and swollen joints remained substantially improved between 36 months and 84 months (Figure 1).

The number of individual patients who responded to MTX therapy was determined using the arbitrary definitions described above. There were no remissions as defined by the ACR criteria (14). Of the 12 patients who remained in the study at 84 months, 10 (83%) demonstrated a "marked" improvement in the joint pain index, 11 (92%) in the joint swelling index, 5 (42%) in the physician assessment, and 6 (50%) in the patient assessment of disease activity. Five of these 12 patients exhibited the most "substantial" response to MTX at their last visit, achieving a marked improvement in the joint pain index, joint swelling index, and physician and patient assessments of disease activity. There was no unique difference in demographic profile, prednisone therapy, or disease activity at entry in the patients who achieved a "response" compared with the other patients. Of the 14 patients who withdrew from the study, 9 (64%) demonstrated a "marked" improvement in the joint pain index, 7 (50%) in the joint swelling index, 3 (21%) in the physician assessment, and 6 (43%) in the patient assessment of disease activity at their last study visit.

The mean ± SEM weekly dosage of MTX was 8.9 ± 0.99 mg (range 2.5–15) at 48 months, 9.5 ± 1.1 mg (range 5.0–15.0) at 60 months, 10.0 ± 1.1 mg (range 5.0–15.0) at 72 months, and 10.2 ± 1.1 mg (range 5.0–15.0) at 84 months. Fourteen patients were receiving prednisone at study entry, at a mean ± SEM dosage of 7.1 ± 0.8 mg/day. At the last study visit, the mean dosage of prednisone in these 14 patients was 2.7 ± 0.9 mg/day, which was a significant reduction ($P = 0.0005$). Seven of the 14 patients had been able to discontinue prednisone completely, with no increase in disease activity. Of the 12 patients who remained in the study, 5 of the 12 were taking prednisone (5.5 ± 1.2 mg/day) at study entry. At 84 months, the mean dosage of prednisone in these 5 patients was 2.8 ± 1.1 mg/day ($P = 0.09$). Two of the 5 patients discontinued prednisone therapy, and no patient required an increase in prednisone dosage, or initiation of pred-

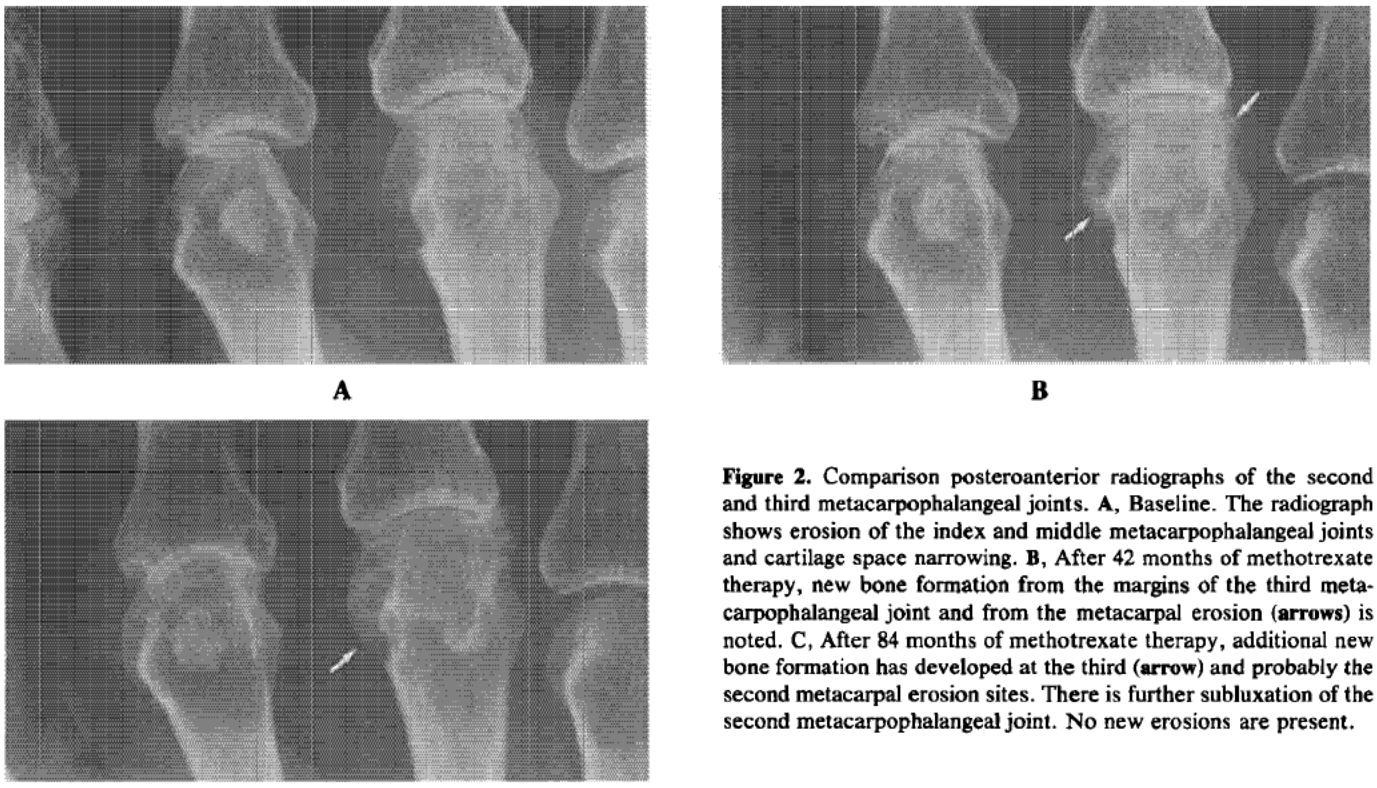

Figure 2. Comparison posteroanterior radiographs of the second and third metacarpophalangeal joints. **A**, Baseline. The radiograph shows erosion of the index and middle metacarpophalangeal joints and cartilage space narrowing. **B**, After 42 months of methotrexate therapy, new bone formation from the margins of the third metacarpophalangeal joint and from the metacarpal erosion (**arrows**) is noted. C, After 84 months of methotrexate therapy, additional new bone formation has developed at the third (**arrow**) and probably the second metacarpal erosion sites. There is further subluxation of the second metacarpophalangeal joint. No new erosions are present.

nisone therapy, during the study. Of the 12 patients who remained in the study, 4 were able to stop taking NSAIDs and another 3 had the NSAID dosage reduced by 50% without an increase in disease activity. In 1 additional patient, NSAID treatment was discontinued due to an adverse reaction.

Ten patients had radiographic evaluations of the hand and wrist performed at entry to the randomized trial, after a mean ± SEM of 41 ± 1.4 months (range 28–42 months) of MTX therapy, and again after 81 ± 1.7 months (range 70–84 months) of MTX. Six of these patients exhibited disease progression on this latest radiograph compared with the earlier radiograph (mean 40 months of therapy), with an increase in the number and size of erosions, deformity, and joint space narrowing. Three patients showed no progression with no new erosions, and 1 patient continued to demonstrate erosion healing with associated joint space narrowing (Figure 2). All 5 of the patients who exhibited progression on the first series of radiographs continued to show progression on this latest set of radiographs. Of the 3 patients who exhibited healing of erosions on the earlier radiographs, 2 did not develop new erosions and 1 continued to show erosion healing with joint space narrowing. The 4 patients who did not demonstrate progression over the 84 months of therapy had a "substantial" clinical response with MTX therapy.

Findings on liver biopsy. Liver biopsies were performed in 17 patients at 24 months, in 15 patients at 48 months, and in 10 patients at 72 months. There were no complications, and no patient required overnight hospitalization or blood transfusion. At the time of the first biopsy, after 24 months of therapy and a mean ± SEM cumulative dose of MTX of 1,082 ± 104.0 mg (range 695–2,088), there was no evidence of fibrosis or cirrhosis. In the 15 patients who underwent a second biopsy after 48 months of therapy, the cumulative dose of MTX at the time of this biopsy was 2,006 ± 193 mg (range 1,152–3,572). Results on 13 of the biopsies were graded as class I, 1 as class II, and 1 as class IIIA (mild fibrosis). At the time of the third liver biopsy, performed in 10 patients after 72 months of therapy, the cumulative dose of methotrexate was 3,095 ± 315 mg (range 1,597–4,635). Seven specimens were graded as class I, 2 as class II, and 1 as class IIIA. Three patients exhibited a change in classification: 2 from class I to class II, and 1 from class I to class IIIA (Table 2). The

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