Methotrexate in the treatment of rheumatoid arthritis

Pilot study

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The spectrum of disease severity in rheumatoid arthritis is as varied as the number of people who are afflicted with the disease. Many patients with rheumatoid arthritis require only supportive therapy consisting of rest, physical therapy, and salicylates or nonsteroidal anti-inflammatory drugs. A few patients with more active disease require suppressive drugs and highly anti-inflammatory drugs such as hydroxychloroquine, parenteral gold, penicillamine and/or low-dose corticosteroids. A minority of patients have severe, progressive disease that does not respond to these more conservative measures. For these patients with malignant rheumatoid arthritis more effective but more dangerous drug choices exist. These are the immunosuppressive cytotoxic drugs.

Cyclophosphamide, an alkylating agent, and azathioprine, a purine analogue, have both been shown to suppress the activity of rheumatoid arthritis.[1–4] Unfortunately, these drugs are not without short- and long-term hazards. The folic acid antagonist methotrexate has not been studied in the treatment of rheumatoid arthritis despite the fact that its short-term toxicity can usually be controlled and its long-term toxicity, with special regard to carcinogenicity, appears to be negligible.[5–10] Methotrexate, however, has been found use-

ful in the treatment of psoriatic arthritis.[11, 12]

The present study was designed to investigate the short-term efficacy and toxicity of low doses of oral methotrexate in the treatment of active rheumatoid arthritis.

Materials and methods

The study population consisted of six patients whose sex, age, duration of disease, total American Rheumatism Association criteria and drug therapy are given in the *Table.* All patients had classic or definite rheumatoid arthritis. In addition, each patient showed incomplete response to previous therapy as judged by the presence of prolonged morning stiffness (>1 hr), at least eight active joints, and an elevated Westergren sedimentation rate (>30 mm/hr). In four patients methotrexate was added to the preexisting regimen, which remained constant for the study period. In patient 1 methotrexate replaced D-penicillamine and in patient 2, methotrexate replaced cyclophosphamide. In addition, patient 1 received one injection of intramuscular triamcinolone (40 mg) and ACTH (40 units) 2 weeks before methotrexate therapy and patient 2 received an intraarticular injection of corticosteroids in one knee joint at the initiation of methotrexate therapy. All

Table. Treatment of rheumatoid arthritis with methotrexate in combination with other drugs

Patient	Sex	Age yr	Disease duration yr	Total no. ARA criteria	Concomitant therapy	Therapy with other drugs before methotrexate mo
1	F	66	6	7	Cyclophosphamide, 75 mg/day* Prednisone, 2.5 mg three times a day ASA, 6–8 grains five times a day	60
2	M	58	16	6	D-penicillamine, 250 mg three times a day† Hydroxychloroquine, 200 mg twice a day Prednisone, 2.5 mg three times a day ASA, 6-8 grains five times a day	60
3	F	45	6	7	Sulindac, 150 mg twice a day Prednisone, 5 mg every morning Hydroxychloroquine, 200 mg/day	3
4	F	71	10	8	Prednisone, 2.5 mg three times a day ASA, 10 grains four times a day Naproxen, 250 mg at bedtime Ibuprofen, 800 mg three times a day	36
5	F	54	4	7	Prednisone, 5 mg every morning, 2.5 mg at bedtime Hydroxychloroquine, 200 mg twice a day	20
6	F	57	2	6	Hydroxychloroquine, 200 mg twice a day Prednisone, 2.5 mg three times a day ASA, 8–12 grains five times a day	6

* Discontinued 2 weeks before methotrexate therapy.
† Discontinued 3 weeks before methotrexate therapy.
ARA criteria = American Rheumatoid Arthritis criteria.

patients were informed of the potential adverse side effects of methotrexate.

Methotrexate was administered on Monday of each week at a dose of 7.5 mg, orally. The patients were instructed to take the drug in a single dose at approximately the same time each week. Additionally, folic acid weekly in a dose of 6 to 9 mg, orally, was administered 5 days after ingestion of the methotrexate. The patients were evaluated at the beginning of the study, at 6 and 12 weeks. Data collected at each visit included (a) duration of morning stiffness, (b) time of afternoon fatigue, (c) grip strength (right and left), (d) joint count, (e) Westergren erythrocyte sedimentation rate, (f) circulating immune complexes (as determined by Clq binding), (g) complete blood count, and (h) serum glutamic oxaloacetic transaminase. Adverse reactions were recorded as they were observed. The dose of methotrexate remained constant in all patients.

Results

There were no adverse effects of any kind observed during the study period. *Figure 1–3* summarize the improvement in subjective data, physical assessment, and laboratory values at 6 and 12 weeks. As indicated, statistical improvement was noted in joint count, grip strength, and duration of morning stiffness. A general improvement in hemoglobin, sedimentation rate, afternoon fatigue, and Clq binding was noted, although these did not achieve statistical significance.

Conclusions

In this pilot study methotrexate appears to be useful in the control of rheumatoid arthritis. The relatively rapid onset of action compares favorably with parenteral gold, penicillamine, azathioprine, and cyclophosphamide. Good patient compliance can be expected since the drug is taken only one day of each week. We document no toxicity in our patients. Although treatment with methotrexate has been associated with alopecia, stomatitis, bone marrow depression, pulmonary disease, and hepatotoxicity, these problems generally occur at higher weekly doses.[12] Pulmonary toxicity has not been detected in patients receiving less than 20 mg of methotrexate weekly.[13] The incidence of hepatic toxicity can be minimized by giving the drug only one day per week and by instructing the patient concerning consumption of alcoholic beverages.[12, 14]

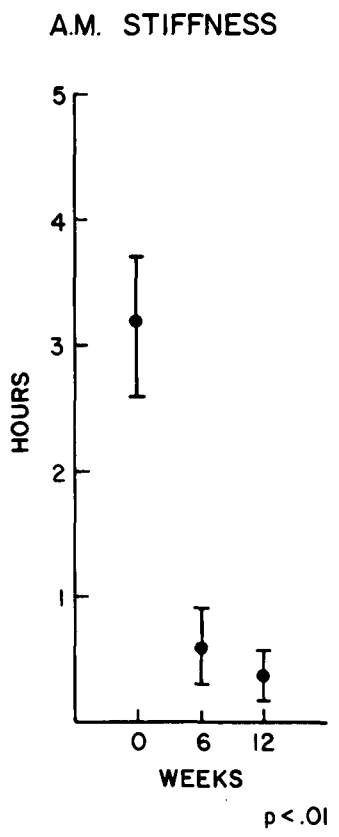

Fig. 1. Decrease in stiffness after treatment with methotrexate.

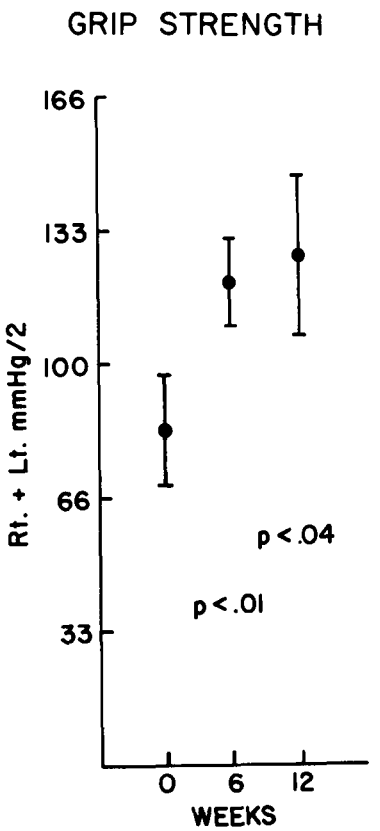

Fig. 2. Improvement in grip strength after treatment with methotrexate.

The recent study by Grünwald and Rosner[5] suggests that there is little or no association between the use of methotrexate and future leukemia.

The mechanism(s) by which methotrexate exerts its effects on rheumatoid disease may include supression of the primary immune response at the cellular proliferation stage,[15] an inhibition of mononuclear cell exudation,[16] the suppression of the formation of antibodies,[17, 18] and other effects.[19] However, all of these studies have employed higher doses of the drug than we have used in the treatment of our patient population. For this reason these mechanisms may not be directly applicable to our study.

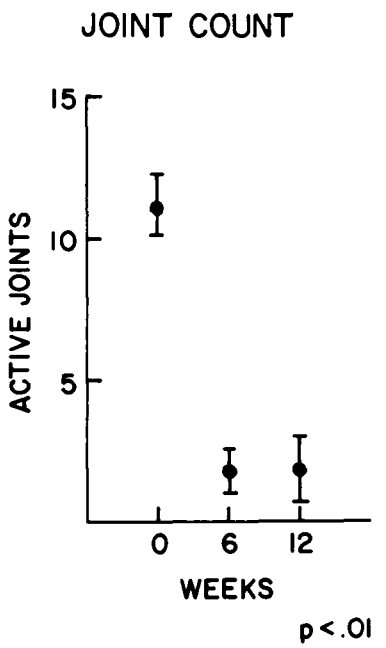

Fig. 3. Active joint count after treatment with methotrexate.

At this time a large, double-blind, controlled study to determine the efficacy of methotrexate in the treatment of active rheumatoid arthritis is underway at our institution. We hope to be able to demonstrate the usefulness and short-term safety of this drug and to study better its effects on the cellular and chemical mediators of rheumatoid inflammation.

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