BRIEF REPORT

WEEKLY INTRAVENOUS METHOTREXATE IN THE TREATMENT OF RHEUMATOID ARTHRITIS

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Patients with rheumatoid arthritis who are unresponsive to antiinflammatory drugs and slow-acting agents such as gold, hydroxychloroquine, and D-penicillamine, pose a therapeutic challenge. This report details the effectiveness of weekly intravenous methotrexate in 14 such patients resistant to standard therapy.

PATIENTS AND METHODS

There were 6 women and 8 men in the study group ranging in age from 48 to 66 years. All met the American Rheumatism Association criteria for the diagnosis of classic rheumatoid arthritis (1). Each participant gave informed consent before entering the program. All had clinical evidence of active disease and had failed to respond to both gold and hydroxychloroquine. In addition, 6 patients were unresponsive to D-penicillamine. Two had failed to improve with immunosuppressive therapy; 1 with azathioprine and the other with cyclophosphamide. Patients were allowed to continue corticosteroid and any non-steroidal antiinflammatory agents on a stable dosage. Excluded from this study were patients with liver disease, renal insufficiency, active infections, known alcohol abuse, abnormal white blood cell or platelet count, and women with childbearing potential.

Prior to the study, each patient had a complete history, physical examination, and chest roentgenogram. Joint index (sum of the number of swollen, tender, and warm joints), grip strength, and an assessment of morning stiffness were determined initially and at monthly intervals. A complete blood count and platelet count were performed weekly; Westergren sedimentation rate, reticulocyte count, serum glutamic-oxaloacetic transaminase (SGOT), serum glutamic-pyruvic transaminase (SGPT), alkaline phosphatase, total bilirubin, creatinine, albumin, and globulins were determined monthly.

Methotrexate was administered intravenously at weekly intervals. The initial dose was 10 mg. If this was well tolerated, the dosage was increased to a maximum of 50 mg. Once a satisfactory response had been achieved, the frequency of methotrexate administration was reduced to a maintenance schedule of one injection every 2 to 4 weeks depending upon activity of disease. Before each injection the patients were checked for stomatitis, sore throat, skin rash, fever, shortness of breath, and gastrointestinal symptoms. The methotrexate dose was reduced or withheld if evidence of toxicity developed.

RESULTS

The findings in all patients while on weekly intravenous methotrexate therapy are shown in Table

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Table 1. Response of individual patients on weekly intravenous methotrexate therapy

Patient	Duration of therapy, weeks	Total dose methotrexate, mg	AM stiffness, hours		Joint index		ESR		SGPT, U/ml		Toxicity	Concurrent drug therapy
			Start	End	Start	End	Start	End	Start	End		
1	13	460	4	2	59	16	62	19	8	19	Nausea, vomiting	Ibuprofen, diphenylhydantoin
2	9	245	5	0	67	45	53	18	6	18	Mild nausea; liver	Prednisone, enteric coated aspirin, diphenylhydantoin
3	9	360	3	1	38	27	20	30	8	30	Liver; oral ulcers	Aspirin, reserpine
4	7	260	2.5	1	35	17	80	50	8	50	Nausea; vomiting	Fenoprofen, prednisone, furosemide, conjugated estrogens
5	16	735	1	1	51	22	67	35	9	19	None	Fenoprofen
6	11	510	12	0	48	2	82	38	14	38	Liver; mild nausea	Prednisone, acetaminophen
7	10	145	2	0	40	21	104	79	23	50	Liver	Fenoprofen
8	10	380	2	0.25	70	35	55	33	18	23	Mild nausea	Choline salicylate
9	9	435	5	5	81	65	61	45	14	11	None	Prednisone, sulindac
10	20	715	12	0	41	8	40	42	10	42	Oral ulcers	Hydroxychloroquine, ibuprofen, acetaminophen
11	14	560	1.5	0	68	15	95	35	12	35	Mild nausea; oral ulcers	Naproxen, prednisone, furosemide, aspirin
12	9	385	12	12	62	50	65	43	11	43	Nausea; vomiting	Ibuprofen, acetaminophen
13	10	215	12	12	63	69	60	52	3	52	Liver; nausea oral ulcers	Aspirin, naproxen, prednisone, diazepam
14	7	285	12	1	75	73	40	25	18	25	Abdominal pain; diarrhea	Enteric coated aspirin, isosorbide dinitrate

1. Ten of 14 patients received at least 2 months of consecutive weekly injections without interruptions for toxicity. The data for patients 1–9 are presented in Figure 1. Patient 10 is not included because he missed a scheduled injection.

The remaining 4 patients required dose modification or withholding of the medication during the first 2 months of therapy because of either oral ulcerations, gastrointestinal symptoms, or liver enzyme abnormalities. Methotrexate was withheld for 1 week from patient 11 and then reduced to 25 mg at weeks 5 and 6 because of oral ulcerations. Subsequent weekly injections of 50 mg were not associated with recurrence of the ulcerations in this patient. His morning stiffness decreased from 2 to 0 hours at 2 months; joint index was reduced from 50 to 5 at 2 months. Although he had failed to respond to cyclophosphamide therapy, this patient has continued receiving 40 mg of methotrexate every 2 weeks for over 18 months with excellent control of his disease. Patients 12 through 14 were withdrawn from the study because of toxicity and/or failure to improve. After 7 weeks of therapy, patient 14 developed abdominal pain and diarrhea which recurred with reinstitution of methotrexate.

Nausea occurred in 8 of 14 patients, usually within 24 hours of injection. Only once (patient 12) was it severe enough to cause discontinuation of treatment. Mild elevations in SGPT (less than two times normal) were noted in 4 patients, all receiving 50 mg of methotrexate each week. This also contributed to discontinuation of therapy in patient 13.

While receiving 25 mg of methotrexate weekly and aspirin, patient 2 developed a mild elevation in SGPT of 58 U/ml (normal < 45 U/ml). After aspirin was discontinued and sulindac substituted, subsequent SGPT values were within normal range on continued weekly methotrexate therapy. This patient had previously been unresponsive to an 8-month course of azathioprine. Patient 3 had an SGPT increase to 54 U/ml, but because she was doing well on therapy, the dose interval was increased to 2 weeks and her SGPT level returned to normal. Patient 6 developed an increase in SGPT to 164 U/ml. At this point the patient's arthritis was quiescent so methotrexate was discontinued. However, his arthritis flared while off methotrexate, and 10 months later the drug was resumed at a dose of 15 mg each week. His clinical response was excellent and immediate (within 3 weeks). During the next 8 months of therapy, there was no recurrence of liver enzyme elevation. No

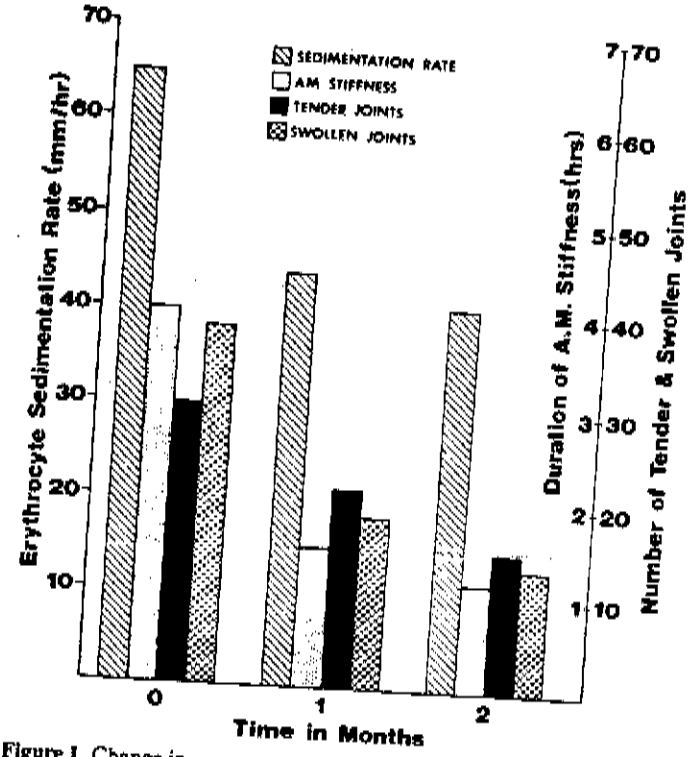

Figure 1. Change in parameters of disease activity during methotrexate therapy.

patients experienced leukopenia, thrombocytopenia, increased anemia, or changes in blood urea nitrogen or creatinine.

DISCUSSION

The patients chosen for inclusion in this study all had persistent arthritis unresponsive to conventional therapy. Two of them had failed to respond to other immunosuppressive agents. Eleven patients showed objective evidence of improvement within 2 months of starting methotrexate therapy, and most did so by 1 month. All patients reported subjective improvement. Although this was not a double-blind study, it is unlikely that improvement would have occurred spontaneously in this group of patients with very resistant disease.

The favorable response of our patients to intravenous methotrexate suggests that further studies to determine the optimal dose and route of administration should be performed. Two recent studies suggest that oral methotrexate is also effective for rheumatoid arthritis (2,3). Currently it is not known which route of administration is safer or more effective in inducing remission. If intravenous methotrexate proves to be more effective than oral methotrexate for inducing remission, it would be important to investigate the best method of maintaining this remission.

Short-term toxicity with weekly intravenous methotrexate is relatively easily controlled by altering the dose; more importantly, this drug's carcinogenic potential appears to be minimal (4). A few of our patients did experience mild elevations in liver enzymes. Significant histologic liver disease has been demonstrated in psoriatic patients on oral methotrexate therapy, despite normal results of serologic tests for liver injury (5). Therefore, if methotrexate is to be used on long-term basis for the treatment of rheumatoid arthritis, some investigators have suggested yearly liver biopsies (6).

The intention of this study was not to determine the smallest effective dose of methotrexate but rather to gain preliminary information on the usefulness of this drug in refractory rheumatoid arthritis. Doses of methotrexate lower than those used in this study may be equally effective with the added advantage of producing less toxicity. The intravenous route of administration allows the physician control over the amount of drug administered and reduces concern over the continuation of a potentially toxic drug without adequate monitoring.

We know of no other study in which a parenteral cytostatic agent has been used in the treatment of rheumatoid arthritis. Our preliminary data indicate that intravenous methotrexate is an effective drug for treating the active synovitis of rheumatoid arthritis which has been resistant to conventional medications.

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