Methotrexate Therapy in Rheumatoid Arthritis: 15 Years Experience

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An increasing amount of clinical data indicates that low-dose methotrexate therapy for rheumatoid arthritis is both effective and free of serious side effects. Since 1967 we treated 78 patients with definite or classic rheumatoid arthritis who showed inadequate response to conventional therapy. Up to 15 mg of methotrexate was given weekly by the intramuscular route. Morning stiffness, severity of pain at rest and with activity, extent of active synovitis, functional capacity, change in steroid dosage, complete blood count, erythrocyte sedimentation rate, and gamma glutamyl transpeptidase were monitored. Overall assessment indicated that 45 of the 78 (58 percent) patients showed marked improvement or complete remission, usually within four weeks. When maximum improvement was obtained, most patients were switched to oral therapy with a variable degree of success, and dosage was decreased as tolerated. No serious toxicity was noted. In 34 patients a total of 67 liver biopsy specimens were obtained, some after as long as 15 years of therapy. Minor changes observed are the same as in patients with rheumatoid arthritis not treated with methotrexate. Because the risks did not appear justified, routine annual biopsies were discontinued. In contrast to other cytotoxic drugs, no carcinogenesis has been demonstrated with methotrexate. It appears that methotrexate is approximately as effective as intramuscular gold and D-penicillamine but that it has a quicker onset of response and less serious toxicity.

Cytotoxic drugs have clearly been shown to be effective in modifying the course of rheumatoid arthritis. Cyclophosphamide, azathioprine, and chlorambucil have been the most widely used. Their effectiveness compares favorably with gold and penicillamine [1]. The oncogenic potential of cyclophosphamide and chloramabucil has caused them to be abandoned in the therapy of rheumatoid arthritis with few exceptions. The association of oncogenesis with the use of azathioprine in organ transplantation is well established. It remains to be proven that this will be a problem in azathioprine treatment of rheumatoid arthritis [2]. Methotrexate has been shown to be an effective agent in the treatment of rheumatoid arthritis [3–7] as well as psoriatic arthritis [8] and Reiter's disease [9].

In 1972 we presented a preliminary report of our first five years experience with low weekly doses of methotrexate in rheumatoid arthritis [3]. The purpose of this report is to review our continuing observations on the efficacy and toxicity encountered in this ongoing study.

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TABLE I Functional Classification (ARA) of 78 Patients with Adult-Onset, Classic Rheumatoid Arthritis

ARA Classification	Functional Capacity	Patients (n)
Zero	Full activity	None
I	Most activities	17
II	Light activities	45
III	Mainly chair and bed	16

ARA = American Rheumatism Association.

METHODS

Patients. All patients admitted to the study have had adult-onset, classic rheumatoid arthritis. All had unsatisfactory response to nonsteroidal anti-inflammatory drugs and intramuscular gold therapy. Most had failed penicillamine and hydroxychloroquine therapy as well. Patients with a history of hepatic disease, alcoholism, active peptic ulcer disease, renal insufficiency, or child-bearing potential were not considered to be candidates for methotrexate therapy. Patients were permitted to continue taking prednisone or other anti-inflammatory drugs.

During the past 15 years, 78 patients have entered the study. All but nine were seropositive for rheumatoid factor. Their average age was 61 years (range 18 to 80 years) with the average duration of disease being nine years. All patients were judged to have moderately severe (41) or severe (37) disease. The functional capacity of the patients as shown in **Table I** is also indicative of the advanced nature of their disease at the start of treatment.

Treatment. A single dose of 10 to 15 mg methotrexate was administered intramuscularly every seven days. When maximum benefit appeared to have been reached, some patients were allowed to try changing to the same dosage orally. Patients have been continued on the lowest dosage that will maintain the response achieved.

Assessment of Disease Activity. Patients have been seen initially at two and four weeks, and monthly thereafter. When optimum improvement has been reached, frequency of assessments usually has been every two to three months. The following information has been recorded at most visits: (1) duration of morning stiffness; (2) pain relative to activity; (3) number of painful joints; (4) number and severity of swollen joints; (5) functional capacity; (6) estimate of severity of disease activity by the examiner; (7) estimate of improvement; and (8) change in prednisone dosage.

Laboratory. Initially we obtained a baseline complete blood count (including platelet estimate), urinalysis, SMA 12/60, erythrocyte sedimentation rate, rheumatoid factor, and fluorescent antinuclear antibody. Subsequently, a complete blood count was repeated at two and four weeks, and monthly thereafter. Erythrocyte sedimentation rate has been obtained at irregular intervals depending on the patient's response. The frequency with which liver function studies and biopsies were obtained has changed with the evolution of our understanding of the hepatotoxicity seen in some patients treated with methotrexate. (See discussion under "Toxicity.")

RESULTS

A numerical grade from zero to three was placed on duration of morning stiffness, amount of activity producing pain, disease severity (based mainly on degree of active joint inflammation), and functional capacity. This numerical grade at onset of therapy was compared with that measured when the patient reached a maximal response, usually after two to six months. A change of three grades was considered a marked or outstanding improvement, two grades a moderate or very good improvement, and one grade mild. The improvement according to this scheme is shown in **Table II.**

Figures 1 and 2 profile the duration of therapy for patients continuing to take methotrexate, and for those who had discontinued.

Forty-four patients dropped out of the study permanently (**Table III**). Approximately one-third had an inadequate or declining response; another one-third were in remission, and the final third gave miscellaneous reasons.

A total of 12 patients have died, none as a known consequence of methotrexate therapy. Their average age at death was 71 years (range 55 to 84 years). Seven deaths were related to arteriosclerotic cardiovascular disease. The three patients who died during therapy were in this group. The other five died of miscellaneous causes, that is, cerebral vasculitis (one patient), odontoid compression of brain stem (one patient), terminal pneumonia associated with senile dementia and general debility (two patients), and recurrent pneumonia and severe pulmonary fibrosis secondary to rheumatoid arthritis (one patient). The latter death could conceivably

TABLE II Numbers of Patients Showing Various Degrees of Improvement in Grade with Therapy

Parameters Measured	Change			
	None	Mild	Moderate	Marked
Morning stiffness	7	26	29	16
Activity producing pain	3	29	38	8
Severity of disease activity	3	25	36	14
Functional capacity	11	36	27	4

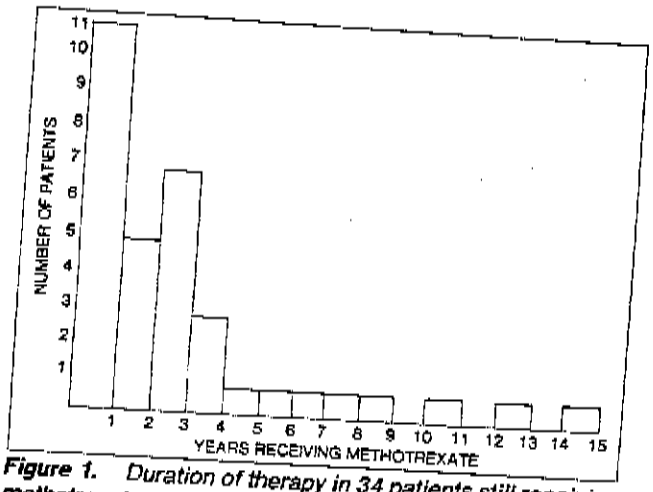

Figure 1. Duration of therapy in 34 patients still receiving methotrexate.

be related to methotrexate therapy; however, the fibrosis was present prior to therapy. In none was the pneumonitis of the type attributed to methotrexate toxicity present [10].

Sixty-four of the patients were receiving up to 10 mg of prednisone daily. Forty-six of these have been able to reduce their dosage. No patient continues to take more than 5 mg of prednisone daily.

Improvement should be apparent after three to six months of therapy. Therefore, we have compared the initial erythrocyte sedimentation rate values with one obtained after at least three months. Because erythrocyte sedimentation rate studies were not carried out on a regular basis, these data are available in only 54 patients. Forty-four of these had an average initial erythrocyte sedimentation rate of 47 mm per hour, which decreased to 21 mm per hour after three to six months of therapy. In the remaining 10 patients, the erythrocyte sedimentation rate increased from an average of 21 to 28 mm per hour.

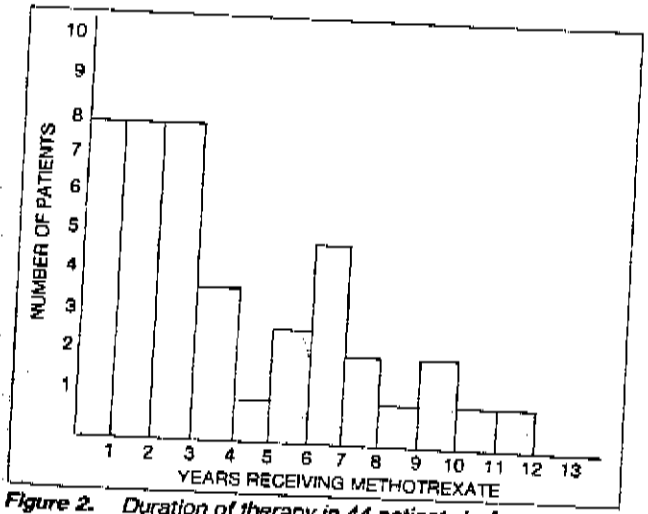

Figure 2. Duration of therapy in 44 patients before stopping methotrexate therapy.

TABLE III Reasons for Stopping Methotrexate Permanently

Reason	Number of Patients
Complete remission	15
Lost effect	4
Inadequate response	10
Uncooperative	1
Excess alcohol intake	1
Moved away	3
Toxicity	7
Died	3
Total	44

Similarly, we have determined change in count of active joints after four to six months of therapy. The average initial joint count of 18 fell dramatically to four. In only six of the 78 patients did the joint count not decrease.

An estimate of overall improvement was made based on all the data presented plus the patients' own assessment (**Table IV**). Little or no improvement was noted in 14 patients, as opposed to marked improvement in 45. Of the latter group, 28 were judged to be in complete remission. Our criteria for complete remission are morning stiffness lasting less than 30 minutes, lack of active synovitis on examination, pain related only to old damage rather than active disease, and a normal erythrocyte sedimentation rate. In 15 of the 28 patients it has not been possible to maintain remission without therapy.

Toxicity. A total of 67 liver biopsy specimens have been obtained from 34 patients. Twenty-four of these were from patients who had been receiving therapy for three or more years. Seven of the specimens were obtained from six to 15 years after the continuous use of methotrexate. Twenty-one patients have undergone between two and five biopsies. Each specimen was stained with three different stains, that is, hematoxylin and eosin, periodic acid-Schiff, and a reticulum stain.

Fifty biopsy specimens were normal. The remaining

TABLE IV Overall Improvement

None	3 (4%)
Mild	11 (14%)
Moderate	19 (24%)
Marked	45 (58%)

17 showed mild to moderate degree of fatty metamorphosis in all, mild increase in portal fibrosis in seven, a few lymphocytes in five, and slight variation in size of hepatocyte nuclei in five. In none of the specimens was the pathologist able to find evidence of necrosis or cirrhosis. Of the 10 patients who underwent biopsy at the onset of therapy, mild to moderate fatty change was found in three, and in the remaining seven the findings were normal. None of the patients whose specimens showed increased fibrosis had had prior normal biopsies.

Mild elevations of SGOT (five patients) or gamma-glutamyl transpeptidase (one patient) occurred in only six patients. Methotrexate therapy was stopped in all six but resumed in four without persistent abnormal levels. The other two patients were switched to penicillamine. Interestingly, in only one patient did leukopenia develop, and she had similar temporary responses during gold and penicillamine therapy also. Other side effects encountered have been minor although occasionally troublesome. Occasional patients complain of stomatitis, headache, nausea, or increased aching for one or two days following the weekly dose. Only six patients terminated therapy for one of these reasons. Other patients noted some of these same symptoms, occasionally requiring a reduction in dosage that was usually temporary. One patient has complained of thinning hair, and one of increased frequency of bowel movements.

COMMENTS

Despite approximately 30 years of treating rheumatoid arthritis with cytotoxic drugs [11,12] their mode of action in the connective tissue diseases remains uncertain. Methotrexate is a potent antimetabolite by virtue of its inhibiting effect on folic acid synthesis. It might exert its action by inhibition of DNA, RNA and protein synthesis, by immunosuppression, by anti-inflammatory effects, or by other actions still to be elucidated.

Problems with toxic side effects, especially hepatic, have discouraged more widespread use of methotrexate. However, with the use of pulse therapy and lower doses, as well as denying therapy to persons with a history of liver disease or alcoholism, significant liver damage has not occurred. Obesity and diabetes may also predispose patients to a decreased tolerance for methotrexate [13] due to a high incidence of mild histologic changes in liver biopsy specimens from these patients. Weinstein [14] reviewed several prospective studies involving a total of 309 patients in which the findings on biopsy were compared before and after one to four years of methotrexate therapy for psoriasis. These data showed that in approximately 3 percent of the patients cirrhosis developed in the first few years of therapy. The lack of cirrhosis in any of our patients may be due to the use of doses lower than those generally employed in psoriasis. It has been well established that mild to moderate liver damage can be present on biopsy before significant liver enzyme changes occur. The minor histologic changes we found in liver biopsies are commonly found in patients with rheumatoid arthritis not treated with methotrexate [15]. The liver can be involved in rheumatoid arthritis as evidenced by the demonstration of rheumatoid factor in liver cells [16], and by the frequent reduced albumin levels seen in patients with severe disease. Although the changes we noted are likely unrelated to methotrexate therapy, it must be kept in mind that patients with these changes may be predisposed to methotrexate-induced hepatic damage. The place of leucovorin in preventing toxicity to methotrexate is not well defined [17].

There does not appear to be any evidence that methotrexate is carcinogenic [18]. Certainly the antimetabolites seem less likely than the alkylating agents to promote oncogenesis. Delayed wound healing and increased susceptibility to infection may be a problem, especially when combined with the use of corticosteroids, but has not been observed with the low doses used in this study.

There is ample evidence in the literature that the antimetabolic effect as well as toxicity of methotrexate depends on the length of time the drug is present in the blood stream. Freeman-Narrod and associates [19] studied serum concentrations achieved with the four usual methods of administrating methotrexate, that is, orally, intramuscularly, orally in three divided doses eight hours apart, and intravenously. They found the intramuscular route resulted in higher and more prolonged serum levels than the same doses taken orally. The intravenous route produced the highest levels, but they decreased more rapidly. The divided dosage method provided lower serum concentrations but over a longer period of time. We have preferred the intramuscular route mainly because of known variation in gastrointestinal absorption of oral methotrexate. Forty-eight patients were switched to oral therapy after they appeared to have obtained maximal effect with intramuscular therapy. In 10 of these, their condition deteriorated but improved promptly when returned to intramuscular therapy. The divided dosage method given once weekly was devised specifically to provide drug effect correlating with the very rapid rate of epidermal cell proliferation in psoriasis [20].

It is of interest that of 10 patients who were changed to penicillamine therapy seven believed they had superior results with methotrexate.

CONCLUSIONS

The increasing enthusiasm for methotrexate in rheumatoid arthritis would appear justified. During the 15-year span of this study 78 patients have received a total of 327 patient-years of therapy. The efficacy of these low doses given weekly compares well with that reported for intramuscular gold, penicillamine, and hydroxychloroquine [21, 22]. This group of patients had severe, resistant disease. Perhaps an unselected group would have an even more impressive response to methotrexate. In our experience it is seldom beneficial to continue therapy beyond four to six months if a satisfactory response is not achieved.

Up to this time, serious toxicity has not been reported with similar trials in rheumatoid arthritis using low-dose pulse therapy. The possibility of producing serious liver damage appears unlikely with this protocol, but only further experience can answer this question. Other potentially hepatotoxic agents should be avoided. We instruct patients to avoid all alcoholic beverages for 48 hours after the weekly dose and to ingest no more than two ounces of hard liquor, or the equivalent, per day. Unfortunately, there is no simple test for early detection of significant hepatotoxicity. Although some would disagree, we believe the risks involved in liver biopsies do not justify their routine use in following these patients. The gamma glutamyl transpeptidase appears to be too sensitive to be useful on a routine basis. We have recently returned to the serum glutamic pyruvate transaminase as a screening test. If it is persistently increased, and other potential sources of liver toxicity have been eliminated, the clinician must then choose between (1) monitoring liver enzymes while reducing the dose of methotrexate, (2) obtaining a liver biopsy, or (3) discontinuing the drug.

Methotrexate should probably continue to be reserved for patients unresponsive to conventional therapy until more prolonged observations regarding liver toxicity have been accumulated.

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