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EFFICACY OF LOW-DOSE METHOTREXATE IN RHEUMATOID ARTHRITIS

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Abstract Twenty-eight patients with refractory rheumatoid arthritis completed a randomized 24-week double-blind crossover trial comparing oral methotrexate (2.5 to 5 mg every 12 hours for three doses weekly) with placebo. The methotrexate group had significant reductions ($P<0.01$ as compared with the placebo group) in the number of tender or painful joints, the duration of morning stiffness, and disease activity according to physician and patient assessments at the 12-week crossover visit; reductions in the number of swollen joints ($P<0.05$) and 15-m walking time ($P<0.03$) also occurred. These variables, as well as the grip strength and erythrocyte sedimentation rate, showed significant ($P<0.01$) improvement at 24 weeks in the population crossed over to methotrexate. A significantly increased frequency ($P<0.03$) of the HLA-DR2 haplotype occurred in the eight patients with the most substantial response to methotrexate. Adverse reactions during methotrexate therapy included transaminase elevation (21 per cent), nausea (18 per cent), and diarrhea (12 per cent); one patient was withdrawn from the trial because of diarrhea. One patient died while receiving the placebo. Methotrexate did not affect measures of humoral or cellular immunity.

We conclude that this trial provides evidence of the short-term efficacy of methotrexate in rheumatoid arthritis, but the mechanism of action is unknown. Longer trials will be required to determine the ultimate safety and effectiveness of this drug. (N Engl J Med 1985; 312:818-22.)

CERTAIN cases of rheumatoid arthritis are refractory to conventional therapies because of lack of benefit or the occurrence of unacceptable side effects. The antimetabolite methotrexate was reported to produce favorable effects on rheumatoid arthritis by Gubner et al. in 1951,[1] and since that time, other open trials have suggested that the drug is effective in this disease.[2,3] This experience prompted the following randomized double-blind crossover study of low-dose oral weekly methotrexate for patients with severe adult-onset rheumatoid arthritis in whom gold-salt therapy had failed to produce a response or had been toxic.

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METHODS

Patients

Thirty-five patients with rheumatoid arthritis fulfilling the American Rheumatism Association's criteria for definite or classic disease[4] gave informed consent and entered the study. All had received gold-salt therapy; 28 (80 per cent) had received penicillamine, 23 (66 per cent) hydroxychloroquine, and 2 azathioprine. These drugs had been discontinued because of ineffectiveness or toxicity.

Other criteria for entry were onset of the disease after the age of 16 and the presence of active disease, defined by at least three of the following: 3 or more swollen joints, 6 or more tender joints, 45 minutes or more of morning stiffness, a Westergren erythrocyte sedimentation rate of 28 mm per hour or higher, and a mean grip strength for both hands of 192 mm Hg or less in men and 146 mm Hg or less in women, averaged from three measurements.[4] Two bone radiologists agreed that the anatomic stage of disease[3] was II or greater in all patients, according to plain radiographs of the hands obtained at entry. Women either had no childbearing potential or were practicing contraception.

Excluded from the study were patients with a serious concomitant medical illness, judged to be in Functional Class IV by the criteria of the American Rheumatism Association,[4] or with a history of cancer, liver or renal disease, insulin-dependent diabetes, obesity (more than 10 kg above ideal body weight), liver enzyme levels at least twice the upper limit of normal, white-cell counts of less than 3500 per cubic millimeter, platelet counts below 1.5×10^5 per cubic millimeter, or therapy with methotrexate or total lymphoid irradiation.[4] Patients were not accepted into the trial until gold, penicillamine, or hydroxychloroquine had been withdrawn for at least two months and azathioprine for at least six months.

During the study each patient remained under the care of his or her personal rheumatologist, abstained from alcohol, and continued to receive stable doses of aspirin or another nonsteroidal antiinflammatory drug; those taking prednisone at entry were maintained on a stable dose not exceeding 10 mg a day.

Study Design

This was a double-blind crossover study of 24 weeks' duration. Patients were randomly assigned in blocks of four to receive initially indistinguishable tablets consisting of either methotrexate (2.5 mg) or placebo for 12 weeks (Period 1). Tablets were ingested in equal numbers on three consecutive occasions at 12-hour intervals beginning on the same day of each week. For the first 6 weeks, three tablets were taken weekly; at 6 weeks, the dose could be increased to six tablets weekly if a satisfactory response was not noted by the physician investigator. At 12 weeks, crossover occurred; patients initially assigned to methotrexate received placebo for the final 12 weeks of the study (Period 2), and patients originally assigned to placebo received methotrexate. Again, elective increases in dosage were incorporated into Week 6 of Period 2. Patients and their rheumatologists, as well as the investigators, remained unaware of drug assignments until the study was completed.

Clinical Assessments

Each patient was examined by the same physician investigator every three weeks, and pill counts were performed; the entry, crossover, and final visits occurred early in the morning. The clinical disease variables determined at each visit consisted of (1) the number among 66 diarthodial joints with swelling; (2) the number among 68 joints with tenderness on pressure or pain on passive motion (or both); (3) the joint-swelling index, expressed as a sum in which each joint was graded for swelling as 0 (none), 1 (mild), 2 (moderate), or 3 (severe); (4) the joint-tenderness/pain index, representing the sum for joints graded according to the above scale; (5) mean grip strength for both hands; (6) 15-m (50-ft) walking time without assisting devices; (7) the duration of morning stiffness; (8) the physician's assessment of disease activity graded as 0 (asymptomatic), 1 (mild), 2 (moderate), 3 (severe), or 4 (very severe); and (9) the patient's assessment of disease activity graded on the same scale.

Overall responses to treatment were derived with the following arbitrary designations modified from those proposed by Williams et al.[6,7]: (1) therapeutic remission, defined by the preliminary criteria of the American Rheumatism Association[8]; (2) marked improvement in the joint-swelling index and in the joint-tenderness/pain index, defined as a decrease of 50 per cent or more in their values at the 12-week or 24-week visit, as compared with their values at entry or crossover; (3) moderate improvement, defined as decreases of 30 to 49 per cent in these indexes; (4) no change, if the value for an index remained within 30 per cent of the original value; and (5) worsening, if the value for an index increased 30 per cent or more. Improvement and worsening in the physician and patient assessment of disease activity represented changes of at least 2 integers in their five-point scales.

Laboratory Assessments

Every three weeks, a complete blood count, including platelets and the erythrocyte sedimentation rate, and liver-enzyme tests, consisting of measurement of serum aspartate and alanine aminotransferase, alkaline phosphatase, and total bilirubin, were obtained; serum creatinine was measured every six weeks. Patients were withdrawn from the study if the white-cell count decreased to less than 3300 per cubic millimeter, the polymorphonuclear leukocyte count decreased to less than 1200 per cubic millimeter, the platelet count decreased to less than 1.5×10^5 per cubic millimeter, or the creatinine level rose above 1.8 mg per deciliter (160 μmol per liter). If the values for liver enzyme increased to more than twice the upper limit of normal, the tablets were withheld and the tests were repeated weekly. Abnormalities persisting for more than three weeks also led to withdrawal. Typing for HLA-A, B, C, and D polymorphism was performed in the tissue-typing laboratory of the Department of Rheumatology and Immunology; the reagents included antiserums tested during the 8th Histocompatibility Workshop.[9]

Immunologic Assessments

At the entry, crossover, and final visits, 80 ml of blood was obtained for immunologic studies. Serum aliquots were analyzed for titers of rheumatoid factor by nephelometry and for concentrations of immune complexes by C1q binding.[10] Cytofluorographic enumeration of blood mononuclear cells by surface antigens was performed as described elsewhere.[4] Anti-T3 reacted with all mature T cells, whereas anti-T4 and anti-T8 identified functionally distinct T-cell subsets.[4] Anti-Ia reacted with activated T cells as well as cells of B-lymphocyte and monocyte lineage.[11] Anti-B1 identified B lymphocytes,[12] and anti-Mo_1 reacted with monocytes and a majority of null cells.[13] Anti-$TI1_3$ and anti-Ta_1 identified T-cell–specific markers of activation.[14,15] Tritiated thymidine incorporation by blood mononuclear cells in response to an optimal quantity of the mitogens phytohemagglutinin and concanavalin A and the antigens streptokinase–streptodornase, candida, and purified protein derivative of tuberculin was also measured.[10]

Statistical Analysis

Continuous disease variables were analyzed as the difference in group means between the crossover visit and entry visit, as well as between the final visit and the crossover visit, by covariance.[16] Other indexes were analyzed in terms of their group means (by Student's two-tailed t-test), and dichotomous variables by their proportionate group frequencies (by the chi-square test). P values smaller than 0.01 are not given.

Results

Patients and Study Course

Of the 35 patients enrolled, 17 were initially assigned to receive methotrexate and 18 to placebo (Table 1). All but two patients had their dose of test medication increased to six tablets; the two patients were receiving methotrexate. Pill counts suggested a high degree of compliance with the prescribed regimen.

There were four withdrawals before the crossover visit; the data from these patients were excluded from the efficacy analyses in Table 2. Two of these patients were receiving placebo; one was withdrawn because of a cerebrovascular accident and the other because of a protocol violation (a persistent elevation in alkaline phosphatase was detected after entry into the trial). One of the patients receiving methotrexate was withdrawn at Week 9 because of diarrhea, and the other withdrew after one week of treatment with methotrexate, during an exacerbation of rheumatoid arthritis requiring hospitalization. Three patients, all receiving placebo, did not finish Period 2. One withdrew because of an arthritic flare at Week 18, after benefiting from methotrexate. One was withdrawn at Week 21

Table 1. Demographic and Clinical Characteristics of the Patients at Study Entry.*

Variable	Medication Sequence	
	Methotrexate–Placebo (N = 17)	Placebo–Methotrexate (N = 18)
Age (yr)		
Average	60	59
Range	45–70	44–73
No. female	10	15
No. white	16	17
Disease duration (mo)		
Average	100	128
Range	21–320	48–352
Functional class		
II	11	8
III	6	10
Rheumatoid factor (titer ≥1:160)	16	18
HLA-DR4	9	8
Prednisone (≤10 mg per day)	8	12
Previous hip, knee, or ankle arthroplasty	6	7

*Patients were grouped according to whether they were randomly assigned to methotrexate in Period 1, with subsequent crossover to placebo in Period 2, or received these test medications in the reverse sequence during these two periods. The values listed did not differ significantly between the groups.

because of not keeping a visit appointment, and the other (a 66-year-old woman who had moderate improvement in the joint-swelling index and joint-tenderness/pain index and had alopecia during treatment with methotrexate) died suddenly at Week 18 during a recrudescence of arthritis. A patient taking placebo had an intraarticular injection of a glucocorticoid into a knee in Period 1; this joint was excluded from analysis in the study.

Effects on Disease

When the 15 patients receiving methotrexate and 16 patients receiving placebo who completed the initial 12-week trial were compared, significant degrees of improvement were found in the methotrexate group, versus the placebo group, in all the clinical variables measured except the grip strength (Table 2). There was no significant change in the sedimentation rate, hematocrit, total white-cell count, platelet count, or absolute lymphocyte count.

Analysis of the 16 patients crossed over to methotrexate and the 12 crossed over to placebo who completed Period 2 revealed a significant ($P<0.01$) improvement in all variables, including the sedimentation rate, in the methotrexate group. Again, there was no change in blood-cell components in this period. Because of the crossover design, patients who received methotrexate initially were examined for a change in the measured variables at the end of Period 2. In this subgroup, a significant ($P<0.01$) flare in rheumatoid arthritis was noted, as measured by the joint-swelling index, grip strength, morning stiffness, and physician assessment of disease activity; the walking time ($P<0.04$) and patient assessment of disease activity ($P<0.02$) had also worsened.

A total of 33 patients received methotrexate during this study. The number who responded to the drug was calculated by using the arbitrary definitions, and the frequency and degree of these responses were compared with those observed in a control group consisting of 18 patients randomly assigned to placebo in Period 1 (Table 3). No remissions occurred with methotrexate therapy, but there was a marked improvement in the joint-tenderness/pain index in 18 patients (54 per cent) and a moderate improvement in 6 (18 per cent). Thus, 24 of the patients (73 per cent) receiving methotrexate had at least a 30 per cent improvement in the joint-tenderness/pain index. A marked or moderate improvement in this index was found at Week 3 of methotrexate therapy in 36 per cent of the patients. A marked improvement in the joint-swelling index occurred in 13 (39 per cent) of the patients taking methotrexate, and a moderate improvement occurred in 7 (21 per cent). Thus, 20 patients (61 per

Table 2. Clinical and Laboratory Variables in Patients Completing Period 1 of the Study.*

Variable	Treatment †	Value at Entry Visit	Difference at Crossover Visit ‡	P Value §
		mean ±S.E.		
No. of joints swollen	Methotrexate (15)	34±3	14±2	<0.05
	Placebo (16)	28±2	5±2	
No. of joints tender to pressure or painful on passive motion	Methotrexate (15)	37±4	26±4	<0.01
	Placebo (16)	36±3	4±4	
Joint-swelling index	Methotrexate (15)	51±5	30±3	<0.01
	Placebo (16)	40±4	10±3	
Joint-tenderness/pain index	Methotrexate (15)	58±8	46±7	<0.01
	Placebo (16)	52±4	6±6	
Grip strength (mm Hg)	Methotrexate (15)	61±6	−21±7	NS
	Placebo (16)	43±5	−4±3	
15-m (50-ft) walking time (sec)	Methotrexate (15)	17±1	5±1	<0.03
	Placebo (13)	22±2	3±1	
Duration of morning stiffness (min)	Methotrexate (15)	182±60	134±58	<0.01
	Placebo (16)	103±18	−36±32	
Physician assessment of disease activity	Methotrexate (15)	2.7±0.2	1.5±0.2	<0.01
	Placebo (16)	2.6±0.2	0.0±0.2	
Patient assessment of disease activity	Methotrexate (15)	2.8±0.2	1.6±0.2	<0.01
	Placebo (16)	2.7±0.2	0.1±0.2	
Erythrocyte sedimentation rate (mm/hour)	Methotrexate (15)	77±9	17±7	NS
	Placebo (14)	50±7	−4±5	

*Period 1 encompasses the initial 12 weeks of the study.
†Figures in parentheses are numbers of patients in whom the variable was analyzed.
‡Positive values represent a decrease in the difference from the mean.
§P values were determined by analysis of covariance using adjusted means. NS denotes not significant.

cent) taking methotrexate had at least a 30 per cent improvement in the joint-swelling index. Again, a marked or moderate improvement in this index was present at Week 3 in 24 per cent of the patients. An improvement in the physician's assessment of disease activity occurred with methotrexate in 36 per cent of the patients, and an improvement in the patient's assessment occurred in 42 per cent.

Eight (24 per cent) of the 33 patients had the most substantial response to methotrexate, which was arbitrarily defined as achieving a marked improvement in the joint-swelling and joint-tenderness/pain indexes as well as improvement in both the physician and patient assessments of disease activity. No patient taking placebo fulfilled these criteria. There was no significant difference in the demographic or disease variables at study entry, or in the frequency of concomitant prednisone therapy, between these 8 patients and the other 25 patients. Of potential interest, 4 of these 8 patients with a substantial response were typed as HLA-DR2, as compared with 3 (12 per cent) of the 25 patients who did not have such a response (chi-square = 5.2, $P<0.03$).

Adverse Occurrences

Side effects occurred with equal frequency during treatment with the 7.5-mg and 15-mg doses of methotrexate, except that nausea developed only at the higher dose. During methotrexate administration, 17 (52 per cent) of the 33 patients had one or more types of adverse reactions, chiefly gastrointestinal, that were considered to be attributable to the drug; similar reactions were noted in 5 (15 per cent) of the 33 patients during administration of placebo ($P<0.01$) (Table 4). The one patient withdrawn from the trial because of a drug reaction had severe diarrhea after nine weeks of methotrexate therapy (cumulative dose, 90 mg); without the drug, the diarrhea resolved during a seven-day hospitalization. The side effects in the other patients were clinically mild. Elevated serum levels of aspartate and alanine aminotransferase occurred in seven (21 per cent) of the patients taking methotrexate and returned to within normal limits after the medication was withheld for one to three weeks. One patient taking placebo had a transient elevation of both enzymes.

Table 4. Adverse Occurrences.*

Morbid Event	During Administration of:	
	Methotrexate (N = 33)	Placebo (N = 33)
	no. of patients	
Abnormal transaminase	7 (21%)	1 (3%)
Nausea	6 (18%)	3 (9%)
Diarrhea	4 (12%)	0
Alopecia	2	0
Stomatitis	2	0
Headache	2	0
Skin infection	2	1
Anorexia	1	0
Vomiting	1	1
Rash	2	4 (12%)
Back pain	2	0
Cough	2	1
Chest pain	2	1
Stroke	0	1
Death	0	1
Abdominal pain	0	1
Depression	0	1

*There were 383 patient-weeks of methotrexate administration and 369 patient-weeks of placebo administration in this study. The rashes, back or chest pain, and cough were not considered to be drug-related.

Immunologic Studies

There were no significant differences between the methotrexate group and the placebo group in the mean titers of rheumatoid factor, the level of immune complexes, or the number and percentage of blood mononuclear cells expressing the phenotypic and activation markers measured in either Period 1 or 2 of the trial (data not shown). No functional indication of methotrexate-attributable immunosuppression was found in the thymidine-incorporation assays. Likewise, no distinguishing immunologic alterations occurred in the subgroup of eight patients with dramatic responses to methotrexate. Six (18 per cent) of the 33 patients who received methotrexate in the trial had stimulation indexes of less than 2 in response to all antigen challenges at study entry. These anergic patients had a lower T4/T8 ratio at entry than the 27 patients with responses to antigens in vitro, although this tendency was not statistically significant (mean ratio ±S.E., 1.6±0.7 for the

Table 3. Patients' Responses to Treatment.*

Variable	Treatment	Degree of Response				
		Marked Improvement	Moderate Improvement	Improvement	No Change	Worsening
		no. of patients				
Joint-swelling index	Methotrexate	13 (39%) †	7	—	13	0
	Placebo	2 (11 %)	2	—	14	0
Joint-tenderness/pain index	Methotrexate	18 (54%) ‡	6	—	9	0
	Placebo	3 (17%)	0	—	12	3
Physician assessment	Methotrexate	—	—	12 (36%) ‡	21	0
	Placebo	—	—	0	17	1
Patient assessment	Methotrexate	—	—	14 (42%) ‡	19	0
	Placebo	—	—	1 (6%)	16	1

*The frequency of responses was determined for 33 patients who received methotrexate in either Period 1 or Period 2 of the study, and was compared with the pattern observed in a control group of 18 patients randomly assigned to placebo at entry. The degree of response represents either the change observed after 12 weeks of test medication or, for the two patients given methotrexate and the two given placebo who did not complete 12 weeks of treatment, the response recorded at the final visit.

†$P<0.05$.

‡$P<0.01$.

anergic group vs. 2.4±0.2 for the immunocompetent group). This functional alteration in immunocompetence was not associated with prednisone therapy.

Discussion

The results of this study confirm uncontrolled reports of the antiinflammatory effect of low-dose methotrexate in patients with advanced rheumatoid arthritis that is resistant to conventional therapy.[2,3] The recrudescence of the disease after methotrexate therapy and the significant methotrexate-associated difference in disease variables between the groups at crossover make it difficult to determine the degree of benefit attributable to the drug in the Period-2 trial. Gastrointestinal problems were the most common adverse reactions to methotrexate in this short-term trial. The relatively small number of patients involved may explain why the more serious adverse reactions that can occur with low-dose methotrexate administration — e.g., bone-marrow suppression[17] or acute pulmonary toxicity[18,19] — were absent in this study. Transaminase elevation occurred in 21 per cent of the patients receiving methotrexate. The importance of these enzyme elevations is uncertain; long-term administration of low doses of methotrexate may be associated with hepatotoxicity.[17,20]

One important question is whether subsets of patients with rheumatoid arthritis will have a better response to methotrexate. There was no indication that patients receiving concomitant low-dose prednisone therapy benefited more from methotrexate than patients not taking this glucocorticoid. The results of this study are consistent with the proposal that a small subpopulation of anergic patients with rheumatoid arthritis exists[21,22]; the response of the patients to methotrexate did not exceed that of the immunocompetent participants, and they remained anergic after therapy with this drug. The observation, which requires confirmation, that patients with the HLA-DR2 haplotype respond markedly to low-dose methotrexate therapy is of interest. Earlier reports have related HLA-DR2/Dw2 with a better outcome in rheumatoid arthritis.[23,24]

This trial, as well as the initially reported results of a randomized multicenter study,[25] provides evidence of the short-term value of low-dose methotrexate in patients with rheumatoid arthritis uncontrolled by more conventional therapy. Lengthy prospective trials are required to determine the ultimate benefits and disadvantages of this treatment.

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