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Methotrexate Therapy in Psoriatic Arthritis

Double-Blind Study on 21 Patients

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A double-blind study comparing the response of 21 patients with psoriatic arthritis to a series of three parenteral injections of methotrexate at 10-day intervals with the response to a similar series of three placebo injections has been reported. Methotrexate was found to be effective in suppressing the skin manifestations, decreasing joint tenderness and swelling, improving joint range of motion, and decreasing the erythrocyte sedimentation rate. Side effects included anorexia or nausea in 13 patients, burning sensation in the skin in ten, depression of the white blood cell count below 4,000/cu mm in seven, oral ulcerations in two, and mild hair loss in one. This therapy should be reserved for patients with severe disabling disease who have failed to respond to more conservative measures.

IN 1951 Gubner and co-workers [1] reported good results from oral administration of sodium aminopterin in six of seven patients with rheumatoid arthritis. They also treated six patients with psoriatic arthritis; skin lesions improved in all and the arthritic condition improved in three. However, these workers concluded that "the toxic effects of sodium aminopterin place practical limitations on its use as a therapeutic agent."

The present authors reported preliminary experience with another antifolic agent, methotrexate, in the treatment of psoriatic and rheumatoid arthritis in 1962.[2] The initial observation of favorable response in psoriatic, but not rheumatoid, arthritis encouraged us to design and conduct a double-blind study comparing the effects of methotrexate and a placebo in the treatment of patients with psoriatic arthritis. The results of this study form the basis of this report.

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Design of Study

Patients age 18 years and over were admitted to the study, provided that both psoriasis and inflammatory joint disease were present, and that either disorder was of at least one year's duration. Excluded from the study were patients who had severe renal or liver disease, severe infection, or a hematological disorder, such as neutropenia, severe anemia, or thrombocytopenia. Pregnancy was also cause for exclusion. Participation in the study required a minimum hospital observation period of 80 days.

The first 20 days provided time for adequate assessment of skin and joint involvement, stabilization of the clinical state, and complete, pretreatment radiographic and laboratory evaluation. Throughout the study the patients were treated with local applications of a bland ointment (Eucerin) to the skin. When patients had previously received either corticosteroid or salicylate therapy or both, dosage was reduced to a level at which a slight increase in skin lesions or joint symptoms occurred. This minimum maintenance dosage then remained constant throughout the study. Although their activity was not otherwise limited, patients were not permitted to be exposed to sunlight.

During the first 14 days each patient received a single 25-mg parenteral dose of methotrexate to test for hypersensitivity to this preparation. A profound reaction to this dose would have excluded the patient from further study, but no such reaction occurred. From the first bottle, either methotrexate or a placebo according to a randomized schedule, each patient then received a series of three injections (intravenous when possible, otherwise intramuscular) at intervals of 10 days. The schedule included progressively increasing doses from 1 to 3 mg per kilogram of body weight. When clinical improvement occurred prior to the

third injection, the third dose was kept at 2 mg/kg. If at any time the white blood cell (WBC) count fell below 4,000/cu mm or the platelet count fell below 100,000/cu mm, the next scheduled dose was withheld. On completion of the first series of injections, three successive injections of the alternate preparation were administered at the same dosage schedule, again at intervals of 10 days.

During the entire study the status of skin and joint involvement was evaluated twice weekly by the same observer. The area of skin involved was estimated and expressed as a percentage of total body surface. Joints were evaluated and scored on a 0 to 3 scale for pain on motion, tenderness, and swelling; the total score for all joints for all three variables comprised the "joint index." The range of motion (ROM) of hips, knees, ankles, shoulders, elbows, and wrists was measured weekly, and the score expressed as a percentage deficit of the normal. Westergren erythrocyte sedimentation rate (ESR) was determined and WBC and platelet counts were performed twice weekly. Blood urea nitrogen (BUN) and serum glutamic oxalacetic transaminase (SGOT) determinations were made weekly. Sulfobromophthalein excretion (BSP), and alkaline phosphatase, cholesterol, and serum protein levels were determined monthly.

Composition of Series

Twenty-one patients participated in this double-blind study, 11 females and ten males (Table 1). The ages ranged from 29 to 62 years. One woman, who participated in the methotrexate phase only and showed dramatic improvement in skin and joint manifestations, was dropped from the series when after three injections she developed severe thrombophlebitis, and it was considered unwise to continue the double-blind regimen.

Duration of psoriasis ranged from 2 to 49 years; the mean duration was 16 years. The extent of skin surface affected was 6% in one patient, between 11% and 25% in five, between 26% and 50% in another five, between 50% and 75% in four, and over 76% in six; five of the latter six had between 90% and 100% skin surface involvement. In every case, scalp and nail lesions of psoriasis were observed. Eleven of the patients exhibited appearance of a psoriatic lesion at the site of trauma (Koebner phenomenon).

All patients had had arthritis ranging in duration from six months to 30 years (three for only six months). The mean duration of arthritis was eight years. All 21 patients had clinical signs of involvement of the small joints of the hands and, in all but one patient, distal interphalangeal joints were affected. Symptoms of spinal involvement, most frequently in the cervical region, were present in 12 patients. The knees were affected in 15.

Table 1.—Composition of Series

Age Group, Yr	Duration of Psoriasis, Yr					
	2-5	6-10	11-15	16-20	21-25	>26
20-29		1 F†				
30-39	3 M*		1 F 1 M			
40-49		1 F 1 M	1 M	1 M	2 F	
50-59		1 F 2 M			1 F	3 F
60-69			1 M			1 F

*M — male; †F — female.

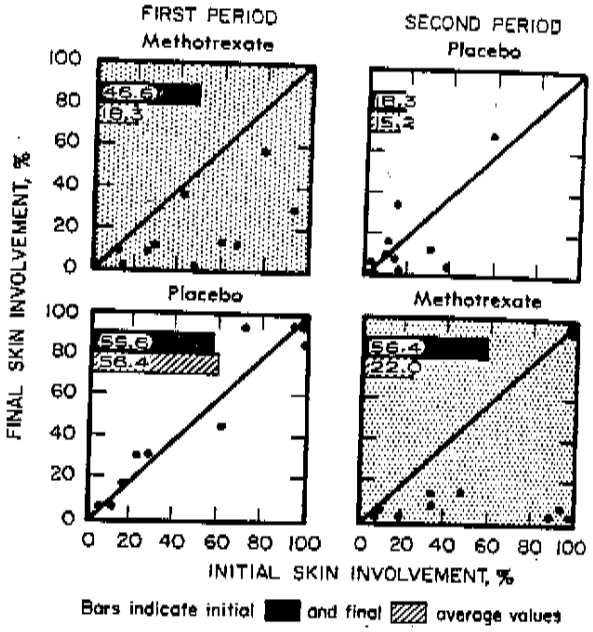

Fig 1.—Changes in percentage of skin involvement during double-blind study. Degree of improvement reflected by distance at which plotted point falls below diagonal line.

Fourteen of the patients reported a synchronous relationship between exacerbations of skin involvement and increasing severity of joint disease; abatement of arthritis followed recession of skin lesions, either spontaneously or in response to treatment. All 21 patients had morning stiffness; none had subcutaneous nodules. The bentonite flocculation test for rheumatoid factor yielded repeatedly negative results in 20 of the 21 patients. In the one patient with a positive result, the titer was 1:64; this patient had extensive psoriasis and distal interphalangeal joint involvement. Lupus erythematosus cell preparations gave negative results in all cases.

All 21 patients had previously received topical medication (usually tar ointment) for the psoriasis. All but one had received systemic corticosteroid therapy with inadequate or unsatisfactory improvement in the skin or joint disorder. Four patients had previously received chloroquine phosphate for treatment of their arthritis; three of these four had experienced a marked exacerbation in skin disease following administration of this drug; in one, the exacerbation occurred after only nine days of therapy.

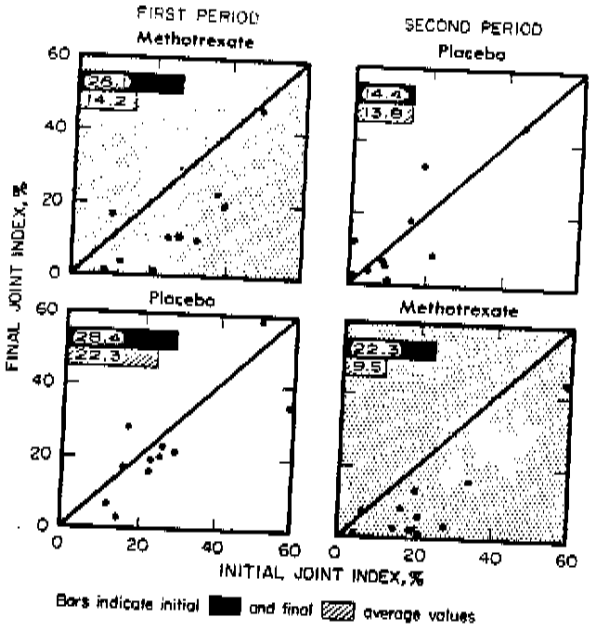

Fig 2.—Changes in severity of joint involvement during double-blind study.

Results

By random selection, ten patients, six men and four women, received a course of methotrexate prior to the placebo (group AB). The remaining four men and seven women received a placebo before methotrexate (group BA). An attempt was made to reduce or withdraw the corticosteroid medication in all patients receiving these compounds prior to the study. In eight patients, it was necessary to continue corticosteroid administration during the trial in doses varying from a minimum of 6 mg of triamcinolone daily to a maximum of 20 mg of prednisone daily. Three of these eight patients were in group AB and five were in group BA. Four of these patients also received aspirin daily. Two patients in group AB and three in group BA received maintenance dosage of aspirin without a corticosteroid during the period of observation.

The response to methotrexate was favorable in most instances. Figure 1 shows the changes in skin involvement during the double-blind study. The upper two diagrams illustrate the response of the ten patients who received the antifolic compound prior to a placebo (group AB). The percentage of skin surface involved prior to drug administration is plotted along the horizontal axis, and that at the end of the study is plotted on the vertical. If, hypothetically, no improvement would occur in a given patient, then the point plotted for that patient would fall exactly on the 45° diagonal. The degree of improvement, therefore, is reflected by the distance at which a plotted point falls below the diagonal line. It will be noted that the average area of skin involved prior to administration of methotrexate in this first group was more than 46%, whereas the final involvement averaged 18%. Very little change was observed during the placebo period, the average changing from 18% to 15%. In group BA there was no change in the area of skin involved during the placebo phase; however, when the drug was given the average extent of skin involvement fell from 56% to 22%.

In both groups the most pronounced improvement occurred after the second injection of methotrexate (between 10 and 20 days after the first injection). It is of interest that some changes in the skin often followed the first injection; first, there was a decrease in the amount of scale formation, followed by a softening in the texture of the skin, but a persistence of erythema. A decrease in the area of skin involvement was not recorded until the area of erythema showed clearing. Four patients in the entire series failed to show improvement in their skin condition during the administration of the antifolic compound. One of these was in group AB, receiving methotrexate first and the placebo later. This patient was treated at a later date with methotrexate and showed complete clearing of skin manifestations. The other three patients were in group BA, receiving the placebo first. One of these patients, described later, died. One other was treated at a later date and responded with complete clearing of the skin. The remaining patient was not retreated.

Figure 2 illustrates the changes that took place in the severity of joint involvement in these patients. The joint index prior to the start of the study is plotted along the horizontal axis and the final score along the vertical axis. It will be noted in Fig 2 that in both groups AB and BA there was a decidedly greater decrease in the average joint index during methotrexate administration than during the placebo periods. In general, the joint improvement occurred somewhat less rapidly than did the favorable change in the skin.

Table 2.—Undesirable Side Effects of Methotrexate in Treatment of 21 Patients With Psoriatic Arthritis

Side Effect	No. of Patients
Gastrointestinal (in 16 of 21 patients)	
Decreased appetite	14
Nausea	13
Abdominal pain (mild)	2
Oral ulceration	2
Dermatological	
Burning sensation (skin)	10
Bleeding from skin	4
Mild hair loss	1
Hematological (in 7 patients)	
WBC less than 4,000/cu mm	7
Platelets less than 100,000/cu mm	1
Hemoglobin less than 10 gm%	3
Disturbance in hepatic function	
Increase in BSP	1
Transient elevation in SGOT	3

Improvement in ROM of joints was observed in all patients during the study. The average percentage deficit in ROM decreased from 16.5 to 13.2 in the patients receiving the drug first. There was little change during the placebo period, the average changing from 13.2% to 12.7%. The second group of patients showed little change during the early stage of the placebo period, the score varying from 18% to 17.2%. During the drug phase the score changed from 17.2% to 15%.

The ESR was determined twice weekly. In group AB the average ESR fell from 55 to 39 mm per hour during methotrexate administration and changed from 43 to 45 mm per hour during the placebo period. In group BA the average ESR fell from 71 to 64 mm per hour during the placebo phase and from 64 to 48 mm per hour during the methotrexate phase.

Statistical Analysis.—Statistical analysis of the data was performed by Wilcoxon's ranking method,[3] as modified by White,[4] to compare two treatments where the numbers in two groups are not necessarily the same. Since the response data are not normally distributed along the "bell-shaped" curve, conclusions drawn from an analysis of variance based on normal distribution are invalid. Wilcoxon's test, however, makes no assumptions as to the underlying distribution, and although there is some loss of information with "ranking," the conclusions are valid. The tables used in calculating the significance are those of Mainland.[5]

The overall significance of treatment A (methotrexate) was compared to treatment B (placebo) by ranking the difference in improvement scores of group AB (A minus B, which should be positive if A is effective) and group BA (B minus A, which should be negative if A is effective). The results were effect on the joints, $p=0.01$; effect on skin, $p<0.01$; effect on ESR, $p<0.01$; and effect on ROM, $p=0.01$. Response to treatment by methotrexate was definitely superior to that from the placebo in all parameters measured.

Adverse Side Effects and One Death.—Side effects observed in the group of patients during treatment with methotrexate fall in four general categories and are listed in Table 2. Gastrointestinal symptoms occurred in 16 of the 21 patients; decrease in appetite was the most frequent complaint, and nausea occurred in 13 patients. Two patients had mild abdominal pain and two others developed buccal ulcerations. Ten patients reported a burning sensation of the involved skin areas during the 24- to 48-hour period following injection of methotrexate. The sensation was relatively mild in all but four patients who experienced bleeding from the skin at the site of previous psoriatic plaques. One patient had mild hair loss, a symptom which gradually decreased after the last dose of the drug. Seven patients showed a decrease in WBC count to less than 4,000/cu mm; in one patient the leukocyte count fell to less than 1,000/cu mm and platelets to below 100,000/cu mm. In all cases the changes were transitory and recovery was complete within one week. In three patients an elevation in SGOT levels was observed. This was transient, returning to normal within ten days following the injection. One patient showed an increase in BSP retention to 20%, detected six days following an intravenous injection of 100 mg of methotrexate. In spite of this abnormality methotrexate was administered on three subsequent occasions (twice in a dosage of 150 mg) and three days after the last injection, the BSP retention was only 7%.

One patient, a 39-year-old male, died during the period of methotrexate administration. This patient had had psoriasis for 13 years and arthritis for six months. During the eight months preceding the patient's admission he had received prednisone, 30 mg daily, for his psoriasis. Three doses (50 mg, 100 mg, and 150 mg) of methotrexate were administered intravenously at ten-day intervals. On the day prior to the third dose, the patient's WBC count was 9,000/cu mm, SGOT, 8 units, and platelets, normal value. Four days after the injection the WBC count fell to 1,200/cu mm, on the sixth day to 600/cu mm, reaching 400/cu mm on the seventh day. Platelets fell to 26,000/cu mm. At this time the patient developed abdominal pain, and aspirate from the stomach was dark brown and contained blood (guaic-positive). Two WBC transfusions from donors with chronic myelogenous leukemia and platelet transfusions were administered. There was a progressive rise in the WBC count to 5,400/cu mm on the tenth post-injection day, 8,400/cu mm on the next day, and 18,000/cu mm on the 12th day. The SGOT value during this period reached a peak of 200 units. Cortisone acetate was given, 300 mg daily intramuscularly, during this period of stress. On the 13th post-injection day, the patient had an episode of hematemesis and died. In addition to generalized pustular psoriasis and chronic arthritis, autopsy revealed a single massive and multiple small pulmonary emboli. The marrow showed a leukemoid reaction. Subacute ulcerative esophagitis was found, with an estimated 500 ml of blood in the bowel. Focal areas of central lobular necrosis were observed in the liver. Death was believed to be due to the large pulmonary embolus. Although a primary relationship between the administration of methotrexate and his death could not be established (the bone marrow was observed to have fully recovered prior to the patient's death), the fact remains that this death did follow immediately after a profound and serious reaction to the drug.

Follow-Up

The subsequent course of the 21 patients who have been treated with methotrexate in the double-

blind study is of considerable interest. In addition to the death already mentioned, a second patient died of cerebral thrombosis one month after completion of the study.

Two patients have received prolonged therapy with the drug in doses of 40 mg intramuscularly every 10 to 14 days; they have been observed over a six- and eight-month period, respectively, and have experienced no recurrence of their skin or joint manifestations.

For the remaining 17 patients, treatment was suspended upon completion of the double-blind study. Recurrence of skin and joint manifestations occurred in all—in 12 patients, within one to four months. Among the other five patients the shortest interval of remission was two weeks and the longest was 15 months. Six of these 17 patients have received intermittent doses of 40 to 60 mg of methotrexate following recurrence of their disease. In three of these six patients it was possible to reduce concomitant corticosteroid therapy by at least 50%. They were observed for periods of 1 to 12 months and in each case suppression of disease was maintained.

Comment

The biochemistry and mechanism of action of the folic acid antagonists has been reviewed recently by Holland.[6] The mechanism of action of these agents depends on inhibition of folic reductase, the enzyme which catalyzes the conversion of folic acid to citrovorum factor. Folic acid antagonists exert a potent inhibitory effect upon cell reproduction in rapidly growing tissue such as the bone marrow and certain neoplasms, especially choriocarcinoma.

The hazards of administration of folic acid antagonists—both reported and potential—are of considerable magnitude. This type of therapy therefore requires unusual caution—a conservative calculation of risks versus expected benefits, judicious selection of patients, and very close and alert observation of the patient during treatment. The dosage schedule adopted by us, consisting of relatively small individual and aggregate doses, long intervals between injections, and parenteral administration, was designed to minimize incidence and severity of toxic reactions. They were not eliminated, however, and one patient in our group died after a series of three injections of methotrexate.

Sodium aminopterin has been used to induce abortions. In those cases in which pregnancy continued, some newborns exhibited anomalies.[7] Folic acid antagonists are, therefore, contraindicated in pregnancy. These drugs also cause oligospermia.[8] Some leukemic children treated with these agents have developed fibrosis of the liver;[9] hepatic fibrosis has also been reported in an adult following methotrexate therapy for psoriasis,[10] although in this latter instance a direct causal relationship has not been established.

The clinical response in most patients treated by us was quite impressive, but nevertheless palliative, since the drug merely suppressed the disease. Relapses occurred in all cases after variable intervals following a course of three injections given at 10-day intervals. Fortunately, almost all patients continued to respond well to repeated courses. Although many totally disabled patients were restored to an ambulatory and employable state, there is as yet no evidence that the course of the disease was altered by methotrexate.

The authors are currently engaged in developing and evaluating a relatively safe, long-term regimen of treatment of severe psoriatic arthritis with antifolic acid agents. The fact that extensive cutaneous disease has been safely controlled with methotrexate administered at regular intervals for periods up to several years now suggests that this may be feasible.[11]

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Dr. Donald Mainland, Professor of Medical Statistics at the School of Medicine, New York University, assisted in the statistical design and interpretation of this study.

Generic and Trade Names of Drugs

Sodium aminopterin—*Aminopterin Sodium.*
Chloroquine phosphate—*Aralen Phosphate.*
Triamcinolone—*Aristocort, Kenacort.*
Prednisone—*Deltasone, Deltra, Meticorten, Paracort.*
Cortisone acetate—*Cortisone Acetate, Cortogen Acetate, Cortone Acetate.*

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