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METHOTREXATE IN RESISTANT JUVENILE RHEUMATOID ARTHRITIS

Results of the U.S.A.–U.S.S.R. Double-Blind, Placebo-Controlled Trial

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Abstract *Background.* The antimetabolite methotrexate has been shown in placebo-controlled trials to be effective in adults with rheumatoid arthritis. Methotrexate may also be effective in children with resistant juvenile rheumatoid arthritis, but the supporting data are from uncontrolled trials.

Methods. Centers in the United States and the Soviet Union participated in this randomized, controlled, double-blind trial designed to evaluate the effectiveness and safety of orally administered methotrexate. Patients received one of the following treatments each week for six months: 10 mg of methotrexate per square meter of body-surface area (low dose), 5 mg of methotrexate per square meter (very low dose), or placebo. The use of prednisone (≤10 mg per day) and two nonsteroidal antiinflammatory drugs was also allowed.

Results. The 127 children (mean age, 10.1 years) had a mean duration of disease of 5.1 years; 114 qualified for the analysis of efficacy. According to a composite index of several response variables, 63 percent of the children who received low-dose methotrexate improved, as compared with 32 percent of those in the very-low-dose group and 36 percent of those in the placebo group ($P = 0.013$). As compared with the placebo group, the low-dose group also had significantly larger mean reductions from base line in the number of joints with pain on motion (−11.0 vs. −7.1), the pain-severity score (−19.0 vs. −11.5), the number of joints with limited motion (−5.4 vs. −0.7), and the erythrocyte sedimentation rate (−19 vs. −6 mm per hour). In the methotrexate groups only three children had the drug discontinued because of mild-to-moderate side effects; none had severe toxicity.

Conclusions. Methotrexate given weekly in low doses is an effective treatment for children with resistant juvenile rheumatoid arthritis, and at least in the short term this regimen is safe. (N Engl J Med 1992;326:1043-9.)

JUVENILE rheumatoid arthritis is the most common rheumatic condition of childhood, with an annual incidence of about 1.4 cases per 10,000 children under the age of 16 years in the United States, and a prevalence of roughly 1 per 1000.[1,2] Three types of onset of juvenile rheumatoid arthritis are recognized, each of which has a characteristic clinical, epidemiologic, and genetic pattern.[3] The systemic-onset form produces a rheumatoid rash and intermittent fever (temperature, >39.4°C, with daily return to normal); anemia, pericarditis, and hepatosplenomegaly are common. The arthritis usually involves multiple joints. Polyarticular onset is characterized by arthritis in five or more joints, and oligoarticular onset (also referred to as pauciarticular) is characterized by arthritis in fewer than five joints. Rheumatoid rash and intermittent fever are absent in the polyarticular and oligoarticular forms, although other systemic manifestations may occasionally be present.

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Approximately one third of all patients with juvenile rheumatoid arthritis achieve adequate control of their disease with nonsteroidal antiinflammatory drugs; the remainder are candidates for more aggressive therapy with second-line agents. In large randomized trials in adults with refractory rheumatoid arthritis, the antimetabolite methotrexate has had therapeutic advantage over placebo, with an acceptable safety profile.[4,5] Long-term studies have shown that the therapeutic effect of methotrexate may persist for extended periods.[6-11] Anecdotal reports and the results of uncontrolled trials of the efficacy and safety of low-dose methotrexate in juvenile rheumatoid arthritis have been encouraging.[12-17] For these reasons the Pediatric Rheumatology Collaborative Study Group (PRCSG), in conjunction with colleagues in the then Soviet Union, conducted this double-blind, randomized, placebo-controlled trial to assess the therapeutic effects of two different doses of methotrexate in children with resistant juvenile rheumatoid arthritis.

METHODS

The study was conducted under the Cooperation in Medical Science and Public Health Agreement (signed on May 23, 1972, in Moscow) and was a collaborative effort between physicians and scientists in the United States and the Soviet Union. A total of 23 pediatric rheumatology centers in the two countries participated (18 in the United States and 5 in the Soviet Union).

Study Design

The investigation was designed as a prospective, parallel, multicenter, placebo-controlled, randomized, double-blind clinical trial of six months' duration. Randomization was in blocks of three

as 40 percent in the rate of response between the active drug and placebo was considered important to detect as statistically significant. We estimated that approximately 30 percent of the patients given placebo would be classified as improved. According to the tables presented by Gehan and Schneiderman,[28] and assuming the use of two-tailed tests, a minimum of 30 patients were required in each group.

We tested proportional data for significance using the chi-square test or, where appropriate, Fisher's exact test. Statistical significance by the chi-square test was required for tables with more than 1 degree of freedom before partitioning. For continuous variables, mean values were compared by one-way analysis of variance. When multiple-range tests became appropriate, Dunnett's method for making multiple comparisons with a placebo[29] was used. Two-way analysis of variance was used to test for the effects of drug and country on the change in articular indexes. The Bonferroni correction was used to adjust for the testing of multiple hypotheses ($n = 12$) among secondary variables and in the analysis of response in subgroups of patients. Both unadjusted and adjusted values are shown, however, if a P value was significant (≤ 0.05) before correction, and the results are referred to as statistically significant.

Emphasis was placed on the intention-to-treat analysis rather than the analysis of those who completed the entire six-month trial. The intention-to-treat technique used the values of response variables at the final visit, whether or not the patient completed the entire trial. This approach offered several advantages: more patients were available for the analysis of efficacy, data on those who dropped out before completion could be included, and it more closely reflected how physicians evaluate a therapeutic agent in the clinical setting, outside an experimental protocol.

Results

A total of 127 patients (96 girls and 31 boys) were enrolled in the trial (66 in the United States and 61 in the Soviet Union). Age and duration of disease at entry averaged 10.1 and 5.1 years, respectively. The disease course was systemic in 32 patients (25 percent), all of whom also had polyarthritis. Forty-six children received low-dose methotrexate, 40 received very-low-dose methotrexate, and 41 were given placebo. Randomization worked well; there were no significant differences among the treatment groups in any of the demographic or disease characteristics shown in Table 1. Patients from the two countries were distributed about equally among the three treatment groups. Those from the United States had a higher mean (±SE) number of joints with active arthritis (27±2 vs. 20±2, $P<0.046$), but the mean articular-severity score (112) was the same for the two countries.

Indomethacin was the most frequently used concurrent nonsteroidal drug (26 percent), followed by naproxen (18 percent), tolmetin sodium (17 percent), diclofenac sodium (16 percent), aspirin (16 percent), and other agents (6 percent).

Efficacy

Patients were included in the analysis of efficacy if they met all eligibility criteria, received the study drug in blinded fashion for a minimum of one month, were 100 percent compliant with the prescribed regimen during at least 80 percent of the follow-up period, and complied with the other specifications of the protocol regarding restrictions on other medications and return visits to the clinic.

Table 1. Demographic and Clinical Characteristics of the Patients at Entry, According to Study Group.

Characteristic*	Low-Dose Methotrexate (N = 46)	Very-Low-Dose Methotrexate (N = 40)	Placebo (N = 41)
Age (yr)			
Average	10.1	9.6	10.6
Range	2.5–17.5	3.3–17.4	3.2–17.8
Disease duration (yr)			
Average	4.8	4.8	5.8
Range	0.6–13.5	0.5–11.8	0.5–14.4
No. (%) female	33 (72)	29 (73)	34 (83)
No. (%) taking low-dose prednisone	15 (33)	15 (37)	14 (34)
No. (%) taking two NSAIDs†	5 (11)	3 (7.5)	3 (7.3)
No. (%) with systemic-onset disease	9 (20)	11 (28)	12 (29)
Mean (±SE) no. of joints with active arthritis‡	27 (2)	21 (2)	24 (2)

*There were no significant differences among the treatment groups in any of the characteristics.

†NSAID denotes nonsteroidal antiinflammatory drug.

‡See the Methods section for a definition of active arthritis.

Of the 127 enrolled patients, 114 (90 percent) qualified for the analysis of efficacy, including 38 (83 percent) of the 46 in the low-dose group, 37 (92 percent) of the 40 in the very-low-dose group, and 39 (95 percent) of the 41 who took placebo. Among the 13 patients excluded from the efficacy analysis, 8 violated the specified doses for concurrent nonsteroidal agents, 3 violated the prednisone regimen, 1 was noncompliant in taking the study medication, and 1 was discovered to have had fewer than three joints that met the criteria for active arthritis at the base-line visit.

Only 11 of the 114 children in the efficacy subgroup took two concurrent nonsteroidal agents during the trial. These patients were equally divided among the treatment groups, and their data were not considered separately. A total of 40 patients in the efficacy subgroup received low-dose prednisone during the trial, including 14 who were given low-dose methotrexate and 13 in each of the other two groups. Since the numbers were small and the dose low and constant, data for those who received prednisone were not analyzed separately.

Among the 127 randomized patients, 108 completed the entire six-month trial, including 97 (85 percent) of the 114 in the efficacy subgroup.

Global Assessment

Figure 1 shows the percentages of patients at each return visit who had clinical improvement from their base-line condition, according to the physician's global assessment. Both methotrexate groups had consistently higher proportions of patients with improvement than the placebo group. According to the physician's final global assessment, a significantly higher proportion of patients improved in the low-dose group than in the placebo group (χ^2 with 2 df = 7.53, P = 0.023). Those in the very-

tion of the oral mucosa accompanied by headache and gastrointestinal problems. Five of the 41 patients who took placebo (12 percent) had side effects, all of which were gastrointestinal. All side effects were graded as either mild or moderate in severity, except for two episodes of stomach pain graded as severe in a patient receiving placebo. No patient had evidence of methotrexate-induced pulmonary disease during the trial.

Laboratory Evidence of Toxicity

Patients who received methotrexate had more abnormal results on laboratory tests that were judged to be clinically important and possibly, probably, or definitely related to the study medication than those given placebo. Fifteen patients who received low-dose methotrexate, 15 who were given very-low-dose methotrexate, and 5 who were given placebo had such results. Among the patients given methotrexate, the most frequent abnormal results were alterations in the differential white-cell count, hematuria, pyuria, and the elevation of serum aminotransferase levels. Elevations of aminotransferase levels and anemia were the most frequent abnormal results among the patients given placebo. Other clinical-chemistry data were unremarkable.

Dropouts

A total of 19 patients (10 in the United States and 9 in the Soviet Union) discontinued therapy before completing the six-month trial (Table 3). Two patients in the low-dose group dropped out because of adverse effects: persistent elevations of serum aspartate and alanine aminotransferase (levels up to 120 IU per liter) in one and persistent hematuria in the other. Both problems resolved quickly after the discontinuation of the study medication. One patient given very-low-dose methotrexate had a persistent skin rash and was dropped from the study one month after entry. The total numbers of dropouts were not significantly different among the groups.

Discussion

The results of this trial confirm anecdotal reports and evidence from uncontrolled trials that low-dose methotrexate has antiinflammatory activity and clinical effectiveness in resistant juvenile rheumatoid arthritis. We also found a trend toward a dose–response relation in the low-dose and very-low-dose methotrexate groups, similar to that reported by Furst et al.[30] in adult rheumatoid arthritis. The favorable findings from the present study should be encouraging news for clinicians faced with managing a child's disease that has failed to respond adequately to nonsteroidal drugs. Methotrexate has distinct advantages over other second-line agents, including its oral route of administration, once-a-week dosage, lack of known oncogenicity, and lack of long-term effects on fertility. The choice of which second-line agent to use initially has become more difficult in recent years, after controlled trials and long-term prospective studies showed a lack of efficacy among the agents in common use.[19-21,31] Parenteral gold remains a therapeutic option, but its considerable toxicity[32] and inconvenience must be considered. Furthermore, injectable gold salts have never been assessed in a controlled trial in children with arthritis. Thus, the tendency among pediatric rheumatologists to consider the use of methotrexate earlier in the disease, and before other second-line agents, is likely to continue.

There was a consistent trend in this study toward greater improvement in the low-dose group across all indexes of articular disease; some of the mean changes were not statistically significant, however. The variability of the changes within the treatment groups, the limited sample size, the corrections for testing of multiple hypotheses, and the high rate of response to placebo in all previous PRCSG studies undoubtedly affected our ability to detect some changes as statistically significant. The recent development of a childhood health-assessment questionnaire and functional-ability tool may provide more sensitive measures of response in future trials.[33,34] Nevertheless, the results obtained here represent by far the most encouraging data from a trial of a second-line agent undertaken by the PRCSG.

The equality of response across treatment groups in the subgroup of patients with severe disease is unexplained. Since all three groups showed dramatic improvement in the articular-severity score, it is possible that there was a greater regression toward the mean in these children with severe disease that effectively blurred any difference in response produced by methotrexate.

The concurrent administration of aspirin is known to slow systemic and renal clearance and increase the unbound fraction of methotrexate, perhaps resulting in greater toxicity.[35] We did not observe such an association among the 20 children (16 percent) who took aspirin. Among the 14 children who had clinically important physical adverse effects while receiving methotrexate, 2 (14 percent) were taking aspirin. Among the 30 children treated with methotrexate who had substantial abnormalities in laboratory indexes of toxicity, 4 (13 percent) were receiving aspirin.

Although mild elevations of serum aminotrans-

Table 3. Reasons Patients Left the Study, According to Study Group.

Reason	Low-Dose Methotrexate (N = 46)	Very-Low-Dose Methotrexate (N = 40)	Placebo (N = 41)
	no. of patients (%)		
Ineffectiveness of drug	0 (0)	2 (5)	5 (12)
Adverse effects	2 (4)	1 (2)	0 (0)
Intercurrent illness	2 (4)	2 (5)	1 (2)
Administrative reasons	2 (4)	0 (0)	1 (2)
Noncompliance with protocol	1 (2)	0 (0)	0 (0)
Total	7 (15)	5 (12)	7 (17)

ferase levels were common in all the study groups, only four children in the low-dose group, one in the very-low-dose group, and one in the placebo group had markedly elevated (more than two times the upper limit of normal) enzyme levels (range, 85 to 134 IU per liter). Possible explanations for the lack of hepatotoxic effects include the duration of the trial, the administration schedule of a single dose per week, and the low cumulative doses to which the children had been exposed. Also, previous concern about the hepatic toxicity of methotrexate may have been exaggerated.[36] A prospective study of the children who received methotrexate during this study is now under way to evaluate long-term outcome and safety.

In conclusion, methotrexate at a dose of 10 mg per square meter per week appears to have greater clinical effectiveness than placebo in children with juvenile rheumatoid arthritis. The short-term safety profile is acceptable. Given the results of previous trials by the PRCSG, the use of methotrexate as the initial second-line agent in resistant juvenile rheumatoid arthritis appears to be justified.

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