Efficacy of Methotrexate in Ankylosing Spondylitis: A Randomized, Double Blind, Placebo Controlled Trial

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ABSTRACT. ***Objective.*** To evaluate the efficacy and safety of methotrexate (MTX) compared with placebo in patients with active ankylosing spondylitis (AS).

Methods. This 24 week, double bind, randomized, placebo controlled trial compared the response between MTX 7.5 mg/week or placebo in patients with active AS. The primary outcome measure was a composite index of improvement in 5 of the following scales: severity of morning stiffness, physical well being, the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), the Bath Ankylosing Spondylitis Functional Index (BASFI), the Health Assessment Questionnaire for Spondyloarthropathies (HAQ-S), and physician and patient global assessment of disease activity.

Results. Seventeen patients received MTX and 18 placebo. In the intention-to-treat analysis at 24 weeks, 53% of patients in the MTX group had a treatment response, compared with 17% in the placebo group ($p = 0.03$). We observed significant improvements with MTX in physical well being ($p = 0.009$), BASDAI ($p = 0.02$), BASFI ($p = 0.02$), physician global assessment ($p < 0.001$), patient global assessment ($p = 0.03$), and HAQ-S ($p = 0.02$). In the adjusted analysis only MTX determined the improvement in the primary outcome. At the end of the trial, one patient with MTX withdrew due to a lack of compliance, and one with placebo due to a lack of efficacy. We did not observe significant differences in rates of side effects between the 2 groups.

Conclusion. MTX is safe and effective for patients with AS. Longterm studies are needed to evaluate the permanence of its benefit. (J Rheumatol 2004;31:1568–74)

Key Indexing Terms:
ANKYLOSING SPONDYLITIS METHOTREXATE RANDOMIZED CONTROLLED TRIAL

Ankylosing spondylitis (AS) is a chronic inflammatory disorder of the axial skeleton, affecting mainly the sacroiliac joints and the lumbar spine, leading in severe cases to spinal ankylosis[1]. No disease controlling antirheumatic drugs currently used to treat AS are considered the gold standard. Sulfasalazine is useful for many patients, improving morning stiffness, pain, and general well being[2]. Its efficacy is more often observed in patients with peripheral joint manifestations, but is discussed in patients with axial manifestations[3]. In contrast, during followup a high proportion of patients treated with this drug may develop a lack of response or unacceptable side effects requiring other therapeutic options. Recently, placebo controlled studies have described the efficacy of infliximab[4] and etanercept[5] for active spondyloarthropathies (SpA). Nevertheless, the high cost of these biological therapies constitutes an important limitation for many patients[6].

Methotrexate (MTX) is a synthetic analog of folic acid, used successfully in a variety of inflammatory connective tissue diseases, mainly rheumatoid arthritis (RA). Case reports and uncontrolled studies suggest that MTX may be an effective drug for AS[7-11]. In a Medline search from 1966 to March 2003, using the key words "methotrexate" and "ankylosing spondylitis," we were able to find only 2 controlled studies[12,13]. Both studies showed no benefits of MTX compared with the control group. However, one of the studies was not blinded, and neither used a composite index for efficacy; therefore, the power of both studies for detecting differences was insufficient. Evidence provided by double blind controlled clinical trials is required to calculate the effect size of disease controlling antirheumatic treatments in this disease. We conducted a 24 week, randomized, double blind placebo controlled trial to evaluate the efficacy and safety of MTX in the treatment of AS.

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MATERIAL AND METHODS

Patients. The study was conducted from January 2000 to June 2002. Patients were recruited from an outpatient rheumatology clinic in Guadalajara, Mexico. Patients with AS were eligible if they met the modified New York criteria[14] and since diagnosis had a duration of AS of at least one year. Patients were required to have active disease at the time of the baseline evaluation. Activity was defined by the combination of 3 conditions: (1) a disease activity score of at least 30 mm on a 0 to 100 mm visual analog scale (VAS) as assessed by the physician, based on the question, "How would you describe the current level of disease activity in this particular patient with ankylosing spondylitis?" (0 mm representing absence of disease activity and 100 mm very severe activity); (2) presence of inflammatory back pain (stiffness and pain worsening with rest and improving with exercise); (3) plus at least one of the following indicators: (i) morning stiffness ≥ 45 minutes [question 6 of the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)[15]], and/or (ii) presence of peripheral arthritis (based on the 44-joint count). Patients had to be 18 years of age or older. Additionally to be eligible, patients were required to be receiving stable doses of antiinflammatory drugs. Disease controlling antirheumatic drugs were not allowed for at least 8 weeks before entry. Patients of childbearing potential during the trial were required to have both a negative pregnancy test result and to follow an appropriate contraceptive method.

Patients were not eligible if they had previously been treated with MTX or had history of hepatitis or pneumonitis or diagnosis of anemia with a hemoglobin level < 11 g/dl, active infections, alcohol or drug abuse, mental or psychiatric disorders, or if they required treatment with intravenous methylprednisolone, oral corticosteroids or immunosuppressive drugs. All patients provided written informed consent before entering the study.

Study design. The study was a 24-week, single center, randomized, double blind, placebo controlled trial comparing MTX and placebo in treating AS. The study protocol and the consent form were approved by the Research and Ethics Committee of the participating hospital (approval number IMSS 98/259/043).

Randomization. An independent investigator from the Department of Public Health at the University of Guadalajara generated a simple randomization through a computer generated random list. A numerical code was assigned to every patient, then each number was randomly assigned in a 1:1 distribution to one of the 2 treatment groups. The sequence of numbers was given to a researcher from the Department of Pharmacology at the University of Guadalajara who prepared the sequentially numbered identical containers according to the allocation sequence. All medication was provided by an independent researcher who was not involved in the randomization. The patients and researchers involved in administration of the interventions, clinical evaluations, and statistical analyses were blinded to the treatment assignment for the duration of the trial. The code was open to the researchers once recruitment, data collection, and statistical analysis of the final results were completed.

Study drug administrations. After the randomization every patient was assigned to receive orally 3 identical capsules, each containing MTX 2.5 mg (Ledertrexate™, Wyeth-Ayerst Lederle Inc.) or placebo administered weekly. All patients were instructed to select a single day of the week for taking 2 capsules in the morning and one capsule at night. The doses of MTX or placebo were kept stable throughout the study.

Preparation of MTX and placebo. To assure blindness of the study all the capsules were identical (red and white color) and coded by personnel outside the study. The codes were kept blinded until the end of the trial.

Cointerventions. All patients continued receiving nonsteroidal antiinflammatory drugs (NSAID) during the trial. The use of analgesics for pain was allowed. Administration of intramuscular diclofenac 75 mg twice a day for 3 days was allowed during episodes of peripheral arthritis based on an arbitrary clinician judgment of the severity of the arthritis. All doses of intramuscular diclofenac were administered after the assessment of the response at each visit. The clinicians were free to prescribe folic acid supplements of 1 mg/day administered orally to those patients who developed gastrointestinal side effects; the decision to prescribe this drug was made independently of the investigator who evaluated the clinical response.

Efficacy: primary outcome. Based on the utility shown by the 20% improvement in the composite index proposed by the American College of Rheumatology to assess clinically significant responses in RA trials[16], and the lack of standard composite indexes to evaluate therapeutic response in AS at the time this study started, we designed our own index based on a combination of domains recommended by the Assessments in AS Working Group[17]. We tested the hypothesis that MTX would improve the response in a prespecified composite index for AS with no severe side effects. In order to consider response in the composite index, the improvement was required to be equal to or greater than 20% of at least 5 of the following scales: (A) Severity of morning stiffness was measured on a 100 mm VAS (where 0 = without stiffness and 100 = very severe stiffness). (B) Physical well being was measured on a 100 mm VAS (0 = feeling very well and 100 = feeling very bad). (C) Disease activity was evaluated with the BASDAI[15]. (D) Functioning was evaluated with the Bath Ankylosing Spondylitis Functional Index (BASFI)[18]. (E) Functioning was also evaluated with the Health Assessment Questionnaire for Spondyloarthropathies (HAQ-S)[19]. (F) Physician global assessment of disease activity was measured with a 100 mm VAS, 0 representing absence of disease activity and 100 very severe activity. (G) Patient global assessment of disease activity was measured using a VAS similar to that used by the physician based on the question, "How would you describe the current level of activity of your illness" (0 mm representing the absence of disease activity and 100 mm very severe activity). Additionally, classification as a responder required no worsening in any of the scales (> 20% worsening compared to baseline values).

Efficacy: secondary outcomes. Secondary efficacy variables included changes from baseline to endpoint in each of the individual components of the composite index. We also recorded the percentage of patients in each group achieving a BASDAI improvement of 20% and 50%. Additionally, we analyzed the changes in spinal pain using the mean improvement in the second question of the BASDAI. Other secondary outcomes were changes in erythrocyte sedimentation rate (ESR) and hemoglobin from baseline to the end of the trial.

Clinical and laboratory assessments were obtained at baseline and at 4, 12, 20, and 24 weeks. All clinical evaluations were performed by the same investigator. To increase the reliability of the measurements this investigator was trained in the application of the clinical scales.

Compliance. At every visit each patient was asked about the medication that was taken. Each was given a container of the total number of placebo or MTX capsules required until the next visit. The capsules were counted at each visit by an independent monitor.

Safety: adverse drug reactions. During the study, patients answered a self-assessment questionnaire on side effects associated with the medication. Every patient was trained to fill out the questionnaire at home and to return it at each visit. The assessment of side effects included changes in blood count, leukocytes, platelets, aspartate aminotransferase (AST), aspartate alaninotransferase (ALT), urinalysis, and chemistry profile evaluated at every visit. Mild adverse effects were considered the presence of any infection that did not require hospitalization for treatment, no serious oral ulcerations, headache, nonsevere diarrhea, transitory liver function abnormalities, transitory nausea and vomiting, or mild upper abdominal pain. Stopping rules were hepatotoxicity (AST or/and ALT values > 2 times the upper limit of normal in at least 2 independent determinations) or the presence of serious adverse events defined as thrombocytopenia (decrease of platelets to < 100,000/mm^3), leukopenia (decrease of leukocytes to < 3000/mm^3), severe infections requiring hospitalization, or renal toxicity (increase in creatinine > 1.5 mg/mm^3).

Statistical analysis. As the prespecified primary outcome measure we used improvement in the composite treatment index. As described above, response was considered when the patients had ≥ 20% improvement in at least 5 of the 7 scales evaluated. The study was designed to detect an

absolute difference of 45% in the composite treatment index between the MTX and placebo groups using a critical level of 0.05 (2-sided test). The sample size for the study was calculated assuming that 10% of patients receiving placebo would improve in the composite treatment index. We assumed a dropout rate of 20% and considered this rate in calculating the sample size. Using these data, a sample size of 17 patients in each group would provide 80% power to detect difference. An intention-to-treat (ITT) analysis was used for all patients in the group to which they were assigned by randomization. We followed all patients to the end of the study, even if they had dropped out of the study medication. For patients who missed a visit, we imputed the value of the previous visit.

The primary outcome measure of the 2 groups was compared by chi-square test. For effect size and precision we computed differences in the proportions of response in the composite index and 95% confidence intervals (CI) for these differences. Due to the small sample size the Wilson method was preferred over the traditional method for the calculation of 95% CI[20]. The number needed to be treated (NNT) to obtain an additional benefit was also calculated. We compared continuous variables between the MTX and placebo groups using the Student t-test for independent samples. For comparisons in nominal variables between groups we used chi-square tests (Fisher exact test when required). The Wilcoxon rank-sum or Mann-Whitney U test was used for ordinal measures. For comparisons between differences at baseline and 6 months we used paired t-tests. Logistic regression analysis was used to evaluate the differences of response in the composite index between both groups, adjusting for variables at baseline that were considered clinically important for the primary outcome. In the adjusted model the covariates included were treatment group, age, sex, duration of disease, and the presence of peripheral arthritis. Stepwise variable selection was used, and a p value < 0.2 was the selection criterion for the entry of the variables. All statistical tests were 2-sided, and the p value for significance was 0.05. All analyses were made by a statistician who was blinded to the assignment group, and the code was broken only after the analysis was complete. Most analyses were conducted using SPSS for Windows, version 8.0. For calculation of differences in proportions and their 95% CI we used Confidence Interval Analysis software, version 2.0.

RESULTS

Patient population. Figure 1 shows the trial praofile. We evaluated 70 patients for eligibility; 40 met the criteria for study entry, but 5 patients declined to participate for the following reasons: unwillingness to risk receiving placebo (3 patients), a wish to become pregnant (one patient), and concern about the side effects of MTX (one patient). Table 1 shows baseline characteristics of the patients. Of 35 patients enrolled, 17 were randomly assigned to receive MTX and 18 placebo. Peripheral joint involvement at study entry was 60%. Clinical characteristics were similar at baseline. There was no significant difference in hemoglobin level (14.6 ± 2 MTX group vs 14.5 ± 1 placebo; p = 0.8) or ESR (19 ± 13 MTX vs 19 ± 11 placebo; p = 0.8). Six (33%) patients with MTX and 5 (29%) with placebo had received sulfasalazine before entering the study, with no satisfactory response (p = 1.0).

Efficacy in the primary outcome measure. Table 2 describes the response rates in the composite index. A trend favoring MTX was observed as early as the 16th week; however, a statistical difference was reached only at the 24th week. The response rate at the 24th week was 53% in the MTX group versus 11% in the placebo group (p = 0.01).

In the ITT analysis at the 24th week, assuming no response in the patient receiving MTX who withdrew from the study and response in the patient with placebo who withdrew, the statistical difference continued to favor the MTX group (p = 0.03).

Using the data of the ITT analysis to compute the NNT, we would require only 3 patients to be treated with MTX in order to obtain an additional response in the composite index.

Secondary outcome measures. Table 3 shows within-group comparisons for the different secondary outcome measures. The changes from baseline to Week 24 favored the MTX group in the following variables: physical well being (p = 0.009), BASDAI (p = 0.02), BASFI (p = 0.02), physician global assessment (p < 0.001), patient global assessment (p = 0.03), and HAQ-S (p = 0.02). In the placebo group we observed statistical differences only in BASDAI (p = 0.01). In the laboratory measures, we detected no statistical differences between baseline and end of trial for the hemoglobin, platelet count, or ESR. Nine of 11 patients (81%) taking MTX and 8 of 10 (80%) placebo who had peripheral arthritis at baseline had disappearance of the arthritis during the trial.

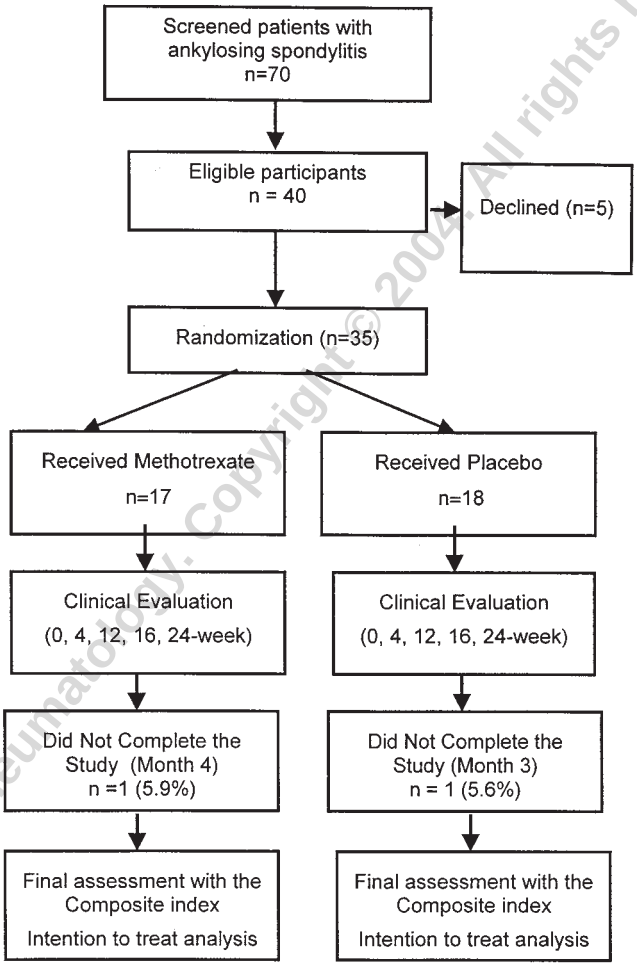

Figure 1. Trial profile of patients with AS.

Table 1. Baseline characteristics of the patients.

Characteristics	Methotrexate, n = 17	Placebo, n = 18	p†
Male, n (%)	13 (76)	11 (61)	0.3
Age, yrs*	32 ± 10	38 ± 10	0.1
Duration of disease since first symptoms, yrs*	9.5 ± 8	5.7 ± 5	0.1
Duration of disease after diagnosis, yrs*	5.8 ± 7	2.3 ± 5	0.2
Previous treatment with sulfasalazine, n (%)	6 (33)	5 (29)	1.0
Inflammatory back pain, n (%)	14 (82)	16 (89)	0.7
Previous peripheral joint involvement, n (%)	14 (78)	12 (71)	0.7
Peripheral joint involvement at time of study, n (%)	11 (65)	10 (56)	0.6
Morning stiffness > 45 min, n (%)	8 (47)	4 (22)	0.2
Morning stiffness, 0 to 100 mm VAS*	47 ± 30	30 ± 28	0.09
Physical well being, 0 to 100 mm VAS*	53 ± 20	52 ± 21	0.9
BASDAI*	5.0 ± 2	4.4 ± 2	0.4
BASFI*	4.7 ± 3	3.5 ± 2	0.1
Physician global assessment, 0 to 100 mm VAS*	49 ± 30	30 ± 20	0.2
Patient global assessment, 0 to 100 mm VAS*	46 ± 31	46 ± 28	0.9
HAQ-S	1.7 ± 0.5	1.5 ± 0.3	0.2

* Values expressed as means ± standard deviations. † Comparisons at baseline between means were calculated with Student t-test and between proportions with Fisher exact test.

Table 2. Number (%) of patients in each group achieving a treatment response in the composite index.

Time	Methotrexate, n = 17	Placebo, n = 18	Difference (95% CI)	p
4 weeks	4 (24)	1 (6)	18 (–7 to 42)	0.17
12 weeks	5 (29)	2 (11)	18 (–9 to 43)	0.22
16 weeks	7 (41)	2 (11)	30 (1 to 54)	0.06
24 weeks	9 (53)	2 (11)	42 (11 to 64)	0.01
Intention to treat (24 weeks)	9 (53)	3 (17)	36 (5 to 60)	0.03

Comparisons were calculated using chi-square with Fisher exact test. Differences and 95% confidence intervals (95% CI) were computed using the Wilson method.

Efficacy for spinal pain was evaluated using the second question of the BASDAI. In the MTX group, the mean spinal pain score decreased from 5.5 ± 2.4 at baseline to 3.7 ± 2.9 at Week 24 (p = 0.03). In the placebo group the decrease was not significant (from 5.4 ± 2.0 to 4.6 ± 2.3; p = 0.12). Eleven (65%) MTX treated patients experienced 20% improvement in the BASDAI at Week 24 compared with 6 (33%) placebo patients; however, this difference did not achieve statistical significance (p = 0.09). The number of responders achieving a BASDAI improvement of 50% was only 6 (35%) in the MTX group and 3 (17%) in the placebo group (p = 0.26).

Cointerventions, contamination, and changes in medication. Folic acid was prescribed for 6 (33%) patients in the placebo group and 7 (41%) in the MTX group (p = 0.9). Analgesics were received by 12 (67%) placebo patients and 8 (47%) taking MTX (p = 0.4). Intramuscular diclofenac was prescribed during at least one of their visits for 9 (50%) placebo patients and 5 (29%) taking MTX (p = 0.4). Two patients in the placebo group and one in the MTX group received prednisone indicated by their family physician (doses 5–7.5 mg/day). Four patients in each group received benzodiazepine and one additional patient in each group was taking imipramine.

Adjusted analysis. After adjusting for sex, age, years since the diagnosis of AS, and peripheral arthritis at baseline, only treatment with MTX remained significant as a determinant of the response in the composite index (p = 0.021). In the adjusted model, use of intramuscular diclofenac or folic acid did not influence the response for MTX in the composite index.

Withdrawals and adverse drug reactions. Thirty-three patients (16/17 in the MTX group, 17/18 placebo group) completed the trial. The proportion of patients developing side effects was similar between groups. There were no serious adverse effects or withdrawals due to side effects. One patient in the MTX group withdrew due to a lack of compliance and one in the placebo group due to a lack of response. Side effects are described in Table 4.

Table 3. Secondary outcomes at baseline and at 24 weeks.

Characteristic	Methotrexate, n = 17	p	Placebo, n = 18	p
Morning stiffness				
Baseline	47 ± 30		30 ± 28	
24 weeks	38 ± 30	0.3	32 ± 25	0.6
Physical well being				
Baseline	53 ± 20		52 ± 21	
24 weeks	37 ± 20	0.009	44 ± 22	0.08
BASDAI				
Baseline	5.0 ± 2		4.4 ± 2	
24 weeks	3.4 ± 2	0.02	3.5 ± 2	0.01
BASFI				
Baseline	4.7 ± 3		3.5 ± 2	
24 weeks	3.4 ± 2	0.02	3.1 ± 2	0.2
Physical global assessment				
Baseline	49 ± 30		30 ± 20	
24 weeks	17 ± 10	< 0.001	30 ± 27	0.9
Patient global assessment				
Baseline	46 ± 31		46 ± 28	
24 weeks	33 ± 25	0.03	34 ± 21	0.09
HAQ-S index				
Baseline	1.7 ± 0.5		1.5 ± 0.3	
24 weeks	1.5 ± 0.5	0.02	1.5 ± 0.4	0.9

Comparisons are the values in each outcome measure between baseline and 24 weeks. P values are based on paired-samples t-test comparing 24 weeks minus baseline within group.

Table 4. Side effects.

Adverse Effects	Methotrexate, n = 17 (%)	Placebo, n = 18 (%)	p
Mild headache	9 (53)	8 (44)	0.7
Oral ulcerations	9 (53)	5 (28)	0.2
Upper abdominal pain	5 (29)	5 (28)	1.0
Nausea and vomiting	2 (12)	7 (39)	0.1
Nonsevere, transitory diarrhea	2 (12)	5 (28)	0.4
Transitory liver function abnormalities	2 (12)	2 (11)	1.0
Loss of hair	1 (5.9)	0 (0)	—
Mild infections	1 (5.9)	1 (5.6)	1.0
Withdrawals*	1 (5.9)	1 (5.6)	1.0

Comparisons between groups were calculated by chi-square (Fisher exact test). * One patient taking MTX withdrew due to a lack of compliance and one taking placebo due to lack of efficacy.

DISCUSSION

Our double blind, randomized, placebo controlled study demonstrates that MTX is effective for treating patients with ankylosing spondylitis. Benefits of MTX started to be evident in the composite index after 16 weeks of therapy and became statistically significant at the 24th week of therapy compared with the placebo group. Treatment with MTX led to significant improvement in physical well being, BASDAI, BASFI, physician global assessment, patient global assessment, HAQ-S, and spinal pain. These findings are important because they were observed even in patients with prolonged duration of disease, as well as in patients with peripheral joint involvement or with axial involvement. Evidence of the benefits of MTX even in patients with prolonged disease duration is encouraging, since longer duration of disease is a negative factor for functional prognosis in patients with AS[21]. An interesting finding in our study is the improvement in spinal pain in patients taking MTX, since other disease controlling antirheumatic drugs, such as sulfasalazine, seem not to offer clear benefits for patients with predominant axial involvement[3]. However, this finding needs to be corroborated by further studies, because currently only the biological agents have shown effectiveness in improving back pain in AS[4,5,22].

No serious toxicity was observed with MTX at doses used during the trial and adverse drug reactions were mild and transitory. Nevertheless, in patients who would require higher dose MTX or a longer treatment time the proportion of side effects may increase.

Our results regarding the efficacy of MTX support the observations of several uncontrolled studies that used low dose MTX for treating AS[9-11]. Creemers, *et al*[10] described benefits in pain, swollen joint count, Ritchie articular index, spinal mobility, functioning, and laboratory measures. Sampaio-Barros, *et al*[9] observed a clinical response in 53% of their patients, and most of these responders had peripheral joint involvement. Biasi, *et al*[11] found improvement after 3 months of therapy with MTX in pain, well being, and spinal mobility, but not in peripheral arthritis. Nevertheless, the lack of a comparison group in these studies limits their consideration for clinical decision making.

We were able to find reports of only 2 randomized controlled trials[12,13]. One was a 12 month randomized, nonblinded controlled trial that evaluated the efficacy of the combination of MTX (7.5 mg/week) plus naproxen versus naproxen alone[12]. That study did not show statistical improvement in spinal mobility, enthesis index, functioning, morning stiffness, pain, patient global assessment of disease activity, and laboratory measures. Only the physician global assessment of disease activity improved significantly in the group using MTX. In the second study[13], 30 patients were randomized to receive MTX 10 mg weekly or placebo in a double blind design. That study did not show improvement in BASDAI and Bath AS Mobility Index (BASMI). These 2 studies had drawbacks decreasing the strength of their conclusions. First, neither used a prespecified composite index to evaluate the response between treatment groups. The lack of a composite index has several disadvantages: it increases difficulties in standardizing outcomes across the trials and decreases the power to detect differences between therapies (including placebo and active drug), requiring increased sample sizes to show differences. We encountered a similar limitation, when we analyzed only the percentage of improvement of BASDAI as a measure of response.

Although we did not detect significant differences between MTX and placebo, a trend was evident favoring MTX using the BASDAI improvement criteria of 20% and 50%. On the basis of this trend, it is likely we would have observed statistical differences between groups with a larger sample.

Recently, use of a primary endpoint based on a composite index has been suggested; this approach allows detection of important clinical differences even in trials with a small sample size, enhancing their statistical power[16]. The ASAS Working Group has suggested the use of a composite index for defining improvement during trials with disease controlling antirheumatic drugs[17,23]. An approach for defining improvement with disease controlling antirheumatic drugs was used by Gorman and coworkers in a trial with etanercept[5]. They constructed a composite index defined as the improvement of ≥ 20% in at least 3 of 5 measures. Similarly, we constructed our primary outcome measure using the improvement of ≥ 20% in at least 5 of 7 scales.

Besides the use of a composite index, we have some methodological differences compared to the 2 other controlled trials of MTX in AS. One of these trials had an unblinded design[12]. This limitation increased the probability of biases that may influence the report of responses to treatment. In contrast, in our study the double blind placebo design minimized the likelihood of expectancy biases. In the second trial[13], a larger sample size would have been required to show differences, since that trial was designed to test a primary outcome based on the changes in scores of BASDAI or BASMI.

Another difference between our study and the 2 other trials[12,13] would rest on the clinical characteristics of the study population: we included a group of patients who had a higher proportion of peripheral arthritis and were younger than previous studies. Studies with sulfasalazine have shown that patients with peripheral joint involvement are more likely to exhibit a response than patients with pure axial involvement[3]. However, we cannot confirm that the response in the composite index was influenced by the presence of arthritis, since both groups had similar rates of improvement in this outcome.

A higher proportion of patients in the placebo group improved in the BASDAI; one explanation for this result was the concomitant use of nonsteroidal antiinflammatory drugs that may contribute to decreasing differences in response between the groups. Also, patients in the placebo group received analgesics and intramuscular diclofenac more frequently; however, this trend was not significantly different in the multivariate analysis.

Several limitations in our study need to be considered. Due to the exploratory design we used low doses of MTX. Since the MTX doses were not increased, we ignored the effect of higher doses such as 15 or 20 mg per week. Whether an increase in the MTX dose would lead to an increase in the response rate in the composite index is an issue that requires further study. Also, we did not determine if the efficacy of this disease modifying antirheumatic drug (DMARD) would remain significant in longterm studies. However, on the basis of the observed trend of increased improvement over time, it is possible that the rate of responders to MTX would be increase in longterm studies. An important issue for future studies is evaluation of the effects of MTX on the radiological progression of AS.

MTX offers a safe and effective option as an antirheumatic drug in AS. This drug needs to be taken into account since a high proportion of patients treated with sulfasalazine did not achieve significant improvements, and the use of biological therapies such as etanercept or infliximab is limited by their cost. Further studies are needed to determine the longterm effects of MTX, its relative potency, and safety in regard to other DMARD. Trials comparing MTX with sulfasalazine and biological therapies are needed; additional studies comparing efficacy between low and high doses and its utility as a combined therapy in AS are required.

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