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Methotrexate in Severe Ankylosing Spondylitis: An Open Study

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ABSTRACT. Objective. To study the efficacy and toxicity of methotrexate (MTX) for patients with ankylosing spondylitis (AS) in a 36 week, open, single observer study.

Methods. Patients were selected for study if they had evidence of active disease and had failed to respond to treatment with nonsteroidal antiinflammatory drugs (NSAID) and sulfasalazine. Eleven patients entered the study, and 9 were evaluated at the end. Oral MTX (7.5–15 mg weekly) was given for at least 24 weeks; NSAID were kept at a stable dose. Efficacy was evaluated by calculating the relative difference of assessed variables between Weeks 0 and 24 and by patient evaluation.

Results. Assessed variables showed good relative improvement. Four patients decided to continue MTX; 3 used a lower dose of NSAID; one stopped NSAID. Five patients discontinued MTX: 3 of these had disease flares and restarted MTX. Side effects were mild and reversible.

Conclusion. Results of our study showed that the majority of our patients with AS taking MTX had beneficial effects. (*J Rheumatol* 1995;22:1104–7)

Key Indexing Terms:

SPONDYLOARTHROPATHIES
METHOTREXATE

ANKYLOSING SPONDYLITIS
SLOW ACTING ANTIRHEUMATIC DRUGS
DISEASE MODIFYING ANTIRHEUMATIC DRUGS

Ankylosing spondylitis (AS) is a chronic inflammatory condition of the axial skeleton and sacroiliac joints that may lead to spinal ankylosis¹. Peripheral arthritis and extraarticular features occur in a small proportion of cases and are bad prognostic factors^{1,2}. Up to now treatment of AS mainly comprises nonsteroidal antiinflammatory drugs (NSAID). Of second line drugs, only sulfasalazine³ efficacy has been established in AS. Significant clinical improvement with methotrexate (MTX) administered weekly has been reported in 16 patients with severe AS^{4–7}. The aim of our study was to determine the efficacy and toxicity of MTX in patients with severe AS in an open, single observer, 36 week interventional study.

MATERIALS AND METHODS

The study was conducted at the rheumatology departments of University Hospital Nijmegen, St. Radboud and St. Maartenshospital Nijmegen with a full ethical committee approval.

Patients with severe AS fulfilling the modified New York criteria⁸, of either sex, aged 18 to 60 years, were included. They were excluded in cases of (1) serious systemic disease, malignancies, impaired organ function, or serious infections like tuberculosis; (2) mental disorders; (3) alcohol or drug

abuse; (4) pregnancy or breast feeding; (5) history of intestinal disease. Severe or refractory AS was defined as a failure on treatment with NSAID and sulfasalazine; as well, active disease had to be present, defined as the presence or persistence of at least 2 of the following features: (1) morning stiffness at least 30 min; (2) disturbed sleep due to pain and stiffness; (3) peripheral arthritis; (4) erythrocyte sedimentation rate (ESR) \geq 30 mm, or C-reactive protein (CRP) \geq 20 mg/l, or IgA \geq 3.9 mg/l; (5) spinal pain; (6) stiffness and pain of thorax at movement or during normal breathing; (7) pain in both buttocks during the night or day. A stable NSAID dose and discontinuation of sulfasalazine were required, both for at least 4 weeks before study entry. Adequate contraception during and 6 months after MTX treatment was recommended.

Study design. This was an open, single observer, 36 week study of MTX efficacy and toxicity. Patients were seen every 4 weeks for 36 weeks and variables for disease activity and toxicity were measured at each visit. Medication for nonrheumatic chronic conditions and intercurrent acute illnesses was allowed, except for antifolate drugs (e.g., sulfonamide derivatives), allopurinol, immunosuppressive treatment, and second line drugs. MTX was taken orally 7.5 mg/week. At Week 12, MTX dose was increased to 15 mg/week in case of lack of response. At Week 24, efficacy was evaluated based on patients' global assessment: (1) if patients judged that MTX was clearly effective, MTX was kept at a stable dose and NSAID dose was reduced; and (2) if patients judged efficacy of MTX was moderate or absent (see below), MTX was discontinued and NSAID kept at a stable dose. If the disease flared subsequently, judged by the patients' global assessment and according to predefined criteria for disease activity, MTX was restarted. In case of severe side effects, MTX was stopped; in milder cases the dose was decreased or 1 mg folic acid was administered^{9–11}.

Measurements. Every visit the following variables were assessed. (1) Objective clinical variables: occiput-wall distance, chest expansion, Schober's 10 cm test¹², fingertip-to-floor distance, an entheses index¹³, number of swollen joints, Ritchie Articular Index¹⁴. Extraarticular manifestations were carefully monitored. (2) Subjective variables: visual analog scales (VAS) ranging from 0 to 100 mm, corresponding with "none" to "has never been worse," were used for spinal pain, chest pain, general well being, and tiredness. Next, duration of morning stiffness after arising was assessed. (3) Functional assessment: a Dutch Functional Index (DFI) for AS¹⁵. (4) Laboratory variables: ESR, CRP, complete blood cell count, serum creatinine, liver function tests, albumin, immunoglobulin A, G, and M, creatinine

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phosphokinase. (5) Side effects related to study medication were assessed by direct questioning or as spontaneously reported complaints.

Response. The relative difference between Weeks 0 and 24 was calculated, and response was defined as follows: good, if improvement $\geq 50\%$ was present in the majority of variables; moderate, if this improvement was between 15 and 50%; and no response, in case changes were smaller or absent. Variables not abnormal at the start of the study or during the study were defined as "not affected" (NA) and left out of the evaluation.

RESULTS

In total, 11 patients were enrolled in the study; all had NSAID failure, 9 failed to respond to sulfasalazine treatment and 2 could not tolerate sulfasalazine, one patient used corticosteroids (15 mg/week) and continued this throughout the study. Patients' characteristics are shown in Table 1. After 12 weeks of treatment, MTX was increased to 15 mg weekly in 9 patients. Generally, response, if present, could be observed after 4 to 12 weeks of MTX treatment. Two patients dropped out at Week 16 because of protocol violating changes in treatment: one due to a flare of the disease, the other due to development of a peptic ulcer, for which oral steroids were stopped as well.

Table 1. Patients' characteristics at start of the study

	No. Patients
Male:female	8:3
HLA-B27 positivity	11
Peripheral arthritis	3
Enthesitis	5
Iridocyclitis	2
Age (yrs)*	35 \pm 8 (21-47)
Disease duration	14 \pm 9 (3-26)

* Mean \pm standard deviation (range).

After 24 weeks, 9 patients were evaluable, with a mean weekly MTX dose of 13.3 mg over a period of 24 weeks. Improvement could be seen in most assessed variables (Table 2 and Figure 1). CRP and ESR improved equally. Immunoglobulin A, elevated in 4 patients, decreased. Anemia (Hb: 5.7 to 6.7 mmol/l), present in all 3 patients with peripheral arthritis, improved at least 1.0 mmol/l. The course of iridocyclitis (2 patients, 3 episodes) appeared not to be influenced by MTX. Efficacy was good in 5 patients: 4 continued MTX treatment and the NSAID dose could be reduced ($n = 3$) or stopped ($n = 1$). The 5th patient stopped MTX treatment despite good clinical response, but deteriorated within 4 weeks, and MTX was readministered. In the remaining 4 patients MTX was stopped because of moderate or absent efficacy, and 2 of them deteriorated within 4 weeks.

Side effects were abdominal discomfort ($n = 2$), nausea ($n = 1$), transient oral ulcers ($n = 1$), reversible liver function elevations ($n = 3$), for which 2 patients experienced benefit with folic acid 1 mg.

DISCUSSION

MTX was studied in severe AS in a 36 week open study. Regarding enthesitis, peripheral arthritis, and duration of the disease, patients were quite different. Data were not analyzed statistically because of this heterogeneity and the small sample size. Efficacy was evaluated in 2 different ways: objectively, i.e., the relative difference of assessed variables between Weeks 0 and 24 (Table 2); and subjectively, by deciding at Week 24 to either continue ($n = 4$) or stop MTX ($n = 5$) based on patients' global assessment. One patient was able to stop NSAID treatment, 3 were able

Table 2. Relative improvement*

Variables	Patients									
	1	3	4	5	6	7	8	9	10	
Disease duration (yrs)	23	26	8	8	5	22	16	11	3	
Disease characteristics**		P		P		P		I		
Spinal pain	++	+	++	-	+	+	-	-	++	
Chest pain	++	++	-	++	-	++	-	-	++	
General well being	++	+	++	++	+	++	-	-	-	
Tiredness	++	++	++	+	-	-	-	-	-	
Morning stiffness	++	++	++	++	-	-	-	-	++	
Occiput-to-wall distance	+	++	++	NA	NA	-	NA	NA	NA	
Fingertip-to-floor distance	++	-	-	++	-	-	-	-	++	
Chest expansion	++	-	++	++	-	-	-	++	+	
Schober's 10 cm test	++	++	++	++	-	++	-	-	++	
Ritchie Articular Index	++	++	NA	++	+	++	NA	-	NA	
Number of swollen joints	NA	+	NA	++	NA	++	NA	NA	NA	
Enthesis index	++	++	++	++	-	++	-	-	NA	
Dutch Functional Index	++	-	++	++	++	+	-	-	-	
ESR	++	+	-	++	NA	+	NA	-	-	

* Relative improvement: ++ improvement $\geq 50\%$; + improvement 15-49%; - no improvement or $< 15\%$; NA = not affected.

** P = peripheral arthritis; I = iridocyclitis.

Patients 2 and 11 dropped out; both had enthesitis, Patient 2 also had iridocyclitis.

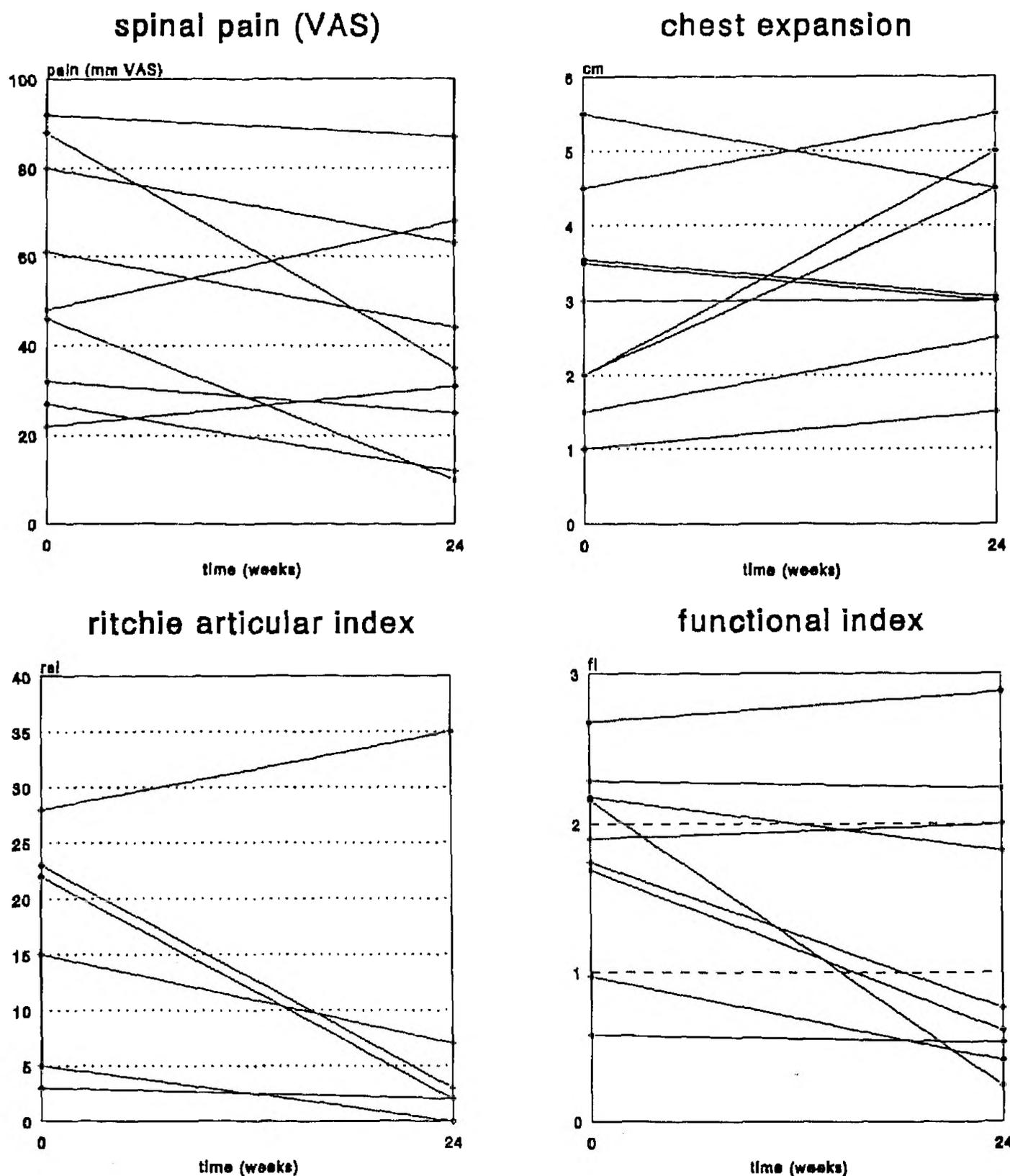


Fig. 1. Response in the 9 evaluable patients (Week 0-24).

to reduce the NSAID dose, and 4 patients deteriorated after discontinuation of MTX and chose to restart. Side effects were reversible or transient, and no severe side effects were seen. There was no obvious difference in response between patients with peripheral arthritis and patients with involvement of the axial skeleton only. Thus, although numbers were small, this study provides circumstantial evidence that the majority of patients experienced beneficial effects after taking MTX. In future, a double blind, placebo controlled study should corroborate these data.

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