Clin Rheumatol (2000) 19:114–117

Clinical
Rheumatology

Original Article

Efficacy of Methotrexate in the Treatment of Ankylosing Spondylitis: A Three-Year Open Study

D. Biasi, A. Carletto, P. Caramaschi, M. L. Pacor, T. Maleknia and L. M. Bambara

Dipartimento di Medicina Clinica e Sperimentale, University of Verona, Italy

Abstract: The aim of the study was to evaluate the efficacy of methotrexate treatment in patients with ankylosing spondylitis in a 3-year open trial. Seventeen patients, 14 men and three women (mean age 32.7 $\pm$ 8.9 years), suffering from ankylosing spondylitis and non-responders to treatment with sulphasalazine, were enrolled in our study. Sixteen of them were evaluable at the end of the study. Methotrexate (7.5–10 mg/week) was administered for 3 years. Efficacy was evaluated on the basis of clinical and laboratory variables, radiographic signs of disease progression and daily dosage of indomethacin. We obtained a good and relatively prompt clinical response except for peripheral arthritis and iridocyclitis; in fact, after 3 months of methotrexate treatment a significant amelioration of the following parameters was observed: visual analogue scale for the evaluation of both night pain and general well-being, Shober's test, occiput-wall distance, fingertip to floor, erythrocyte sedimentation rate, C-reactive protein level and daily dose of indomethacin. A further improvement was obtained during the subsequent period. Radiographs of the spine and sacroiliac joints did not show any signs of disease progression. Side-effects were a transitory elevation of transaminases (four cases) and slight hypogammaglobulinaemia (one case). Methotrexate treatment may be useful in ankylosing spondylitis, but a combined treatment might be indicated for patients with peripheral arthritis.

Keywords: Ankylosing spondylitis; Methotrexate; Therapy

Correspondence and offprint requests to: Domenico Biasi, Dipartimento di Medicina Clinica e Sperimentale, Via delle Menegone, 37134 Verona, Italy. Tel: 045/8074410; Fax: 045/580111.

Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory disease of unknown aetiology. It affects mainly the axial skeleton and, the sacroiliac joints, but peripheral arthritis and extra-articular manifestations, such as enthesopathies and anterior uveitis, may be present and are considered to be important features. The disease is also closely linked to HLA-B27 [1].

The aim of treatment is to facilitate a normal and autonomous life. Education of the patient is important, as well as pharmacological therapy, which comprises non-steroidal anti-inflammatory drugs (NSAIDs) and second-line drugs.

Among the NSAIDs, indomethacin is the more commonly used drug in AS [2]; among the second-line drugs, sulphasalzine has demonstrated a significant, but not great, benefit in AS, even if it has not been established whether long-term sulphasalazine treatment can modify the natural history of the disease [3–7]. Recent studies with methotrexate (MTX), administered weekly, have shown a significant clinical improvement for the treatment of severe AS [8–12].

The aim of our study was to evaluate the efficacy of MTX treatment, based upon clinical features and disease progression, in a 36-month prospective open study.

Materials and Methods

Seventeen patients, 14 men and three women, between the ages of 21 and 52 years (mean 32.7 $\pm$ 8.9 years), suffering from active AS and non-responders to treatment with sulphasalazine, who fulfilled the modified New York criteria [13], were admitted to our study. All the patients were HLA-B27 positive. The mean disease

Table 1. Patients' characteristics at the start of methotrexate therapy

Males	14
Females	3
Age (years)	32.7 ± 8.9
Disease duration (years)	4.8 ± 0.9
HLA-B27 positivity	17 (100%)
Peripheral arthritis	6 (35.3%)
Enthesitis	7 (41.2%)
Iridocyclitis	2 (11.8%)
Radiographic changes	
Sacroiliitis	17 (100%)
Blurring of subchondral bone plate	17 (100%)
Sclerosis and erosion of bone	3 (17.6%)
Ankylosis	1 (5.9%)
Lumbosacral and thoracolumbar spine involvement	12 (70.5%)
Squarring	12 (100%)
Syndesmophytes	4 (33.3%)

duration was 4.8 ± 0.9 years; six patients had peripheral arthritis, seven patients had enthesitis and two patients suffered from iridocyclitis. In all the patients, radiographic signs of sacroiliitis were present; 12 of them also showed radiographic signs of lumbosacral and/or thoracolumbar junction involvement. None of the patients was affected by psoriasis or inflammatory bowel disease. The characteristics of the patients are reported in Table 1.

Patients affected by renal or hepatic diseases, severe infections, myelosuppression, peptic ulcer, cancer, psychiatric disorders or other diseases contraindicating the use of MTX were not admitted to our study. Uncooperative patients were also excluded from this study, as well as pregnant women. All the patients gave their consent, after being informed about both the disease severity and the adverse reactions of the drug.

The patients were defined as non-responders to sulphasalazine when the disease was still active after 6 months of treatment at the daily dose of 2–3 g. AS was defined as active in the presence of at least three of the following features: (a) disturbed sleep due to pain and stiffness; (b) peripheral arthritis; (c) spinal pain; (d) thoracic stiffness and pain during movement or normal breathing; (e) pain in both buttocks during the night or day; (f) erythrocyte sedimentation rate (ESR) $\geqslant 30$ mm/h, or C-reactive protein (CRP) $\geqslant 20$ mg/l.

A stable indomethacin administration and discontinuation of sulphasalazine treatment were required before entry to the study. None of the patients was receiving intra-articular or systemic steroid therapy. Folic or folinic acid supplementation was not administered.

On admission, the patients underwent a physical examination (occiput-wall distance, Schober's test, fingertip-to-floor distance, swollen and tender joint counts) and laboratory evaluation, including ESR, CRP, fibrinogen, complete blood count, hepatic and renal function tests, immunoglobulin levels, rheumatoid factor, antinuclear antibodies and urinalysis. Radiography of the spine (lateral and frontal radiographic projections) and of the sacroiliac joints (anteroposterior and anteroposterior with 30° cephalic angulation of the central ray) was performed. Laboratory tests and radiography were all carried out in our hospital.

Initially the patients were treated for 3 years with oral MTX 7.5 mg/week and indomethacin 100 mg/day. Each patient underwent a clinical assessment every 3 months by the same physician. If the disease was still active after 12 weeks, the MTX dose was increased to 10 mg/week. If the treatment was not efficacious after 24 weeks, MTX administration was discontinued definitively on the basis of the physician's and patient's evaluations.

Efficacy was evaluated using the following parameters:

1. Laboratory variables: ESR and CRP values. These parameters were measured at entry and every 3 months thereafter.
2. Radiographic signs of progression of the disease: radiographs of the spine and sacroiliac joints were performed at entry and were repeated after 3 years and read by the same radiologist. The radiologist, who was blinded to the clinical and laboratory findings, made a reading of the radiographs in chronological sequence; he evaluated subjectively if, after 3 years of treatment, the radiographs showed any sign of damage progression or not.
3. Clinical variables: Schober's test, fingertip-to-floor distance, occiput-wall distance, number of swollen and tender joints. Moreover, a visual analogue scale (VAS) ranging from 0 to 100 mm, corresponding with 'none' to 'has never been worse', was used for spinal pain and general well-being. These parameters were measured at entry and every 3 months thereafter.
4. Daily dose of indomethacin. This parameter was evaluated every 3 months.

To evaluate adverse reactions to MTX, we performed complete blood cell counts, hepatic and renal function tests and urinalysis after 1, 2 and 4 weeks and then monthly; the immunoglobulin level was evaluated every 6 months. MTX treatment was definitively discontinued if aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels were higher than 80 U/l, haemoglobin <9 g/dl, white blood cell count <3500/mm^3 and platelet count <130 000/mm^3 and in the presence of other relevant side-effects. Minor side-effects, such as elevation of AST and ALT to above 80 U/l, determined the temporary suspension of the drug or its reduction in dosage. The non-parametric Wilcoxon test for paired data was used for the statistical evaluation.

Results

Seventeen patients were enrolled in this study. At the 3-month visit, the MTX dose was increased to 10 mg/week in four patients; one patient left the study at month 6 because of the lack of benefit. At the 12-month visit, the three patients treated with MTX 10 mg/week reduced the dosage to 7.5 mg/week, because there was a good

Table 2. Clinical and haematochemical parameters under basal conditions and after 6, 12, 18, 24, 30 and 36 months

	Basal	6 months	12 months	18 months	24 months	30 months	36 months
VAS, night pain (16 patients)	57.2±9.2	33.2±7.2*	9.7±7.4*	1.9±3*	0*	0*	0*
VAS, general well-being (16 patients)	62.6±8.9	34.2±9.5*	10.8±7.9*	6±7.5*	4.3±5.7*	3.7±5*	3.7±4*
Schober's test (16 patients) (cm)	2±0.4	3.1±0.6*	4.2±0.4*	4.4±0.3*	4.6±0.3*	4.7±0.3*	4.9±0.2*
Occiput-wall distance (16 patients) (cm)	11.6±2.4	8.7±2.3*	7.4±2.2*	6.9±1.4*	5.7±1.4*	5.3±1.5*	5±1.6*
Fingertip to floor (16 patients) (cm)	33±8	20.4±6.5*	14.2±2*	12.2±2*	10.1±1.4*	9.6±1.2*	7.1±4*
Number of pSJ (6 patients)	5±1.4	3.8±1.5	3.3±1	3.3±0.8	2.5±1.1	2.8±1	2.1±1.3
Number of pTJ (6 patients)	8.2±2.3	5.2±1.7	4.2±1.7	4.2±0.7	3.9±0.8	3.3±2	3.3±2.1
ESR (16 patients) (mm/h)	37.4±7.5	23.7±5*	16.3±4.9*	14.2±3.3*	13.6±3.4*	15.3±10.6*	11.8±3.1*
CRP (16 patients) (mg/l)	37.8±13.3	20.9±8.3*	10.4±4.8*	7±3.6*	4.9±3.7*	4.8±1.2*	4.2±2.2*
Dose of indomethacin (mg/day)	100±0	81.7±11.4*	60±12.6*	40.8±12*	35.9±14.9*	21.6±19.7*	15±18*

VAS, visual analogue scale; pSJ, peripheral swollen joints; pTJ, peripheral tender joints; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.
* $p<0.005$.

clinical response. After 3 years, 16 patients were evaluable. The mean dose of MTX after 1, 2 and 3 years of treatment was 7.6, 7.3 and 7.3 mg/week, respectively.

Table 2 shows the data concerning efficacy parameters. All the clinical and haematochemical parameters that were considered had improved after 6 months and a further amelioration was observed after 12, 18, 24, 30 and 36 months, except for the number of tender and swollen joints. In fact, patients with peripheral arthritis experienced a persistence of pain and swelling in small number of joints after 3 years of therapy. The mean value of the indomethacin daily dose progressively decreased. At the end of the study, indomethacin was discontinued in nine patients.

The course of iridocyclitis was not influenced by MTX treatment. Two patients had iridocyclitis at entry into the study and were treated with local steroid therapy, as suggested by the eye specialist. During the study these patients had multiple relapses of iridocyclitis (three episodes in one case and two episodes in the second case), which was treated again with local steroid therapy.

The spine and sacroiliac joint radiographs did not show any signs of progression in our patients. Five patients experienced minor side-effects: a slight and transitory elevation of AST and ALT (four cases) and slight hypogammaglobulinaemia (one case). No major side-effects were observed, even when patients did not receive folic or folinic acid supplementation.

Discussion

During the past 20 years, MTX has been largely employed for the treatment of chronic inflammatory arthropathies, including spondyloarthropathies [14]. The use of MTX in AS has increased in the past few years although further prospective, multicentre and controlled studies are necessary to evaluate the usefulness of this treatment. In 1995, in a small pilot study, Creemers and co-workers [12] reported the results obtained in 11 patients suffering from AS treated with MTX for 36 weeks. At the end of the study the efficacy was considered to be good in five patients and side-effects were mild and reversible.

The aim of our prospective study was to evaluate not only the clinical benefit of MTX, but also the usefulness of this treatment in arresting or delaying the involvement of the axial skeleton. We prolonged the study duration to 3 years to obtain credible information.

All the patients except one showed a significant clinical amelioration with improvement of their quality of life; consequently, they could considerably reduce the dose of indomethacin. In four patients the MTX dosage was increased during the first year of treatment. The drug was well tolerated by all the patients. In our opinion the lack of serious side-effects was due to the careful follow-up: the frequency of the clinical and haematochemical controls allowed us to adapt suitably the dosage of the drug in case of minor side-effects. Moreover, both the initial selection of the patients and the limited use of NSAIDs may have contributed to our results.

It is important to underline that we observed a very important improvement of the variables concerning inflammation and spinal function; in contrast, we cannot confirm the same results for the course of peripheral arthritis and iridocyclitis. Moreover, the radiographs of the spine and sacroiliac joints did not show any sign of disease progression in our patients. In our opinion this observation is of great interest, even if AS is a chronic disease characterised by a slow evolution; therefore, the anatomical damage needs to be visualised by radiography over a long period of time. Obviously, larger and controlled studies are necessary to confirm our results.

Our study is not controlled and the number of subjects considered is small, nevertheless our results show that the majority of our patients with AS taking MTX has beneficial effects. It is surprising that in patients with peripheral arthritis and iridocyclitis the efficacy of MTX affects mostly the axial skeleton; in these cases higher doses of MTX or a combined treatment with sulphasalazine might be indicated.

Acknowledgements. The work was supported by a grant from 'Progetto Sanità' 1996–1997, Fondazione Cassa di Risparmio di Verona, Vicenza, Belluno ed Ancona.

References

1. Van der Linden S. Ankylosing spondylitis. In Kelley WN, Harris ED, Ruddy S, Sledge C, editors. Textbooks of rheumatology. Philadelphia: WB Saunders, 1997:969–82.
2. Calin A, Elswood JA. Prospective nationwide cross-sectional study of NSAID usage in 1331 patients with ankylosing spondylitis. J Rheumatol 1990;17:801–3.
3. Dougados M, Boumier P, Amor B. Sulphasalazine in ankylosing spondylitis: a double blind controlled study in 60 patients. Br Med J 1986;293:397–9.
4. Feltelius N, Hallgren R. Sulphasalazine in ankylosing spondylitis. Ann Rheum Dis 1986;45:396–9.
5. Fraser SM, Sturrock RD. Evaluation of sulphasalazine in ankylosing spondylitis: an interventional study. Br J Rheumatol 1990;29:37–9.
6. Ferraz MB, Tugwell P, Goldsmith CH, Atra E. Meta-analysis of sulphasalazine in ankylosing spondylitis. J Rheumatol 1990; 17:1482–6.
7. Clegg DO, Reda DJ, Weisman MH, Blackburn WD, Cush JJ, Cannon GW, et al. Comparison of sulphasalazine and placebo in the treatment of ankylosing spondylitis. Arthritis Rheum 1996;39:2004–12.
8. Handler RP. Favourable results using methotrexate in the treatment of patients with ankylosing spondylitis. Arthritis Rheum 1989;32:234.
9. Bosi Ferraz M, Carrica da Silva H, Atra E. Low dose methotrexate with leucovorin rescue in ankylosing spondylitis. J Rheumatol 1991;18:146–7.
10. Yamane K, Saito C, Natsuda H, Yuhara T, Akama T, Suzuki H, Kashiwagi H. Ankylosing spondylitis successfully treated with methotrexate. Intern Med 1993;32:53–6.
11. Creemers MC, van Riel PL, Franssen MJ, van de Putte LB, Gribnau FW. Second-line treatment in seronegative spondylarthropathies. Semin Arthritis Rheum 1994;24:71–81.
12. Creemers MC, Franssen MJ, van de Putte LB, Gribnau FW, van Riel PL. Methotrexate in severe ankylosing spondylitis: an open study. J Rheumatol 1995;22:1104–7.
13. Van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis: a proposal for modification of the New York criteria. Arthritis Rheum 1984;27:361–8.
14. Gutierez-Urena S, Espinoza LR. Methotrexate. The agent of choice for chronic inflammatory disorders: a perspective ten years later. Clin Exp Rheumatol 1995;13:281–4.

Received for publication 26 January 1999
Accepted in revised form 25 August 1999