Efficacy and Safety of Mesalazine (Salofalk®) in an Open Study of 20 Patients with Ankylosing Spondylitis

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ABSTRACT. ***Objective.*** Mesalazine (Salofalk®) was found to be effective and showed low toxicity in patients with inflammatory bowel disease. The association of gut lesions and spondyloarthropathy (SpA) is well known and we studied the efficacy and safety of a relatively high dose of mesalazine in patients with ankylosing spondylitis (AS).

Methods. In an open study, mesalazine (3–4 g/day) was prescribed for 24 weeks to 20 patients (aged 18–70 yrs) with active AS, defined as the presence of at least one clinical criterion (morning stiffness > 30 min, peripheral synovitis, enthesopathy, or pain score > 2 on a visual analog scale of 10 cm) and one laboratory criterion [erythrocyte sedimentation rate (ESR) > 20 mm/h or C-reactive protein (CRP) > 20 mg/l]. Data on toxicity and disease activity variables (ESR, CRP, BASDAI, BASFI, BASMI, global assessment, and joint count) were obtained at baseline and after 4, 12, and 24 weeks, and analyzed on an intention-to-treat basis.

Results. Study patients had a mean age of 41 years, with mean disease duration of 7.9 years and a mean ESR at baseline of 29 mm/h. After a mean of 9.3 weeks (range 2–22), 8 of the 20 patients prematurely stopped the medication because of adverse effects, mainly gastrointestinal complaints. Twelve patients completed the 24 weeks of the study using a mean dose of 3.2 g/day (range 1–4) mesalazine. Analysis of the data showed improvement in ESR, CRP, and physician's global assessment, but only the change in ESR (29 mm/h on baseline and 25 mm/h at week 24) reached statistical significance ($p = 0.03$). No change was observed in the other disease activity variables.

Conclusion. No significant improvement in any disease activity variable of active AS was observed during treatment with Salofalk® except for the ESR. Many side effects were seen. (J Rheumatol 2003;30:1558–60)

Key Indexing Terms:
ANKYLOSING SPONDYLITIS MESALAZINE

Treatment of patients with ankylosing spondylitis (AS) consists mainly of exercise therapy and nonsteroidal antiinflammatory drugs (NSAID). A considerable number of studies have assessed the efficacy and safety of sulfasalazine (SSZ) in AS[1-8]. SSZ (2–3 g/day) was proven to be more effective than placebo in active spondyloarthropathy (SpA), especially in decreasing the peripheral arthritis[6-8].

SSZ is metabolized in the large intestine into sulfapyridine and mesalazine (5-aminosalicylic acid, 5-ASA). The latter is the active drug in the treatment of inflammatory bowel disease (IBD). Based on the hypothesis that the gut plays an important role in the onset of AS and because mesalazine is less toxic than SSZ, mesalazine seemed to be an attractive candidate in the treatment of AS. Mesalazine was used previously in some AS patients with various results[9-11]. The results of a randomized controlled study of treatment with either SSZ, mesalazine, or sulfapyridine suggested that sulfapyridine and not mesalazine is the active moiety in SpA[11]. However, in that study a very low dose of mesalazine (Asacol® 0.8 g/day) was used. For IBD, it is common practice to use doses up to 6 g/day of mesalazine. Our aim was to assess the efficacy and safety of a relatively high dose (up to 4 g/day) of mesalazine (as Salofalk®) in patients with AS.

MATERIALS AND METHODS

Study design. In an open pilot study, 20 patients with AS were treated with mesalazine over 24 weeks. Patients with active AS were included if they fulfilled the modified New York criteria for AS, were aged between 18 and 70 years, and showed active disease defined as the presence of at least one clinical criterion [morning stiffness > 30 minutes, or peripheral synovitis, or enthesopathy, or pain score > 2 on a visual analog scale (VAS, 0–10 cm)] plus one laboratory criterion [erythrocyte sedimentation rate (ESR) > 20 mm/h or C-reactive protein (CRP) > 20 mg/l]. Previous use of mesalazine, treatment with a disease modifying antirheumatic drug (DMARD), including SSZ,

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experimental therapy, or corticosteroids in the previous 4 weeks, known allergy to salicylates or SSZ, pregnancy, severe renal and/or hepatic dysfunction, and history or symptoms of IBD were the exclusion criteria.

After inclusion, mesalazine was prescribed as Salofalk® in 500 mg tablets with an initial daily dose of 3 g (1 g tid). We confirmed with the patients'pharmacy that no other mesalazine formulation was given. In case of intolerance or side effects, the dosage of Salofalk® was decreased to the highest tolerated dose.

After 4 weeks the daily dose was increased to 4 g in case of inefficacy, defined as less than 20% improvement in at least 2 of the following variables: VAS morning stiffness, VAS pain, or ESR.

NSAID were continued during the study if they had been taken in a stable dose from 4 weeks prior to study entry. The type, dosage at entry, and change in dosage or type of the NSAID during the study were recorded.

At baseline and at 4, 12, and 24 weeks the following data were obtained by one of us (JC van D): Bath Ankylosing Spondylitis Functional Index (BASFI), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), global assessment according to the patient and to the doctor (VAS 0–10 cm), Bath Ankylosing Spondylitis Metrology Index (BASMI, new scoring system)[12], tender joint score (TJS, 42 joints), swollen joint score (SJS, 40 joints), laboratory tests, and adverse events.

The following were used as variables for disease activity: ESR, CRP, BASDAI, BASFI, BASMI, global assessment according to the patient and to the doctor, TJS, and SJS. The Assessments in Ankylosing Spondylitis Working Group (ASAS) response criteria were not used because they were not developed when this study was performed[13]. The mean values of the variables at baseline and after 24 weeks were compared using paired t tests. An intention-to-treat analysis of all 20 patients was performed, as well as a separate analysis of the patients who completed the whole study.

The medical ethical committee of the Slotervaart Hospital, Amsterdam, approved the study.

RESULTS

The mean age of the 20 AS patients was 41 years (range 19–69, median 40), 18 were men and 19 were positive for the HLA-B27 antigen. The mean disease duration was 7.9 years (range 0.4–27). The patients had no history of extraarticular manifestations besides acute anterior uveitis (25%) and psoriasis (10%).

Eight out of 20 patients stopped the medication permanently after a mean period of 9.3 weeks (range 2–22) due to adverse effects, despite dose reduction. Several of these patients were not even able to tolerate a dose as low as 0.5 g/day. Most patients (75%) reported side effects, consisting mainly of gastrointestinal complaints, especially diarrhea. Five patients reported no adverse reaction due to the medication (Table 1). Laboratory values showed no adverse effects except a > 3–6-fold increase in hepatic enzymes in one patient, necessitating withdrawal of treatment with mesalazine; the levels normalized after drug discontinuation.

Twelve (60%) of the patients completed the 24-week treatment with mesalazine, using a mean dose of 3.2 g/day (range 1–4). Because of adverse effects, 5 of these 12 patients discontinued the medication during a short period (with a mean duration of 3.2 weeks and in one case 10 weeks because of an intercurrent urological analysis), but completed the study. The 12 completers were younger (mean 34 yrs) and had shorter disease duration (mean 6.0 yrs) compared to the 8 dropouts (mean 52 and 10.7 yrs).

All patients used NSAID during the study; 3 patients increased the dose, 4 used a lower dose, and 3 switched to another NSAID.

Table 1. Number of reported adverse effects in 20 patients with AS taking mesalazine (adverse effects were seen in 15 patients).

Adverse Effect	n
GI disorders	
Nausea	4
Abdominal pain	4
Diarrhea	7
Increased hepatic enzymes	1
Skin disorders	
Pruritus	1
Worsening eczema	1
CNS disorders	
Dizziness	3
Headache	1
Other	
Fever	1
Impotence	1
Arthralgia	2

GI: gastrointestinal, CNS: central nervous system.

The results of the disease outcome variables at baseline and during followup of the total group of 20 patients and of the 12 patients who completed the study are presented in Table 2. Improvement was observed in ESR, CRP, and physician's global assessment, but only the change in ESR reached statistical significance ($p = 0.03$). The other outcome variables did not change favorably.

A secondary analysis of the 12 completers only showed significant improvement of the CRP ($p = 0.03$) and physician's global assessment ($p = 0.02$).

DISCUSSION

In our open pilot study, no significant improvement of active AS was observed during treatment with mesalazine for 24 weeks. The ESR was the only disease activity variable that changed significantly, although the clinical relevance of this finding (mean difference –4 mm/h) was doubtful. A striking number of patients did not tolerate mesalazine, mainly due to gastrointestinal complaints, which improved after cessation of the drug. A separate analysis of the 12 patients who completed the whole study did not show any favorable effect.

Another preparation of mesalazine, Pentasa®, performed better in 2 open studies in patients with SpA, with fewer side effects and improvement of most clinical, physical, and laboratory variables[9,10]. The somewhat lower mean age of the patients in these studies (37.6, 39.1, and 34.4 yrs) compared to our population (41 yrs) might be a possible explanation, because in our study the older patients were more likely to drop out. Also, the higher tolerance of Pentasa® can probably be explained by the more gradual increment of the drug and the lower dose used in these studies. However, in some of our patients even a dose as low as 0.5 g/day in rechallenge was not tolerated.

Table 2. Disease activity variables in 20 patients with AS (data in parentheses for the 12 completers only). Values are given as mean.

	Baseline	4 Weeks	12 Weeks	24 Weeks	p
ESR, mm/h	29 (30)	24	26	25 (27)	0.03 (0.26)
CRP, mg/l	25 (30)	22	28	22 (23)	0.16 (0.03)
BASDAI, 0–10	4.4 (4.4)	4.1	4.4	4.2 (3.7)	0.67 (0.31)
BASFI, 0–10	4.5 (4.1)	4.3	4.5	4.5 (3.8)	0.97 (0.49)
BASMI, 0–10	4.5 (3.9)	4.6	4.7	4.6 (4.2)	0.54 (0.09)
Patient global, 0–10	4.8 (4.9)	4.8	5.1	4.7 (4.3)	0.85 (0.35)
Doctor global, 0–10	5.4 (5.3)	4.8	4.8	4.6 (4.1)	0.09 (0.02)
SJS, 0–40	0.2 (0.2)	0.2	0.3	0.3 (0.3)	0.33 (0.34)
TJS, 0–42	1.2 (1.2)	1.2	1.5	1.3 (0.8)	0.80 (0.17)

Paired t test comparing week 24 to baseline. ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, BASFI: Bath Ankylosing Spondylitis Functional Indesx, BASMI: Bath Ankylosing Spondylitis Metrology Index (new scoring system), SJS: swollen joint score, TJS: tender joint score.

As far as we know there are no studies suggesting that Salofalk® is less tolerated than other formulations of mesalazine. The impaired tolerance of mesalazine in our study, compared to the situation in IBD, is possibly related to the rheumatic disease itself or concomitant use of antiinflammatory drugs.

It can be hypothesized that the apparent difference in efficacy between Pentasa® and Salofalk® could be due to the pharmacological difference between the several preparations of mesalazine. These various preparations are released at different parts of the bowel. The release of Pentasa® starts in the proximal small intestine, whereas Asacol® becomes available only when the pH rises to around 7, typically in the terminal ileum. Salofalk® takes an intermediate place, being released at around pH 6. The mesalazine in SSZ is split from sulfapyridine in the colon by bacterial enzymes. The associations of SpA with enterogenic infection and IBD are well known. Even in undifferentiated SpA and AS, ileocolonoscopic inflammatory lesions in the small and large bowel were found in high frequencies[14]. However, because the exact pathogenic role of the gut in AS is not known, the importance of the differences in delivery characteristics of the forms of mesalazine is not certain, but cannot be excluded.

In summary, we saw no improvement in disease activity variables in patients with AS during treatment with Salofalk®, except for the ESR. There was a high rate of premature discontinuance by patients because of intolerance. Although we cannot exclude the possibility that a lower dose or a different formulation of mesalazine might be better tolerated and more effective, our results suggest that Salofalk® has no role in the treatment of AS.

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