# Limited effect of sulphasalazine treatment in reactive arthritis. A randomised double blind placebo controlled trial

Charlotte Egsmose, Troels Mørk Hansen, Lis Smedegaard Andersen, Jannie Marion Beier, Lene Christensen, Leif Ejstrup, Niels Daugaard Peters, Désirée M F M van der Heijde

**Abstract**

***Objective*—To assess the efficacy and safety of sulphasalazine in reactive arthritis.**

***Methods*—Double blind placebo controlled trial of six months duration comparing sulphasalazine 2-3 g per day (n = 37) with matching placebo (n = 42) in adults with active reactive arthritis (age 19-57 years, median 34). Treatment response was evaluated once a month by changes in erythrocyte sedimentation rate (ESR), pain, peripheral arthritis, tender iliosacral joints, entesopathy, extra-articular manifestations, and working ability.**

***Results*—15 patients in the sulphasalazine group and eight in the placebo group withdrew from the study prematurely. Adverse events, primarily gastrointestinal, were the main reason for withdrawal in the actively treated group. Intention-to-treat analyses showed significant improvements over time in both groups in ESR, pain, and number of swollen joints ($P < 0.01$). Number of days on sick leave decreased significantly in the sulphasalazine group only ($P < 0.01$). No significant differences between the two groups were present after six months. Among the patients completing the trial according to protocol, persistent complete remission had occurred within two months in five (23%) of the actively treated, but in no placebo treated patients ($P = 0.013$).**

***Conclusions*—Sulphasalazine seemed to improve only the very short term outcome of reactive arthritis. The possible beneficial effect of the drug should also be weighed against the risk of adverse events. Although these were mainly mild, almost 25% of the patients in the actively treated group gave up treatment for this reason.**

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**Department of Rheumatology, Copenhagen Municipal Hospital, Copenhagen and GentofteUniversity Hospital, Hellerup, Denmark**
C Egsmose

**Department of Rheumatology, Herlev University Hospital, Herlev, Denmark**
T M Hansen

**Department of Rheumatology, King Christian X Rheumatism Hospital, Graasten, Denmark**
L S Andersen

**Department of Rheumatology, Odense University Hospital, Denmark**
J M Beier
L Ejstrup

**Department of Rheumatology, Hjørring Hospital, Denmark**
N D Peters

**Department of Rheumatology, University Hospital Maastricht, The Netherlands**
D M F M van der Heijde

Correspondence to:
Charlotte Egsmose, Department of Rheumatology B4, Slagelse County Hospital, DK-4200 Slagelse, Denmark.

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The traditional treatments in reactive arthritis consist of non-steroidal anti-inflammatory drugs and physiotherapy. Such treatments can only be considered palliative and have not been shown to change the course of the disease. No disease modifying agent is currently available for patients with aggressive disease.

The clinical entity of reactive arthritis bears some resemblance to the HLA-B27 related arthropathies, ankylosing spondylitis and psoriatic arthritis (HLA-B27 association, spondylitis, extra-articular manifestations), and also to rheumatoid arthritis (peripheral arthritis), in which a beneficial effect of sulphasalazine has been shown.[1 2]

In addition, inflammatory lesions have been found in the ileum and colon of patients with reactive arthritis, even in the absence of intestinal symptoms.[3–6] These lesions resemble those found in the classical inflammatory bowel diseases, where sulphasalazine is an established treatment.[7]

Open studies and retrospective analyses have suggested an effect of the drug in reactive arthritis.[3 8 9–11] Recently, a double blind placebo controlled trial of sulphasalazine in spondylarthropathies has suggested a marked effect of the active drug in psoriatic arthritis, but not in the subgroup classified as having reactive arthritis.[12]

The present prospective, double blind, placebo controlled study was undertaken in order to evaluate the effect of sulphasalazine in patients suffering from reactive arthritis.

## Methods

Five centres participated in the study. Patients above the age of 18 years with active reactive arthritis were eligible for the trial. This condition was defined as the presence for at least four weeks of at least one peripheral swollen joint despite non-steroidal anti-inflammatory drug (NSAID) treatment, and providing rheumatoid arthritis, septic arthritis, crystal arthropathies, ankylosing spondylitis, psoriasis, inflammatory bowel diseases, and acute intermittent porphyria had been excluded. Axial involvement, extra-articular manifestations, and history of urethritis, cervicitis, or enteritis were not obligatory. Further exclusion criteria were a history of glucose-6-phosphate dehydrogenase deficiency, known allergy to salicylic acid or sulphonamides, low neutrophil count ($<1.5 \times 10^9$ litre$^{-1}$), low platelet count ($<100 \times 10^9$ litre$^{-1}$), significant impairment of hepatic or renal function, previous sulphasalazine treatment, and oral or intra-articular glucocorticoid treatment within the past four weeks. Pregnant and lactating women and patients planning to conceive within the study period were also excluded.

The trial period was six months.

Trial medication consisted of sulphasalazine (Salazopyrin EN tablets) and matching placebo and was kindly supplied by Pharmacia AS, Denmark. The dose regimen was one 500 mg tablet twice daily in the first week, two tablets twice daily in the second week, and three

*Table 1 Baseline characteristics of the 79 patients included in the trial*

| | *Sulphasalazine (n=37) mean/n (%)* | *Placebo (n=42) mean/n (%)* | *Range* |
|---|---|---|---|
| Age (years) | 33.1 | 35.2 | 19–57 |
| Disease duration (total, months) | 4.7 | 3.9 | 1–315 |
| Duration of present attack (months) | 2.5 | 2.8 | 1–65 |
| Experiencing 1st attack | 26 (70) | 30 (71) | |
| EXAM* | 14 (38) | 15 (36) | |
| HLA-B27 positive | 20 (54) | 27 (64) | |
| Pathological *x* rays | | | |
| Iliosacral joints | 4 (11) | 5 (12) | |
| Peripheral joints | 9 (24) | 6 (14) | |
| Positive serology/culture | 12 (32) | 14 (33) | |
| Yersinia | 4 | 3 (1 also chlamydia) | |
| Borrelia | 1 | 0 | |
| Salmonella | 1 | 1 | |
| Chlamydia | 6 | 11 | |
| Gonococci | 0 | 1 (also chlamydia) | |
| ESR | 30 | 32 | 1–120 |
| Pain (mm VAS) | 46 | 46 | 0–95 |
| No of swollen joints | 3.2 | 3.5 | 1–10 |
| No of patients on sick leave** | 23 (62) | 31 (74) | |

*EXAM = presence of extra-articular manifestations (conjunctivitis, uveitis, urethritis, balanitis, skin/mucous membrane manifestations, entesopathy)
**Within past 4 weeks, due to reactive arthritis.
VAS, visual analogue scale.

tablets twice daily from the third week onwards. In the event of side effects, or of sufficient effect at a lower dose, the daily dosage could be reduced or maintained at a lower level.

Date of onset of the present and any previous attacks of arthritis was recorded. *X* rays of the iliosacral joints and of affected peripheral joints were taken, and the patients were tested for HLA-B27 and serum titres of *Yersinia enterocolitica*, *Borrelia burgdorferi*, and salmonella/shigella (Widal). Urethral/cervical smears were also cultured for chlamydia and *Neisseria gonorrhoeae*.

The patients were evaluated at entry and once a month for six months. Clinical assessments consisted of recording the number of swollen joints (sternoclavicular, acromioclavicular, shoulder, elbow, wrist, metacarpophalangeal, proximal interphalangeal, distal interphalangeal, knee, ankle, metatarsophalangeal/toes; thus the maximum possible number of active joints was 52), and the presence of fever (37.5°C or more rectally), conjunctivitis (as evaluated by the treating rheumatologist), uveitis (confirmed by an ophthalmologist if necessary), urethritis (defined as dysuria), balanitis, other skin/mucous membrane manifestations (as evaluated by the treating rheumatologist), entesopathy (tender, swollen entheses), and tender ileosacral joints. Pain (axial, joints, and entheses combined) was recorded on a 100 mm visual analogue scale (VAS). Laboratory determinations comprised erythrocyte sedimentation rate (ESR), and, as a safety measure, haemoglobin, white blood count and full differential count, platelet count, serum creatinine, alkaline phosphatase activity, and aspartate aminotransferase. The patients were questioned about adverse events at every visit, and concomitant treatment was recorded.

*Table 2 Reasons for premature withdrawal from the study*

| | *Sulphasalazine (n=37)* | *Placebo (n=42)* |
|---|---|---|
| Lack of effect | 0 | 1 |
| Recovered | 2 | 1 |
| Adverse event | 9 | 3 |
| Consent withdrawn | 0 | 3 |
| Other reason | 3 | 0 |
| Lost to follow up | 1 | 0 |
| Total | 15 | 8 |

*Table 3 Most frequently reported adverse events in the two treatment groups summarised by body system*

| | *Sulphasalazine (n=37)* | *Placebo (n=42)* |
|---|---|---|
| Gastrointestinal disorders | 13 | 10 |
| CNS disorders | 9 | 7 |
| Skin disorders | 4 | 4 |
| Leucopenia | 2 | 1 |
| Total number of adverse events | 39 | 30 |
| Total number of patients with adverse events | 22 | 19 |

The primary efficacy variables consisted of pain (VAS scale), number of swollen joints, ESR, whether or not the patient was still on sick leave because of the joint disease, and "complete remission" defined as absence of fever, peripheral arthritis, tender iliosacral joints, entesopathy, extra-articular manifestations (conjunctivitis, uveitis, urethritis, balanitis, skin/mucous membrane manifestations) and normal ESR. For each patient, outcome measures were collected by a single observer. Compliance was checked by asking the patients at every visit whether they had taken their pills as prescribed.

The study was approved by the local ethics committees, and oral informed consent according to the Declaration of Helsinki II was obtained from all the patients.

SAMPLE SIZE AND STATISTICAL ANALYSIS.
Calculations of sample size showed a need for 76 subjects in order to achieve a statistical power of 0.80 with a two tailed $\alpha$ of 0.05 assuming a difference of 40% in the percentage of patients in remission and with an expected drop out rate of 20%.

Data were analysed according to the intention-to-treat principle, and also as patients completing the trial per protocol. The statistical methods employed were the log rank test, the Wilcoxon rank sum test, the Fisher exact test, and analysis of variance (ANOVA).

Based on the literature, a remission rate of 25% after six months was expected in the placebo group.[8]

## Results

Eighty three patients were allocated. Four of these were excluded from analysis, either because they did not meet the inclusion criteria or because they withdrew before the one month control. Thus data from 79 patients were available for statistical analysis. Thirty seven (13 women, 24 men) were allocated to sulphasalazine and 42 (eight women, 34 men) to placebo. Baseline data of the patients appear in table 1. The two treatment groups were comparable at baseline. A little more than one half of the patients were HLA-B27 positive, and the probable triggering micro-organism could be identified in one third of the cases (one half, if low titres of the serological tests were considered positive). One third of the

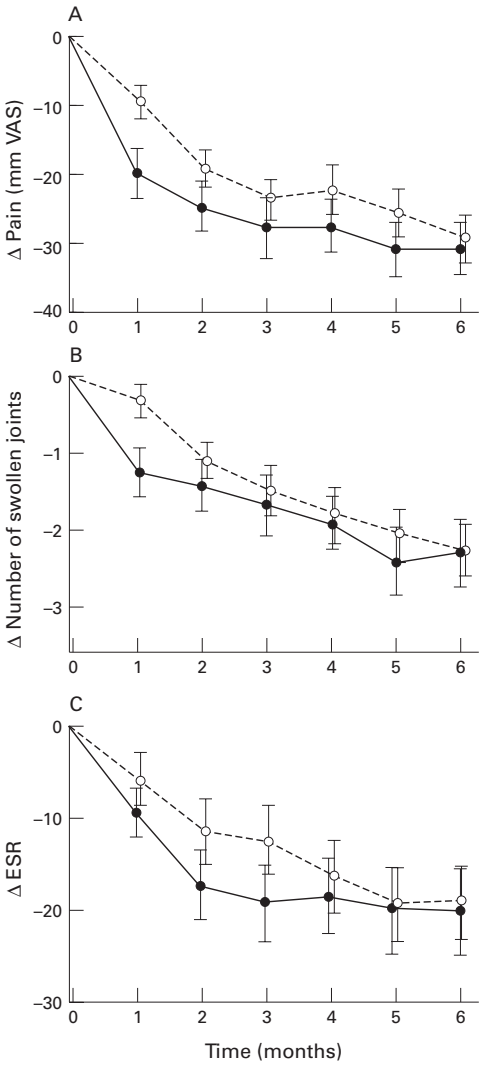


*Figure 1 Changes over time in pain (A), number of swollen joints (B), and ESR (C) in patients treated with sulphasalazine (n = 37) and placebo (n = 42). Intention-to-treat analysis. Values are means, error bars = SEM. Decrease over time: P < 0.01 in both groups for all three variables. Difference between groups over time: NS. Sulphasalazine • ; placebo ◦*

patients fulfilled the preliminary criteria for Reiter syndrome[13] and two thirds the preliminary criteria for spondylarthopathy,[14] which include reactive arthritis.

Trial medication dosage remained at 2 g daily (two tablets twice daily) in seven sulphasalazine and in 10 placebo treated patients and was reduced after having reached 3 g daily in four patients.

Twenty three patients withdrew from the study prematurely, 15 in the sulphasalazine group and eight in the placebo group. Reasons for withdrawal are shown in table 2. Adverse events were the main reason for withdrawal in the actively treated group.

INTENTION-TO-TREAT ANALYSIS.

Significant improvements over time were registered in pain, number of swollen joints, and ESR in both groups (P < 0.01), fig 1A-C. There was no significant difference between the two groups. The number of days on sick leave decreased significantly in the sulphasalazine group (P < 0.01) but not in the placebo group. Complete remission as defined above was present at end point in 13 patients in the sulphasalazine group and 11 in the placebo group (35% and 26%).

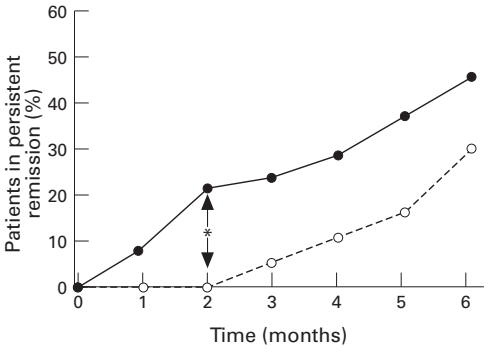


*Figure 2 Number of patients in persistent complete remission (for definition see text) in patients treated with sulphasalazine (n = 22) and placebo (n = 34). Completer analysis. Sulphasalazine • ; placebo ◦ . *P = 0.013*

Patients with positive serology/culture showed the same treatment response as those who were negative. The same held true when comparing HLA-B27 positive and HLA-B27 negative patients and patients with (n = 22) and without (n = 57) axial involvement.

Adverse events were reported by 22 sulphasalazine and 19 placebo treated patients. Details are shown in table 3. Two cases of mild, reversible leucopenia were seen in the sulphasalazine group, and one in the placebo group. No serious biochemical abnormalities were registered.

COMPLETER ANALYSIS

Fifty six patients completed the study per protocol, 22 in the sulphasalazine group and 34 in the placebo group. The baseline characteristics of these patients did not differ from the original intention-to-treat population (data not shown).

Changes over time in pain, number of swollen joints, number of patients on sick leave, and ESR were essentially similar to those seen in the intention-to-treat analysis (data not shown). The cumulative number of days on sick leave (time course effect) constituted 20% of the total study period in the sulphasalazine group and almost twice as many (38%) in the placebo group (P = 0.14).

The first remission set in earlier in the actively treated patients (log rank test, P = 0.055). Twenty five (45%) of the patients completing per protocol experienced no remission at all — six (27%) in the sulphasalazine group and 19 (56%) in the placebo group (P = 0.054).

After two months, persistent complete remission had occurred in five sulphasalazine treated patients (23%) but in no placebo treated patients (P = 0.013), fig 2. After six months, 10 patients in the sulphasalazine group and 11 in the placebo group were in complete remission (P = 0.40). Among these

patients, median time to persistent complete remission was 3.3 months versus 5.4 months (P = 0.13).

## Discussion

The optimistic results of previous open studies of sulphasalazine in reactive arthritis cannot quite be confirmed.[3 9 10] In the first place, one third of the patients completing per protocol in the placebo arm (or a little over 25% evaluated by intention-to-treat analysis) went into remission within six months reflecting the spontaneous course of the disease. In the second place, success rate—expressed as percentage of patients experiencing complete remission—was only half of that reported by Mielants and Veys[3] and Trnavský *et al*.[10] In those studies, 15 *v* 18 patients with reactive arthritis were followed for three to 36 months (median 8) *v* 9 months. Remission rate in the present study corresponded to that found by Mielants *et al*,[8] who followed 32 patients with reactive arthritis and 16 patients with ankylosing spondylitis for three to 24 months (mean 10). Possible differences between patient groups were not examined. Stroehmann *et al*,[9] investigating patients with reactive arthritis, psoriatic arthropathy, and ankylosing spondylitis, reported a "profound improvement" in the first mentioned group. In a retrospective analysis of 101 patients with various subtypes of spondylarthropathy resistant to NSAID treatment, Dougados *et al*[11] found sulphasalazine to be of "clinically relevant benefit" (defined as continued use of the drug for at least six months) in 59% of the patients. A recent double blind placebo controlled trial of sulphasalazine in spondylarthropathies[12] failed to show any benefit of the active drug over placebo in the reactive arthritis subgroup (n = 81). Disease duration was somewhat longer in some of the patients [5 (SD 8.2) years] than in the present study, but the decrease in pain (VAS) observed in both actively and placebo treated patients over the six month observation period corresponded almost exactly to the changes in the present study. This suggests that the short term (six months) course of the disease was not influenced by total disease duration, and that the fact that sulphasalazine did not prove significantly superior to placebo in the present study was not due to the inclusion of patients with mild, self limiting disease.

Disease duration in previous open studies was also generally longer[9 10] than in the present study, or not clearly stated.[3 8 11]

In the present study, reactive arthritis was defined in the same manner as in daily clinical practice, that is, in part as a diagnosis of exclusion. Others have used classification criteria as suggested by Wilkens *et al* for Reiter syndrome[13] or Dougados *et al* for spondylarthropathy.[14] We found these criteria too limited for our purpose, however, as we did not wish only to include patients with posturethritic arthritis[13] or with axial involvement.[14] Thus some of the patients could be classified as having seronegative oligoarthritis or undifferentiated arthritis, which may not be identical to reactive arthritis. Analysis of treatment response in subgroups, however, with or without signs of a precipitating infection and with or without signs of spondylarthopathy, did not suggest that the broad definition used in the present study had any influence on the results.

Compliance was only checked by asking the patients whether they had taken their medication as prescribed. Thus compliance may actually have been poorer than estimated. It was our clinical impression that the patients, generally young and previously healthy, had some difficulty in accepting their role as patients, and persuading them to meet their appointments (physician, laboratory, *x* rays) proved difficult. When free of symptoms, they wished to avoid medication and hospital contact.

Remission occurred within the first two months in almost 25% of the sulphasalazine treated patients who completed the trial according to the protocol, but not in any of the patients in the placebo group. Despite the small number of patients available for statistical analysis, a significant difference between the two treatment groups was present at this time point, suggesting that the drug actually does shorten the duration of the disease in certain patients.

The drop out rate in the present study was unexpectedly high, almost 30%. Thus, if the sample size had been larger, differences between the groups in the efficacy variables investigated may have been more pronounced.

Adverse events were reported by more than half of the patients in the actively treated group, and by over 45% in the placebo group, confirming the findings of Dougados *et al*.[12] Apart from reversible leucopenia, adverse events were much more frequent than found in open studies,[3 8 9–11] and—although the adverse events reported generally were mild in nature—almost 25% (nine out of 39) of the sulphasalazine treated patients were withdrawn from the present study for this reason. This withdrawal frequency is also somewhat larger than previously reported,[3 8 9–12] where withdrawals were seen in 0%, 0%, 0%, 17%, 14%, and 18% respectively. The daily sulphasalazine dose employed in all the studies including ours has ranged between 2 g and 4 g. Thus different dose regimens cannot explain the findings. The discrepancies in reported adverse events and in withdrawal rates may reflect patient selection (and in most of the previous studies, patient subgroups cannot be identified) rather than true differences in frequency.

The divergence between the present study and previous open studies in response rate, adverse event reporting, and withdrawals, and the high rate of adverse event reporting in the placebo treated patients, stresses the importance of performing double blind, randomised, placebo controlled trials when evaluating the effect and the toxicity of new drugs, or new indications for existing drugs.

In conclusion, sulphasalazine may improve the short term outcome in some patients with reactive arthritis. The possible beneficial effect

of the drug should, however, be weighed against the risk of adverse events. Although these were mainly mild in nature, almost 25% of the patients in the actively treated group gave up treatment for this reason.

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1 McConkey B, Amos RS, Durham S, Forster PJG, Huball S, Walsh L. Sulphasalazine in rheumatoid arthritis. BMJ 1980;280:442–4.
2 Pullar T, Capell HA. Sulphasalazine: a "new" antirheumatic drug. Br J Rheumatol 1984;23:26–34.
3 Mielants H, Veys EM. HLA-B27 related arthritis and bowel inflammation. Part 1. Sulphasalazine (Salazopyrin) in HLA-B27 related reactive arthritis. J Rheumatol 1985; 12:287--93.
4 Mielants H, Veys EM, Cuvelier C, De Vos M, Botelberghe L. HLA- B27 related arthritis and bowel inflammation. Part 2. Ileocolonoscopy and bowel histology in patients with HLA-B27 related arthritis. J Rheumatol 1985; 12:294–8.
5 Mielants H, Veys EM, Joos R, Cuvelier C, de Vos M. Repeat ileo-colonoscopy in reactive arthritis. J Rheumatol 1987; 14:456–8.
6 Mielants H, Veys EM, Goemaere S, Goethals K, Cuvelier C, De Vos M. Gut inflammation in the spondyloarthropathies: clinical, radiological, biological and genetic features in relation to the type of histology. A prospective study. J Rheumatol 1991;18:1542–51.
7 Peppercorn MA. Sulphasalazine: pharmacology, clinical use, toxicity and related new drug development. Ann Intern Med 1984;101:377–86.
8 Mielants H, Veys EM, Joos R. Sulphasalazine (Salazaopyrin) in the treatment of enterogenic reactive synovitis and ankylosing spondylitis with peripheral arthritis. Clin Rheumatol 1986;5:80-3.
9 Stroehmann I, Wüstenhagen E, Martini M. Die Therapie seronegativer Oligo-artritiden mit Salazopyrin. Z Rheumatol 1987;46:79--82.
10 Trnavský K, Peliskova Z, Vácha J. Sulphasalazine in the treatment of reactive arthritis. Scand J Rheumatol 1988;suppl 67:76–9.
11 Dougados M, Maetzel A, Mijiyawa M, Amor B. Evaluation of sulphasalazine in the treatment of spondyloarthropathies. Ann Rheum Dis 1992;51:955–8.
12 Dougados M, van der Linden S, Leirisalo-Repo M, Huitfeldt B, Juhlin R, Veys E, et al. Sulphasalazine in the treatment of spondylarthopathy. Arthritis Rheum 1995; 38:618–27.
13 Wilkens RF, Arnett FC, Bitter T, Calin A, Fisher L, Ford DK, et al. Reiter's sydrome. Evaluation of preliminary criteria for definite disease. Arthritis Rheum 1981;24:844–9.
14 Dougados M, van der Linden S, Juhlin R, Huitfeld B, Amor B, Calin A, et al. The European spondylarthropathy study group preliminary criteria for the classification of spondylarthropathy. Arthritis Rheum 1991;34:1218–27.