Is Sulfasalazine Effective in Ankylosing Spondylitis? A Systematic Review of Randomized Controlled Trials

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ABSTRACT. ***Objective.*** To evaluate the efficacy and toxicity of sulfasalazine (SSZ) for the treatment of ankylosing spondylitis (AS).

Methods. We searched randomized and quasi-randomized trials in any language comparing SSZ with placebo in treatment of AS. Two reviewers independently selected the studies and assessed the methodological quality. Data were extracted from the chosen studies and metaanalysis was conducted with RevMan software.

Results. We identified 11 trials, in which a total of 895 patients were treated for periods ranging from 12 weeks to 3 years. The pooled analysis showed that differences between SSZ and placebo were statistically significant only in erythrocyte sedimentation rate (ESR) and the severity of spinal stiffness, favoring SSZ over placebo. Weighted mean differences were ESR –4.79 mm/h (95% CI –8.80 to –0.78) and spine stiffness –13.89 mm (95% CI –22.54 to –5.24) on 100 mm visual analog scale (where 0 = no stiffness, 100 = severe stiffness). Nissila 1988 is the only trial in which SSZ showed benefit in primary outcome analyses, including back pain, chest expansion, occiput-to-wall test, and patient's general well-being. Compared with other trials, patients in this trial had the shortest disease duration and highest level of baseline ESR, and it had the greatest proportion of patients with peripheral arthritis. Significantly more withdrawals for side effects (relative risk 1.47, 95% CI 1.01 to 2.13) were found in the SSZ than in the placebo group, although severe side effects were rare.

Conclusion. Across all patients with AS, SSZ showed some benefit in reducing ESR and easing spinal stiffness, but no evidence of benefit in physical function, pain, spinal mobility, enthesitis, or patient and physician global assessment. Patients at an early stage of disease, with higher level of ESR (or active disease) and peripheral arthritis, might benefit from SSZ. (J Rheumatol 2006;33:722–31)

Key Indexing Terms:
ANKYLOSING SPONDYLITIS SULFASALAZINE METAANALYSIS

Sulfasalazine (SSZ) has been used in inflammatory arthritis for decades, and has been confirmed to be effective in rheumatoid arthritis (RA)[1]. Although it has been extensively studied, its efficacy in treating ankylosing spondylitis (AS) remains unclear. In 1990, Ferraz, *et al*[2] conducted a meta-analysis of 5 randomized controlled trials comparing SSZ with placebo, and concluded that SSZ significantly relieved pain and morning stiffness. But this result could not be confirmed by subsequent larger randomized clinical trials[3,4]. On the other hand, a wide range of adverse effects related to SSZ has been reported[5]. Severe side effects are estimated to be about 39 per one million prescriptions[6]. Therefore, it is necessary to verify the efficacy of SSZ in the treatment of AS.

MATERIALS AND METHODS

Criteria for considering studies for this review. We evaluated randomized and quasi-randomized trials in any language comparing SSZ with placebo in treatment of AS. The participants were patients with AS. Studies of patients with spondyloarthropathies (SpA)/spondyloarthritis were included if data were available assessing the outcomes specific to patients with AS. According to the core set for the evaluation of disease controlling antirheumatic treatment (DC-ART) proposed by ASsessment of Ankylosing Spondylitis (ASAS) Working Group[7,8], the primary outcomes were: (1) physical function; (2) pain; (3) spinal mobility; (4) peripheral joints/entheses (pain, swelling, and tenderness); (5) changes in spine radiographs; and (6) patient and physician global assessment. The secondary outcomes were: (1) changes in hip radiograph; (2) spinal stiffness; (3) fatigue; and (4) level of acute-phase reactants, including erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). For the assessment of adverse effects related to SSZ, we included: (1) any side effects reported in the included studies; (2) toxicity related withdrawals; (3) total number of withdrawals and dropouts.

Search strategy for identification of studies. We searched CENTRAL (Cochrane Central Register of Controlled Trials, Issue 2, 2003), Medline (1966 to June Week 4 2003), Embase (1980 to 2003 Week 26), CINAHL (1982 to June Week 3 2003), and the reference sections of retrieved articles. The search strategies were offered by the Cochrane Musculoskeletal Group.

Methods of review. Potential studies for inclusion were identified from the search results. Unblinded trial reports were reviewed independently by 2 reviewers according to the selection criteria. Disagreements on inclusion of studies were resolved, where necessary, by recourse to a third reviewer. The methodological quality of included studies was independently assessed by the same reviewers on randomization, concealment, blindness (patients, care providers, and outcome investigators), description of withdrawals and dropouts, and intention-to-treat analysis. For allocation concealment, we scored as A (adequate), B (unclear), C (inadequate), and D (not used). For other criteria, we scored as A (yes), B (unclear), and C (no).

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RevMan software was used for metaanalysis. Data extracted from the included studies were entered independently by 2 reviewers. Only outcomes specified above were included in the review. Continuous data (e.g., visual analog scales for pain) were entered as means and standard deviations (SD), and dichotomous outcomes (e.g., response, improvement) as number of events. Results were combined using both random and fixed effects models as weighted mean difference (WMD) for continuous data and relative risk (RR) for dichotomous data (given the event is not rare). The origins of heterogeneity, if present, were analyzed according to differences in methodological quality, characteristics of participants, and intervention. Sensitivity analyses were performed on methodological quality.

RESULTS

Description of studies. Eleven studies[3,9-18] (Table 1) met the inclusion criteria. Twelve studies[19-30] were excluded from the review. Six of them[19-24] were duplicate publications. In 5 studies[25-29], participants were patients with SpA and the outcomes specific for AS patients were not given separately. One study[30] did not assess the outcome relevant for the present review.

These 11 trials treated a total of 895 patients, 469 receiving SSZ and 426 placebos. In the trials where gender information was given (Taylor, *et al*[17] did not present information on the sex distribution of participants), 86% of participants were male. Depending on the trial, age and duration of disease were reported as a mean or median value. The age ranged from 26.9 to 45.7 years and duration of disease ranged from 3.8 to 21.9 years. Zero to 68% of patients had disease complicated with peripheral arthritis. All studies claimed that they included patients with active disease, but the definitions of active disease varied. The dosage of SSZ (or placebo) was 2.0 g/day or up to 3.0 g/day depending on the efficacy and tolerance. The duration of treatment ranged from 12 weeks to 3 years. The sample size ranged from 30 to 264.

More than 30 outcomes were assessed, including primary outcomes, secondary outcomes, and outcomes for adverse effects. The outcomes in continuous data were presented as change from baseline or endpoint value or both. In our metaanalysis, we first subtotaled changes from baseline and endpoint values and then pooled them. For those outcomes from studies presenting both change from baseline and endpoint values[3,12], we analyzed the results twice, first using change from baseline and then endpoint value. This was to test whether these 2 values would give different results. We found that the pooled estimates were similar. So we selected the first analysis for presentation.

Several studies presented their results in a form that did not allow analysis in RevMan. In Corkill, *et al*[9], most outcomes were given as means for intervention groups and 95% confidence intervals (95% CI) of differences between them, while standard deviations of each intervention group were not presented. In Dougados, *et al*[11], all continuous data outcomes were given as medians and 95% CI for each intervention group. In conducting our metaanalysis, we assumed that these medians were equal to means and calculated the standard deviations (SD) from confidence intervals. In addition, we performed sensitivity analyses to determine whether these assumed or calculated values affected the final results. In 2 reports[12,13], only graphs were presented for most outcomes. Time to event data were also used to describe peripheral joint symptoms in one study[13]. Attempts to date to obtain unpublished data have been unsuccessful. For the sake of completeness and concision, we describe the main results in Table 1.

Only one study[18] presented outcome data for subgroups (patients with and those without peripheral arthritis).

Methodological quality of studies

Randomization and allocation concealment. All these studies claimed randomized allocation. The allocation concealment was adequate in 5 trials[3,9,11,13,17], but was unclear in others.

Blinding. Nine studies[3,9-12,14-17] were reported as double-blind and one[18] as single-blind. One study[13] did not report blinding, but was found to have triple-blinding (patients, care providers, and outcome observers) upon personal communication with the investigators. Blind outcome assessment was confirmed in 6 reports[3,9-11,13,17], but remained uncertain in others.

Dropouts and intention-to-treat analysis. There were clear descriptions of withdrawals and dropouts in all studies. Four studies[11-13,16] had more than 20% and 2[13,16] had more than 30% of patients dropping out. In our review, all the dichotomous data were analyzed according to intention-to-treat analysis. For the continuous data, 7 trials[3,9-13,18] were reported to include only patients who completed the trial, while others were not. We also considered these trials to include only patients who completed the trial because there was no explanation of the outcomes of those dropping out.

Primary outcomes. Twenty-four outcomes (Table 2) were available for analysis. They assessed physical function, pain, spinal mobility, peripheral joints/entheses, and patient and physician global assessment. Twelve of these outcomes were assessed in only one study. Pooled data showed that the difference between treatment groups was statistically significant only in chest expansion, favoring SSZ over placebo. The WMD was 0.31 cm (95% CI 0.17 to 0.44 cm; Figure 1). No significant heterogeneity was found among the trials (chi-square = 3.57, $I^2 = 0\%$, $p = 0.74$). However, the results in one study[11] were highly variable. In one study[11], a trial with 36% dropouts, a weight of 89.2% was described in metaanalysis. When this trial was deselected, the difference was nonsignificant (Figure 1). Statistically significant heterogeneity ($p < 0.20$) was found among the included studies in the outcomes for Schober's test, occiput-to-wall test, improvement in patient, and physician global assessment. Again, when the Schmidt[16] trial was deselected, the heterogeneity became nonsignificant.

Secondary outcomes. Spinal stiffness and acute phase reactants were the only secondary outcomes available for analysis (Table 2). For spinal stiffness, the pooled estimate for severi-

Table 1. Randomized controlled trials comparing sulfasalazine with placebo.

Study, Duration of Treatment	No. Patients and Characteristics	Outcomes Assessed	Results Reported	Results in the Present Analysis
Clegg[3], 36 wks	264 (SSZ 131, placebo 133); 29% with PA DD, yr: 18.5 ± 11.6 ESR, mm/h: 26.4 ± 18.0 SSZ, 25.2 ± 22.0 placebo CRP, μg/ml: 1.9 ± 2.3 SSZ, 1.9 ± 2.2 placebo	Primary outcomes included response to treatment, improvement in PhGA, PGA, back pain, and morning stiffness. Secondary outcomes included night pain (event), duration of morning stiffness, back pain VAS, spondylitis function index, joint/tenderness score, joint swelling score, dactylitis score, enthesopathy index, spondylitis articular index, chest expansion, Schober's test, occiput-to-wall test, finger-to-floor test, ESR, and CRP	Dropouts: 19.3% Both endpoint value and change from baseline were presented for all continuous outcomes No difference between treatment groups in all outcomes except ESR, which declined more in SSZ than placebo group ($p < 0.0001$). Comparing SSZ responders with nonresponders, the former had greater decrease in ESR ($p < 0.04$) Subgroup analysis showed that in patients with PA, 55.9% of SSZ group and 30.2% of placebo group had peripheral response ($p = 0.023$)	All results reported have been confirmed except subgroup analysis because no information about treatment allocation was available MD for ESR (change from baseline) was –3.10 mm/h, 95% CI –4.85 to –1.35 mm/h, favoring SSZ group
Corkill[9], 48 wks	62 (SSZ 32, placebo 30); 19% with PA DD, yr: 12.3 ± 8.2 SSZ, 16.1 ± 11.4 placebo ESR, mm/h: 15 ± 16 SSZ, 24 ± 26 placebo	Spinal pain VAS, spinal stiffness VAS, peripheral joint pain VAS, Schober's test, chest expansion, cervical flexion, cervical rotation, and ESR	Dropouts: 1.6% No significant difference between treatment groups	Because SD were not given for all outcomes, these results could not be analyzed
Davis[10], 3 mo	30 (SSZ 15, placebo 15) 23% with PA DD, yr: 8.6 SSZ, 8.4 placebo ESR, mm/h: 24±7.8 (95%CI) SSZ, 26.4±8 placebo CRP, mg/l: 27 (median) SSZ, 17 placebo	Pain VAS, spinal stiffness VAS, sleep disturbance (event), occiput-to-wall test, finger-to-floor test, ESR, and CRP	Dropouts: 6.7% In SSZ group, all clinical outcomes significantly improved when initial and 3-mo results were compared	Pain VAS, spinal stiffness VAS, and CRP could not be analyzed because means and SD were not given No significant difference found in any other outcome
Dougados[11], 6 mo	60 (SSZ 30, placebo 30) None with PA DD, yr, median: 10 ESR, mm/h, median: 13.5 SSZ, 11.0 placebo	PGA, score of daily NSAID, pain VAS, joint index, frequency of nocturnal awakening, function index, Schober's test, finger-to-floor test, chest expansion, ESR	Dropouts: 21.7% PGA was greater in SSZ than in placebo group (15/30 vs 6/30, $p < 0.05$) SSZ resulted in significant reduction in score of daily NSAID ($p < 0.05$) and significant improvement of function index (p not given) compared with placebo. No significant difference found in other outcomes	All continuous outcomes presented as median and 95% CI. For RevMan analysis, we assumed that mean is equal to median for each outcome and calculated SD from 95% CI and sample size Success in PGA was greater in SSZ than in placebo group (RR 2.5, 95% CI 1.12 to 5.56) No significant difference found between treatment groups in other outcomes
Feltelius[12], 12 wks	37 (SSZ 18, placebo 19) 5% with PA DD, yrs, median: 12.1 SSZ, 10.4 placebo ESR, mm/h: 24.3 ± 17.4 SSZ, 28.5 ± 19.5 placebo	Duration of morning stiffness, spinal stiffness VAS, pain VAS, general well-being VAS, chest expansion, Schober's test, sleep disturbance (event), sacroiliac pain VAS, ESR	Dropouts 21.6% Spinal stiffness VAS, chest expansion, and sleep disturbance significantly improved in SSZ compared with placebo group	All outcomes presented as graphs; no data were available for analysis except ESR, which showed no significant difference between treatment groups
Kirwan[13], 3 yrs	89 (SSZ 44, placebo 45) 28% with PA DD, yr: 19 ±12 SSZ, 21.9 ± 11.7 placebo ESR not given	Primary outcomes:Schober's test, chest expansion, and lateral cervical flexion. Secondary outcomes: function (HAQ), back pain VAS, consumption of antiinflammatory drugs, sleep disturbance VAS, PGA, episodes of peripheral arthritis, episodes of heel pain, flares in general AS symptoms, episodes of iritis	Dropouts: 30.3% No significant difference between treatment groups in all outcomes except occurrence of peripheral joint symptoms. Episodes of PA were 0.289 episodes/yr in SSZ; 0.392 episodes/yr placebo group ($p < 0.05$)	There were significantly more dropouts for any reason in SSZ than in placebo group. RR 2.43 (95% CI 1.19 to 4.96) No data available for analysis in any other outcomes

Table 1. Continued.

Krajnc[14], 24 wks	95 (SSZ 71, placebo 24) 66% with PA DD not given ESR mm/h: 41 ± 19 SSZ, 43 ± 18 placebo	Duration of morning stiffness, Schober's test, chest expansion, finger-to-floor test, number of painful/swollen joints, and ESR	Dropouts: 14.3% In SSZ group, duration of morning stiffness, chest expansion, no. of painful/swollen joints, and ESR showed significantly improved when initial and 24 wk results were compared	No significant difference between treatment groups in all outcomes except ESR (MD –17.00 mm/h, 95% CI –26.99 to –7.01 mm/h, favoring SSZ)
Nissila[15], 26 wks	85 (SSZ 43, placebo 42) 68% with PA DD, yr: 3.8 ± 4.3 SSZ, 5.4 ± 7.3 placebo ESR, mm/h: 42 ± 20 SSZ, 46 ± 19 placebo CRP, g/l*: 26 ± 18 SSZ, 30 ± 26 placebo *We suspected the unit was a mistake	Duration morning stiffness, spinal stiffness VAS, chest expansion, Schober's test, finger-to-floor test, occiput-to-wall test, number of painful joints, number of swollen joints, general well-being VAS, ESR, and CRP	Dropouts: 12.2% Significant differences between treatment groups in morning stiffness VAS ($p = 0.02$), chest expansion ($p = 0.03$), and ESR ($p = 0.02$) favoring SSZ. No significant difference in other outcomes We suspected results of chest expansion were errors because they were impossible to be about 40–50 cm; we divided them by 10 for analysis	Significant differences found in morning stiffness VAS (MD –14.00, 95% CI –23.78 to –4.22), chest expansion (MD 1.00 cm, 95% CI 0.10 to 1.90 cm), occiput-to-wall test (MD –0.80 cm, 95% CI –1.55 to –0.05 cm), ESR (MD –19.00 mm/h, 95% CI –29.65 to –8.35 mm/h), and general well-being VAS (MD –11.00, 95% CI –19.84 to –2.16) favoring SSZ. No significant difference found in other outcomes
Schmidt[16], 26 wks	70 (SSZ 34, placebo 36) 36% with PA DD, yr: 16.7 ± 7.2 SSZ, 16.3 ± 7.8 placebo ESR, mm/h: 23.1 ± 3.2 SSZ, 20.4 ± 2.4 placebo CRP, mg/l: 19.8 ± 3.7 SSZ, 13.8 ± 2.3 placebo	Back pain VAS, nocturnal awakening (event), pain/tenderness score, duration of morning stiffness, no. painful joints, no. swollen joints, spondylitis function index, PGA, PhGA, Schober's test, finger-to-floor test, chin–sternum distance, chest expansion, ESR, CRP	Dropouts: 36% No significant difference reported between treatment groups. There were more dropouts in SSZ than in placebo (38% vs 11%)	All continuous outcomes analyzed as change from baseline. Significant differences found between treatment groups in back pain VAS (MD –2.30, 95% CI –4.44 to –0.16), chest expansion (MD 0.30 cm, 95% CI 0.16 to 0.44 cm), Schober's test (MD 0.50 cm, 95 CI 0.44 to 0.56 cm), duration of morning stiffness (MD –0.39 h, 95% CI –0.48 to –0.30 h), ESR (MD –3.10 mm/h, 95% CI –4.85 to –1.35 mm/h), and CRP (MD –2.50 μg/ml, 95% CI –4.70 to –0.30 μg/ml), favoring SSZ group. But in occiput-to-wall test, the difference (MD 0.70 cm, 95% CI 0.32 to 1.08 cm) favored placebo over SSZ. No significant difference found in other outcomes Significantly more withdrawals for side effects and dropouts for any reason in SSZ than in placebo. RR 3.44 (95% CI 1.24 to 9.52) and 2.42 (95% CI 1.14 to 5.15), respectively
Taylor[17], 1 yr	40 (SSZ 20, placebo 20) 15% with PA DD, yr): 11 ± 1.6 SSZ, 10.7 ± 1.6 placebo ESR, mm/h,mean: 27 SSZ, 25 placebo	Back pain VAS, finger-to-floor test, chest expansion, sleep disturbance (event), forced vital volume, occiput-to-wall test, Schober's test, spinal stiffness VAS, reduction or stop of NSAID (event)	Dropouts: 17.5% No significant difference between treatment groups in all outcomes except pain VAS ($p < 0.05$) favoring SSZ	No significant difference between treatment groups in all outcomes including pain VAS
Winkler[18], 24 wks	63 (SSZ 31, placebo 32) 33% with PA DD, yr, median: 10.8 SSZ, 11.2 placebo ESR, mm/h: 33.4 ± 20.4 SSZ, 26.9 ± 16.4 placebo	ESR, duration of morning stiffness, back pain VAS, score of sleep disturbance, chest expansion, Schober's test, finger-to-floor test, disease severity in PGA	Dropouts: 22.2% Advantage of SSZ over placebo significant only in duration of morning stiffness ($p < 0.05$) and score of sleep disturbance ($p < 0.05$). In subgroup analysis, the same results were found in patients with axial form disease ($n = 34$). In patients with peripheral arthritis ($n = 15$), articular index showed significant improvement in SSZ over placebo ($p < 0.05$)	No significant difference between treatment groups in all outcomes. In subgroup analysis of patients with axial form, we found significant difference favoring SSZ over placebo in back pain VAS (MD –9.20, 95% CI –17.81 to 0.59

CRP: C-reactive protein, DD: duration of disease, ESR: erythrocyte sedimentation rate (baseline), HAQ: Health Assessment Questionnaire, MD: mean difference, NSAID: nonsteroidal antiinflammatory drugs, PA: peripheral arthritis, PGA: patient global assessment, PhGA: physician global assessment, RR: relative risk, SD: standard deviation, SSZ: sulfasalazine, VAS: visual analog scale.

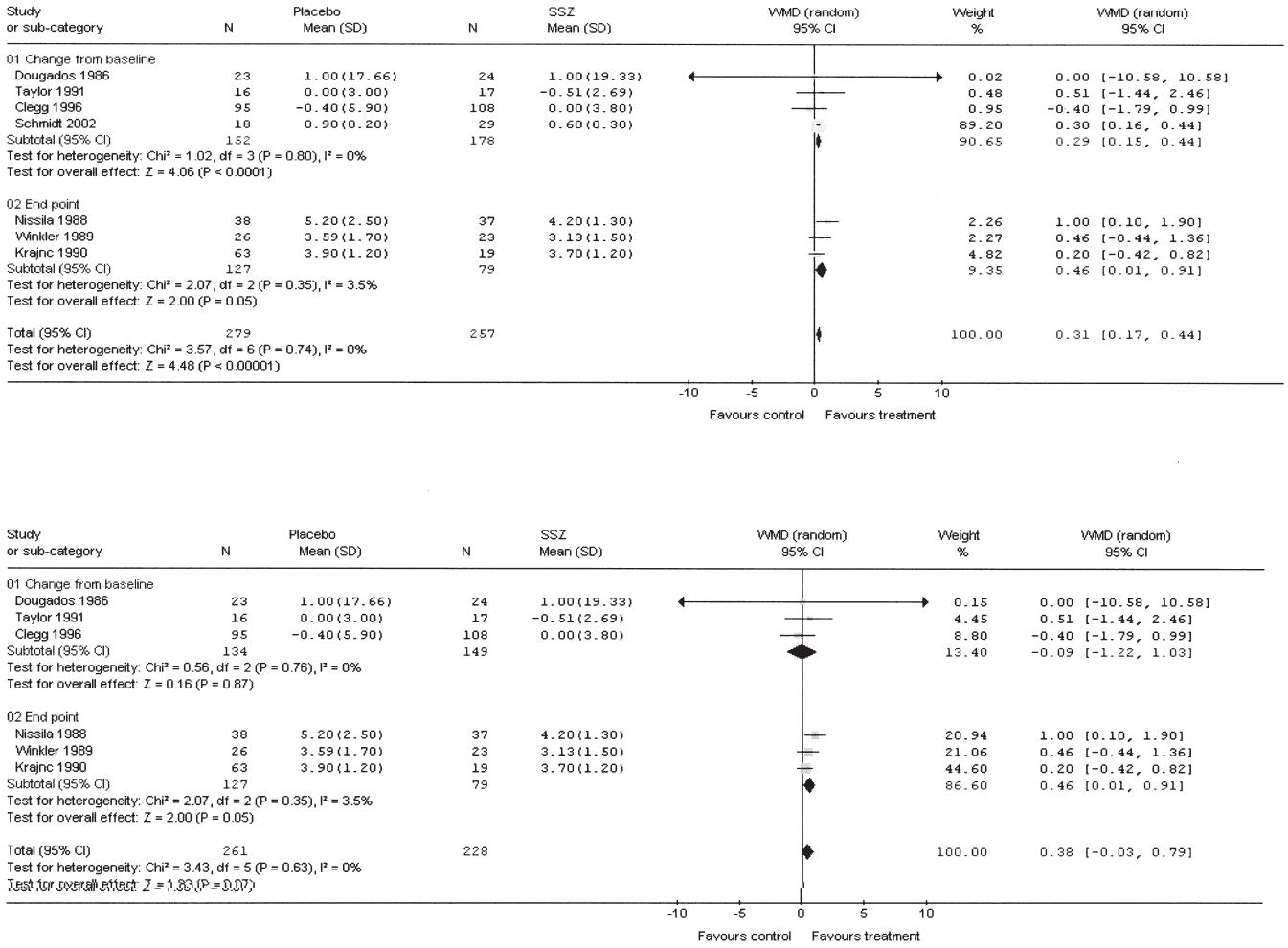

Figure 1. Pooled estimates of chest expansion (cm). Upper panel: data from Schmidt, *et al*[16] were included. Lower panel: data from the same study were excluded.

ty measured on a visual analog scale (VAS; 0–100 mm, where 0 = no stiffness and 100 = severe) showed statistically significant difference between treatment groups favoring SSZ over placebo. The WMD was –13.89 mm (95% CI –22.54 to –5.24 mm). No statistically significant heterogeneity was found among the included trials (chi-square = 0, I^2 = 0%, p = 0.96; Figure 2). However, the pooled estimate of difference for the duration of morning stiffness was not significant: the WMD was –0.20 h (95% CI –0.39 to 0 h). Statistically significant heterogeneity was found among the included trials (chi-square

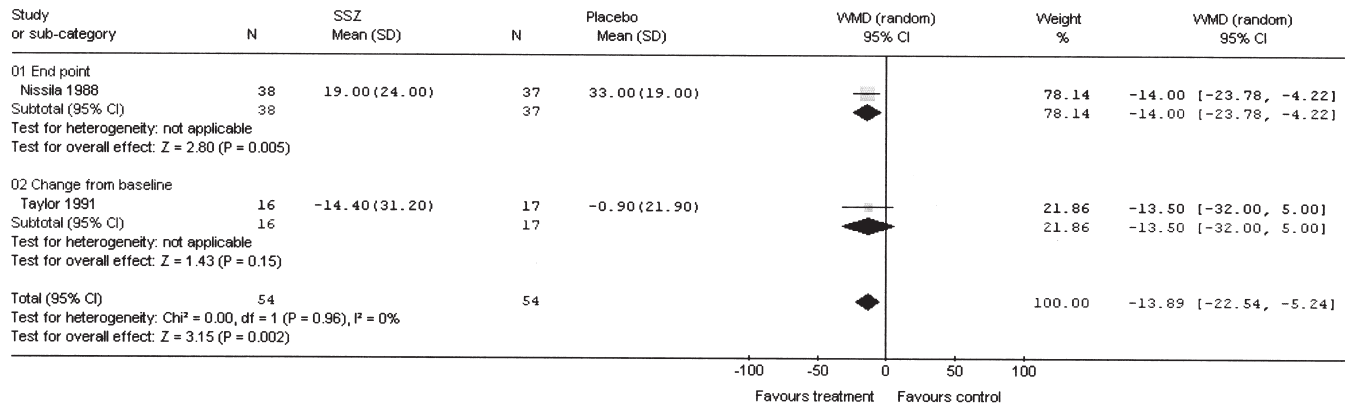

Figure 2. Pooled estimate of spinal stiffness (100 mm VAS: 0 = no stiffness, 100 = severe).

Table 2. Pooled estimates of outcomes comparing sulfasalazine with placebo.

Outcomes	Studies	Participants	Statistical Method	Effect Size (95% CI)
1. Primary outcomes				
Spondylitis function index (score 0–40, 0–44; 0 = best, increasing score = worse function)	3	297	WMD (random)	0.20 (–0.77, 1.18)
Improvement in back pain	1	264	RR	0.87 (0.58, 1.32)
Back pain (100 mm VAS; 0 = no pain, 100 = severe)	6	454	WMD (random)	–2.38 (–5.78, 1.03)
Night pain (not troublesome)	4	404	RR (random)	1.08 (0.80, 1.47)
Sleep disturbance (0–4; 0 = no disturbance, 4 = severe disturbance)	1	49	MD	–0.36 (–0.90, 0.18)
Frequency of nocturnal awakening	1	47	MD	0 (–5.26, 5.26)
Score for daily NSAID (usual dosage as 10)	1	47	MD	–3.80 (–23.3, 15.7)
Reducing or stopping NSAID	1	40	RR	0.86 (0.35, 2.10)
Chest expansion, cm	7	536	WMD (random)	0.31 (0.17, 0.44)*
Forced vital volume, l/min	1	33	MD	212.0 (–332.6, 756.6)
Modified Schober's test, cm	7	536	WMD (random)	0.12 (–0.21, 0.45)
Occiput-to-wall test, cm	5	386	WMD (random)	–0.03 (–0.84, 0.79)
Finger-to-floor test, cm	7	517	WMD (random)	–0.71 (–2.18, 0.75)
Chin-sternum distance, cm	1	47	MD	0 (–0.18, 0.18)
Joint pain/tenderness score (0–198, higher score = more severe disease	2	278	WMD (random)	–0.15 (–0.38, 0.09)
Joint swelling score (0–198, higher score = more severe disease)	2	278	WMD (random)	0 (–0.29, 0.29)
Dactylitis score (change from baseline, 0–3; 0 = normal, 3 = severe)	1	203	MD	0.10 (–0.07, 0.27)
Enthesopathy index (0–90, 0–66, 0–90 (higher score = more severe disease	3	297	WMD (random)	0.11 (–0.12, 0.34)
Spondylitis articular index (0–90, higher score = more severe disease)	1	203	MD	0 (–0.96, 0.96)
Improvement in patient global assessement	3	394	RR (random)	1.53 (0.78, 2.99)
Patient assessment of disease severity (100 mm VAS; 0 = very good, 100 = very poor)	1	49	MD	–4.80 (–18.41, 8.81)
General well-being (100 mm VAS; 0 = very good, 100 = very poor)	1	75	MD	–11.00 (–19.84, –2.16)*
Improvement in physician global assessment	2	334	RR (random)	1.35 (0.58, 3.15)
Response to treatment (based on patient and physician assessment)	1	264	RR (random)	1.06 (0.77, 1.45)
2. Secondary outcomes				
Duration of morning stiffness, h	5	456	WMD (random)	–0.20 (–0.39, 0)
Spinal stiffness (100 mm VAS, 0 = no stiffness, 100 = severe)	2	108	WMD (random)	–13.89(–22.54, –5.24)*
Improvement in morning stiffness	1	264	RR	1.10 (0.85, 1.43)
ESR, mm/h	8	560	WMD (random)	–4.79 (–8.80, –0.78)*
CRP, μg/ml	3	325	WMD (random)	–1.39 (–3.85, 1.07)
3. Outcomes for adverse effects				
Withdrawal for side effects	11	895	RR (random)	1.47 (1.01, 2.13)*
Withdrawal for ineffectiveness	10	833	RR (random)	0.82 (0.39, 1.70)
Dropout for any reason	10	833	RR (random)	1.33 (1.03, 1.73)*

*Statistically significant. CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, MD: mean difference, NSAID: nonsteroidal antiinflammatory drugs, RR: risk ratio, VAS: visual analog scale, WMD: weighted mean difference.

= 11.25, I^2 = 64.4%, p = 0.02). Leaving out Schmidt, *et al*[16], the heterogeneity for duration of morning stiffness was not significant (chi-square = 0.56, I^2 = 0%, p = 0.90) and the WMD was –0.10 h (95% CI –0.25 to 0.05 h).

Pooled data for acute phase reactants showed the difference between treatment groups was statistically significant in the outcome for ESR, but nonsignificant for CRP. The WMD for ESR was –4.79 mm/h (95% CI –8.80 to –0.78; Figure 3). Statistically significant heterogeneity was found among included trials in both ESR and CRP outcomes (for ESR, chi-square = 22.11, I^2 = 68.3%, p = 0.002; for CRP, chi-square = 6.54, I^2 = 69.4%, p = 0.04). This could be due to the large difference at baseline levels among the studies (Table 1).

Adverse effects. A statistically significant difference between treatment groups was found in pooled data of withdrawals for side effects (RR 1.47, 95% CI 1.01 to 2.13) and dropouts for any reason (RR 1.33, 95% CI 1.03 to 1.73), favoring placebo over the SSZ group. Pooled data of withdrawals for ineffectiveness showed no significant difference between treatment groups (RR 0.82, 95% CI 0.39 to 1.70; Table 2). Among 469 patients receiving SSZ, a severe adverse reaction was reported in one patient who developed a generalized, erythematous, raised, pruritic eruption that was associated with nausea, anorexia, and insomnia[3].

Sensitivity analysis. We first conducted sensitivity analyses for concealment and blind assessment. Five of 11 trials examined[12,14-16,18] were unclear on the allocation concealment and blind outcome assessment. Another trial[10] was unclear for allocation concealment alone. After withdrawal of these 6 trials, the WMD for chest expansion, spinal stiffness by VAS, and ESR outcome was no longer statistically significant. Pooled RR of withdrawal for side effects also became statistically nonsignificant.

As continuous data included only the patients who completed the trials, post hoc sensitivity analysis was conducted to determine if these dropouts affected the results. Two studies[13,16] had more than 30% of patients dropping out. After withdrawing the Schmidt study[16] (no continuous data were available in the study of Kirwan, *et al*[13]), we found that the WMD for chest expansion became nonsignificant, as noted above. Other outcomes remained similar. Continuous data from another study[11] were assumed and calculated from the original report, and are possibly inaccurate. In sensitivity analyses, however, we found no obvious difference when this trial was excluded from metaanalysis.

Subgroup data. Studies used in our review could not be grouped according to the characteristics of interventions and participants. Only one study[18] presented data for subgroups (patients with and without peripheral arthritis). In patients with peripheral arthritis (N = 15), no significant difference was found between intervention groups in back pain, score for sleep disturbance, chest expansion, Schober's test, finger-to-floor test, articular index, degree of joint swelling, patient assessment of disease severity, duration of morning stiffness, and ESR. For patients without peripheral arthritis (N = 34), no significant difference was found in these outcomes (but articular index and degree of joint swelling were not assessed), except the back pain VAS (0 = no pain, 100 mm = severe), which was found to significantly favor SSZ over placebo (mean difference –9.20, 95% CI –17.81 to –0.59). Another study[3] has separately analyzed the results of patients with peripheral arthritis, and, based on patient and physician global assessment, found more improvement in the SSZ treatment group than the placebo group (55.9% vs 30.2%, respectively; p = 0.023); but we did not analyze them because the information for treatment allocation was not given.

DISCUSSION

The efficacy of SSZ in AS has been controversial for decades. In 1990, Ferraz, *et al*[2] conducted a metaanalysis of 5 studies[9-12,15] treating a total of 272 patients with AS, and found that the pooled estimate of clinical benefit significantly favored SSZ over placebo in duration and severity of morning stiffness, severity of pain, general well-being, and ESR. In this review,

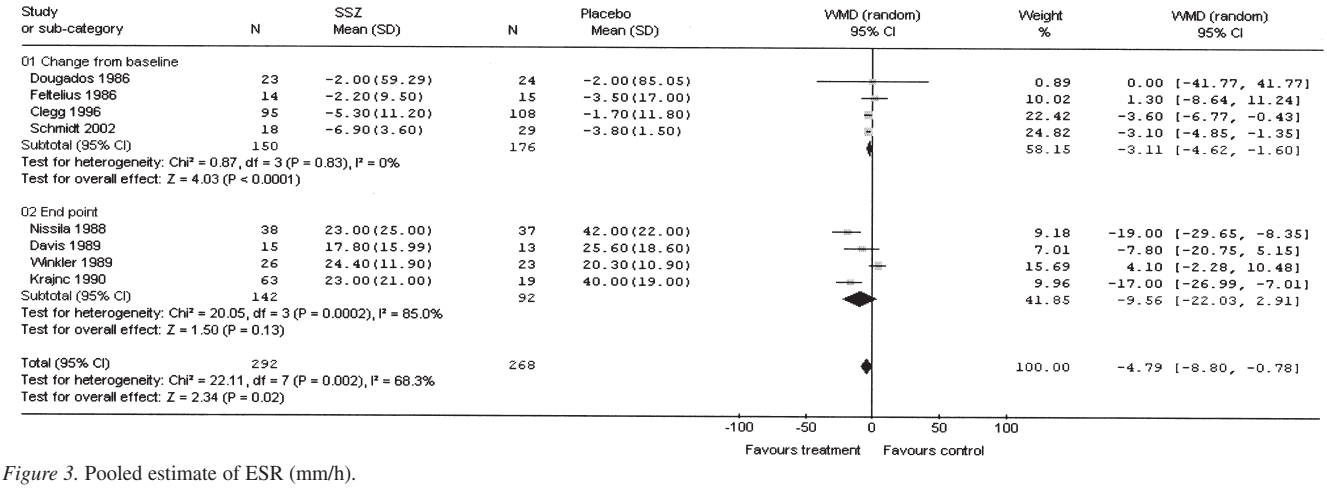

Figure 3. Pooled estimate of ESR (mm/h).

we added 6 other studies and increased the number of participants to 895. More than 30 outcomes were assessed. None of these studies used ASAS improvement criteria for AS[31,32], because they were conducted before the criteria were published. The metaanalysis showed that the difference between treatment groups was statistically significant in chest expansion, the severity of spinal stiffness, and ESR, but not statistically significant in other outcomes. In sensitivity analysis, however, the difference for chest expansion was no longer significant after the study with 36% dropouts[16] was excluded. For the sensitivity analysis, according to the allocation concealment and blind outcome assessment, the results were difficult to explain because few trials and participants left behind after the studies with unclear allocation concealment and blind outcome assessment were excluded. Therefore, SSZ had a statistically significant effect only in the severity of spinal stiffness and ESR (both are secondary outcomes). The WMD between treatment groups were 13.89 mm (on 100 mm VAS) and 4.79 mm/h, respectively, favoring SSZ over placebo.

A limitation of our review is that most outcomes include only a few trials (less than 5) and have a small sample size (less than 400). Because of this, the pooled data should not be the sole basis for a conclusion, and scrutiny of individual studies is also important (Table 1).

First, we examined those studies with high methodological quality, larger sample size, and longer period of treatment. For methodological quality, all trials reviewed were rated A or B in both concealment and blinding assessment, but the proportion of dropouts differed among the trials. Clegg, *et al*[3] conducted the trial with the largest sample size, 264 (there were fewer than 100 in all other trials), and treatment duration of 36 weeks. The proportion of dropouts was 19.3%. They assessed some 30 outcomes and found that ESR declined in the SSZ group compared with the placebo group ($p < 0.0001$). In our analysis, the mean difference was –3.60 mm/h (95% CI –6.67 to –0.43 mm/h; Figure 3). No significant difference was found in other indicators. In subgroup analysis, Clegg, *et al*[3] found that patients with peripheral arthritis experienced more improvement (events) taking SSZ than those in the placebo group ($p = 0.023$). The Kirwan study[13] lasted 3 years (all other trials lasted not more than one year) and included 89 participants; 30.3% dropped out. They found that the occurrence of peripheral joint symptoms was lower in the SSZ group (0.298 episodes/yr) than in placebo group (0.392 episodes/yr) ($p < 0.05$). No difference was found in Schober's test, chest expansion, and cervical spine lateral flexion (no available data for our analysis). These 2 studies confirmed that SSZ is effective in reducing ESR, but ineffective in other outcomes. Both studies indicated that patients with peripheral arthritis might benefit from SSZ.

Next, we went through the other 9 studies and scrutinized those in which SSZ was effective in AS. Five trials[10-12,14,15] reported that SSZ was effective. In 2 trials[10,14], the conclusion was based on comparisons between the initial and endpoint results. In our analysis, the effectiveness of SSZ was confirmed only in studies by Nissila, *et al*[15] and Dougados, *et al*[11]. In Nissila, *et al*[15], the severity of pain, chest expansion, patient general well-being, morning stiffness, and ESR were confirmed to be significantly improved. Dougados, *et al*[11] reported more successes of treatment (judged by patients), reduced use of daily nonsteroidal antiinflammatory drugs, and improved function index. However, only more successes of treatment were confirmed in our analysis. In those studies[9,16-18] where SSZ was reported to be ineffective, we found there was a statistically significant difference between treatment groups for the outcomes of chest expansion, Schober's test, duration of morning stiffness, ESR, and CRP in Schmidt study[16]. However, attrition bias was strongly suspected here, because more patients dropped out from the SSZ than from the placebo group (RR 2.42, 95% CI 1.14 to 5.15; Table 1). On the whole, Nissila, *et al*[15] was the only study where efficacy of SSZ was confirmed in our analysis (Table 1).

Finally, to determine why SSZ was effective in Nissila, *et al*[15] but not in other studies, we looked into this study more closely. Nothing was special about the intervention; but participants' characteristics were different (Table 1), as follows. (1) The mean (or median) duration of disease was the shortest, 3.8 years in the SSZ and 5.4 years in the placebo group (in other studies, it ranged from 8.4 to 21.9 yrs). (2) The mean (or median) level of baseline ESR was the highest, 42 mm/h in the SSZ and 46 mm/h in the placebo group (in other studies, this ranged from 41 in SSZ and 43 in placebo to 13.5 in SSZ and 11.0 in placebo). (3) The proportion of patients with peripheral arthritis was the highest, at 68% (range 66% to 0% in other studies). Only the Krajnc study[14] could match the Nissila study[15] in these aspects (the duration of disease was not given, baseline ESR was 41 mm/h for SSZ and 43 for the placebo group, patients with peripheral arthritis comprised 66%). The imbalance in treatment allocation (71 patients taking SSZ and 24 patients in the placebo group) could be the reason for the observed negative results in this study.

These findings, combined with the results of pooled data and the 2 most impressive trials[3,13], could have important clinical implications, as follows: (1) SSZ management might be useful in early AS, possibly with disease duration less than 5 years; and (2) SSZ management might be effective in patients with higher ESR (possibly > 30 mm/h). Higher ESR indicates active disease, but the current definition of active disease is equivocal. In our review, all studies selected patients with active disease, but the definition was quite different among the studies. Additionally, many studies used patient's subjective assessments as markers, e.g., duration of morning stiffness, pain severity which is subject to investigators' bias. Differences of selection criteria could be one reason why SSZ was effective in some studies but not in others; and (3) SSZ might be effective in patients with peripheral arthritis. This remains to be examined further by separately analyzing patients with peripheral arthritis. In our review, only one

study[18] gave separate data for patients with peripheral arthritis, but the sample size was small (N = 15). Most studies presented the data for AS patients as a whole, in which some outcomes, e.g., score and number of painful joints, score and number of swollen joints, were insensitive to change because patients without peripheral arthritis would be recorded as zero.

With regard to the side effects of SSZ, we found statistically significantly more withdrawals for side effects (RR 1.47, 95% CI 1.01 to 2.13) and dropouts for any reason (RR 1.33, 95% CI 1.03 to 1.73) in the SSZ than in the placebo group (Table 2). Among the 469 patients taking SSZ, one was reported to develop a severe skin reaction[3]. These results showed that adverse effects of SSZ were obvious in some patients, although severe side effects were rare.

Across all patients with AS, SSZ demonstrated some benefit in reducing ESR and easing spinal stiffness, but there was no evidence of benefit in physical function, pain, spinal mobility, enthesitis, or patient and physician global assessment. Patients with early-stage disease, higher ESR (or active disease), and peripheral arthritis might benefit from SSZ.

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