A Comparison of Cyclosporine, Sulfasalazine, and Symptomatic Therapy in the Treatment of Psoriatic Arthritis

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ABSTRACT. ***Objective.*** To compare the efficacy and tolerability of cyclosporine (CSA) with that of symptomatic therapy (ST) alone and sulfasalazine (SSZ) in the treatment of psoriatic arthritis (PsA).

Methods. Twelve rheumatology centers recruited 99 patients with active PsA in a 24 week, prospective, randomized, open, controlled study. The patients were treated with CSA (3 mg/kg/day) or SSZ (2000 mg/day) plus ST, or ST alone (nonsteroidal antiinflammatory drugs, analgesics, and/or prednisone ≤ 5 mg/day). The primary endpoint was the 6 month change in pain. Analyses were on the basis of the intention-to-treat principle.

Results. In comparison with both SSZ and ST, there was a statistically significant difference in favor of CSA in terms of the mean changes in the pain score ($p < 0.05$), which was considered the primary response variable. A significant decrease in favor of CSA versus ST alone was also observed for swollen joint count ($p = 0.05$), tender joint count ($p = 0.01$), joint/pain tenderness score ($p = 0.002$), patient and physician global assessment by at least one point ($p = 0.04$ and 0.01, respectively), total Arthritis Impact Measurement Scale score ($p = 0.002$), and spondylitis functional index ($p = 0.002$). There was a statistically significant difference in the ACR 50% and ACR 70% response rates between the CSA and ST groups ($p = 0.02$, 0.05). Comparing the SSZ and ST alone groups, only the spondylitis functional index decreased significantly in the SSZ treated patients ($p = 0.03$). The Psoriasis Area and Severity Index was significantly lower in the CSA than in the ST and SSZ groups ($p = 0.0001$ and 0.01, respectively). Decrease in erythrocyte sedimentation rate was significant only in the SSZ versus the ST group ($p = 0.02$), whereas reduction in C-reactive protein was significant in the CSA treated patients compared with the ST group ($p = 0.006$). The most common adverse event in the CSA group was mild, reversible kidney dysfunction.

Conclusion. The results of this open trial confirm that CSA is well tolerated by patients with PsA and suggest that it is more efficacious than ST or SSZ. (J Rheumatol 2001;28:2274–82)

Key Indexing Terms:
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Psoriatic arthritis (PsA) used to be considered a relatively mild nondeforming arthropathy. Its treatment consisted of nonsteroidal antiinflammatory drugs (NSAID) and local corticosteroid injections, with second-line drugs reserved for NSAID resistant or progressively destructive forms. However, this view has been challenged over the last decade. One of the largest PsA series revealed the development of erosive and deforming arthritis in 40% of cases, a rate that is similar to that observed in rheumatoid arthritis (RA)[1-3].

As in RA, early and aggressive treatment with symptom modifying antirheumatic drugs (SMARD) may be efficacious in controlling the progression of PsA. Methotrexate (MTX), sulfasalazine (SSZ), and cyclosporine (CSA) are the most widely used SMARD in the treatment of PsA, but only a few well designed and controlled studies have been conducted[4-7], and the effect of SMARD on axial disease has been evaluated rarely[8,9].

A recent metaanalysis of the efficacy of SMARD in PsA has shown that MTX and SSZ are active[10], but this has not been confirmed in all studies[11,12].

In the 1980s, studies evaluating the use of CSA in severe cases of psoriasis documented improvement in the associated arthritis[13-15]. Subsequent open prospective studies included patients with active peripheral arthritis. Improvement in clinical measures was noted at initial CSA doses of 3–6 mg/kg/day, but the absence of controlled studies does not permit any conclusions on the efficacy of CSA in PsA[16]. Furthermore, no studies have evaluated the efficacy of CSA on axial disease, and only one exploratory study considered the progression of radiological damage[17]. Double blind studies of the efficacy of CSA in PsA might be impossible because of the drug's known effect on psoriatic skin lesions[15].

SMARD and symptomatic treatments (ST) have rarely been compared, although this is the only way of establishing the added benefit offered by second-line therapy. This comparison is particularly important when assessing the efficacy of SMARD therapy in PsA. In their metaanalysis, Jones, *et al*[10] demonstrated that the placebo group in all the published controlled studies, usually on therapy with ST, improved considerably over baseline, and so a positive effect of ST may be erroneously attributed to SMARD.

We evaluated the 24 week efficacy and safety of CSA versus SSZ and ST in the treatment of PsA with or without axial involvement.

MATERIALS AND METHODS

Study design. This was a 24 week, multicenter, randomized, open, controlled study comparing the efficacy and tolerability of CSA 3 mg/kg/day (Sandimmun Neoral, Novartis AG), SSZ 2000 mg/day (Salazopyrin EN, Upjohn-Pharmacia Ltd.), and ST alone (NSAID, analgesics, prednisone equivalent ≤ 5 mg/day).

The study was supervised by an executive committee consisting of the study chairman, the study biostatistician, selected participating investigators, and a consultant responsible for data source verification and data management.

Eligibility criteria. Patients with PsA aged 16–65 years were considered eligible for study if they had one of the following clinical characteristics: distal interphalangeal (DIP) joint involvement, asymmetrical peripheral arthritis, or symmetrical polyarthritis with or without axial involvement (sacroiliitis and/or spondylitis). The diagnosis of psoriasis had to be confirmed by a dermatologist.

At study entry, patients were required to have at least 3 swollen and tender joints and active disease of at least 6 weeks' duration that did not respond to NSAID. Active disease was defined as morning stiffness of at least 30 min duration, pain on a visual analog scale (VAS) > 20 mm, and patient global assessment of disease activity ≥ 2 on a 5 point ordinal scale. Patients who had failed a previous course with antimalarials, parenteral or oral gold salts, etretinate, MTX, or photochemotherapy could be included in the study. All patients had a Steinbrocker functional and anatomical grade < IV and mild/moderate cutaneous psoriasis, defined as a Psoriasis Area and Severity Index (PASI) score ≤ 15[18].

Patients were excluded from the study if they had any of the following characteristics: positive rheumatoid factor (RF), PsA exclusively involving the DIP joints, previous treatment with CSA and SSZ, oral corticosteroids (daily dosage > 5 mg prednisone equivalent), intraarticular corticosteroid use in the previous 3 weeks, photochemotherapy in the previous 4 weeks, retinoid therapy in the previous 3 months, uncontrolled arterial hypertension, active or previous neoplasms, relevant active infections, thrombocytopenia (< 150,000/mm^3), leukopenia (< 3500/mm^3), neutropenia (< 1500/mm^3), pregnancy, lactation or inadequate contraception, epilepsy, drug or alcohol abuse, or renal or hepatic dysfunctions. Patients with chronic illnesses that would limit their successful participation in the trial were also excluded.

The study protocol was reviewed and approved by ethics committees of each of the 12 participating centers. Before entering the trial, each potential participant was informed of the nature, duration, and purpose of the study and all the potential benefits, inconveniences, and hazards that could reasonably be expected.

Study medication. Patients were randomly allocated to receive either CSA at an initial dose of 3 mg/kg/day or enteric coated SSZ tablets 500 mg twice daily, or NSAID/corticosteroids/analgesics alone, according to a prearranged centralized randomization plan, balanced for each center. In addition, patients treated with CSA or SSZ were allowed to receive a stable dose of NSAID/corticosteroids/analgesics.

An increase in CSA dose to a maximum 5 mg/kg/day was allowed at Weeks 4, 8, and 12 in the case of insufficient response. The dose was halved if serum creatinine levels increased by more than 30% of baseline value, blood CSA through levels increased by more than 200 ng/ml at 2 consecutive visits, serum potassium levels increased above the upper normal limit, or if liver enzymes (SGOT, SGPT, gammaglutamyltransferase, alkaline phosphatase) or bilirubin levels were twice the upper normal limit, or systolic or diastolic blood pressure were > 160 or > 95 mm Hg at 2 consecutive visits.

The SSZ treatment was started at 2 tablets daily for one week, and was then increased by one tablet per day each week up to 4 tablets given in 2 divided doses per day. This could be increased to a maximum of 6 tablets per day in the case of insufficient response. Patients were withdrawn from SSZ if they had a white blood cell count < 3000/mm^3, polymorphonuclear cell count < 1500/mm^3, platelet count < 100,000/mm^3, an acute or progressive decrease in hemoglobin or hematocrit, proteinuria > 500 mg/24 h, or significant rash.

Patients who took NSAID during the trial were required to have been taking a stable dose for one month before entry. Patients in the ST alone group were allowed to receive full doses of NSAID. Systemic corticosteroid at doses ≤ 5 mg/day prednisone equivalent and analgesics (paracetamol) were allowed in all 3 treatment arms. The doses of NSAID, corticosteroids, and analgesics were modified according to the clinical activity of the disease.

Compliance. A tablet/capsule count of the trial medication was carried out at each visit to monitor compliance.

Clinical assessment. The outcome measures of disease activity were evaluated at the time of screening (not more than 4 weeks before study entry), at randomization (Week 0), and after 2, 4, 8, 12, 16, 20, and 24 weeks. At each center, each patient was clinically assessed by the same investigator.

The patient self-assessment measures included (1) severity of pain (current global level of pain) evaluated using a 100 mm VAS; (2) duration of morning stiffness (including spinal stiffness); (3) global disease assessment graded on a 5 point scale (0 = none, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe); (4) the validated Italian version of the Arthritis Impact Measurement Scale (AIMS)[19,20]; and (5) the spondylitis functional index[21].

The clinical assessments included (1) the number of tender and swollen joints (57 and 54 sites, respectively); (2) the joint pain/tenderness score graded on a 4 point scale (0 = none, 1 = positive response on questioning, 2 = spontaneous response elicited, 3 = withdrawal on examination); (3) the number of fingers showing dactylitis, defined as the presence of tenderness and swelling of entire digits; (4) mobility impairment related to axial involvement, as evaluated by chest expansion, modified Schober test, finger to floor distance, and cervical spine flexion/extension distances[22];

and (5) a physician global disease assessment graded on a 5 point scale (1 = none, 2 = mild, 3 = moderate, 4 = severe, 5 = very severe).

After being instructed by an experienced dermatology metrologist at a training session, the same dermatologist evaluated the extension and severity of cutaneous psoriasis at each visit. The evaluation was performed using the PASI, which summarizes the degree of erythema, desquamation, and infiltration and the percentage of body surface area involved[18].

Laboratory evaluations were made at every visit and included biochemical surveys, routine hematologic variables, urinalysis, the Westergren erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) levels.

HLA-B27 typing, rheumatoid factor determination, and pelvis radiographs (anteroposterior views) were performed at the screening visit.

The patients were screened for adverse events at every visit.

Definition of clinical response. Each patient was considered a treatment responder or nonresponder on the basis of 2 sets of criteria: the American College of Rheumatology (ACR) improvement criteria for RA with 20%, 50%, and 70% improvement[23,24], using ESR or CRP; and the core set for endpoints in ankylosing spondylitis proposed by the Assessments in Ankylosing Spondylitis (ASAS) working group for studies on SMARD[25]. The following 5 variables were considered: spondylitis functional index[21], pain score, modified Schober test[22], morning stiffness duration, and patient global disease assessment, with improvement defined as a 20%, 50%, or 70% improvement in any 4 of the 5 variables.

Statistical analyses. The within-patient difference in the pain score (VAS 0–100 mm) was taken as the primary efficacy variable for sample size calculation. On the basis of the available information from double blind, placebo controlled studies of SSZ in PsA[5,8], the study was sized to reject the null hypothesis for a between-group difference in the reduction in the mean pain score ± SD of at least 20 ± 25 mm, with a significance level of 5% and power of 80%.

It was calculated that 30 patients per arm were needed, but the total number of patients was increased to 99 to allow for an expected dropout rate of 10% due to adverse events or inefficacy.

Analyses were carried out on an intention-to-treat (ITT) sample, which included all the enrolled eligible patients who had been treated at least once and had at least one post-baseline value for the efficacy variables[26].

Changes in the primary and secondary outcome measures from baseline to the last available followup were expressed as mean values (SD) with their 95% confidence intervals, and were analyzed using t tests for continuous data and chi-square and Fisher exact tests for ordinal and categorical data.

Maintenance on the initially prescribed treatment ("survival on treatment") was evaluated as the number of days from randomization to the discontinuation of the treatment or trial. The product-limit method was adopted to estimate survival on treatment, and between-group comparisons were made using the log rank test[27].

Analyses were made using SPSS version 8[28]. The statistical tests were 2 sided and $p \leq 0.05$ was considered statistically significant.

RESULTS

Patient population. Ninety-nine patients entered the study and constituted the intent-to-treat population: 36 were randomized to receive CSA, 32 to receive SSZ, and 31 to receive ST alone. Table 1 shows patients' baseline demographic, clinical, and laboratory variables.

The duration of arthritis was 2.2 (3.8) years. Clinical and/or radiological evidence of axial involvement was associated with peripheral arthritis in 17 patients. Thirty-six patients had dactylitis, and 5 cases were HLA-B27 positive.

Twenty of 99 patients had previously been treated with SMARD. A previous course of prednisone ≤ 5 mg/day had been received by 10 patients. Two patients had received etretinate. There were no statistically significant differences in baseline variables between the 3 groups of patients.

Study therapies. The initial dose of 3 mg/kg/day CSA was increased in 5 of the 36 patients, permanently decreased in 3 patients, and withdrawn in 6 cases. The mean maintenance dose was 2.9 mg/kg/day.

Twenty-five of 32 patients treated with SSZ received the standard maintenance dose of 2000 mg/day, which was subsequently decreased in 3 patients and withdrawn in 3 cases for poor tolerability/noncompliance. The remaining 7 patients received a maintenance dose of 3000 mg/day.

During the trial, systemic corticosteroids were given to 5 patients in the CSA group, 8 in the SSZ group, and 17 in the ST alone group.

There were no significant changes in NSAID, corticosteroid, or analgesic use in the 3 treatment groups.

Compliance and adherence to trial treatments. Compliance was high in all 3 groups, with about 90% of the prescribed medication being taken.

Twenty patients (6 CSA, 3 SSZ, 11 ST alone) withdrew from the trial because of adverse events or concomitant diseases (5 cases: 3 CSA, 2 SSZ), inefficacy (7 cases, all ST alone), or other reasons (8 cases: 3 CSA, one SSZ, 4 ST alone).

The probability of continuing the trial treatments, including all the events occurring within 180 days of randomization, is illustrated in Figure 1. The differences between the CSA or SSZ groups were significant ($p < 0.05$) versus the ST alone group.

Outcome measures. Table 2 shows the clinical outcome measures in the intention-to treat set. Considering the last-visit analysis, there was a statistically significant difference in favor of CSA in terms of the mean changes (95% CI) in the pain score (VAS) versus both SSZ and ST alone ($p < 0.05$). There were no significant differences between the SSZ and ST alone groups.

A statistically significant decrease in favor of CSA versus ST alone was also observed for the following secondary variables: swollen joint count ($p = 0.05$), tender joint count ($p = 0.01$), joint pain/tenderness score ($p = 0.002$), spondylitis functional index ($p = 0.002$), total AIMS ($p = 0.007$), patient global assessment by at least one point (61% vs 33%; $p = 0.04$), physician global assessment by at least one point (66% vs 32%; $p = 0.01$), physician global assessment by at least 2 points (24% vs 0%; $p = 0.005$) (the last 3 measures are not shown in Table 2).

Comparing decreases in the secondary variables between the CSA and SSZ groups, the total AIMS ($p = 0.04$) and the physician global assessment by at least 2 points (24% vs 3%; $p = 0.03$) were significantly higher in the CSA patients.

In the comparison of secondary variables between SSZ and ST alone groups, only the spondylitis functional index decreased significantly in the SSZ treated patients ($p = 0.03$).

Table 1. Demographic, clinical, and laboratory characteristics of the study patients at baseline. Unless otherwise indicated, values are means (SD).

Characteristics	Cyclosporine, n = 36	Sulfasalazine, n = 32	Symptomatic Therapy Only, n = 31
Age, yrs	49 (12)	46 (10)	48 (11)
Females/males	14/22	10/22	13/18
Disease duration, yrs	1.9 (4.0)	2.7 (4.3)	2.0 (3.1)
Previous use of			
Systemic corticosteroids, no. of patients	2	6	2
SMARD, no. of patients	8	7	5
Etretinate, no. of patients	0	0	2
Current status			
Axial involvement, no. of patients	8 (22%)	4 (13%)	5 (16%)
PASI	4.8 (3.9)	5.7 (4.6)	6.0 (6.1)
Tender joint count	14.8 (11.4)	14.6 (9.0)	15.1 (8.0)
Swollen joint count	9.2 (6.1)	9.6 (6.8)	8.4 (5.2)
Joint pain/tenderness score	12.1 (8.5)	12.2 (8.8)	11.9 (6.6)
Pain score (VAS), mm	60.8 (16.7)	53.2 (15.8)	60.7 (16.6)
Patient global disease assessment > 2, no. of patients	16 (44%)	13 (41%)	13 (42%)
Physician global disease assessment > 2, no. of patients	6 (17%)	4 (13%)	5 (16%)
Morning stiffness, min	84.1 (77.2)	80.8 (73.4)	88.7 (69.1)
Spondylitis functional index	11.2 (6.3)	9.4 (5.0)	9.6 (4.6)
Total AIMS test	23.0 (7.5)	21.5 (6.2)	22.3 (6.5)
Erythrocyte sedimentation rate, mm/hour	38.2 (24.5)	35.2 (24.7)	34.6 (17.7)
C-reactive protein, mg/dl	2.6 (2.7)	2.8 (3.1)	2.6 (2.6)

AIMS: Arthritis Impact Measurement Scales, SMARD: symptom modifying antirheumatic drugs, PASI: Psoriasis Area and Severity Index, VAS: visual analog scale.

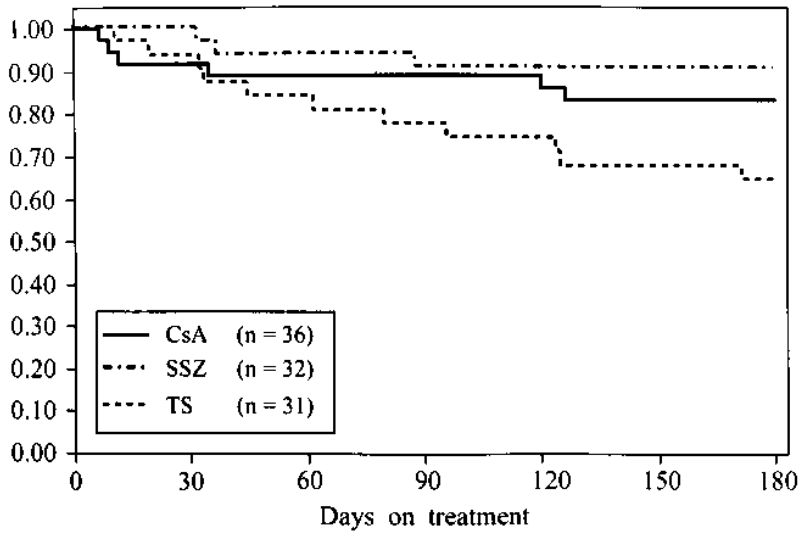

Figure 1. Probability of continuing in the cyclosporine (n = 36), sulfasalazine (n = 32), or symptomatic treatment group (n = 31) for 24 weeks. The between-group differences were significant ($p < 0.05$). All the events leading to discontinuation of treatment occurred within 180 days of randomization.

There was only a trend toward improvement in the majority of axial measures in favor of CSA versus both SSZ and ST alone.

Longitudinal analysis of our data showed that CSA acted more rapidly than SSZ in improving the primary and secondary outcomes (Figure 2).

Only 4 patients developed new episodes of dactylitis during the study period (2 CSA, one SSZ, one ST alone).

The reduction in PASI was significant in the CSA group in comparison with ST alone ($p = 0.0001$) and SSZ ($p = 0.01$). SSZ also had a significantly greater effect on the PASI than ST alone ($p = 0.004$).

The decrease in ESR was significant only in the SSZ versus the ST alone group ($p = 0.02$); reduction in CRP levels was significant in the patients taking CSA versus those treated with ST alone ($p = 0.006$).

There was a statistically significant difference in the ACR 50% and ACR 70% response rates between the CSA and ST groups (Table 3); no statistically significant differences were observed between the SSZ and ST alone groups. The percentage of ACR 70% responders was significantly higher in the CSA than in the SSZ group.

There were no statistically significant differences in the response rates measured using the ASAS working group criteria for improvement in AS.

Adverse events. Twenty-one of the 36 patients treated with CSA (58%), 14 of 32 treated with SSZ (44%), and 10 of 31 treated with ST alone (32%) experienced at least one side effect. These were sufficiently severe to warrant premature withdrawal of treatment in 3 patients taking CSA (one for moderate hypertension, one gastrointestinal disturbances, and one concomitant disease) and 2 patients taking SSZ

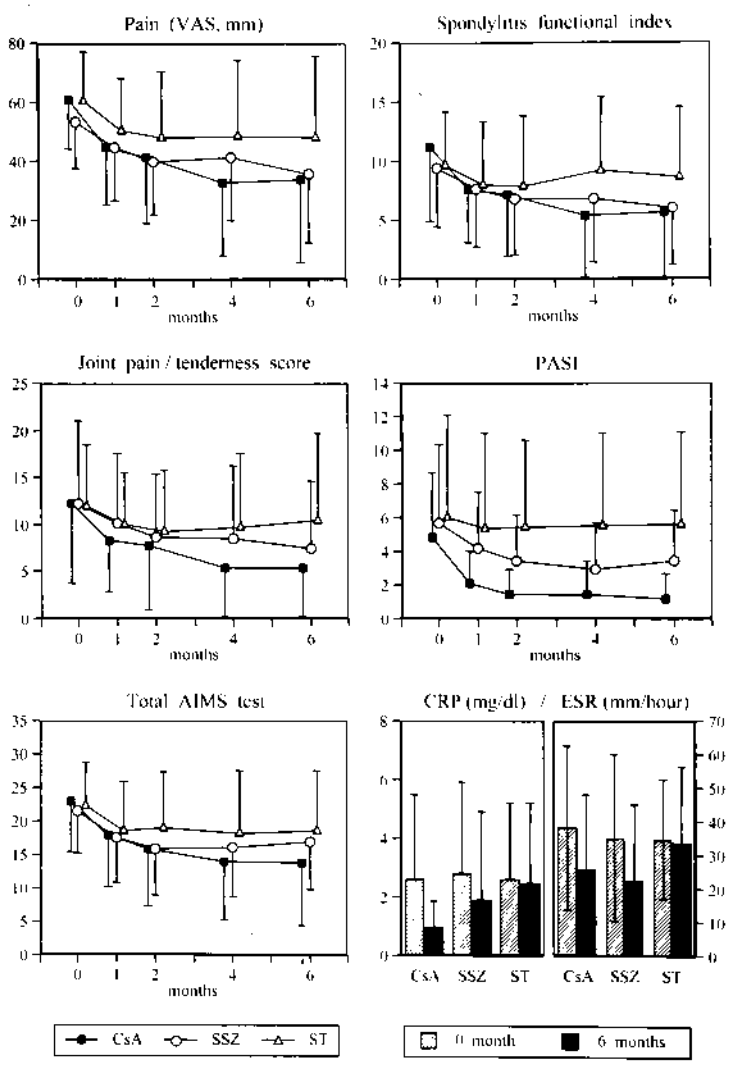

Figure 2. Comparison of disease activity variables of the cyclosporine (CSA), sulfasalazine (SSZ), and symptomatic treatment (ST) groups. Mean values ± SD.

Table 2. Clinical outcome in the intention-to-treat set.

Outcome Measure	Change at 24 Weeks: Cyclosporine, n = 36 Mean	SD	95% CI	Sulfasalazine, n = 32 Mean	SD	95% CI	Symptomatic Therapy Only, n = 31 Mean	SD	95% CI
Pain score (VAS), mm	–27.2	31.9	–38.6; –15.9	–17.3	18.0	–23.8; –10.8	–12.5	22.8	–20.9; –4.2
Swollen joint count	–4.8	7.5	–7.4; –2.1	–4.4	5.8	–6.5; –2.4	–1.8	5.5	–3.8; 0.2
Tender joint count	–7.6	10.4	–11.3; –3.9	–5.7	6.9	–8.2; –3.2	–3.5	8.1	–6.5; –0.6
Joint pain/tenderness score	–6.9	8.8	–10.1; –3.8	–4.8	6.7	–7.2; –2.3	–1.5	8.1	–4.5; 1.4
Morning stiffness, min	–41.5	61.5	–63.3; –19.7	–45.9	84.4	–76.4; –15.5	–37.1	84.6	–68.1; –6.1
Total AIMS test	–9.2	9.0	–12.4; –6.0	–4.8	6.3	–7.1; –2.5	–3.8	8.3	–6.8; –0.7
Spondylitis functional index	–5.7	6.8	–8.1; 3.3	–3.5	3.9	–4.9; 2.1	–0.9	5.3	–2.9; 1.0
Schober test, cm	1.3	11.3	–2.9; 5.6	–1.8	10.8	–5.7; 2.1	0.0	12.3	–4.7; 4.7
Finger-to-floor test, cm	1.0	5.3	–1.0; 3.0	0.0	4.5	–1.6; 1.6	2.9	14.0	–2.4; 8.3
Cervical spine flexion test, mm	–2.9	17.0	–9.3; 3.6	1.8	9.4	–1.6; 5.2	0.8	8.1	–2.3; 3.8
Cervical spine extension test, mm	3.3	16.3	–2.9; 9.5	–4.8	17.9	–11.3; 1.6	–1.2	18.6	–8.3; 5.8
Chest expansion, mm	7.0	14.8	1.4; 12.6	2.7	11.0	–1.2; 6.7	3.3	11.7	–1.1; 7.8
PASI	–3.6	3.7	–4.9; 2.3	–2.3	3.4	–3.5; 1.1	–0.4	3.9	–1.8; 1.1
ESR, mm/h	–12.4	19.5	–19.3; 5.4	–12.9	25.7	–22.2; 3.6	–0.9	23.3	–10.0; 8.1
CRP, mg/dl	–1.6	2.3	–2.4; 0.8	–0.9	3.4	–2.2; 0.3	–0.1	2.3	–1.0; 0.8

AIMS: Arthritis Impact Measurement Scales, PASI: Psoriasis Area and Severity Index, VAS: visual analog scale.

Table 3. Response rates of 99 patients with PsA treated with cyclosporin A (CSA), sulfasalazine (SSZ), or symptomatic therapy (ST) only, categorized according to the different response criteria on the basis of ITT analysis.

Response Criteria	CSA, n = 36, %	SSZ, n = 32, %	ST, n = 31, %	CSA versus SSZ, p	CSA versus ST, p	SSZ versus ST, p
ACR20 (ESR)	44.4	43.8	35.5	NS	NS	NS
ACR20 (CRP)	44.4	37.5	32.3	NS	NS	NS
ACR50 (ESR)	25.0	12.5	3.2	NS	0.02	NS
ACR50 (CRP)	27.7	12.5	3.2	NS	0.02	NS
ACR70 (ESR)	13.8	0.0	0.0	0.05	0.05	NS
ACR70 (CRP)	13.8	0.0	0.0	0.05	0.05	NS
ASAS20	47.2	40.0	29.0	NS	NS	NS
ASAS50	16.6	12.5	9.7	NS	NS	NS
ASAS70	5.5	0.0	0.0	NS	NS	NS

ACR: American College of Rheumatology criteria; ASAS: Assessments in Ankylosing Spondylitis Working Group criteria.

Table 4. Adverse events (number of patients) recorded over 24 weeks.

Adverse Event	Cyclosporine, n = 36	Sulfasalazine, n = 32	Symptomatic Therapy Only, n = 31
Impaired renal function*	10	1	1
GI intolerance**	4	6	4
Neurological disturbances***	7	3	3
Hypertrichosis	2	0	0
Hypertension	5	1	1
Gingival hyperplasia	2	0	0
Increased liver enzymes	1	4	1
Bacterial infections	1	0	0
Altered blood cell counts	1	0	0
Neoplasia	0	0	0

* Serum creatinine levels > 30% above baseline at 2 consecutive measurements; blood urea nitrogen, uric acid, and potassium above normal limits. ** Dyspepsia, nausea, vomiting, gastric pain, and diarrhea. *** Hyper- or paresthesia, tremors, headache, vertigo, insomnia, drowsiness, asthenia, myalgia, depression.

(one for GI disturbances, one for liver function abnormalities). Table 4 summarizes the adverse events.

There were more GI complaints in the SSZ treated patients than in the other 2 groups. Central/peripheral nervous system symptoms were more frequently observed in the CSA treated group.

Bacterial infection occurred in one CSA patient, but was not considered to be related to the trial drug.

Five patients receiving CSA experienced an increase in diastolic blood pressure (≥ 95 mm Hg): a return to baseline values was achieved with calcium antagonist therapy.

Transiently abnormal liver function was observed in 4 patients treated with SSZ.

The most common adverse event in the CSA group (10/36, 27.7%) was mild, reversible kidney dysfunction (serum creatinine levels > 30% above baseline values at 2 consecutive measurements). The mean (SD) serum creatinine levels were 0.92 (0.13) mg/dl at baseline and 1.03 (0.19) mg/dl after 24 weeks in the CSA treated patients. All the cases of kidney dysfunction normalized after a CSA dose reduction.

DISCUSSION

Previous open studies suggested that CSA may be an effective and safe therapy in PsA patients with active peripheral arthritis[29-31], but only 2 prospective controlled studies have been published. The first compared CSA with azathioprine (AZA) and placebo for 6 months, but the results suffered from poorly defined inclusion criteria, outcome variables, and side effects[32]. The second showed that CSA and MTX were equally effective in the treatment of peripheral PsA, but the study was limited by the small number of patients who completed it[33].

We compared CSA with SSZ because there is clinical evidence the latter is efficacious in treatment of PsA. SSZ has recently been shown to be superior to placebo in 6 double blind, randomized, placebo controlled studies[4,5,8,34–36]; these results are supported by a meta-analysis of randomized controlled therapeutic trials[10].

One of the aims of this study was to evaluate the efficacy of CSA treatment on axial disease. Although the results were not encouraging, SSZ is the only drug whose efficacy on axial symptoms in spondyloarthropathy (SpA) has been evaluated[8,9].

PsA is a heterogeneous disease characterized by a different degree of axial and peripheral involvement, and so the choice of criteria to evaluate treatment response is much more complicated than in RA. A core set of variables for endpoints in studies of SMARD and disease controlling antirheumatic therapy (DC-ART) has recently been defined in ankylosing spondylitis by the ASAS Working Group[25]. As members of the ASAS group, 2 of the authors decided to use these criteria to evaluate the clinical response to treatment.

Pain was taken as the primary response variable because it is common to the whole spectrum of PsA, it was considered a primary efficacy variable in most controlled therapeutic trials in PsA[4,5,7,8,10,34,35], and it was selected by the ASAS Working Group as one of the important domains for assessing the symptomatic outcome of AS[25].

Our results show that CSA is more effective in treating PsA than SSZ or ST alone. A significant difference in primary outcome measure was observed only between CSA and ST alone and not between SSZ and ST alone.

In comparison with ST alone, CSA also significantly improved all the secondary outcome variables, with the exception of the duration of morning stiffness. In relation to SSZ, the total AIMS and physician global assessments were significantly better in the patients treated with CSA. Only the spondylitis functional index improved significantly more in the SSZ treated patients than in those treated with ST alone. This absence of any clear difference between SSZ and ST alone in SpA has previously been observed in various clinical trials using single outcome measures[8,34,35]; SSZ was significantly more effective than placebo only when a composite index was used[4]. The effect of SSZ on SpA is more pronounced in the subgroup of patients with peripheral joint involvement, and it has no effect on the indices of axial disease[9]. In our study, the results of the Schober and flexion-extension cervical tests and chest expansion were better in the patients treated with CSA than in those treated with SSZ, even if the differences were not significant.

CSA and SSZ significantly improved ESR at the end of the study, although only the patients treated with SSZ showed a significant difference in comparison with ST alone. On the other hand, reduction in CRP levels was significant only in the CSA treated patients, and the difference in comparison with ST alone was also significant. The better effect of CSA on CRP than ESR is consistent with the findings of studies in RA[37]. The prognostic value of changes in the levels of ESR and CRP in the SpA is still unclear. On the basis of current literature, neither measure is clearly more valid than the other in longitudinal clinical trials[38].

The efficacy of CSA was evident as early as the 8th week of treatment, whereas the effect of SSZ on the spondylitis functional index was apparent only after 24 weeks. However, Clegg, *et al*[4] found that the efficacy of SSZ in PsA was evident only after 36 weeks, and remained limited until week 28. The short duration of the treatment period in our study could therefore partially explain the weak effect of SSZ.

Our study makes it possible to evaluate the efficacy of CSA as a SMARD according to the spondyloarthropathy criteria set mentioned above[25]. However, the number of criteria and the percentages of improvement that need to be satisfied to define a patient as a responder have not yet been defined. We therefore arbitrarily selected 3 levels of response (20%, 50%, and 70%) in 4 of the 5 core set

measures considered by the ASAS Working Group as defining a SMARD. The responses to CSA and SSZ were superior, although not significantly, at all levels of the ASAS Working Group criteria. The high response rate among the patients undergoing ST alone may have influenced the statistical significance of intergroup comparisons.

Because all the patients had peripheral arthritis, we also used the ACR improvement criteria for RA to define the response to the 3 different treatments. There was no significant difference in the response rates at the 20% level, but CSA was superior to the SSZ and ST alone when both the ACR 50% and ACR 70% criteria were used.

The differences in the response rates using peripheral arthritis and axial disease criteria could be explained by the low rates of response at the levels of 50% and 70% for the axial variables in the groups treated with CSA and SSZ. Conversely, the patients treated with ST alone showed almost no response in terms of peripheral disease at the 2 highest levels. These data confirm that CSA and SSZ were more efficacious in controlling peripheral arthritis than axial disease.

Both SSZ and CSA were well tolerated, and the rate of withdrawals due to adverse events was similar in the 2 groups. The most frequent side effect of CSA was kidney dysfunction (i.e., serum creatinine levels of > 30% above baseline values at 2 consecutive measurements), which was well controlled by CSA dose reduction. No patient discontinued CSA because of nephrotoxicity. These data confirm the short term safety of CSA treatment in PsA described in a review by our group[16]; only 6% of the 170 CSA treated patients in 16 studies discontinued the drug because of nephrotoxicity.

Potential irreversible nephrotoxicity is a major concern with the longterm use of CSA. Furthermore, RA and PsA patients, who are often also treated with NSAID, may be more sensitive to the renal effect of CSA. The risk of renal damage is known to be related to the CSA dose and to the maximum increase in serum creatinine[39,40]. The strategies used in RA, such as the careful selection of patients, a low CSA dose of 2.5–4 mg/kg/day using the microemulsion formulation, and a reduction in dose to limit any increase in serum creatinine to less than 30% of baseline levels, have efficiently minimized CSA induced nephrotoxicity[39,40]. Renal biopsies of 60 patients with RA treated for a period of 87 months showed that pathological findings consistent with CSA induced nephropathy were surprisingly rare. None of the 22 patients who had received < 4 mg/kg/day as a starting dose showed any pathological changes or signs of functional deterioration[41]. Data concerning the longterm safety of CSA in PsA are lacking; however, the longterm use of CSA in RA showed that survival on treatment was better in the CSA than in the SMARD control group after 3 years[42].

The percentages and types of side effects observed in the patients treated with SSZ were mild and similar to those reported in other series of patients with PsA or spondyloarthropathy treated with this drug[4,8,34-36].

In comparison with the ST alone group, there was an expected significant improvement in skin disease (evaluated by PASI) in the CSA treated group after only 2 months of therapy. A more limited but still significant improvement in the PASI was also observed in the SSZ treated patients after 2 months of therapy. Previous open and double blind studies reported a significant effect of SSZ on clearing of psoriatic cutaneous lesions[43,44], but others have not confirmed this observation[34,35]. There was no favorable evolution of the skin disease in the ST alone group in our study, but the use of systemic steroids had no detrimental effect.

Given the unblinded nature of the protocol, our results need to be confirmed by a double blind study. However, it is very difficult to use a blind design to compare a drug that is known to be very active with other drugs that are much less active or inactive on cutaneous psoriasis. Another possible criticism is the short duration of the trial, but 6 months is generally considered sufficient to confirm the effect of a drug as a SMARD.

The results of this open trial confirm that cyclosporine is well tolerated by patients with psoriatic arthritis, and suggest that it is more efficacious than symptomatic therapy or sulfasalazine.

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