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Efficacy and Safety of Leflunomide in the Treatment of Psoriatic Arthritis and Psoriasis

A Multinational, Double-Blind, Randomized, Placebo-Controlled Clinical Trial

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Objective. **Current treatment options for psoriatic arthritis (PsA) are limited. Leflunomide, an oral pyrimidine synthesis inhibitor, is highly effective in the treatment of rheumatoid arthritis, and small studies have suggested similar efficacy in PsA. We undertook this double-blind, randomized, placebo-controlled trial to evaluate the efficacy and safety of leflunomide in patients with PsA and psoriasis.**

Methods. **One hundred ninety patients with active PsA and psoriasis (at least 3% skin involvement) were randomized to receive leflunomide (100 mg/day loading dose for 3 days followed by 20 mg/day orally) or placebo for 24 weeks. The primary efficacy end point was the proportion of patients classified as responders by the Psoriatic Arthritis Response Criteria (PsARC). Additional efficacy (joint and skin involvement), safety, and quality-of-life assessments were performed.**

Results. **At 24 weeks, 56 of 95 leflunomide-treated patients (58.9%; 95% confidence interval [95% CI] 48.4–68.9) and 27 of 91 placebo-treated patients (29.7% [95% CI 20.6–40.2]) were classified as responders by the PsARC ($P < 0.0001$). Significant differences in favor of leflunomide were also observed in the proportions of patients achieving modified American College of Rheumatology 20% improvement criteria, improvement in the designated psoriasis target lesion, and mean changes from baseline in Psoriasis Area and Severity Index scores and quality-of-life assessments. Diarrhea and alanine aminotransferase increases occurred at higher rates in the leflunomide group. No cases of serious liver toxicity were observed.**

Conclusion. **Leflunomide is an effective treatment for PsA and psoriasis, providing a safe and convenient alternative to current therapies.**

Psoriatic arthritis (PsA) is a potentially disabling inflammatory condition that affects 5–30% of patients with psoriasis (1,2), a skin condition found in ~1–3% of the population (3). It is likely that PsA is underdiagnosed (4), and thus, the true prevalence may be higher. PsA is associated with significant disability, increased mortality, and reduced quality of life (5–8). Pathophysiologically, PsA is characterized by the presence of activated T cells, particularly in joint fluids and synovial tissues (9,10). T cell activation has also been implicated in psoriasis (11) and rheumatoid arthritis (RA) (12), suggesting a common pathway linking these disorders.

Effective treatment options for patients with PsA are limited. A recent National Psoriasis Foundation

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survey found that ~25% of patients are dissatisfied with the treatment they receive for PsA (4). Most disease-modifying antirheumatic drugs (DMARDs) used to treat PsA have been employed because of evidence supporting their use in RA; very few controlled studies have demonstrated their efficacy and safety in PsA. In a meta-analysis of PsA clinical studies, only high-dose parenteral methotrexate (MTX; 1–3 mg/kg every 10 days) (13) and sulfasalazine were found to be significantly more efficacious than placebo (14). These agents, as well as other treatment options such as low-dose oral MTX (≤15 mg/week), cyclosporine, and intramuscular gold, often fail to improve joint and skin symptoms or are poorly tolerated (14–16). Recently, a tumor necrosis factor (TNF) inhibitor, etanercept, has demonstrated significant efficacy in the treatment of PsA and psoriasis (17), and preliminary data suggest the same for the TNF inhibitor infliximab (18). Another biologic agent, alefacept, a lymphocyte function–associated antigen 3 fusion protein that blocks T cell activation, is available for the treatment of psoriasis and may also be useful in PsA (19). These biologic agents must be administered by injection or infusion and are costly. There remains a need for an easy-to-administer, effective, and well-tolerated therapy for PsA and psoriasis.

Leflunomide is a DMARD that inhibits de novo pyrimidine synthesis. Because activated lymphocytes require a large pyrimidine pool, leflunomide preferentially inhibits T cell activation and proliferation (20) and thus has the potential to address underlying pathophysiologic events in RA, PsA, and psoriasis. Leflunomide has been approved for the treatment of RA in the US, countries of the European Union, and numerous other countries for several years. In patients with RA, controlled clinical trials have demonstrated that leflunomide reduces symptoms and radiographic progression (21–23). Followup studies indicate that safety and efficacy have been maintained for up to 5 years (24–26). Leflunomide has also demonstrated promising activity in PsA and psoriasis in small open-label studies and case reports (27–29). Here, we report data from the Treatment of Psoriatic Arthritis Study (TOPAS), a multinational, double-blind, randomized, placebo-controlled clinical trial examining the safety and efficacy of leflunomide in the treatment of PsA and psoriasis.

PATIENTS AND METHODS

Patients. Male and female patients between the ages of 18 and 70 years diagnosed as having at least one of the subsets of PsA (distal interphalangeal involvement, polyarticular involvement, arthritis mutilans, asymmetric oligoarticular arthritis, or ankylosing spondylitis–like arthritis), and with joint activity involving ≥3 swollen joints and ≥3 tender joints and psoriasis (≥3% of the total body surface area affected with plaque psoriasis), were eligible for inclusion in this study. Patients were required to discontinue DMARD therapies, investigational drugs, biologic agents, and systemic antipsoriatic treatments 28 days prior to the initiation of study drug administration (baseline); topical treatments for psoriasis had to be discontinued 2 weeks prior to baseline, except for treatments applied to the scalp and genital areas. Only female patients of nonchildbearing potential or who were practicing a medically accepted contraceptive regimen were allowed to enroll. Male participants were also required to practice contraception during the study. Female patients were required to have a negative serum pregnancy test result and not to be breastfeeding at study entry.

Patients with nonpsoriatic inflammatory joint disease or who had experienced arthritis onset prior to 16 years of age were excluded from this study. Other key exclusion criteria included rheumatoid factor positivity, rheumatoid nodules, significant concomitant medical conditions (including serious infections, malignancy, or cardiovascular disease), known human immunodeficiency virus, hepatitis B, or hepatitis C antigen positivity, guttate, pustular, or erythrodermic forms of psoriasis, body weight <45 kg, impaired hepatic function (as judged by any one of the following criteria: alanine aminotransferase [ALT] or aspartate aminotransferase [AST] levels >1.5 times the upper limit of normal [ULN], alkaline phosphatase [AP] level >1.2 times the ULN, or serum albumin level <3.0 gm/dl), impaired bone marrow function (as evidenced by anemia, leukopenia, neutropenia, or thrombocytopenia), impaired renal function, a history of drug or alcohol abuse, or previous treatment with leflunomide.

Study protocol. This 24-week, randomized, double-blind, placebo-controlled trial was designed to evaluate the efficacy and safety of leflunomide (20 mg/day) versus placebo in the treatment of PsA and psoriasis. Thirty-one clinical sites (3 in Australia, 2 in Austria, 1 in Belgium, 5 in Canada, 9 in Germany, 1 in Ireland, 2 in The Netherlands, 1 in New Zealand, and 7 in Spain) were involved in this study. All patients provided written informed consent, and the study protocol was approved by the Independent Ethics Committees or Institutional Review Boards of the participating study sites. The trial was conducted in accordance with the Declaration of Helsinki and abided by good clinical practice as defined by the International Conference on Harmonisation (ICH) (30).

At the baseline visit, patients were randomly assigned to double-blind treatment with placebo or leflunomide by chronological assignment to treatment numbers. The randomization schedule was generated by Aventis on a 1:1 basis with a blocking factor of 4, with each center allocated at least one block of study medication. During the study, the randomization schedule was stored at the Aventis biometric department. Treatment allocation was concealed from all investigators, but in case of an emergency, investigators had access to sealed opaque envelopes containing treatment allocation. No such emergency occurred. Leflunomide (Aventis, Bad Soden, Germany) was supplied as a blister package containing three 100-mg tablets (loading dose) and a bottle containing 20-mg tablets (maintenance dose). Placebo was supplied in an iden-

tical manner except that the tablets contained lactose instead of leflunomide. Treatment consisted of a loading dose of 100 mg leflunomide or matching placebo administered orally once daily for 3 days. For the remainder of the 6-month trial, patients received a dose of 20 mg leflunomide or matching placebo orally once daily. No dosage changes were allowed during the study. Patients and investigators were not informed of the treatment assignment.

Patients were not allowed to receive DMARDs, systemic antipsoriatic therapies, or phototherapy during the study. Patients could continue to take nonsteroidal antiinflammatory drugs (NSAIDs) or corticosteroids (prednisone dose of $\leq$10 mg/day or the steroid equivalent administered orally) provided that the dosage had remained stable for at least 28 days prior to study drug administration and remained constant throughout the study. Topical treatments for psoriatic skin lesions on the scalp and genital area were allowed. However, the hands were excluded as an evaluated site for patients who used tar or keratolytic shampoos on the scalp or genital area.

Clinical and laboratory assessments were performed at screening and baseline and at weeks 2, 4, 8, 12, 18, and 24, with exceptions as noted below. Clinical assessments that employed this schedule included the Psoriatic Arthritis Response Criteria (PsARC) and monitoring for concomitant medications and adverse events. Target psoriasis lesions were determined at screening. For the American College of Rheumatology 20% improvement criteria as modified for PsA (modified ACR20), the Functional Disability Index of the Health Assessment Questionnaire (HAQ), the Psoriasis Area and Severity Index (PASI), and the Dermatology Life Quality Index (DLQI), evaluations were performed per schedule except for the absence of a screening assessment. In addition, dermatologic assessments (PASI, DLQI, and target lesion response) were not performed at weeks 2 and 18. Target lesion response and PASI were evaluated by dermatologists.

Physical examinations and 12-lead electrocardiograms were performed at baseline and end point (24 weeks). Laboratory assessments included C-reactive protein (CRP) level, erythrocyte sedimentation rate, blood chemistry, urine analysis, and urine pregnancy test for women of childbearing potential. A serum pregnancy test was performed at screening, and additional urine pregnancy tests were performed at weeks 16 and 22. Assessments of hematology and vital signs (heart rate, blood pressure, temperature, and weight) were performed every 2 weeks throughout the study; liver enzymes (AST, ALT, gammaglutamyl transpeptidase, AP, and bilirubin) were also measured every 2 weeks if clinically indicated. Tablet counts were performed at weeks 2, 4, 8, 12, 18, and 24. Patient compliance was calculated based on the actual number of tablets returned compared with the number expected to be returned. Data were recorded using an electronic case record form. Radiographic evaluations were not performed during this study.

Study end points. The primary efficacy end point was the response rate according to the PsARC, as originally described by Clegg et al (31) (see Appendix A). The PsARC is a composite measure consisting of patient's and physician's global assessments of PsA activity and tender and swollen joint scores. A response according to the PsARC requires improvement in 2 of these 4 parameters, with at least 1 being a joint score, and worsening in none.

Secondary efficacy end points included ACR20 response (32) as modified for PsA (17). The modified ACR20 differs from the conventional ACR20 only in the number of joints evaluated (76 tender joints and 74 swollen joints, rather than 68 tender joints and 66 swollen joints as recommended for RA clinical trials [33]; see Appendix A). The additional joints evaluated were 8 distal interphalangeal joints in the toes. Individual components of the PsARC and modified ACR20 were evaluated as secondary efficacy end points. For individual components, screening values were used if baseline data were missing. However, for the modified ACR20, data for all components were obtained at baseline. Skin efficacy evaluations consisted of the PASI (34) (see Appendix A) and target lesion response. Quality of life was assessed by the HAQ (35) and DLQI (36).

Safety was assessed by monitoring treatment-emergent adverse events. In addition to utilizing criteria for serious adverse events as defined by the ICH (37), additional alert terms were added to aid in safety surveillance, including a neutrophil count of $\leq$1,500 cells/mm^3 and ALT levels $\geq$2 times the ULN. These definitions were added because cases of potentially leflunomide-related severe liver injury and neutropenia occurred in post-marketing observations in patients with RA.

Statistical analysis. Assuming a 55% PsARC response rate for leflunomide (based on efficacy data for leflunomide in RA clinical trials [22]), a 30% response rate for placebo (based on placebo response rates in previous RA and PsA trials after 6 months), and a nonevaluable rate of 25%, it was determined that a sample size of 90 patients in each group (total sample size of 180 patients with 1:1 randomization) would be required to attain 80% power to detect a significant difference between treatments in the primary end point with a 2-sided alpha level of 0.05. For demographic characteristics, the *t*-test was used for continuous variables and the Cochran-Mantel-Haenszel test for categorical data. Efficacy parameters were analyzed by the Cochran-Mantel-Haenszel test adjusted for country. Analysis of variance (ANOVA) values were calculated for efficacy parameters, with treatment and country as fixed effects based on ranked absolute or percentage change from baseline. Clinical variables were analyzed by ANOVA within treatment groups using all scheduled visits; *t*-tests were used to compare individual baseline versus end point changes across treatments. Laboratory parameters were analyzed by the Wilcoxon signed rank test for baseline and individual end point data, and by the Friedman test taking all laboratory visits into account. Quality-of-life data were evaluated by analysis of covariance, taking into account treatment, language/country, and baseline quality of life.

For efficacy evaluations, analyses were performed on the full analysis set (Figure 1). Individual end points were used for patients who left the study prior to the study end point. Safety analyses included all randomized and treated patients for whom data were available.

RESULTS

Disposition of patients. Of the 236 individuals who were screened, 190 met the entry criteria and were randomized to treatment, 98 to the leflunomide group and 92 to placebo (Figure 1). Two patients from the leflunomide group decided not to participate in the

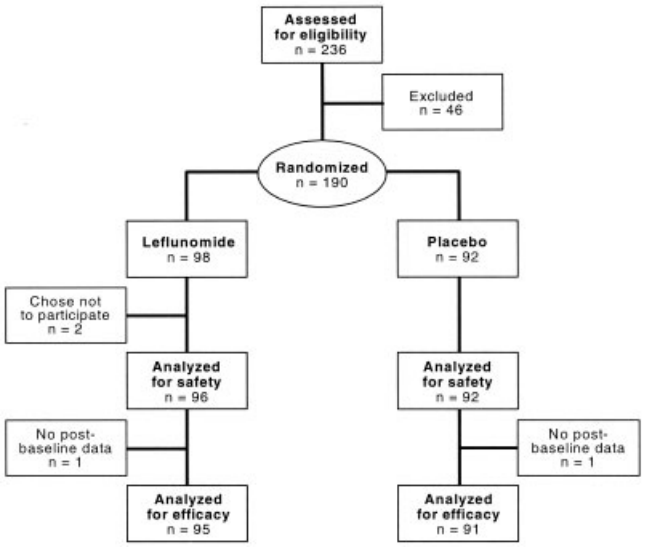

Figure 1. Trial profile showing patient populations analyzed for safety and efficacy. A total of 58 patients in the leflunomide group and 41 patients in the placebo group completed the 6-month treatment phase. Reasons for premature withdrawal were lack of efficacy (leflunomide, n = 19; placebo, n = 33), patient's wish (leflunomide, n = 5; placebo, n = 13), adverse events (leflunomide, n = 10; placebo, n = 2), protocol violation (leflunomide, n = 2; placebo, n = 1), poor compliance (leflunomide, n = 0; placebo, n = 1), and other (leflunomide, n = 2; placebo, n = 1).

study after the baseline visit and received no leflunomide treatment; these 2 patients were excluded from the safety analysis set (leflunomide, n = 96; placebo, n = 92). Two patients, 1 in each treatment group, had no postbaseline data and were therefore excluded from all efficacy analyses. The full analysis set (intention-to-treat analysis) used for efficacy analyses thus included 95 patients in the leflunomide group and 91 patients in the placebo group. During the treatment phase, significantly fewer patients in the leflunomide group (n = 38) than in the placebo group (n = 51) discontinued treatment (P = 0.03). The major reason for withdrawal from the safety analysis set was lack of efficacy (19 in the leflunomide treatment arm [19.8%] and 33 in the placebo treatment arm [35.9%]) (see Figure 1). A total of 58 leflunomide-treated patients and 41 placebo-treated patients completed the study.

Demographic and baseline characteristics. The leflunomide and placebo groups were well matched with respect to baseline demographic characteristics (Table 1), with no significant differences between groups in terms of age, sex, race, or disease duration. Subsets of PsA were found at comparable frequencies in the 2 groups, with the exception of arthritis mutilans, which occurred significantly more frequently in the placebo group (13 patients [14.3%]) than in the leflunomide group (4 patients [4.2%]). Almost half of the patients were DMARD naive at study entry (Table 1). The majority of the remaining patients had

Table 1. Baseline demographic and clinical characteristics of the study patients (full analysis set)*

Characteristic	Treatment group	
	Placebo (n = 91)	Leflunomide (n = 95)
Age, years		
Mean ± SD	46.9 ± 12	48.6 ± 10
Range	20–69	23–68
Men, no. (%)	57 (62.6)	55 (57.9)
White, no. (%)	87 (95.6)	93 (97.9)
Duration of arthritis symptoms, years		
Mean ± SD	10 ± 9	11 ± 9
Range	0.1–52.6	0.2–40.8
Duration of psoriasis, years		
Mean ± SD	19 ± 12	20 ± 13
Range	0.3–43.5	0.6–60.3
DMARD naive, no. (%)	46 (50.5)	37 (38.9)
No. of previous DMARDs		
Mean ± SD	0.84 ± 1.1	0.89 ± 0.9
Range	0–4	0–4
Concomitant therapy during study, no. (%)		
Systemic corticosteroids	9 (9.9)	15 (15.8)
NSAIDs	73 (80.2)	75 (78.9)
Topical agents	23 (25.3)	23 (24.2)

* DMARDs = disease-modifying antirheumatic drugs; NSAIDs = nonsteroidal antiinflammatory drugs.

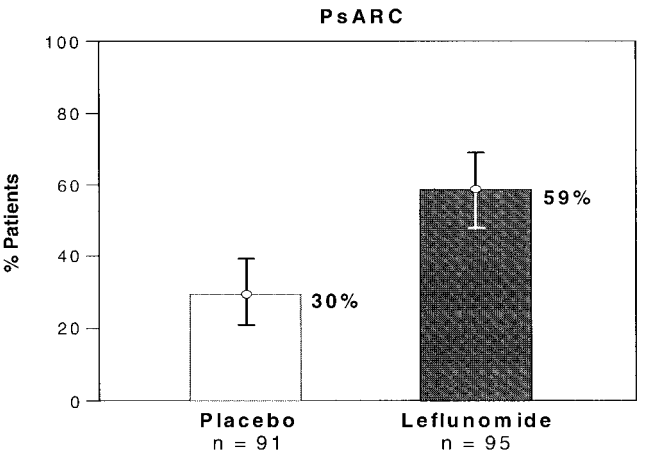

Figure 2. Percentages of patients in the full analysis set who met the Psoriatic Arthritis Response Criteria (PsARC) at study end point (24 weeks). Bars indicate 95% confidence intervals. A significantly greater percentage of leflunomide-treated patients were classified as responders according to the PsARC ($P < 0.0001$ versus placebo-treated patients, by Cochran-Mantel-Haenszel test adjusted for country, with statistical significance set at $P \leq 0.05$).

Table 2. Secondary efficacy outcomes at end point*

Outcome, treatment group	Baseline	End point	Change	*P*
Joint pain/tenderness score†				
Placebo (n = 91)	28.3 ± 23.9	23.7 ± 26.4	−4.6 ± 19.6	0.0022
Leflunomide (n = 95)	28.8 ± 23.3	19.7 ± 22.8	−9.1 ± 21.0	
Joint swelling score‡				
Placebo (n = 91)	18.9 ± 16.5	14.7 ± 15.2	−4.2 ± 13.6	0.0013
Leflunomide (n = 95)	16.8 ± 19.4	9.9 ± 12.9	−6.8 ± 16.8	
Tender joint count†				
Placebo (n = 91)	18.5 ± 13.0	15.5 ± 13.8	−3.0 ± 12.3	0.0006
Leflunomide (n = 95)	20.1 ± 13.7	14.5 ± 16.2	−5.6 ± 10.9	
Swollen joint count‡				
Placebo (n = 91)	13.3 ± 10.6	10.5 ± 11.2	−2.7 ± 9.7	0.0009
Leflunomide (n = 95)	11.6 ± 10.2	7.3 ± 8.9	−4.4 ± 8.6	
CRP level, mg/dl§				
Placebo (n = 89)	20.7 ± 25.9	20.6 ± 26.3	−0.1 ± 14.6	0.0182
Leflunomide (n = 93)	22.2 ± 26.4	14.3 ± 17.3	−7.9 ± 20.8	
HAQ total score				
Placebo (n = 90)	1.14 ± 0.55	1.10 ± 0.69	−0.05 ± 0.46	0.0267
Leflunomide (n = 94)	1.08 ± 0.70	0.89 ± 0.70	−0.19 ± 0.51	
PASI score				
Placebo (n = 90)	9.5 ± 8.8	8.9 ± 8.7	−0.6 ± 6.1	0.0030
Leflunomide (n = 92)	8.7 ± 5.5	6.6 ± 6.5	−2.1 ± 5.9	
DLQI total score				
Placebo (n = 89)	9.1 ± 7.1	8.6 ± 7.7	−0.2 ± 5.1	0.0173
Leflunomide (n = 90)	8.8 ± 6.7	6.8 ± 6.6	−1.9 ± 5.1	

* Values are the mean ± SD for the full analysis set. Mean and SD values were rounded to 1 decimal (2 decimals for the Health Assessment Questionnaire [HAQ] total score) separately for baseline, end point, and change. For change in the Dermatology Life Quality Index (DLQI) total score, n = 87 for the placebo group and n = 89 for the leflunomide group. For all parameters, decreased scores indicate improvement. *P* values are for leflunomide versus placebo by analysis of variance, except for the HAQ and DLQI, which were calculated by analysis of covariance with treatment and country as fixed effects and baseline quality-of-life scores as the covariate. For all efficacy assessments, statistical significance was set at $P \leq 0.05$. CRP = C-reactive protein; PASI = Psoriasis Area and Severity Index.
† 76 joints assessed (see Appendix A).
‡ 74 joints assessed (see Appendix A).
§ Normal range 4.5–50.0 mg/dl.

received prior treatment with 1 DMARD; a few had been treated with up to 4 different DMARDs before study entry. Concomitant therapies during the trial were comparable in the 2 treatment groups, with no statistically significant differences in the proportions of patients receiving corticosteroids, NSAIDs, or topical agents in the leflunomide group relative to the placebo group. The mean ± SD duration of treatment was 19.1 ± 7.5 weeks in the leflunomide group and 17.1 ± 7.6 weeks in the placebo group. Compliance of ≥80% to <110% was reported by 78% of patients in the placebo group and 85% of patients in the leflunomide group. One patient was withdrawn from the placebo treatment arm due to poor compliance.

Efficacy of leflunomide in PsA. Leflunomide was statistically significantly superior to placebo in the primary efficacy end point, the number of patients classified as responders by the PsARC at study end point (Figure 2). Fifty-six of 95 patients in the leflunomide group (58.9%; 95% confidence interval [95% CI] 48.4–68.9) were classified as responders by the PsARC, compared with 27 of 91 patients in the placebo group (29.7% [95% CI 20.6–40.2]) ($P < 0.0001$). This finding was not affected by the different proportions of patients with arthritis mutilans in the 2 treatment groups. Age, sex, and previous MTX intake did not have a statistically significant influence on treatment outcome. Intercenter compatibility was assessed in the 13 centers with at least 6 patients. Compared with placebo-treated patients, a higher percentage of leflunomide-treated patients achieved a PsARC treatment response in 10 of these 13 centers.

Evaluations of secondary efficacy criteria further demonstrated the benefits of leflunomide relative to placebo. Leflunomide was significantly superior to placebo in each of the 4 criteria that compose the PsARC (joint pain/tenderness score, joint swelling score, physician's global assessment, and patient's global self-assessment) (Tables 2 and 3). Leflunomide was also statistically significantly superior to placebo in the pro-

Table 3. Modified ACR20 responses and physician's and patient's assessments at end point*

Assessment, treatment group	Improvement/ response, %	Deterioration, %	P
Modified ACR20			
Placebo (n = 80)	20.0	NA	0.0138
Leflunomide (n = 80)	36.3		
Physician's global assessment			
Placebo (n = 91)	34.1	22.0	0.0001
Leflunomide (n = 95)	52.6	10.5	
Patient's global self-assessment			
Placebo (n = 91)	30.8	24.2	0.0036
Leflunomide (n = 95)	31.6	15.8	
Patient pain assessment			
Placebo (n = 90)	35.6	33.3	0.0042
Leflunomide (n = 90)	46.7	13.3	

* For American College of Rheumatology 20% improvement criteria as modified for psoriatic arthritis (modified ACR20), response rates are shown; for other assessments, the proportions of patients improving or deteriorating (baseline versus end point) are shown. *P* values are for leflunomide versus placebo by Cochran-Mantel-Haenszel test, with statistical significance set at $P \leq 0.05$. NA = not applicable.

portion of patients achieving a modified ACR20 response (Table 3), with 29 of 80 patients in the leflunomide group attaining this response (36.3% [95% CI 25.8–47.8]) compared with 16 of 80 patients in the placebo group (20.0% [95% CI 11.9–30.4]) ($P = 0.0138$). The prospectively planned analysis of ACR20 response could not be performed in 26 patients due to the absence of baseline data. The most common missing component was baseline CRP level (n = 18). Other secondary assessments of disease activity, including joint assessments, also showed statistically significant improvements at end point in the leflunomide group compared with the placebo group (Table 2). During the study, these parameters showed continuing improvements over time.

Efficacy of leflunomide in psoriasis. Dermatologists evaluated psoriasis by use of the PASI and a prospectively defined target lesion. Changes in PASI scores reflect changes in the extent and severity of psoriasis lesions as judged by erythema, desquamation, and infiltration (see Appendix A). Leflunomide resulted in significant improvement in PASI scores during the 24-week study relative to placebo (Table 2). The mean ± SD percentage improvement was 22.4 ± 51.6% in the leflunomide group compared with a deterioration of 2.2 ± 70.4% in the placebo group ($P = 0.0030$). Compared with the placebo group, a significantly greater proportion of patients in the leflunomide group experienced a ≥50% reduction in PASI scores (PASI 50) (30.4% versus 18.9%; $P = 0.050$) and a ≥75% reduction in PASI scores (PASI 75) (17.4% versus 7.8%; $P = 0.048$) from baseline (Figure 3). Leflunomide also showed superiority over placebo in target lesion response, with 44 of 91 patients in the leflunomide group (48.4%) experiencing at least a slight response (~25% improvement) at the end of the study compared with 23 of 90 patients in the placebo group (25.6%) ($P = 0.0048$).

Impact of leflunomide on quality of life. Quality-of-life assessments, including functional status (HAQ total score) and a quality-of-life instrument for dermatologic diseases (DLQI total score), demonstrated that leflunomide was superior to placebo in improving the quality of life in patients with PsA and psoriasis (Table 2). For the DLQI, the greatest difference between leflunomide and placebo was observed in the symptoms-and-feelings subscore.

Safety. Treatment-emergent adverse events were reported in 82 of 96 patients in the leflunomide group (85.4%) and 70 of 92 patients in the placebo group (76.1%). There was no clear association between loading dose administration and the onset or worsening of specific adverse events. Potentially drug-related adverse events were reported in 61 patients in the leflunomide

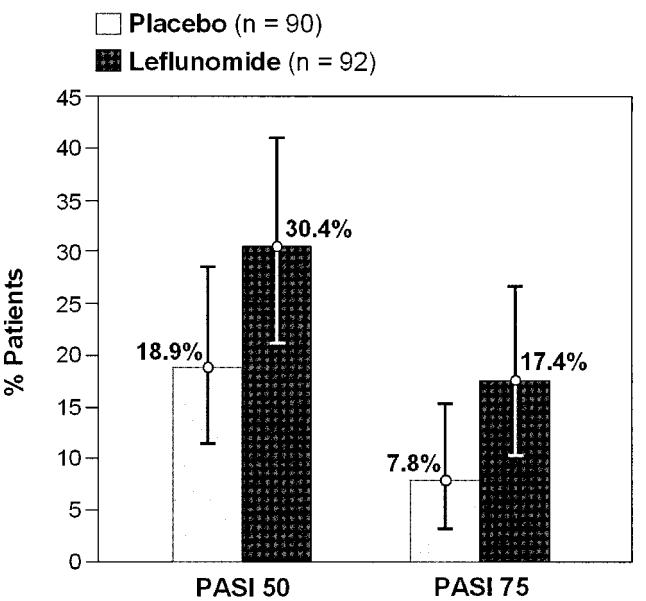

Figure 3. Percentages of patients with ≥50% reduction in scores on the Psoriasis Area and Severity Index (PASI 50) and with ≥75% reduction in PASI scores (PASI 75) at study end point. Bars indicate 95% confidence intervals. Significantly greater percentages of leflunomide-treated patients experienced ≥50% and ≥75% reductions in PASI scores ($P = 0.050$ and $P = 0.048$, respectively, versus placebo-treated patients, by Cochran-Mantel-Haenszel test adjusted for country, with statistical significance set at $P \leq 0.05$).

Table 4. Treatment-emergent adverse events occurring in >5% of patients in the leflunomide treatment group*

Adverse event	Treatment group	
	Placebo (n = 92)	Leflunomide (n = 96)
Diarrhea	12 (13.0)	23 (24.0)
Aggravation reaction†	21 (22.8)	17 (17.7)
Involving PsA	18 (19.6)	9 (9.4)
Unrelated to PsA	3 (3.3)	8 (8.3)
Flu syndrome	12 (13.0)	12 (12.5)
Increased ALT level	5 (5.4)	12 (12.5)
Headache	7 (7.6)	11 (11.5)
Nausea	8 (8.7)	9 (9.4)
Rash	3 (3.3)	7 (7.3)
Joint disorder	5 (5.4)	6 (6.3)
Pruritus	4 (4.3)	6 (6.3)
Gastrointestinal pain	6 (6.5)	6 (6.3)
Tiredness/lethargy	1 (1.1)	6 (6.3)
Skin disorder (other than rash and pruritus)	3 (3.3)	5 (5.2)

* Values are the number (%) of patients. PsA = psoriatic arthritis; ALT = alanine aminotransferase.
† Worsening of any preexisting condition, including PsA.

group (63.5%) and 37 patients in the placebo group (40.2%). Treatment-emergent adverse events were reported as the main reason for withdrawal by 10 patients in the leflunomide group (10.4%) and 2 patients in the placebo group (2.2%). No serious infections or deaths occurred during this trial.

Treatment-emergent adverse events affecting >5% of the leflunomide group are shown in Table 4. The most frequent adverse event in the leflunomide group was diarrhea, while the most frequent adverse event in the placebo group was aggravation reaction, defined as worsening of any preexisting condition. In the majority of placebo-treated patients with aggravation reaction (18 of 21), the condition reported as worsening was related to the underlying PsA. Compared with the placebo group, notably higher incidence rates were observed for diarrhea, ALT increase, and tiredness/lethargy in the leflunomide group. Pain in extremity, alopecia of mild intensity, and decreased white blood cell counts were each reported for 4 patients in the leflunomide group, while none of these were reported in the placebo group. The statistical significance of differences in adverse event rates between the 2 treatment groups was not assessed.

Serious adverse events occurred in 13 of 96 patients in the leflunomide group (13.5%) and 5 of 92 patients in the placebo group (5.4%). In 6 leflunomide-treated patients, serious adverse events were considered by the clinician to be related to treatment (decreased neutrophil count, n = 1; elevated liver enzyme levels [ALT and/or AST], n = 5). The most common serious adverse event was an ALT level ≥2 times the ULN (leflunomide, n = 8; placebo, n = 2). Decreased neutrophil counts reported as serious occurred in 2 leflunomide-treated patients. Other serious adverse events were bone fracture (not spontaneous), infection of left index finger, and actinic keratosis (1 patient each in the leflunomide group). Three of the patients with elevated liver enzyme levels discontinued treatment as required by the study protocol (see below), and the patient with an infected finger temporarily suspended treatment. Treatment for the remaining patients was unchanged. In the placebo group, aggravation reaction (worsening of any preexisting condition), cholelithiasis, and pyoderma gangrenosum affected 1 patient each.

Treatment-emergent transaminase elevations were reported as adverse events in 12 patients in the leflunomide group and 5 patients in the placebo group during the study. The intensity was rated as "mild" in all 5 placebo-treated patients. For leflunomide, 7 cases were considered "mild" and 5 cases were rated "moderate." Five cases of ALT elevations in the placebo group and 8 in the leflunomide group were considered related to treatment. The distribution of patients with ALT elevations ≥2 times the ULN (leflunomide, n = 10; placebo, n = 2) is shown in Table 5 (2 leflunomide-treated patients had ALT elevations ≥2 times the ULN which were not reported as "serious"). Two leflunomide-treated patients and 1 placebo-treated patient were withdrawn from the study because of ALT levels ≥3 times the ULN. In addition, 1 leflunomide-treated patient was withdrawn from the study due to repeated ALT values of 2–3 times the ULN. All

Table 5. ALT elevations ≥2 times the ULN by treatment group*

Maximum ALT value	Treatment group	
	Leflunomide (n = 96)	Placebo (n = 92)
≥2 times to <3 times the ULN	8 (8)	0 (0)
≥3 times to <5 times the ULN	1 (1)	2 (2)
≥5 times to <8 times the ULN	0 (0)	0 (0)
≥8 times the ULN	1 (1)	0 (0)

* Values are the number (%) of patients. According to the clinical study protocol, an alanine aminotransferase (ALT) value ≥2 times the upper limit of normal (ULN) was defined as an alert term, and investigators were requested to report such incidences as serious adverse events, even if the criteria for seriousness as defined by the International Conference on Harmonisation (see ref. 30) were not fulfilled. In 2 such incidences (both in the leflunomide group), the investigators did not do so. As a result, 8 ALT elevations in leflunomide-treated patients and 2 ALT elevations in placebo-treated patients were reported as "serious."

transaminase elevations of ≥3 times the ULN were followed up and found to be reversible, in 1 case after washout of leflunomide with cholestyramine. Liver enzyme values remained normal in the majority of patients, and no cases of severe liver toxicity (jaundice, prothrombin time <50%, hepatic encephalopathy) were observed in leflunomide-treated patients.

Leukocyte, neutrophil, lymphocyte, and platelet counts decreased to a greater extent in the leflunomide group than in the placebo group, a finding consistent with the antiinflammatory activity of leflunomide. Because postmarketing studies had suggested the possibility of neutropenia in leflunomide-treated patients, neutrophil abnormalities were defined as ≤1,500 cells/mm^3 for the purpose of this study, a more stringent standard than commonly used. Treatment-emergent reductions in neutrophil levels to ≤1,500 cells/mm^3 were reported in 4 leflunomide-treated patients. In 3 patients, neutrophil levels of 1,500 cells/mm^3 were noted at 1 study visit only. In the fourth patient, neutrophil counts of 1,100 cells/mm^3 were observed during the first 2 weeks of treatment, but these normalized immediately thereafter. Suspension of leflunomide therapy was not required in any of the patients, and neutrophil decreases were not accompanied by infection or other clinical correlates.

Slight increases in the mean ± SD systolic and diastolic blood pressure were observed in the leflunomide group during the course of the study (1.0 ± 15.3 mm Hg and 2.2 ± 10.4 mm Hg change from baseline to end point, respectively), but values remained stable in most patients. Worsening of hypertension was reported as a treatment-emergent adverse event in 4 leflunomide-treated patients, and was considered to be drug related in all 4 patients. In 2 of these patients, the dosage of antihypertensive comedication was increased as a countermeasure, and in 1 patient enalapril comedication was replaced by hydrochlorothiazide. There were no clinical sequelae related to worsening hypertension in these patients. No other clinically relevant changes in the laboratory variables or physical findings were observed.

DISCUSSION

The treatment of psoriasis and PsA is challenging. Agents used to treat joint symptoms often do little to improve skin lesions, and vice versa, requiring the patient to use multiple therapies for disease control. Some systemic therapies may be useful in treating both PsA and psoriasis, but data from controlled clinical trials are limited. Because of the high placebo response rate in patients with PsA (14), data from uncontrolled trials may be misleading. In addition, discontinuation rates due to lack of response and adverse events are typically high for conventional systemic therapies (38), and long-term safety is a concern (39,40). Two biologic agents, etanercept and infliximab, have recently been shown to be effective in the treatment of PsA, and these agents along with alefacept also reduce psoriasis symptoms (17–19). These therapies require injections or infusions, and cost may be a barrier to their use. Thus, there is still an unmet need for cost-effective, safe, and easy-to-administer systemic therapies that are capable of treating both the skin and joint manifestations of PsA.

In this double-blind, randomized, placebo-controlled clinical trial, we examined the efficacy and safety of leflunomide in patients with active PsA and psoriasis (at least 3% skin involvement). Because only a few controlled clinical trials have been conducted in patients with PsA, a limited number of validated assessment tools are available. We chose to use the PsARC, a composite measure that assesses the patient's global health and joint symptoms, as the primary efficacy evaluation. This assessment has demonstrated the capability to effectively discriminate active treatment from placebo response in trials of patients with PsA receiving sulfasalazine or etanercept treatment (17,31), thereby verifying its clinical relevance. In a recent study, the PsARC (referred to as Clegg improvement criteria) was found to have greater sensitivity than conventional ACR criteria in characterizing treatment response in patients with PsA (41).

The efficacy of leflunomide in RA and its antilymphocytic mode of action suggested that leflunomide might be a promising candidate for the treatment of PsA and psoriasis. The data presented here confirm findings from small, uncontrolled studies of leflunomide in patients with PsA and psoriasis (27–29). Leflunomide was effective in improving both joint and skin symptoms. At study end point, a highly significant difference was observed in the proportion of patients recording a PsARC response in the leflunomide group compared with the placebo group (59% versus 30%; $P < 0.0001$) (Figure 2). Significant differences were also observed in each individual component of the PsARC (Tables 2 and 3) and in the proportion of patients achieving a modified ACR20 response (36.3% versus 20.0%; $P = 0.0138$) (Table 3), a tool that was introduced in the etanercept PsA study (17).

The number of patients included in the modified ACR20 analysis was lower than the number in the PsARC analysis, mostly because of missing CRP values.

However, this did not influence the outcome of the ACR20, as was shown by subsequent analyses. An ad hoc analysis in which screening CRP values were substituted for missing baseline values yielded results almost identical to those in the original analysis, as did an analysis using 4 of 6 ACR response criteria to indicate response if fewer than 7 components were measured and an analysis using a combination of this approach and the use of CRP screening values in order to maximize the number of included patients. These additional analyses thus support the conclusion that fewer patients in both the leflunomide and placebo groups qualified as responders by ACR20 criteria compared with the PsARC. A similar observation was made in the etanercept PsA study (17), suggesting that the PsARC may be a more sensitive tool than the modified ACR20 for assessing treatment effect in patients with PsA.

The impact of leflunomide on skin symptoms was assessed by the PASI (Table 2 and Figure 3), which evaluates the extent and severity of psoriatic lesions, and by changes in a prospectively defined target lesion. Both assessments found significant improvements in leflunomide-treated patients relative to the placebo group. After 6 months of treatment, 30.4% of leflunomide-treated patients had achieved a PASI 50, a level of improvement believed to be clinically significant for most patients (42).

PsA and psoriasis are accompanied by a significant disease burden, affecting both health-related and emotional aspects of a patient's life (8). Accordingly, improving quality of life is a critical goal for therapeutic agents used to treat PsA and psoriasis. Leflunomide was found to result in significant improvements relative to placebo both in functional status, as assessed by the HAQ, and in skin-related quality of life, as assessed by the DLQI, a quality-of-life instrument developed for patients with dermatologic conditions (Table 2).

Data from other studies suggest that these changes were of sufficient magnitude to be clinically significant. A mean HAQ score reduction of 0.19 was observed in this study. This is the same order of magnitude as the 0.22 HAQ score reductions that have been determined to be the minimal clinically important difference in patients with RA (43). The minimal clinically important difference in HAQ score has not been specifically determined in patients with PsA. However, a study involving patients with osteoarthritis, RA, and other forms of arthritis, including PsA, found that a HAQ score difference of 0.2 units was an important symptomatic difference to the average patient (44).

The mean baseline DLQI scores in the patients examined here (8.8 in the leflunomide group, 9.1 in the placebo group) corresponded well to the mean DLQI score of 8.9 determined by Finlay and Khan in the general population of patients with psoriasis (36). At end point, the mean DLQI score in the leflunomide group was 6.8, which represents a 24% improvement over the general population of patients with psoriasis. The mean DLQI score reduction of 1.9 observed in leflunomide-treated patients is similar to the reduction of 2.1 observed in psoriasis patients treated for 1 month with topical corticosteroids (45). In a recent study of DLQI scores in patients with severe psoriasis requiring hospital admission, mean DLQI score reductions of 3.0 were associated with improved clinical status (46). Although the mean DLQI score change was somewhat lower in the present study, the DLQI has been found to have a substantial "floor effect" (i.e., a high number of patients with the lowest possible score) in patients with milder psoriasis (45); therefore, clinically significant change in this population would be expected to result in smaller DLQI score reductions.

The success of leflunomide in treating PsA and psoriasis was further indicated by the observation that significantly fewer patients discontinued treatment in the leflunomide group than in the placebo group. Lack of efficacy (placebo, n = 33; leflunomide, n = 19) was the major reason for withdrawal in both groups and, in the leflunomide group, may reflect the delayed onset of action of leflunomide. Anecdotal evidence suggests that patients and clinicians might have become impatient with the absence of clinical benefit early in the study, leading to a high rate of withdrawals. The completion rate in this study may also have been affected by the requirement to cease all use of topical preparations (except for genital/scalp areas), which may have contributed to patient discomfort and desire to withdraw from the study.

Diarrhea and elevated ALT levels were the most notable events occurring at higher frequencies in the leflunomide group. The increased incidence of diarrhea observed in leflunomide-treated patients may be caused by the inhibition of dihydroorotate dehydrogenase in intestinal epithelial cells, resulting in a high rate of cellular turnover in the gastrointestinal tract (20). Patients with transaminase elevations $\geq$3 times the ULN were followed up, and transaminase elevations were reversible in all cases. Liver enzyme values remained normal in the majority of patients, and there were no cases of severe liver toxicity. These data suggest that, as in RA, leflunomide can be safely used in patients with

PsA and psoriasis with appropriate liver enzyme monitoring.

The efficacy and safety of leflunomide in patients with PsA and psoriasis appear to be similar to the profile of this drug in patients with RA. In particular, the data suggest that liver effects are comparable in these 2 patient populations, with transaminase elevations reported as an adverse event for 14.8% of leflunomide-treated RA patients in a controlled clinical trial (22) compared with 12.5% of leflunomide-treated PsA patients in the current study. This is a potentially important observation given the increased hepatotoxicity of MTX in patients with PsA relative to patients with RA (39). Although long-term data from patients with PsA are not yet available, studies in RA indicate that the efficacy and safety of leflunomide are maintained for at least 5 years (24–26). The long-term tolerability of leflunomide is further supported by an analysis of data from a large US managed-care database which encompassed >45,000 patient-years of exposure to drugs for treatment of RA. This analysis found that leflunomide compared favorably with MTX and other DMARDs in overall adverse event rates, as well as in hepatic and hematologic events (47).

Leflunomide has many advantages to offer in the treatment of PsA and psoriasis: it is well-tolerated in the majority of patients, convenient, and effective in moderating joint and skin symptoms and improving quality of life. In addition, orally administered leflunomide may have benefits in cost and ease of use compared with biologic agents. Because of these characteristics, leflunomide may provide an important treatment option for patients with PsA and psoriasis.

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APPENDIX A: KEY EFFICACY ASSESSMENTS

PsARC (see ref. 31)

Treatment response is defined as improvement in at least 2 of the following 4 measures, one of which must be joint pain/tenderness or swelling, and there must be no worsening in any of the measures:

1. Physician's global assessment, measured on a 5-point Likert scale, with improvement defined as a decrease by ≥1 unit and worsening as an increase by ≥1 unit.
2. Patient's global self-assessment, measured on a 5-point Likert scale, with improvement defined as a decrease by ≥1 unit and worsening as an increase by ≥1 unit.
3. Joint pain/tenderness score on a 4-point scale for each joint (total of 76 joints; see below), with improvement defined as a decrease by ≥30% and worsening as an increase by ≥30%.
4. Joint swelling score on a 4-point scale for each joint (total of 74 joints; see below), with improvement defined as a decrease by ≥30% and worsening as an increase by ≥30%.

Joints Assessed for the PsARC and Modified ACR20 Responses

The following 76 joints were used for tender joint assessments. For swollen joint assessments, the hip joints were excluded (total of 74 joints). In the hands (28 joints bilaterally): distal interphalangeal joints 2–5, proximal interphalangeal joints 1–5, and metacarpophalangeal joints 1–5. In the feet (28 joints bilaterally): distal interphalangeal joints 2–5, proximal interphalangeal joints 1–5, and metatarsophalangeal joints 1–5. Elsewhere (20 joints bilaterally): temporomandibular joints, sternoclavicular joints, acromioclavicular joints, wrists, elbows, hips, knees, ankles, and tarsus joints.

PASI (reproduced, with permission, from ref. 34)

The body is divided into 4 areas (head, trunk, upper extremities, and lower extremities). The extent of involvement in each area is assessed on a 7-point scale (ranging from 0 = no involvement to 6 = 90–100% involvement).

Severity of psoriatic lesions is assessed for erythema, infiltration, and desquamation on a 5-point scale (ranging from 0 = no symptoms present to 4 = exceptionally striking symptoms) for each area of involvement.

To calculate the PASI score for a given area, the severity scores (erythema + infiltration + desquamation) for that area are added, and this total is multiplied by the score assigned for extent of involvement. This number is then adjusted for body area depending on the specific area being assessed (head 10%; trunk 30%; upper extremities 20%; lower extremities 40%). The total PASI score is the sum of the scores for the head, trunk, upper extremities, and lower extremities.