Improved Functional Ability in Patients with Rheumatoid Arthritis — Longterm Treatment with Leflunomide versus Sulfasalazine

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ABSTRACT. ***Objective.*** We previously reported that the new disease modifying antirheumatic drug leflunomide resulted in significant improvement in functional ability compared with placebo and sulfasalazine in a 6 month double blind, randomized, Phase III trial in rheumatoid arthritis (RA). The current study compared functional disability in cohorts of patients with RA from the initial study who volunteered to continue treatment with leflunomide or sulfasalazine.

Methods. The Health Assessment Questionnaire (HAQ) was used to assess functional ability in patients completing 6 months of therapy who chose to continue in double blinded 12 and 24 month extensions. Patients on active regimens continued taking leflunomide 20 mg/day or sulfasalazine 2 g/day; those taking placebo were switched at Month 6 to sulfasalazine.

Results. Leflunomide significantly improved patients' functional ability compared to placebo ($p \leq 0.0001$) and sulfasalazine ($p \leq 0.01$) at 6 months. These changes were seen as early as Month 1, and continued improvements were seen in 12 and 24 month cohorts. Mean HAQ scores were significantly improved with leflunomide compared with sulfasalazine at 24 months (–0.65 vs –0.36; $p = 0.0149$); corresponding changes in HAQ Disability Index (DI) were –0.73 vs –0.56 and were not statistically different. Leflunomide is safe and well tolerated and no unexpected adverse events were noted during the 2 year period; diarrhea, nausea, and alopecia were less frequent with continued treatment.

Conclusion. These longterm data confirm leflunomide improves functional ability as shown by reductions in HAQ scores. The benefit of leflunomide is reflected in other efficacy criteria, such as global assessments and the American College of Rheumatology response rates, all of which showed significantly more improvement with leflunomide than sulfasalazine at 24 months. (J Rheumatol 2001;28:1983–91)

Key Indexing Terms:
RHEUMATOID ARTHRITIS
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Rheumatoid arthritis (RA) is a progressive, debilitating disease characterized by pain and functional loss that results in increased levels of work disability and high medical costs. The goal of RA therapy is to control disease activity, retard radiographic disease progression, and prevent or delay health related functional disability. This may possibly be achieved by the early use of disease modifying antirheumatic drugs (DMARD)[1]; however, longterm use of current DMARD is limited due to a lack of sustained efficacy or because of toxicity[2-4].

Leflunomide, an isoxazole derivative and inhibitor of *de novo* pyrimidine synthesis[5,6], represents a novel class of DMARD. The primary mode of action of leflunomide in RA is thought to be selective inhibition of dihydroorotate dehydrogenase, a key enzyme in *de novo* synthesis of pyrimidine, and subsequent inhibition of RNA and DNA synthesis[7,8]. Activated T lymphocytes, which are hypothesized to play a central role in the pathogenesis of RA[7,9], predominantly synthesize pyrimidines via the *de novo* pathway. Activated T cells expand their pyrimidine pools 8-fold compared to 3-fold expansion of purines[10]. *In vitro* leflunomide treated T cells undergo cell cycle arrest at the G_1/S phase, thus inhibiting clonal expansion of T cells[11]. Recent investigation indicates that leflunomide also blocks tumor necrosis factor mediated

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activation of the transcription factor nuclear factor κB (NF-κB), which is activated in response to proinflammatory cytokines[12]. Efficacy and safety of leflunomide have been demonstrated in Phase II and III studies of patients with RA[13–15].

We reported significantly greater improvement of functional ability following treatment with leflunomide than with either placebo or sulfasalazine after 6 months of therapy[14]. The objective of the current report was to compare functional disability in patients with RA undergoing longterm treatment with leflunomide or sulfasalazine. Health related quality of life was assessed using the Health Assessment Questionnaire (HAQ)[16], a widely used disease-specific instrument for assessing functional ability provided by antirheumatic treatment regimens.

MATERIALS AND METHODS

Patients. The study population was composed of consenting patients ≥ 18 years of age with active RA based on American College of Rheumatology (ACR) criteria and ACR Functional Class I, II, or III. Inclusion criteria at study entry included tender joint count ≥ 6; swollen joint count ≥ 6; physician and patient global assessment: fair, poor, or very poor; C-reactive protein (CRP) > 2.0 mg/dl or erythrocyte sedimentation rate (ESR) > 28 mm/h. Women who were pregnant, breastfeeding, or of childbearing potential who were not taking oral contraceptives were excluded. As concomitant medications, stable doses of nonsteroidal antiinflammatory drugs (NSAID) (including acetylsalicylic acid), oral steroids (prednisolone ≤ 10 mg qd), and up to 3 intraarticular steroid injections, not exceeding an equivalent dose of 60 mg triamcinolone, were permitted. Intraarticular steroid injections were not allowed during the first 6 months.

Study design. This was a multicenter, multinational (sites in Australia, Europe, New Zealand, South Africa), randomized, double blind, placebo controlled (until 6 months), parallel group study. A one week screening period was followed by 24 months of treatment with leflunomide (100 mg qd on Days 1–3, then 20 mg qd) or sulfasalazine (0.5, 1.0, and 1.5 g weekly, respectively, at Weeks 1, 2, and 3; 2.0 g qd from Week 4 to endpoint) and matching placebo for 6 months. At 6 months, completers were invited to continue treatment for a further 6 months, after which they were again invited to continue for a further 12 months. Patients in the leflunomide and sulfasalazine arms continued taking the same dosage while those in the placebo arm switched to sulfasalazine in a blinded manner. Patients in the placebo-sulfasalazine arm received standard dose escalation in increments of 0.5 g weekly to reach 2.0 g. The protocols of the initial 6 month placebo controlled phase as well as the 2 extension phases were approved by the ethics committees of all participating institutions. Before treatment in the extension studies, all patients were informed of the nature, scope, and possible consequences of the extensions and their informed consent was obtained again.

This report presents a secondary analysis of physical function in patient cohorts at 6, 12, and 24 months. Initially, 358 patients were randomized (3:3:2) to leflunomide (n = 133), sulfasalazine (n = 133), and placebo (n = 92). As shown in Figure 1, number of patients evaluable for analyses of function were 310 at 6 months (leflunomide 116, sulfasalazine 113, placebo 81); 160 at 12 months (leflunomide 66, sulfasalazine 62, placebo-sulfasalazine 32); and 117 at 24 months (leflunomide 51, sulfasalazine 45, placebo-sulfasalazine 21).

Assessment of patient function. Functional disability was assessed at baseline and biweekly intervals for the first 2 months, at monthly intervals for Months 2–6, every 3 months for Months 6–12, and every 2 months thereafter until endpoint. The Stanford Health Assessment Questionnaire (HAQ)[16] was used to assess functional disability. All participating countries except Slovenia had previously published language adaptations of the HAQ. The HAQ consists of several questions related to 8 categories of functional ability: dressing and grooming, rising, eating, walking, hygiene, reach, grip, and other activities. Patients rated their ability to perform the various activities stated in questions on a 4 point scale: 0 = without any difficulty; 1 = with some difficulty; 2 = with much difficulty; and 3 = unable to do. Data on functional ability using the HAQ were assessed in 2 ways: (1) the average or mean HAQ scores of all questions in the 8 categories of the HAQ[17,18] (referred to as mean HAQ), and (2) the standard HAQ disability index (HAQ DI), which averages the 8 category scores, each representing the worst/highest item or question score for that category. A decrease in score corresponded to an improvement in functional ability.

Outcome assessment. This report emphasizes functional assessment; however, the primary outcome measures in each phase of the trial included: tender and swollen joint counts, physician and patient global assessment, pain intensity assessment, duration of morning stiffness, Westergren ESR, CRP, rheumatoid factor (RF), and radiographic evaluation of disease progression at study endpoint compared to baseline. Also assessed was ACR responder rate (defined as ≥ 20% improvement from baseline in tender and swollen joint counts and ≥ 20% improvement in 3 of the following 5 criteria: physician global assessment, patient global assessments, pain intensity assessment, HAQ, and CRP/ESR).

Safety. Safety was monitored by physical examination, chest radiography, electrocardiography, blood pressure, pulse rate, body temperature, and body weight measurements. Standard hematological and biochemical tests and urinalysis were done. The occurrence of adverse events was documented and included those spontaneously reported by patients as well as those elicited by general questioning. Investigators recorded adverse events as primary events including the diagnosis, as well as the symptoms accompanying the primary event. Analyses of the adverse events were done on the basis of the primary events.

Laboratory variables were measured at a central laboratory. Statistical analysis included comparison of median values and normalization of changes from baseline to endpoint.

Statistical analyses. Analyses reported were performed on the intent-to-treat (ITT) population of the respective treatment period (0–6 mo, 0–12 mo, and 0–24 mo) and on completers at 6, 12, and 24 months. The primary efficacy analysis during the first 6 months of the investigation compared leflunomide to placebo, and the secondary analysis compared active treatments. The primary efficacy analysis during the extension phases compared active treatments. Baseline categorical variables in the treatment groups were compared by chi-square analysis or Fisher's exact test. All continuous variables including HAQ analysis were compared based on mean changes from baseline to endpoint with the technique of last observation carried forward (LOCF) and analysis of covariance (ANCOVA). Due to the small number of patients per center, centers were pooled for efficacy analysis; pooling was based on geographical regions, language, and treatment regimen. Evaluation of the HAQ DI was performed as an endpoint analysis on the ITT population. Missing HAQ DI values in the 2 year population were replaced by the LOCF approach.

Global assessments were compared by means of the extended Mantel-Haenszel test. All laboratory variables were subjected to descriptive statistics and compared by Wilcoxon signed-rank test. Rates of ACR response were analyzed by logistic regression, adjusted for center effects and disease duration. All statistical tests were 2 sided and significance was defined as $p < 0.05$.

RESULTS

Baseline demographics. The demographic characteristics of the treatment groups were similar; baseline demographic data were obtained only at study entry (Table 1). Patients' mean ages in each of the 3 treatment groups ranged from 58 to 59 years, mean disease duration 5–8 years, and 38–46% had disease for 2 years or less. The majority of patients were of ACR functional class II or III, and 39–53% had no history of

Table 1. Baseline demographics.

	0–6 Months			6–12 Months			12–24 Months		
	LEF n = 133	SSZ n = 133	PL n = 92	LEF n = 80	SSZ n = 76	PL-SSZ n = 41	LEF n = 60	SSZ n = 60	PL-SSZ n = 26
Female, n (%)	101 (76)	92 (69)	69 (75)	60 (75)	50 (66)	31 (76)	49 (82)	41 (68)	19 (73)
Mean age, yrs	58 ± 11	59 ± 11	59 ± 12	58 ± 11	59 ± 11	59 ± 12	58 ± 11	59 ± 11	59 ± 12
Disease duration									
Mean, yrs	8 ± 9	7 ± 10	6 ± 6	6 ± 7	7 ± 9	6 ± 7	7 ± 8	6 ± 9	5 ± 5
≤ 2 yrs, n (%)	50 (38)	56 (42)	41 (45)	33 (41)	32 (42)	19 (46)	25 (42)	26 (43)	12 (46)
> 2 yrs, n (%)	83 (62)	77 (58)	51 (55)	47 (59)	44 (58)	22 (54)	35 (58)	34 (57)	25 (54)
Functional class									
I	10 (7)	6 (4)	3 (3)	5 (6)	3 (4)	1 (3)	3 (5)	1 (2)	0 (0)
II	74 (56)	76 (57)	50 (54)	46 (58)	45 (59)	21 (51)	36 (60)	38 (63)	15 (58)
III	49 (37)	51 (38)	39 (42)	28 (37)	28 (37)	19 (46)	21 (35)	21 (35)	11 (42)
Mean HAQ*	1.14	0.98	1.09	1.15	0.91	0.89	1.10	0.91	0.82
HAQ DI*	1.65	1.50	1.59	1.68	1.42	—	1.6	1.5	—

* In evaluable patients. DI: Disability Index, LEF: leflunomide, PL: placebo, SSZ: sulfasalazine.

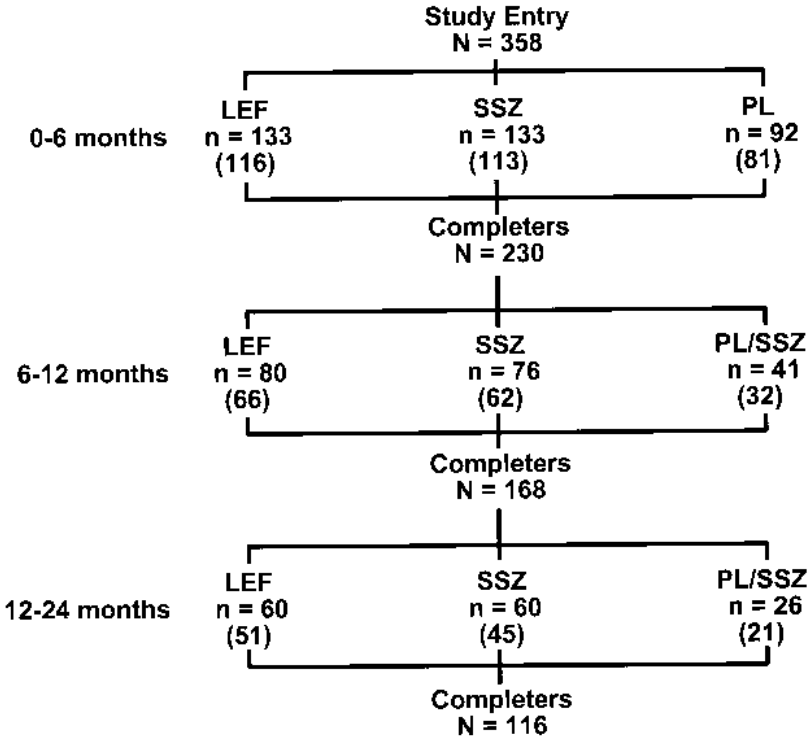

Figure 1. Study design: numbers in parentheses denote number of evaluable patients for analyses of functional disability. LEF: leflunomide, SSZ: sulfasalazine, PL: placebo.

DMARD treatment. Use of NSAID and corticosteroids was similar across groups.

Of the 358 who were randomized, 133 leflunomide, 92 placebo, and 133 sulfasalazine treated patients participated in the first 6 month study period (Figure 1). Of 230 who completed the study at 6 months, 197 patients (80 leflunomide and 76 sulfasalazine, and 41 patients in the placebo group who switched to sulfasalazine) entered the 6–12 month extension.

Of the 168 completers at 12 months, 146 (60 leflunomide, 26 placebo-sulfasalazine, and 60 sulfasalazine) entered the 12–24 month extension. Completers at 24 months included 49 leflunomide, 21 placebo-sulfasalazine, and 46 sulfasalazine treated patients. Patients evaluable for functional assessments at the 3 study periods were as follows: 0–6 months (116 leflunomide, 81 placebo, 113 sulfasalazine), 6–12 months (66 leflunomide, 32 placebo-sulfasalazine, 62 sulfasalazine), and 12–24 months (51 leflunomide, 21 placebo-sulfasalazine, 45 sulfasalazine).

Table 2. Change in mean HAQ scores.

	0–6 Months			0–12 Months			0–24 Months		
	LEF n = 116	SSZ n = 113	PL n = 81	LEF n = 66	SSZ n = 62	PL-SSZ n = 32	LEF n = 51	SSZ n = 45	PL-SSZ n = 21
Baseline									
Mean	1.14	0.98	1.09	1.15	0.91	0.89	1.10	0.91	0.82
SD	0.62	0.55	0.62	0.61	0.52	0.47	0.59	0.57	0.41
Range	0.0–2.7	0.0–2.6	0.0–2.7	0.0–2.6	0.0–2.6	0.0–2.0	0.0–2.5	0.0–2.6	0.0–1.6
Endpoint									
Mean	0.63	0.69	1.05	0.57	0.49	0.59	0.45	0.55	0.62
SD	0.56	0.64	0.70	0.55	0.53	0.58	0.49	0.60	0.55
Range	0.0–2.6	0.0–2.6	0.0–2.9	0.0–2.9	0.0–2.1	0.0–2.4	0.0–2.0	0.0–2.5	0.0–1.7
Change									
Mean	–0.5*†	–0.29*	–0.04	–0.58	–0.41	–0.29	–0.65‡	–0.36	–0.20
SD	0.53	0.46	0.49	0.52	0.49	0.43	0.48	0.53	0.46
Range	–2.2–1.0	–1.5–1.9	–1.5–1.9	–2.3–0.4	–1.5–1.3	–1.5–0.5	–2.4–0.1	–1.6–1.0	–1.1–0.8
% Change	44	30	4	50	45	32	56	45	24

* $p \leq 0.0001$ vs PL; † $p \leq 0.01$ vs SSZ; ‡ $p = 0.0149$ vs SSZ.

In the groups treated with leflunomide and sulfasalazine, continuation in double blinded extensions was on a voluntary basis and was not a reflection of lack of efficacy. For example, of the 33 six-month completers not participating in the 6–12 month extension, 7/16 in the leflunomide group, 3/7 in the sulfasalazine group, and 1/10 in the placebo group were ACR 20% responders. Eighty-three percent of leflunomide treated patients entering the 6 to 12 month extension completed therapy, and 85% completed therapy during the 12 to 24 month extension.

Functional ability assessed by mean HAQ scores. Improvement in functional ability as assessed by changes in mean HAQ scores from baseline at Months 0–6, 6–12, and 12–24 is shown in Table 2. At each consecutive study period, the percentage reductions in the mean HAQ tended to be greater in the leflunomide cohorts (44%, 50%, and 59%) compared with the sulfasalazine (30%, 45%, and 39%), or placebo-sulfasalazine (4%, 32%, and 24%) groups (Figure 2). Significant differences were observed as early as 1 month[14] and at Month 6 with leflunomide compared with placebo (–0.5 vs –0.04; $p \leq 0.0001$) or sulfasalazine (–0.50 vs –0.29; $p \leq 0.01$). Continued improvements were noted in patients in the leflunomide arm at Months 6–12. Although reductions in scores at Months 0–12 were quantitatively greater with leflunomide than sulfasalazine (–0.58 vs –0.41), these changes were not statistically significant. At 0–24 months, changes from baseline mean HAQ scores with leflunomide were again significantly greater than with sulfasalazine (–0.65 vs –0.36; $p = 0.0149$); corresponding changes (discussed below) in HAQ DI at 24 months were –0.73 vs –0.56, which did not prove statistically significant.

Changes in the completers in each treatment group at the end of the 2 year study period are shown in Table 3 and Figure 3. Changes in HAQ scores in the completers show the same trend of reductions observed above. Reductions in HAQ scores seen as early as 6 months with leflunomide (57%) were maintained at 12 (57%) and 24 months (59%).

HAQ subscale scores. Changes in HAQ subscale scores at Months 0–6, 0–12, and 0–24 between leflunomide, sulfasalazine, and placebo-sulfasalazine in each individual category (dressing and grooming, rising, eating, walking, hygiene, reach, grip, other activities) were also compared. At 6 months, improvements in all categories with leflunomide were significantly greater than placebo (Figure 4, upper panel). Additionally, improvements in dressing and arising at 6 months were significantly greater than with sulfasalazine. Continued improvements were seen in all categories with leflunomide and sulfasalazine at Months 0–12 and 0–24. A consistent trend toward greater numerical improvement was seen in patients taking leflunomide compared to the sulfasalazine and placebo-sulfasalazine groups during the entire study period.

HAQ Disability Index. The HAQ Disability Index is calculated by summing the highest scores in each of the 8 categories and dividing this by the number of categories. Changes in HAQ DI are shown in Figure 5. The leflunomide group showed significant improvement at 6 months (34%, ΔHAQ DI –0.56) compared with sulfasalazine (25%, ΔHAQ DI –0.37; $p \leq 0.05$) and placebo (5%, ΔHAQ DI –0.08; $p \leq 0.001$). Proportionately similar trends in improvement were observed in leflunomide cohorts compared to sulfasalazine at Months 0–12 (40% vs 37%) and Months 0–24 (46% vs 37%).

Other efficacy criteria. The level of improvement observed in functional ability with leflunomide and sulfasalazine is reflected in the other primary efficacy criteria (Figure 6). Improvement seen in completers at 6 months in these outcomes is increased or maintained at 24 months with leflunomide. At 24 months, changes from baseline values in global assessments with leflunomide were significantly greater ($p <$

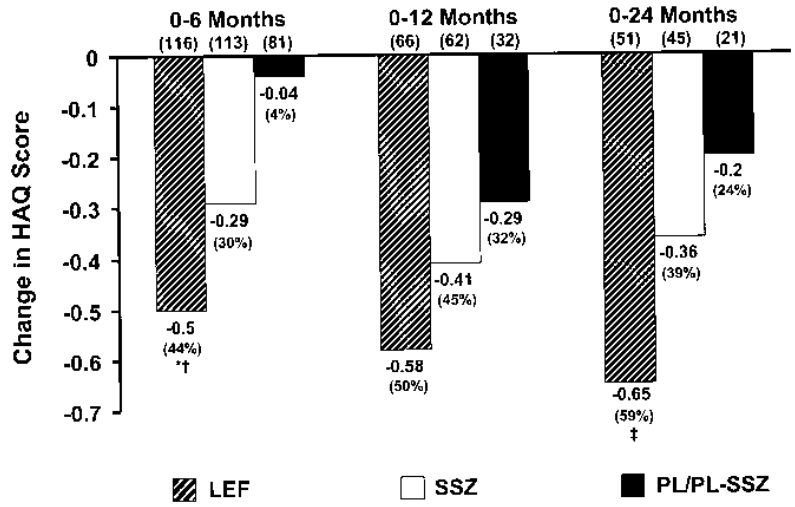

Figure 2. Change in mean HAQ scores in patient cohorts at 0–6, 0–12, and 0–24 month study periods. Numbers in parentheses along the x-axis represent patients evaluable for analysis. Percentages in parentheses represent improvement from baseline. *p ≤ 0.0001 vs placebo (PL); †p < 0.01 vs sulfasalazine (SSZ); ‡p = 0.0149 vs SSZ. Baseline HAQ scores are as shown in Table 1.

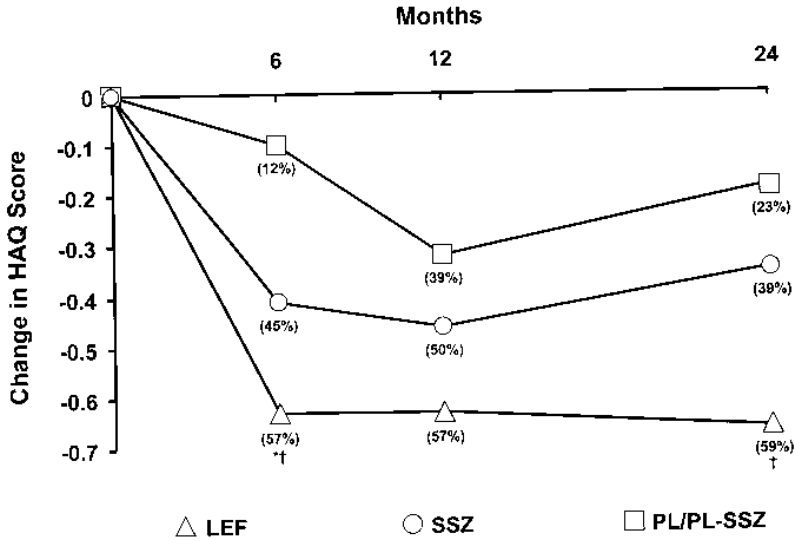

Figure 3. Changes in mean HAQ scores in completers at 24 months: leflunomide (LEF), n = 51; sulfasalazine (SSZ), n = 45; placebo-sulfasalazine (PL-SSZ), n = 21. *p < 0.0001 vs PL; †p = 0.0149 vs SSZ.

Table 3. Change in HAQ scores in completers at endpoint.

	LEF n = 51	SSZ n = 45	PL-SSZ n = 21
Baseline	1.10 ± 0.59	0.91 ± 0.57	0.82 ± 0.41
6 months			
Endpoint	0.48 ± 0.48	0.51 ± 0.58	0.72 ± 0.59
Change	–0.63 ± 0.43*†	–0.41 ± 0.42	–0.1 ± 0.54
% Change	57	45	12
12 months			
Endpoint	0.48 ± 0.47	0.46 ± 0.52	0.50 ± 0.44
Change	–0.63 ± 0.27	–0.46 ± 0.35	–0.32 ± 0.50
% Change	57	50	39
24 months			
Endpoint	0.45 ± 0.49	0.55 ± 0.59	0.62 ± 0.55
Change	–0.65 ± 0.48†	–0.36 ± 0.36	–0.20 ± 0.46
% Change	60	38	23

* p ≤ 0.0001 vs PL; † p ≤ 0.01 vs SSZ.

0.03) than sulfasalazine, resulting in improved physician (42% vs 32%) and patient (44% vs 30%) global scores. Reductions in CRP levels, a good prognostic indicator of functional outcome[19], were seen with both leflunomide and sulfasalazine at Months 6 and 24. Optimal improvement in most efficacy criteria with sulfasalazine appears to be leveling off at 6 months. The overall improvement seen in efficacy outcome with leflunomide as reflected in the ACR 20% response rate at endpoint, including tender and swollen joint counts, was significantly greater with leflunomide than sulfasalazine (82% vs 60%; p = 0.0085).

Safety. As reported[14], during the first 6 months, the most frequent drug related adverse events in the leflunomide group were diarrhea (leflunomide 16%, sulfasalazine 9%), nausea (leflunomide 10%, sulfasalazine 17%), and alopecia (lefluno-

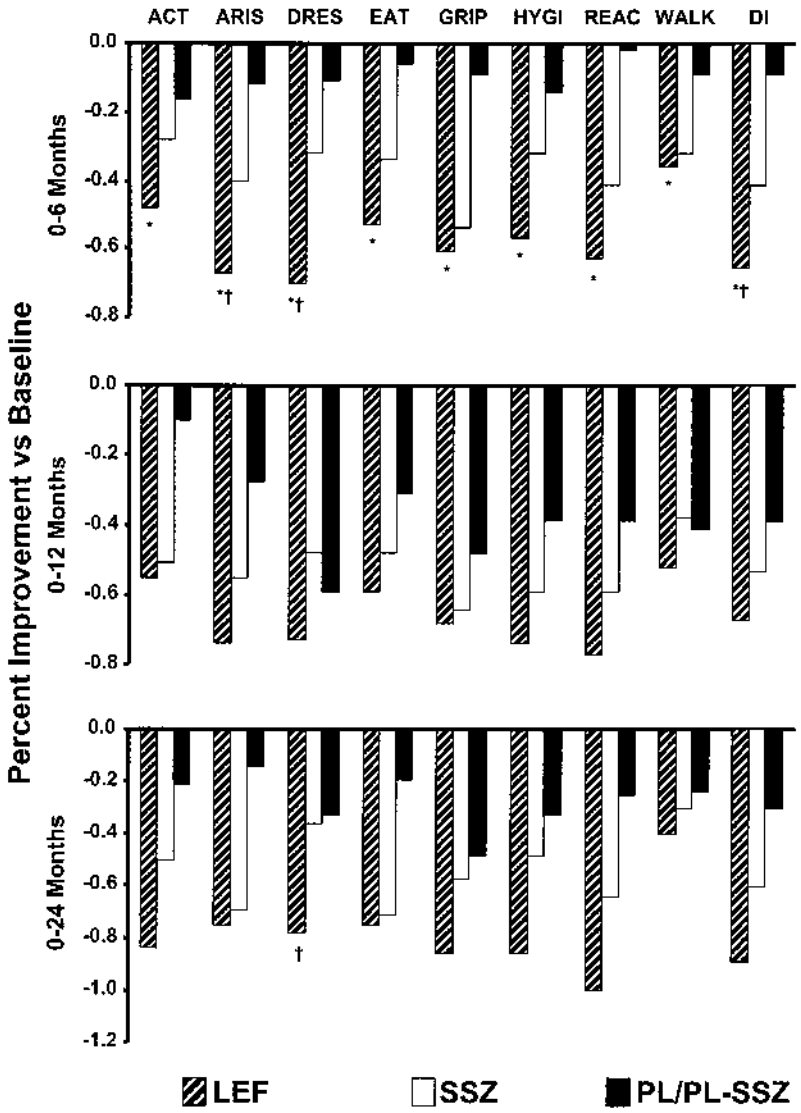

Figure 4. Changes in subscale scores at 6, 12, and 24 months. *p < 0.01 vs PL; †p < 0.05 vs SSZ. DI: HAQ Disability Index; ACT: activities; ARIS: arising; DRES: dressing; EAT: eating; GRIP: gripping; HYGI: hygiene; REAC: reaching; WALK: walking.

mide 8%, sulfasalazine 5%). Three leflunomide and 5 sulfasalazine patients with normal SGOT at baseline had increased SGOT values (> 2 times the upper limit of normal) during treatment with the study medication. Two cases of reversible agranulocytosis in the sulfasalazine group were reported within 6 weeks of treatment initiation and required hospitalization due to infections. No unexpected adverse events occurred with longterm leflunomide treatment; frequency of adverse events tended to subside with decreased incidence of diarrhea (17% to 2%), alopecia (13% to 5%), and nausea (12% to 0%) reported with leflunomide at 6 months compared to 24 months.

During the initial 6 month study, hypertension possibly related to study medication was reported in 2% leflunomide, 1% placebo, and 2% sulfasalazine treated patients; most of these patients had preexisting elevated blood pressure. At 24 months, hypertension possibly related to study medication was observed in 2% of leflunomide treated patients and in no sulfasalazine treated patient. No clinically relevant changes were observed in other laboratory variables.

DISCUSSION

Previously reported 6 month data have shown the efficacy and safety of leflunomide in patients with active RA[14]. Significantly greater improvement in functional ability was seen after 6 months of treatment with leflunomide than with placebo or sulfasalazine. Data at 2 years show that the improvement in functional ability seen with leflunomide at 6 months is maintained; leflunomide was significantly superior to sulfasalazine in improving functional ability at 2 years as assessed by mean HAQ scores.

Patient disposition during the extension phases showed a

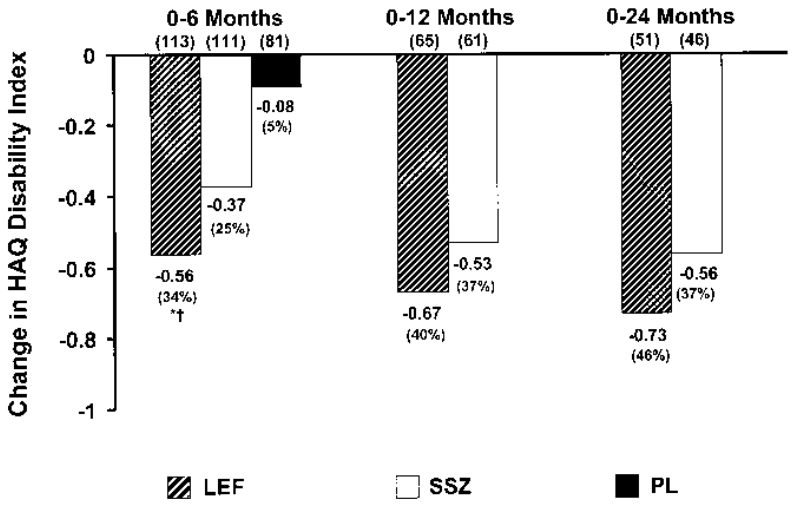

Figure 5. Changes in HAQ Disability Index at 0–6, 6–12, and 12–24 months study periods. *p ≤ 0.001 vs PL, †p ≤ 0.05 vs SSZ. Baseline HAQ DI scores are as shown in Table 1.

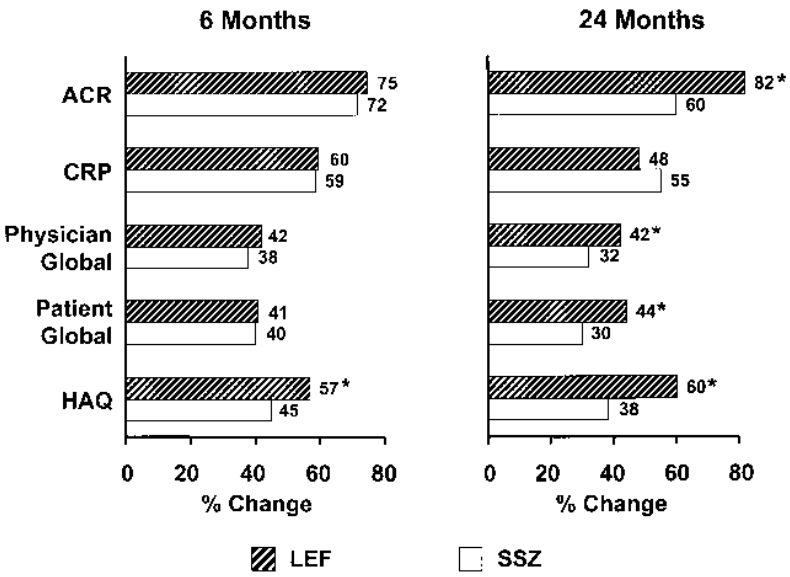

Figure 6. Percentage improvement in efficacy outcomes with leflunomide and sulfasalazine completers at 6 vs 24 months. *Changes from baseline, p < 0.05 vs SSZ.

progressive reduction in patient numbers during each extension. Although difficult to quantify, a recent investigation suggests that pyschosocial and socioeconomic factors are more important determinants of continued participation in longterm research investigations than most clinical disease characteristics[20]. Of the patients declining continued participation in the 0 to 12 month extension, about half were ACR 20% responders. The progressive reduction diminishes the initial statistical power of the trial.

Several instruments are available for measuring physical function[16,21,22]. We utilized the Health Assessment Questionnaire (HAQ)[16], a widely used disease-specific instrument for assessing change in functional ability over time or as a result of treatment. The HAQ was used to compare the effect of auranofin with that of placebo in a 6 month trial; the results favored auranofin[23]. The HAQ was also used in addition to other instruments to compare cyclosporin A and placebo[24]. A recent report showed significant improvement in functional ability and health related quality of life with leflunomide compared to placebo and methotrexate as assessed by the HAQ, the modified HAQ, the Problem Elicitation Technique (PET), and the Medical Outcomes Study Short Form-36 (SF-36)[25].

In the current study, functional ability was measured using both mean HAQ scores and the standard HAQ Disability Index. The mean HAQ score uses the mean score of each category instead of the worst score used to determine the HAQ

DI. There is some suggestion that the disability index does not reflect progress on items whose functional scores are not the worst in that category[17]. The study[17] of 107 patients with RA assessed one year after hospitalization concluded that the mean HAQ scores (because of its statistical properties) was more sensitive than the HAQ Disability Index for documenting changes in functional outcome. This observation was corroborated by Tennant, *et al*, indicating that scoring all 20 items of the HAQ might improve sensitivity and that vital information is lost when scoring only the worst response in each category of the HAQ[26]. As seen in this report, the mean HAQ scores generally correlated to the HAQ Disability Index. However, in the 24 month cohorts, mean HAQ scores were significantly improved with leflunomide compared with sulfasalazine at 24 months (–0.65 vs –0.60; $p < 0.0149$); corresponding changes in HAQ Disability Index were –0.73 vs –0.56 and were not significant.

Outcome Measurements in RA Clinical Trials (OMERACT) guidelines suggest that improvements of 36% above that of baseline or 18% above placebo constitute clinical benefit[27]. Changes in HAQ scores from baseline at 6, 12, and 24 months in leflunomide cohorts (44%, 50%, 56%, respectively) and completers (57%, 57%, 60%, respectively) all exceeded the OMERACT stipulated 36% above baseline improvement. Corresponding changes from baseline with sulfasalazine cohorts at 6, 12, and 24 months were 30%, 45%, and 39%, respectively.

At 6 months, leflunomide showed a 92% improvement above placebo, again exceeding the OMERACT recommended 18% improvement above placebo. Additionally, the magnitude of improvement in all subscales in the leflunomide group at endpoint was clinically meaningful (> 0.22)[28,29]. Changes in almost all subscales with leflunomide at 24 months approached 0.5. A reduction of 7–23% in HAQ scores is considered by patients as clinically important[28], and the changes observed with leflunomide (57% to 60%) in this report substantially exceed this.

Changes in the HAQ DI from baseline at 6, 12, and 24 months in leflunomide cohorts were –0.56, –0.67, and –0.73, respectively; corresponding changes in sulfasalazine cohorts were –0.37, –0.53, and –0.56. An Australian study of early RA noted no change in HAQ disability scores between sulfasalazine and placebo at 6 months[30]. An open trial of patients randomly assigned to either sulfasalazine or D-penicillamine was conducted with the objective of determining the effect of single DMARD therapy on longterm function in established RA[31]. Very few of the patients assigned to the sulfasalazine group continued taking the drug for the duration of the study; however, for the small subset continuing sulfasalazine there was no significant change in HAQ disability scores after 12 years of therapy (baseline 2.13 vs 2.25 at 12 years).

In 2888 RA patients followed prospectively for up to 29 years, Fries and colleagues[1] reported that increased DMARD use was strongly associated with better longterm disability index values. The magnitude of effect was a change of 0.53 disability units between 100% and 0% DMARD use. This is comparable to findings for leflunomide reported in this study, and strongly suggests that effective DMARD such as leflunomide reduce disability and improve longterm disease outcome.

More than 38% of patients enrolled in this study had disease duration of less than 2 years and showed baseline HAQ scores close to or greater than 1. Pain and synovitis may account for the relatively high HAQ scores seen at initial stages of the disease. Levels of CRP correlate with functional outcome, as reported in a prospective study of 109 patients with early RA; low CRP levels were associated with functional improvement, while persistently elevated CRP levels were associated with functional deterioration[19]. This finding suggests that the effect of leflunomide in reducing HAQ could be partially explained by a concomitant reduction in the acute phase response; leflunomide showed reductions (48% to 60%) in CRP levels. Reduction in CRP at Month 6 was significantly greater than with placebo (–2.3 vs –0.2; $p \leq 0.0001$). This observation is consistent with leflunomide improving function through suppression of disease activity.

Over the 2 year period, 20-mg leflunomide was safe and well tolerated. There were no unexpected adverse events during the 2 year period with leflunomide therapy compared to those adverse events observed during the first 6 months. Diarrhea, nausea, and alopecia were less frequent with continued leflunomide treatment. Throughout the full treatment of up to 2 years, no clinically relevant hematological toxicity was observed with leflunomide. No hematologic toxicity was observed with sulfasalazine between 6 and 24 months, after the 2 cases of agranulocytosis reported during the first 6 months. Further, there appears to be no risk of renal toxicity with leflunomide[32].

The data presented indicate that leflunomide significantly improves functional ability at 2 years compared with sulfasalazine. The benefit of leflunomide in improving physical function is reflected in other efficacy criteria of utmost importance to patients, such as the patient global assessment. Global assessment scores and ACR response rate at 2 years with leflunomide were significantly superior to sulfasalazine. Leflunomide shows both an immediate (reductions in HAQ scores at 6 months) and sustained (reductions in HAQ scores at 24 months) effect on HAQ scores, which benefits patients in terms of disability and health status.

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APPENDIX

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REFERENCES

1. Fries JF, Williams CA, Morfeld D, Singh G, Sibley J. Reduction in long-term disability in patients with rheumatoid arthritis by disease-modifying antirheumatic drug-based treatment strategies. Arthritis Rheum 1996;39:616-22.
2. Felson DT, Anderson JJ, Meenan RF. Use of short-term efficacy/toxicity tradeoffs to select second-line drugs in rheumatoid arthritis: a metaanalysis of published clinical trials. Arthritis Rheum 1992;35:1117-25.
3. Pincus T, Marcum SB, Callahan LF. Long-term drug therapy for rheumatoid arthritis in seven rheumatology private practices: II. Second line drugs and prednisone. J Rheumatol 1992;19:1885-94.
4. Wolfe F. Adverse drug reactions of DMARDs and DC-ARTs in rheumatoid arthritis. Clin Exp Rheumatol 1997;15 Suppl 17:S75-S81.
5. Bartlett RR, Anagnostopulos H, Zielinski T, Mattar T, Schleyerbach R. Effects of leflunomide on immune responses and models of inflammation. Springer Semin Immunopathol 1993;14:381-94.
6. Rückemann K, Fairbanks L, Carrey E, et al. Leflunomide inhibits pyrimidine *de novo* synthesis in mitogen-stimulated T-lymphocytes from healthy humans. J Biol Chem 1998;273:21682-91.
7. Fox RI. Mechanism of action of leflunomide in rheumatoid arthritis. J Rheumatol 1998;25 Suppl 53:20-6.
8. Kremer JM. Methotrexate and radiographic disease progression in patients with rheumatoid arthritis. J Rheumatol 1999;26:241-3.
9. Smolen JS, Tohidast-Akrad M, Gal A, et al. The role of T-lymphocytes and cytokines in rheumatoid arthritis. Scand J Rheumatol 1996; 25:1-4.
10. Fairbanks LD, Bofil M, Rückemann K, Simmonds HA. Importance of ribonucleotide availability to proliferating T-lymphocytes from healthy humans. J Biol Chem 1995;270:29682-91.
11. Herrmann M, Frangou C, Kirschbaum B. Effects of leflunomide on early T-cell signaling and cell cycle commitment [abstract]. Rheumatol Eur 1997; 26 Suppl 2:S16.
12. Manna SK, Aggarwal BB. Immunosuppressive leflunomide metabolite (A77 1726) blocks TNF-dependent nuclear factor-k B activation and gene expression. J Immunol 1999;162:2095-102.
13. Mladenovic V, Domljan Z, Rozman B, et al. Safety and effectiveness of leflunomide in the treatment of patients with active rheumatoid arthritis: Results of a randomized, placebo-controlled, phase II study. Arthritis Rheum 1995;38:1595-603.
14. Smolen JS, Kalden JR, Scott DL, et al. Efficacy and safety of leflunomide compared with placebo and sulphasalazine in active rheumatoid arthritis: a double-blind, randomised, multicentre trial. Lancet 1999;353:259-66.
15. Strand V, Cohen S, Schiff M, et al. Treatment of active rheumatoid arthritis with leflunomide compared to placebo and methotrexate. Arch Intern Med 1999;159:2542-50.
16. Fries JF, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. Arthritis Rheum 1980;23:137-45.
17. Borg G, Allander E, Lund B, et al. Auranofin improves outcome in early rheumatoid arthritis. Results from a 2-year, double blind, placebo controlled study. J Rheumatol 1988;15:1747-54.
18. Tomlin GS, Holm MB, Rogers JC, Kwoh CK. Comparison of standard and alternative Health Assessment Questionnaire scoring procedures for documenting functional outcomes in patients with rheumatoid arthritis. J Rheumatol 1996;23:1524-30.
19. Devlin J, Gough A, Huisson A, et al. The acute phase and function in early rheumatoid arthritis. C-reactive protein levels correlate with functional outcome. J Rheumatol 1997;24:9-13.
20. Reisine S, Fifield J, Winkelman DK. Characteristics of rheumatoid arthritis patients: Who participates in long-term research and who drops out? Arthritis Care Res 2000;13:3-10.
21. Meenan RF, Gertman PM, Mason JH. Measuring health status in arthritis. The Arthritis Impact Measurement Scales. Arthritis Rheum 1980;23:146-52.
22. Bergner M, Bobbitt RA, Carter WB, Gilson BS. The Sickness Impact Profile: development and final revision of a health status measure. Med Care 1981;19:787-805.
23. Bombardier C, Ware J, Russell IJ, et al. Auranofin therapy and quality of life in patients with rheumatoid arthritis. Results of a multicenter trial. Am J Med 1986;81:565-77.
24. Bombardier C, Buchbinder R, Tugwell P. Efficacy of cyclosporin A in rheumatoid arthritis: long-term follow-up data and the effect on quality of life. Scand J Rheumatol 1992;21 Suppl 95:29-33.
25. Strand V, Tugwell P, Bombardier C, et al. Function and health-related quality of life. Results from a randomized controlled trial of leflunomide versus methotrexate or placebo in patients with active rheumatoid arthritis. Arthritis Rheum 1999;42:1870-8.
26. Tennant A, Hillman M, Fear J, Pickering A, Chamberlain MA. Are we making the most of the Stanford Health Assessment Questionnaire? Br J Rheumatol 1996;35:574-8.
27. Goldsmith CH, Boers M, Bombardier C, Tugwell P. Criteria for clinically important changes in outcomes: development, scoring and evaluation of rheumatoid arthritis patient and trial profiles. J Rheumatol 1993;20:561-5.
28. Wells GA, Tugwell P, Kraag GR, Baker PRA, Groh J, Redelmeier DA. Minimum important difference between patients with rheumatoid arthritis: the patient's perspective. J Rheumatol 1993;20:557-60.
29. Guzman J, Maetzel A, Peloso P, Yeung M, Bombardier C. Disability scores in DMARD trials. What is a clinically important change? [abstract]. Arthritis Rheum 1996;39 Suppl:S208.
30. Australian Multicentre Clinical Trial Group. Sulfasalazine in early rheumatoid arthritis. J Rheumatol 1992;19:1672-7.
31. Capell HA, Maiden N, Madhok R, Hampson R, Thomson EA. Intention-to-treat analysis of 200 patients with rheumatoid arthritis 12 years after random allocation to either sulfasalazine or penicillamine. J Rheumatol 1998;25:1880-6.
32. Scott DL, Whelton A, Smolen JS, Weaver A, Emery P, Strand V. Renal effects of leflunomide compared with other agents used to treat rheumatoid arthritis [abstract]. Ann Rheum Dis 1999;5:212.