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SAFETY AND EFFECTIVENESS OF LEFLUNOMIDE IN THE TREATMENT OF PATIENTS WITH ACTIVE RHEUMATOID ARTHRITIS

Results of a Randomized, Placebo-Controlled, Phase II Study

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Objective. **To assess the safety and effectiveness of leflunomide versus placebo in patients with active rheumatoid arthritis (RA) treated for 6 months.**

Methods. **Four hundred two patients were randomly assigned to receive placebo or leflunomide at 5 mg, 10 mg, or 25 mg daily. A washout period of 6–12 weeks from prior second-line therapy was required.**

Results. **Statistically significant improvement in primary and secondary outcome measures, as well as by responder analyses, occurred in the 10-mg and 25-mg dosage groups compared to placebo. Twenty-one patients (7.0%) in the active treatment groups withdrew due to adverse events (AEs). The incidence of AEs was higher with leflunomide than with placebo. Gastrointestinal symptoms, weight loss, allergic reactions, skin rash, and reversible alopecia were more common in the 10-mg and 25-mg dosage groups. The incidence of infections was similar between the treatment and placebo groups; no opportunistic infections were seen. Transient elevations in liver function studies were noted in a small number of patients.**

Conclusion. **Leflunomide is effective in daily doses of 10 mg and 25 mg in patients with active RA. Improved efficacy at the 25-mg dose was associated with a higher incidence of AEs. Randomized, placebo-controlled trials using daily doses of 10 mg and 20 mg are under way in the US and Europe to confirm these positive results.**

Rheumatoid arthritis (RA) is an autoimmune disease characterized by severe inflammation of the joints, resulting in destruction of cartilage, bone, and tendon. Several immunosuppressive agents have been shown to be effective in the treatment of RA, including azathioprine (1,2), methotrexate (3–5), cyclophosphamide (1), and cyclosporin A (6,7).

Leflunomide, a novel isoxazole drug with immunosuppressive and antiproliferative properties, has demonstrated prophylactic and therapeutic effects in animal models of autoimmune disease (8–12). In experimental models of chronic graft-versus-host disease (13,14) and solid organ graft rejection (15–17), administration of leflunomide prolonged rejection time or reversed ongoing rejection. In addition, leflunomide has exhibited antiinflammatory, analgesic, and antipyretic activity (8). In experimental septicemia, leflunomide did not alter the resistance of mice to bacterial pathogens (18).

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Table 1. Patient characteristics and concomitant medications at baseline*

	Placebo (n = 102)	Leflunomide 5 mg/day (n = 95)	Leflunomide 10 mg/day (n = 101)	Leflunomide 25 mg/day (n = 104)	Total (n = 402)
No. male/no. female	25/77	16/79	14/87	13/91	68/334
Age, mean (range)	52.8 (28–73)	50.3 (24–74)	51.4 (20–76)	50.0 (21–74)	51.0 (20–76)
RF positive, no.	78	76	78	67	299
Years of RA, mean (range)	8.3 (0.8–26.3)	7.7 (0.8–31.3)	8.5 (0.9–31.8)	8.8 (0.8–37.8)	8.3 (0.8–37.8)
Baseline SJC, mean ± SD	24 ± 12	23 ± 11	24 ± 11	24 ± 10	23.6 ± 10.9
Baseline TJC, mean ± SD	37 ± 15	35 ± 15	35 ± 13	35 ± 15	35.4 ± 14.3
No. of previous DMARDS failed, mean	1.2	1.1	1.1	1.1	1.1
Concomitant NSAID use, %	95	95	97	93	95
Concomitant steroid use, %	37	30	36	39	35

* RF = rheumatoid factor; RA = rheumatoid arthritis; SJC = swollen joint count; TJC = tender joint count; DMARDs = disease-modifying antirheumatic drugs; NSAID = nonsteroidal antiinflammatory drug.

This report summarizes the findings in a randomized, placebo-controlled, phase II study comparing 3 different daily doses of leflunomide to placebo. The study was conducted in 402 patients with active RA in the former Yugoslavia. Clinical outcome, individual responder rates, adverse events, and pharmacokinetics associated with leflunomide administration in this protocol are described.

PATIENTS AND METHODS

Study population and enrollment criteria. Patients were required to have a diagnosis of RA by the American College of Rheumatology (ACR; formerly, the American Rheumatism Association) criteria (19) and to have active disease, as defined by 3 of the following 4 criteria: ≥8 tender joints, ≥8 swollen joints, morning stiffness ≥45 minutes, and Westergren erythrocyte sedimentation rate (ESR) ≥40 mm/hour. Patients were enrolled in 6 study centers in Yugoslavia, Croatia, and Slovenia.

Concomitant medications. Use of nonsteroidal antiinflammatory drugs (NSAIDs) and of corticosteroids in doses ≤10 mg of prednisone (or equivalent) daily were permitted, provided the dosage remained stable during the trial and for at least 4 weeks and 8 weeks, respectively, before enrollment. A washout period of at least 3 months from prior therapy with gold, methotrexate, or azathioprine was required.

Table 2. Reasons for early withdrawal from the study

Treatment	No. of patients randomized	Reason for dropout (no.) Adverse events	Lack of efficacy	Other	No. of patients completed
Placebo	102	2	10	1	89
Leflunomide					
5 mg/day	95	3	3	2	87
10 mg/day	101	7	2	2	90
25 mg/day	104	11	2	0	91
Total	402	23	17	5	357

Treatment regimen. Following oral administration, leflunomide is rapidly metabolized to A77 1726, which is active in vitro and is presumed to be the active drug product. In vitro, A77 1726 inhibits mitogen-stimulated proliferation of human peripheral blood mononuclear cells as well as transformed murine and human cell lines in a dose-dependent manner. This antiproliferative activity was reversed in all test species cells by the addition of uridine to the culture, indicating that A77 1726 acts at the level of the pyrimidine synthesis pathway (18).

In a phase I study of patients with active RA, daily doses of 5 mg, 10 mg, and 25 mg of leflunomide for 6 weeks were associated with improvement in disease activity parameters. The safety profile was acceptable, although steady-state plasma levels were not reached (18). Based on these findings, patients in this phase II protocol received dosages of 5 mg, 10 mg, or 25 mg of leflunomide or placebo daily, following single oral loading doses of 50 mg leflunomide (in the 5-mg daily dose group), 100 mg leflunomide (in the 10- and 25-mg dose groups), or placebo. Due to the long plasma half-life, loading doses were used to achieve steady-state levels more rapidly. A 24-week treatment period was followed by 8 weeks of observation.

Randomization was generated centrally and was site specific; all patients, investigators, and data analysts remained blinded throughout the study. A sample size of 320 evaluable patients was calculated, based on a standard deviation of 35% (α = 0.05, 80% power), to detect a difference of 20% in total joint score between treatment groups. Based on the assumpation that 75% of patients would be evaluable by an intent-to-treat analysis, 402 patients were enrolled.

Primary outcome measures. Primary outcome measures included tender joint count (TJC), swollen joint count (SJC), tender joint score (TJS), and swollen joint score (SJS), using 66 or 68 joints and a scale of 0 (none) to 3 (severe) to assess degrees of swelling and/or tendeness (20). Patient and physician global assessments were performed using a 5-point Likert scale with boxes ranging from "very poor" to "very good" (21).

Table 3. Efficacy analysis: changes from baseline for the primary parameters*

	Placebo (n = 102)	Leflunomide 5 mg/day (n = 95)	Leflunomide 10 mg/day (n = 100)	Leflunomide 25 mg/day (n = 101)
Swollen joint score	−12.8 ± 19	−16.9 ± 20	−20.2 ± 20†	−20.4 ± 16†
Tender joint score	−23.6 ± 29	−25.1 ± 30	−31 ± 28	−35.3 ± 30†
Swollen joint count	−6.5 ± 10.3	−7.6 ± 9.5	−10.4 ± 9.9†	−11.7 ± 9.1†
Tender joint count	−9.7 ± 12.6	−10.5 ± 13.1	−13.6 ± 14.3	−16.5 ± 14.1†
Patient global assessment	0.5 ± 1.2	0.6 ± 1.2	1.1 ± 1.2†	1.0 ± 1.0†
Physician global assessment	0.6 ± 1.0	0.7 ± 1.0	1.1 ± 1.0†	1.1 ± 1.0†

* Negative values for joint counts and scores indicate improvement; positive values for global assessments indicate improvement. Values are the mean ± SD.
† $P < 0.05$ versus placebo.

Secondary outcome measures. Clinical assessment included duration of morning stiffness, grip strength, Health Assessment Questionnaire (22,23), and patient pain score, using a 10-mm visual analog scale (21). Laboratory assessment included Westergren ESR, C-reactive protein (CRP), and rheumatoid factor (RF).

Responder analyses. Four responder criteria were utilized. Two used the primary outcome measures utilized by the Food and Drug Administration, i.e., SJC, TJC, patient global assessment, and physician global assessment. A composite improvement score required 3 of 4 parameters to be improved by ≥20% or 2 of 5 Likert boxes (or from "good" to "very good"); or 2 of 4 to be improved with none worse, as defined in the methotrexate summary basis of approval (24). The Paulus criteria required improvement in 4 of 6 parameters by ≥20% or 2 of 5 boxes (25). The proposed ACR criteria required improvement by ≥20% in 5 of 7 criteria (including both TJC and SJC) (26).

Adverse events. Safety was monitored by physical examination, chest radiography, electrocardiogram (EKG), and standard hematologic and clinical chemistry studies and urinalyses. Adverse events were tabled according to the COSTART (coding symbols for thesaurus of adverse reaction terms) body system and preferred term. The total number of adverse events for each preferred term as well as the number of patients with each type of event are presented. Vital signs, EKG, and radiographic results were tabulated and evaluated.

Laboratory assessment. Data were analyzed by means, mean change from baseline, and shifts from baseline values to followup intervals, i.e., from normal (or abnormal) at baseline to abnormal (or normal) at followup. Contingency tables were constructed for hemoglobin and hematocrit counts, serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), and alkaline phosphatase levels, and blood urea nitrogen (BUN) and creatinine levels, to identify trends in organ system effects.

Other investigations. At the end of the 6-month study period, individual plasma time curves were determined in 89 of 301 patients who received active drug. In selected centers, flow cytometry analyses of peripheral B and T lymphocyte subsets were performed, as well as assays for quantitative levels of IgA, IgG, and IgM; IgA, IgG, and IgM rheumatoid factor; immune complexes by C1q; and C5a and membrane attack complex levels.

Statistical analyses. Results were analyzed on an intent-to-treat basis. All patients with at least 1 assessment in the treatment phase of the study were considered evaluable. All tests were 2-tailed, and the 5% significance level was used. Results of SJC, SJS, TJC, and TJS measures were analyzed for each center to determine whether similar results were seen across the individual study centers. Analyses of baseline disease characteristics (TJC ≥40, SJC ≥20 at entry, disease duration <8 years) and concomitant use of corticosteroids or NSAIDs were conducted to determine whether response was affected.

RESULTS

A total of 402 patients were enrolled and randomly assigned to the following dosage groups: 95 patients received 5 mg leflunomide daily, 101 patients received 10 mg leflunomide daily, 104 patients received 25 mg leflunomide daily, and 102 patients received placebo. There were no statistically significant differences in age, sex, baseline disease characteristics, or concomitant use of NSAIDs or corticosteroids between the treatment groups (Table 1).

Forty-five patients left the study before treatment was completed. Twenty-three patients discontinued therapy due to adverse events, 17 for lack of clinical benefit, and 5 for other reasons (Table 2). All but 4 of the patients were evaluated at the week-4 visit and were therefore included in the intent-to-treat analysis of efficacy. A dose-response was evident: at the higher dosage levels, more patients exited due to tolerability reasons and fewer for lack of efficacy.

Clinical responses. *Primary outcome measures.* Mean (±SD) changes from baseline for the primary outcome measures are presented in Table 3. Statistical

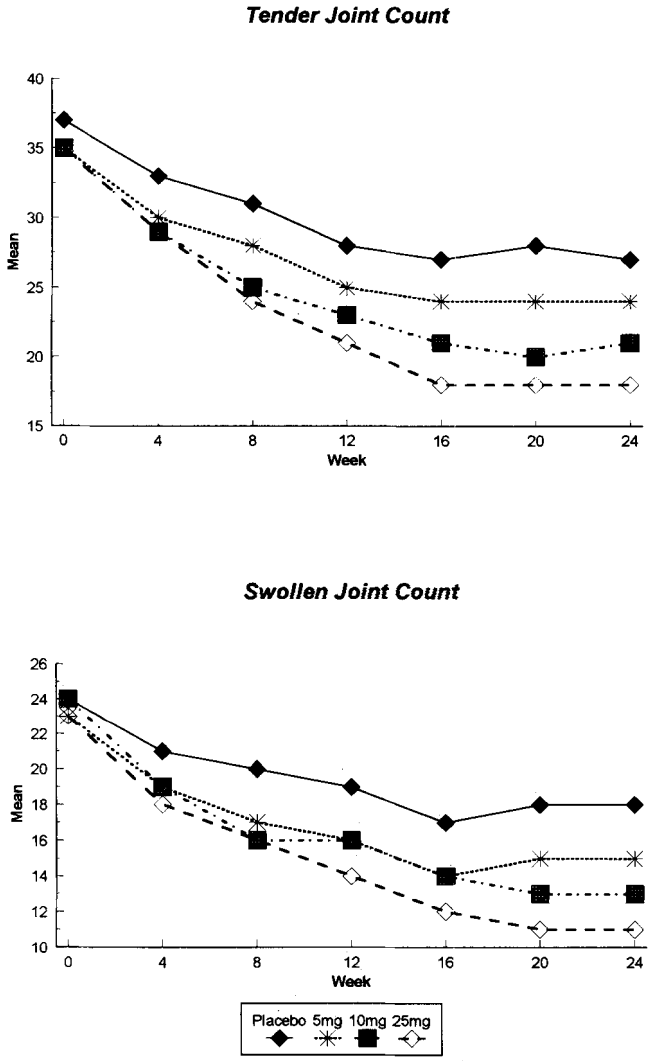

Figure 1. Changes in the mean number of tender joints and swollen joints during the study, by treatment group (placebo or leflunomide at either 5, 10, or 25 mg/day). Mean values are plotted over time. Improvement was evident in all treatment groups at week 4, and continued in the active treatment groups over the course of the study.

analysis of the primary parameters indicated that results in the 25-mg leflunomide group were significantly better than those in the placebo group ($P < 0.05$) for all measurements. Results in the 10-mg leflunomide group were statistically significantly better than those in the placebo group for all outcome parameters except TJC and TJS. Despite the placebo response, a clear dose-response for all of the primary efficacy parameters was evident. Improvement was noted at 4 weeks in all study groups, including the placebo-treated patients (Figure 1).

Secondary outcome measures. Mean (±SD) changes from baseline for secondary outcome measures are presented in Table 4. Although the results in the 5-mg leflunomide group were similar to or worse than those in the placebo-treated group, effects in the 10-mg and 25-mg groups were statistically significantly better than in the placebo group for all parameters, except for morning stiffness in the 10-mg group. Results for patient and physician global assessments and patient assessment of pain paralleled the mean change from baseline in the continuous variables. Although substantial improvement in these parameters occurred in the placebo group, the percentages of improvement in the 10-mg and 25-mg leflunomide groups were statistically significantly greater.

Responder analyses. The numbers of patients meeting responder criteria, by treatment group, are presented in Figure 2. A dose-response was observed, with clear superiority for the 10-mg and 25-mg doses compared to placebo, using all 4 responder analyses ($P < 0.0001$).

Comparison of results across individual study centers and by baseline treatment and disease characteristics. Regression analysis across study centers indicated that results varied among the 6 centers; however, the interaction between leflunomide dosage and center was not statistically significant (data not shown). Although the magnitude of change from baseline in the primary outcome parameters may have differed at each center, the relationship between dosage and response was similar across study centers. Similarly, no effect between clinical outcome and concomitant treatment with NSAIDs and/or steroids or baseline disease characteristics was evident.

Adverse events. Twenty-three patients were withdrawn from the study because of adverse events (2 from the placebo group, 3 from the 5-mg leflunomide group, 7 from the 10-mg leflunomide group, and 11 from the 25-mg leflunomide group). Ten of these events were serious, including 5 attributed to the underlying disease, i.e., septic arthritis, episcleritis, pleuritis, aseptic necrosis, and development of systemic lupus erythematosus with generalized rash, as well as 1 each of anaphylaxis, skin rash, cholecystitis, breast carcinoma, and 1 death by suicide. In total, 387 primary adverse events were reported in 195 patients.

Those adverse events judged to be related to

Table 4. Efficacy analysis: changes from baseline for the secondary parameters*

	Placebo (n = 102)	Leflunomide 5 mg/day (n = 95)	Leflunomide 10 mg/day (n = 100)	Leflunomide 25 mg/day (n = 101)
HAQ score	−8.1 ± 13.0	−5.8 ± 12.6	−14.5 ± 14.2†	−13.6 ± 12.9†
Pain assessment, VAS	0.3 ± 0.9	0.3 ± 1.0	−0.91 ± 1.0†	−1.0 ± 0.81†
Grip strength, mm Hg	14.5 ± 46.7	4.6 ± 43.2	30.8 ± 48.8†	52.4 ± 58.4†
Morning stiffness, minutes	−33.7 ± 93.2	−48.3 ± 115.7	−55.3 ± 64.7	−71.8 ± 80.5†
ESR, mm/hour	3.1 ± 20.6	4.2 ± 19.2	−5.2 ± 23.7†	−5.4 ± 19.3†
CRP returned to normal, no. of patients	14	9	26†	32†

* Negative values indicate improvement except in the case of grip strength, where positive values indicate improvement. Except for C-reactive protein (CRP), values are the mean ± SD. HAQ = Health Assessment Questionnaire; VAS = visual analog scale; ESR = erythrocyte sedimentation rate.
† $P < 0.05$ versus placebo.

study drug administration are presented in Table 5. Potential allergic reactions included 1 episode of nonfatal anaphylaxis in a patient receiving leflunomide after rechallenge of medication. Pruritus and rash occurred more frequently with active treatment (5%) than with placebo (2.9%). Gastrointestinal symptoms, including anorexia, abdominal pain, diarrhea, nausea (with or without vomiting), gastritis, and gastroenteritis, were reported more frequently in patients receiving leflunomide. A review of all cases of weight loss revealed no clinical explanation or correlation with laboratory parameters such as albumin, total protein, serum IgG, cholesterol, or triglyceride levels. Other events reported more frequently with le-

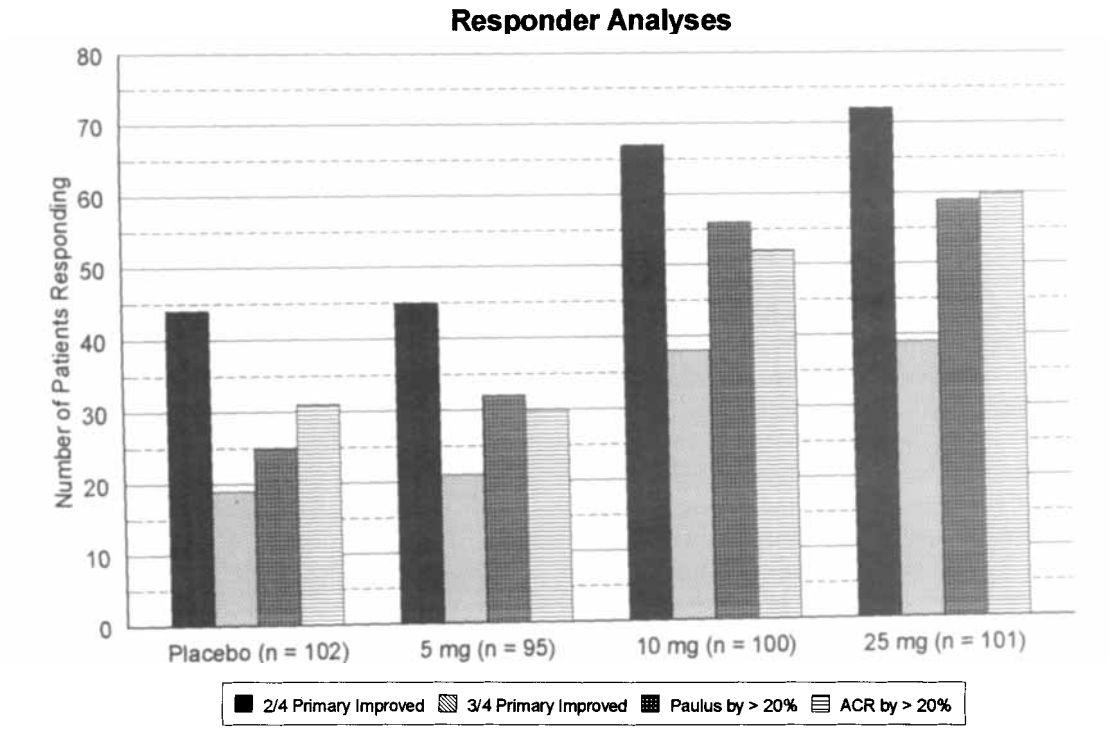

Figure 2. Number of patients who qualified as responders according to the various responder criteria, by treatment group. Compared to placebo, the numbers of responders in the 10 mg/day and 25 mg/day leflunomide groups were statistically significant ($P < 0.0001$) by all response criteria. ACR = American College of Rheumatology. See Patients and Methods for details.

Table 5. Number of patients who had adverse events related to leflunomide administration

	Placebo	Leflunomide		
		5 mg/day	10 mg/day	25 mg/day
Rash/allergic reactions	5	6	4	8
Gastrointestinal symptoms	3	15	10	12
Weight loss	2	2	4	4
Reversible alopecia	1	1	1	7

flunomide treatment were hypertension, dizziness, and reversible alopecia. Given a significant preexisting incidence of hypertension and cardiovascular disease in this patient population, attribution to study drug administration is difficult to assess. Reversible alopecia occurred more frequently in the 25-mg dosage group, and appeared to be related to leflunomide administration.

The incidence of infections was similar between treatment and placebo groups (n = 18 in the placebo group, 23 in the 5-mg leflunomide group, 13 in the 10-mg leflunomide group, and 16 in the 25-mg leflunomide group). No opportunistic infections were noted. Adverse events associated with RA revealed no clear association with leflunomide administration, but were compatible with the severity of the underlying disease and undertreatment of the patients enrolled. Specifically, 2 cases of RA-associated vasculitis were reported.

Laboratory data. Decreases in mean hematocrit and hemoglobin values, although not clinically meaningful, were observed in all 4 treatment groups. No patients experienced leukopenia (white blood cell count <2,000/ml) or neutropenia (polymorphonuclear cells <500/ml). Two patients had transient thrombocytopenia (platelets <100,000/ml) during the study; levels normalized while drug administration continued.

Although mean values for alkaline phosphatase, SGOT, and SGPT increased during the course of the study, they remained within the normal range. A contingency table for elevations in liver function studies demonstrated a higher incidence of abnormalities in the 10-mg and 25-mg leflunomide groups at 24 weeks, compared with placebo (Table 6).

Mean creatinine levels did not change meaningfully during the drug administration period. Three patients (1 each from the placebo, 5-mg leflunomide and 10-mg leflunomide groups) had isolated creatinine values ≥1.8 mg/dl once during the study. Only the patient in the placebo group had a concomitantly elevated BUN level >40 mg/dl; these values were present at baseline and remained stable throughout the study.

Pharmacokinetics. Although substantial individual variability was indicated by the SD and range of individual values, mean concentrations of leflunomide at 6 months were proportional to daily maintenance doses. The pharmacokinetics of the active metabolite, A77 1726, appeared to be linear over the dosage range of 5 mg to 25 mg daily. Mean plasma concentrations were proportional at 9 μg/ml, 19 μg/ml, and 52 μg/ml for the 5-mg, 10-mg, and 25-mg daily dose groups, respectively. Mean plasma half-life was 15–18 days, with total plasma clearance of 0.30 ml/kg/hour. The active metabolite was extensively protein bound (>99%) and was cleared via several metabolic pathways, including biliary and urinary excretion. Administration of cholestyramine or activated charcoal rapidly decreased plasma levels of the active metabolite by 40–50% within 24 hours (18).

Results of other investigations. No significant treatment effect was observed in flow cytometry analyses of peripheral T and B cell subsets, including CD3, CD4, CD8, CD20, CD16, CD38, CD25, and CD4:CD8 ratios. Although statistically significant decreases in quantitative immunoglobulin levels in the 10-mg and 25-mg treatment groups were evident when comparing end-of-study values with baseline values, few patients' levels were below the normal range at

Table 6. Frequency of elevated liver function test results at 24 weeks*

	Placebo	Leflunomide		
		5 mg/day	10 mg/day	25 mg/day
GGTP (>ULN)	2	2	5	8
Alk. phos. (≥1.2 to <3 times ULN)	1	3	8	5
SGOT (≥1.2 to <3 times ULN)	2	1	1	3
SGPT (≥1.2 to <3 times ULN)	2	1	1	6
Total no. of patients with elevations	6	6	13	14

* Values were normal at baseline. GGTP = gamma glutamyl transpeptidase; ULN = upper limit of normal; Alk. phos. = alkaline phosphatase; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase.

Table 7. Changes in RF, CRP, and ASO levels in a subpopulation of 198 patients*

	Placebo (n = 50)	Leflunomide 5 mg/day (n = 47)	Leflunomide 10 mg/day (n = 50)	Leflunomide 25 mg/day (n = 51)
IgA–RF, units	−15.9 ± 137	26.1 ± 228	−26.6 ± 208	−43.6 ± 153
IgG–RF, units	−10.9 ± 147	15.9 ± 204	−27.5 ± 293	−41.4 ± 144
IgM–RF, units	−15.1 ± 147	23.8 ± 245	−26.5 ± 191	−35.8 ± 147
CRP, units	5.3 ± 23.0	2.4 ± 23.0	−14.9 ± 33.0†	−9.5 ± 25.0†
ASO titer	33 ± 317	−32 ± 189	−13 ± 58	−4 ± 113

* Values are the mean ± SD. IgA, IgG, and IgM rheumatoid factor (RF) and C-reactive protein (CRP) were determined by enzyme-linked immunosorbent assay. ASO = antistreptolysin O.
† $P < 0.05$ versus placebo by Kruskal-Wallis nonparametric test, multiple comparison Nemeny.

weeks 12 or 24 (n = 1 in the placebo group; n = 1, 2, and 1 in the 5-mg, 10-mg, and 25-mg leflunomide groups, respectively). A detailed central laboratory determination of IgM-RF by nephelometry and IgA- and IgG-RF by enzyme-linked immunosorbent assay (ELISA), as well as measurement of CRP in 198 patients, suggested a treatment effect of leflunomide at the 10-mg and 25-mg daily dosage levels (Table 7). Antistreptolysin O (ASO) titers were unchanged, providing evidence against a nonspecific hepatotoxic effect mediating the changes in CRP and RF titers.

Open-label extension protocol. Three hundred of the 402 patients in this study subsequently participated in an open-label extension study, which included 50 additional patients from a single-blind randomized study protocol (204 YU) comparing 5 mg, 10 mg, and 25 mg of leflunomide daily with associated pharmacokinetic determinations. Of patients continuing treatment from the present protocol, 74 had received placebo; 67, 76, and 83 had received leflunomide at 5 mg/day, 10 mg/day, and 25 mg/day, respectively. Two hundred four of the 350 patients completed 18 months of treatment with active drug in the open-label study. They received daily doses of 5–25 mg, titrated in increments of 5 mg by the treating physician to achieve maximal clinical benefit and tolerability. The type and incidence of adverse effects were similar to those found in this protocol, and they were highest in the 25-mg dosage group. Evaluation, using mean changes in primary outcome measures and in responder analyses, indicated stabilization of clinical effect as well as improvement in disease activity in patients 6 months after entry into the open-label study. Improvement occurred not only in patients who previously received placebo and then initiated active treatment, but also in patients who previously received low doses of leflunomide (27).

DISCUSSION

In this clinical trial, statistically significant benefit in patients with severe, longstanding RA was observed in primary and secondary measures of clinical outcome at the 2 higher dosages of leflunomide, when compared to placebo. Improvement was evident at 4 weeks, i.e., the first time point when clinical status was assessed after initiation of treatment. When these results are compared with the findings of randomized, placebo-controlled, 18–24-week trials of other disease-modifying antirheumatic drugs (DMARDs), clinical responses in the leflunomide treatment groups are similar to or greater than those reported with methotrexate (3,4,28), sulfasalazine (29–31), injectable gold (31,32), and cyclosporin A (7). Although the response rate in the placebo group was high (mean ± SD decrease in TJC 9.7 ± 12.6, SJC 6.5 ± 10.3; 25% responders by Paulus criteria, 31% by ACR criteria), improvements in the 10-mg and 25-mg leflunomide groups were significantly better. Detailed analyses indicated a dose-response effect in both efficacy and tolerability, which has not been reported with other antirheumatic therapies.

Several factors may have contributed to the high placebo effect. The relatively long duration of disease and small number of previously used DMARDs imply a less aggressive treatment of RA. Further, the trial was initiated just prior to the outbreak of hostilities in the former Yugoslavia, which may have restricted access to care. Thus, patients enrolled in this study may have benefited from more frequent clinical monitoring and assessment of disease activity. Comparable placebo responses have been reported in the US, where patients participating in a clinical trial may receive regular examinations and

laboratory assessments otherwise not covered by third-party payors (33).

Although the duration of this clinical trial was only 6 months, further improvement was shown in patients who continued open-label treatment, with a similar tolerability profile (27). This suggests that long-term administration of leflunomide may maintain benefit and be relatively well tolerated. Phase III trials, under way in the US and Europe, will evaluate 12-month and 24-month administration of leflunomide in patients with active RA.

The reported adverse effects suggest that leflunomide may be similar to methotrexate in several ways. Its mechanism of action may be analogous, inhibiting the pyrimidine (uridine), rather than the purine (adenosine), synthesis pathway in rapidly dividing cells. Leflunomide administration appears to cause elevated liver function studies in a dose-dependent manner. As with methotrexate, the SGPT level appears to be most sensitive to drug effect (34). To date, reported liver function test abnormalities have been transient and have not warranted liver biopsy.

In contrast to methotrexate, signs or symptoms suggestive of interstitial pneumonitis have not occurred with leflunomide treatment. Gastrointestinal symptoms and weight loss appear to be more common with leflunomide, and warrant careful monitoring in continuing trials. Although allergic reactions have been rare, 1 case of nonfatal anaphylaxis following discontinuation of treatment and rechallenge with study drug has been reported. To date, significant alopecia has been observed only at the 25-mg dose (n = 7, compared with 1 in each of the other dosage groups), which was reversed with discontinuation of treatment. The data from the combined safety database of 500 patients treated in the phase II studies do not differ from those on the 402 patients reported here. It must be recognized, however, that uncommon adverse events may yet be seen when a larger number of patients are treated in the phase III protocols.

In conclusion, leflunomide was effective in daily doses of 10 mg and 25 mg in patients with active RA, as shown by statistically significant improvement over placebo in primary and secondary outcome measures, as well as by responder analyses. Although improved efficacy was seen with the 25-mg dose, it was associated with a higher incidence of adverse events. These positive results warrant confirmation in larger randomized, placebo-controlled trials. Phase III studies using daily doses of 10 mg and 20 mg are currently under way in the US and Europe.

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