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The Efficacy and Safety of Leflunomide in Patients With Active Rheumatoid Arthritis

A Five-Year Followup Study

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Objective. **To investigate the efficacy and safety of leflunomide beyond 2 years in a multinational, open-label extension of 2 phase III double-blind studies.**

Methods. **Patients with rheumatoid arthritis (RA) who received leflunomide (100 mg/day for 3 days, 10 mg/day or 20 mg/day thereafter) in the 2 phase III studies and who completed 2 years of treatment were offered inclusion in the open-label extension phase and were maintained on the same dosage of leflunomide. The American College of Rheumatology revised criteria for 20% improvement (ACR20), ACR50, and ACR70 response rates, the Stanford Health Assessment Questionnaire (HAQ) scores, and C-reactive protein (CRP) levels were assessed. Safety measures included monitoring of adverse events and laboratory values.**

Results. **A total of 214 patients (mean age 57 years) were treated with leflunomide for >2 years; 74.8% of the patients were female. The mean disease duration was 4.1 years (range 0.1–26.6 years), and in 44% of patients, RA was first diagnosed within 2 years of entry into the phase III studies. The mean duration of leflunomide treatment was 4.6 years (range 2.8–5.8 years), and 32% of patients had received no previous treatment with disease-modifying antirheumatic drugs. ACR20, ACR50, and ACR70 response rates and HAQ scores at 1 year were maintained through year 4 or until the end point. No new types of adverse events were observed, and liver function was normal at baseline and at the end point in the majority of patients.**

Conclusion. **The improvements in both functional ability and physician-based efficacy measures seen with leflunomide after 1 year were maintained for up to 5 years (maximum treatment duration 5.8 years), demonstrating that the early efficacy of leflunomide in patients with RA is sustained long-term, and that the long-term safety profile of leflunomide is no different from that observed in phase III trials.**

In patients with rheumatoid arthritis (RA), early intervention with disease-modifying antirheumatic drugs (DMARDs) is required to minimize joint damage and retard disease progression (1). However, treatment with the currently available DMARDs is not continued long-term because of a lack of efficacy or related toxicity (2,3).

Leflunomide is a new class of DMARD and is converted on first-pass metabolism through the liver into its active metabolite A77 1726, which has antiinflammatory and immunomodulatory properties. The primary mode of action is thought to be selective inhibition of de novo pyrimidine synthesis by blocking the rate-limiting enzyme dihydroorotate dehydrogenase (4). Activated CD4+ T cells proliferate rapidly during the progression of RA, a process involving de novo pyrimidine synthesis (5). Leflunomide acts to inhibit T cell proliferation by preventing pyrimidine generation and subsequent DNA synthesis (6–8).

Several recent phase III studies demonstrated the

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efficacy and safety of leflunomide for up to 2 years in patients with active RA (9–15). Leflunomide was shown to be more effective than placebo and at least as effective as methotrexate and sulfasalazine in improving individual signs and symptoms of RA (9–12,15). In addition, the American College of Rheumatology 20% (ACR20) response rate (16) was achieved much sooner with leflunomide than with methotrexate or sulfasalazine (9,11). Leflunomide was also shown to be more effective than both methotrexate and sulfasalazine in improving functional activity over a 2-year period (12,13), as measured by the Stanford Health Assessment Questionnaire (HAQ) disability index (17). Furthermore, following 2 years of treatment, leflunomide was shown to be statistically equivalent to methotrexate (12) and numerically superior to sulfasalazine (14,15) in slowing disease progression, as assessed by radiographic analysis of joint damage in the hands and feet. Use of combination therapy with leflunomide and methotrexate has recently been shown to result in even greater responses to treatment, without an increased frequency of adverse events (18).

These shorter-term studies showed that leflunomide, at a dosage of 20 mg/day, is safe and generally well tolerated over a 2-year period (13,15). Adverse events were generally mild to moderate and were more common during the first 6 months, with the frequency decreasing over time. Further data are needed to establish the long-term efficacy of leflunomide and to confirm the absence of unexpected late or cumulative effects.

The aim of the present study was to provide leflunomide to patients with RA who had benefited from leflunomide treatment in 2 previous phase III clinical studies (9,11) and who wanted to continue receiving this treatment regimen until the drug became commercially available. This is the first report on the long-term efficacy and safety of leflunomide in a subset of patients with RA who received leflunomide therapy for up to 5 years.

PATIENTS AND METHODS

Patients. Men and women with RA who were treated with leflunomide (a 100-mg loading dose for 3 days followed by 10 mg/day or 20 mg/day thereafter) in 2 phase III studies and who completed 2 years of treatment were offered inclusion in this open-label, noncontrolled extension study. The 2 phase III studies began in 1996; this extension study began in 1998 and ended in February 2000, when the European Agency for the Evaluation of Medicinal Products and the Committee for Proprietary Medicinal Products recommended leflunomide for European licensing approval.

The first phase III study, MN301 (9), was a 6-month randomized, double-blind, placebo-controlled study of the efficacy and safety of leflunomide compared with sulfasalazine and placebo in 358 patients. Patients were then entered into a double-blind 6-month extension phase during which patients taking placebo were switched to sulfasalazine, and then into a double-blind extension phase for a further 12 months (10,14). Following unblinding, only patients who completed the full 24 months of leflunomide treatment were offered inclusion in the extension study reported here.

The second phase III study, MN302 (11), was a 12-month randomized, double-blind, parallel-group evaluation of the efficacy and safety of leflunomide compared with methotrexate in 999 patients. This double-blind study was then extended to allow all patients to complete 2 years of leflunomide treatment. At the end of this period, blinding was discontinued, and patients who had completed 2 years of leflunomide treatment were offered inclusion in the present extension study.

In the original phase III studies, inclusion criteria at the start of leflunomide treatment included a diagnosis of active RA based on the ACR (formerly, the American Rheumatism Association) criteria (19), and categorization into Steinbrocker functional class I, II, or III (20). Active RA was defined by the presence of at least 6 tender joints and at least 6 swollen joints, based on a 28-joint count; overall assessments by the physician and patient of RA disease activity as being fair, poor, or very poor; a C-reactive protein (CRP) level $\geq$20 mg/liter (normal $<$10 mg/liter); or an erythrocyte sedimentation rate (ESR) $\geq$28 mm/hour. Patients who had previously taken DMARDs were included only if these agents had been discontinued at least 28 days before enrollment in the initial phase III studies. Nonsteroidal antiinflammatory drugs (NSAIDs), including aspirin, and oral corticosteroids, were allowed if the patient had been receiving a stable dosage for at least 30 days before entry in the extension study. Changes in steroid dosages were permitted during the study period.

Women who were pregnant or breastfeeding were excluded, and women of childbearing age were required to use adequate contraception. Men wishing to father children during the course of the study and 6 months thereafter were also excluded.

This study was conducted following the principles of the Good Clinical Practice guidelines of the European Community and the Declaration of Helsinki. The clinical study protocol and study-related documents were approved by an independent ethics committee. Written informed consent from patients was required for study entry.

Study design. This open-label, noncontrolled, multinational study took place in 85 centers across Germany, Norway, Slovenia, South Africa, The Netherlands, Belgium, the UK, Denmark, Finland, France, Hungary, Ireland, and Sweden. Because the patient populations in the 2 phase III studies were similar, and because patients continued receiving the same dosages of leflunomide (10 mg/day or 20 mg/day), the efficacy and safety profiles were expected to be comparable. Therefore, one common protocol was used for all patients in the extension study. Patients continued to receive the same daily maintenance dosage as was used at the end of the original phase III studies. However, patients experiencing clinically significant adverse events or relevant abnormalities on laboratory tests at

any time had the option of decreasing the daily dosage of leflunomide from 20 mg to 10 mg. After dosage reduction, patients were maintained on a dosage of 10 mg/day for the duration of the study, and no further adjustment was allowed. Conversely, the daily dosage could be increased from 10 mg to 20 mg at the discretion of the investigator. A loading dose of 100 mg was given on the first 2 days before the dosage increase. No further dosage increase or reduction was allowed.

Efficacy measures. Patients who completed 2 years of treatment and entered the long-term extension study underwent clinical assessments at the extension baseline and at 6-month intervals thereafter. The end point of this study occurred when leflunomide became commercially available and thus was defined as the last observation made in leflunomide-treated patients. During this extension study, any patient who did not take the study medication for >30 days in a 12-month period was withdrawn.

Efficacy was assessed according to the ACR20 response rate, which indicates the proportion of patients showing a 20% improvement from baseline levels in the number of tender and swollen joints, as well as a 20% improvement in 3 of the following 5 criteria: investigator's global assessment, patient's global assessment, pain intensity assessment, physical disability, and CRP level or ESR. The ACR50 and ACR70 response rates were also evaluated.

Physical function was assessed using the HAQ, a disease-specific instrument that provides a self-assessment of functional ability in daily life for patients with RA. It consists of 20 questions relating to the following 8 categories of functional disability: dressing and grooming, rising, eating, walking, hygiene, reach, grip, and other activities. Patients' answers are graded on a 0–3 scale (0 = without difficulty, 3 = unable to do). A mean score for each category is calculated, and a decrease in the score corresponds to improvement. The HAQ score for each patient was calculated as the mean score for all 8 categories.

Safety measures. Treatment-emergent adverse events, adverse events that were possibly treatment-related, and serious adverse events were observed by the investigator or reported by the patient. Laboratory evaluations, including hematology, blood chemistry, and urinalysis, were performed every month.

Statistical analysis. Because this was an open-label study without a control group, the statistical analysis is descriptive only. Efficacy results are summarized according to the mean (±SD) changes over time. The numbers of patients fulfilling the ACR response criteria were calculated for yearly time intervals. The ACR response rates are expressed as a percentage of responders/patients analyzed, where "patients analyzed" are those who continued treatment and for whom an efficacy assessment was available at that time point. For the safety analysis, the incidence of adverse events and the laboratory findings are described.

RESULTS

Patient demographics. The study design is shown in Figure 1. The baseline demographics of patients from the 2 phase III studies were similar (Table 1), although

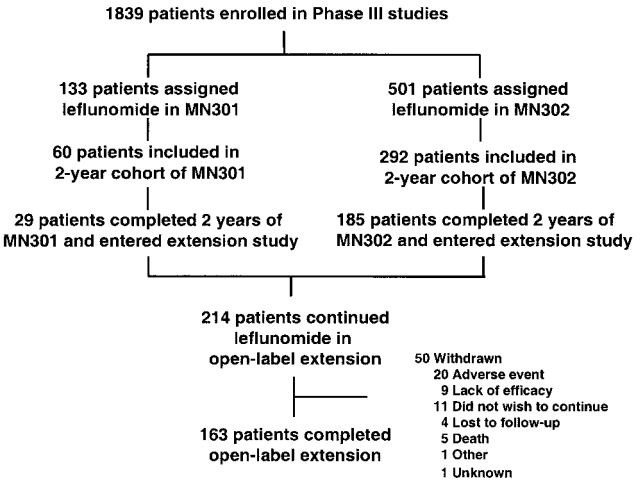

Figure 1. Study design and completion status.

the mean disease duration at the time of entry in MN301 (6.8 years) was greater than that at entry in MN302 (3.7 years), reflecting an increased proportion of patients with longstanding disease (>10 years) in the MN301 patient population. There were no clinically relevant differences between the 2 phase III patient populations with respect to the classification of the severity of RA.

Of the 214 patients (74.8% female) entered into this extension study, 29 were from MN301 and 185 were from MN302. The mean age at the time of enrollment was 57 years (range 29–79 years), and the mean disease duration 4.1 years (range 0.1–26.6 years), with 44% of the patients first being diagnosed <2 years before entry into the MN301 and MN302 trials. The mean duration of leflunomide treatment was 4.6 years (range 2.8–5.8 years); 182 patients continued leflunomide treatment for at least 4 years, with 58 of these patients completing at least 5 years of treatment. In 8 (4%) of the 214 patients, the dosage of leflunomide was decreased from 20 mg/day to 10 mg/day; in 2 of these patients (1%), the 20-mg daily dose was subsequently reinstated. In 2 patients (1%), the dosage of leflunomide was increased from 10 mg/day to 20 mg/day during the course of the study.

Clinical efficacy. Of the 214 patients entering the open-label extension study, 163 (76.2%) received treatment until the study end point. Reasons for withdrawal included adverse events (n = 20; 9.3%), lack of efficacy (n = 9; 4.2%), did not wish to continue (n = 11; 5.1%), lost to followup (n = 4; 1.9%), death (n = 5; 2.3%), unknown (n = 1; 0.5%), and other (n = 1; 0.5%).

The improvements in ACR20, ACR50, and ACR70 response rates observed at year 1 (72.9%, 48.3%, and 14.5%, respectively) were maintained

Table 1. Demographics of the patients enrolled in the extension study of leflunomide therapy*

Characteristic	MN301 (n = 29)	MN302 (n = 185)	Total (n = 214)
Sex, no. (%) women	24 (82.8)	136 (73.5)	160 (74.8)
Mean age, years (range)	55 (29–79)	57 (31–77)	57 (29–79)
No. (%) of patients ≥65 years of age	6 (20.7)	43 (23.2)	49 (22.9)
Mean duration of RA, years (range)	6.8 (0.1–26.6)	3.7 (0.3–11.8)	4.1 (0.1–26.6)
RA diagnosis at phase III study, % of patients			
≤2 years	38	45	44
>2 years but ≤10 years	31	52	49
>10 years	31	3	7
Steinbrocker class, % of patients			
Class I	17.2	23.4	22.5
Class II	41.4	49.5	48.4
Class III	41.4	27.2	29.1
No previous DMARD, % of patients	24	33	32
Mean treatment duration, years (range)	4.8 (3.7–5.8)	4.5 (2.8–5.8)	4.6 (2.8–5.8)

* Rheumatoid arthritis (RA) patients enrolled in the MN301 and MN302 phase III studies who completed 2 years of leflunomide treatment were offered inclusion in this extension study. DMARD = disease-modifying antirheumatic drug.

throughout the study until year 4 or the end point (69.2%, 43.0%, and 19.6%, respectively) (Figure 2). Analysis of the individual components of the ACR criteria, including swollen and tender joint counts, investigator's and patient's global assessments, and CRP, showed an improvement from baseline at year 1, which was maintained until the end point of the study (Figure 3). The duration of morning stiffness was reduced at year 1 (mean 24.7 minutes, median 10 minutes) compared with baseline (mean 145.2 minutes, median 120 minutes), and this improvement was maintained until year 4 or the end point (mean 46.4 minutes, median 15 minutes).

Improvements in the mean CRP level, ESR, and rheumatoid factor level compared with baseline (3.9 mg/dl, 50.3 mm/hour, and 295.1 units/ml, respectively) were observed at year 1 (1.3 mg/dl, 34.3 mm/hour, and 153.4 units/ml, respectively) and were maintained until year 4 or the end point (1.2 mg/dl and 1.4 mg/dl, 33.8 mm/hour and 33.4 mm/hour, and 176.1 units/ml and 176.5 units/ml, respectively).

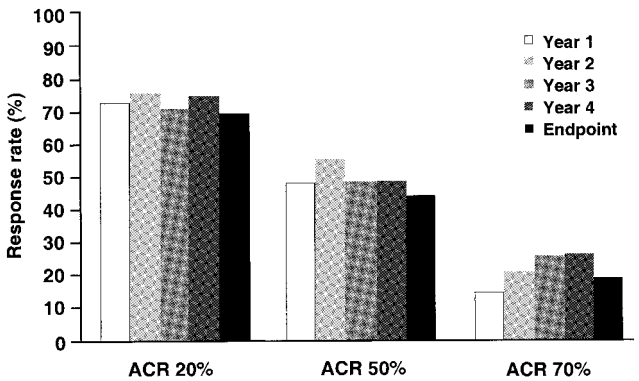

Figure 2. American College of Rheumatology 20% (ACR20), ACR50, and ACR70 response rates for leflunomide-treated patients from year 1 until year 4 or the end point.

An improvement in functional ability as measured by HAQ scores was seen at year 1 (mean change −0.6) and was maintained through year 4 or the end point (mean change −0.5 and −0.5, respectively) (Figure 3). A change of −0.22 in functional ability is considered to be clinically meaningful (17). Seventeen patients could not be assessed by HAQ due to the lack of availability of validated language adaptations of the HAQ in Hungary and Slovenia.

Safety. The overall mean (±SD) duration of exposure to leflunomide in this followup study was 1.33 ± 0.43 years (range 0.03–1.82 years) for all 214 patients. Of these 214 patients, 183 (85.5%) experienced 1 or more treatment-emergent primary adverse events. The most common primary adverse events were upper respiratory tract infection (23.4%), diarrhea (8.4%), back pain (6.5%), and pain in an extremity (6.5%). Individual treatment-emergent adverse events reported in at least 5% of patients are shown in Table 2.

Of the infections reported as being primary adverse events, the most common were upper respiratory tract infection, bronchitis, pharyngitis, and urinary tract infections. Six cases of pneumonia, 1 case of sepsis, and 3 cases of herpes zoster were reported. Of the pneumonia cases, only 2 were considered to be possibly treatment-related; 1 patient recovered, with no further recurrence, and the other patient was withdrawn from the

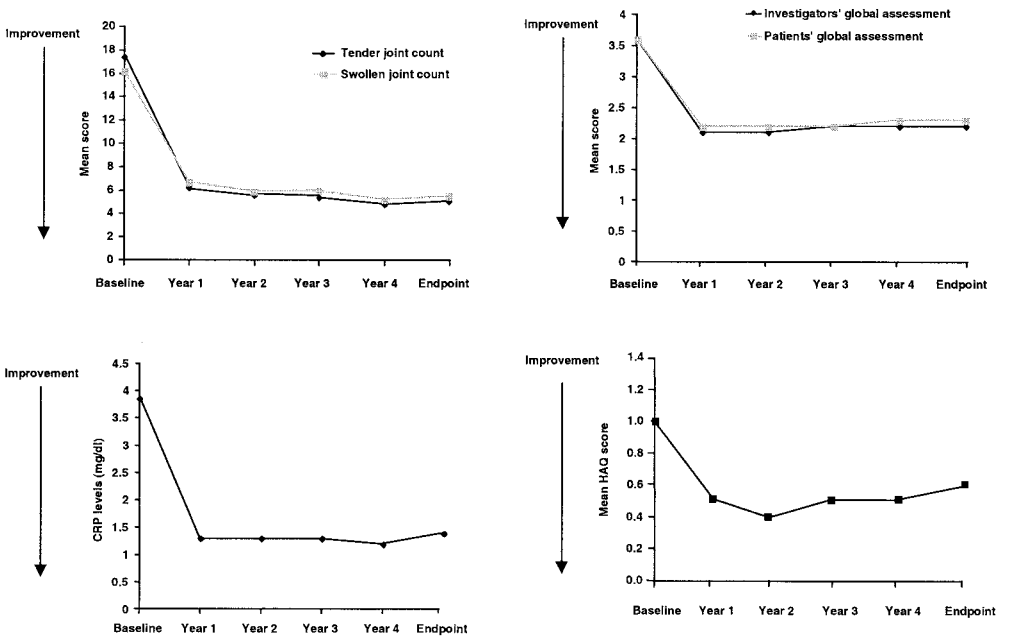

Figure 3. Mean scores for tender and swollen joint counts, investigators' and patients' global assessments, C-reactive protein (CRP) levels, and mean Health Assessment Questionnaire (HAQ) scores for leflunomide-treated patients.

study. Of the other 4 cases of pneumonia, recovery was reported in 3 patients, and 1 patient died. The case of sepsis was mild and was thought not to be related to treatment. Overall, 56 patients (26.2%) experienced primary adverse events that were considered possibly treatment-related, the most frequent of which were diarrhea (5.6%), hypertension (2.8%), abnormal findings on liver function tests (2.8%), rash (2.8%), and eczema (2.3%).

The types of primary adverse events observed in this long-term followup study were very similar to those reported after 2 years of treatment in the 2 phase III studies. The most common adverse events reported in at least 10% of patients at 2 years (upper respiratory tract infection, rash, diarrhea, and alopecia) occurred at lower frequencies during the extension study. In the extension

Table 2. Adverse events and treatment withdrawals*

All adverse events	183 (85.5)
Adverse events occurring in ≥5% of patients	
Upper respiratory tract infection	50 (23.4)
Diarrhea	18 (8.4)
Back pain	14 (6.5)
Pain in extremity	14 (6.5)
Bronchitis	13 (6.1)
Nausea	13 (6.1)
Accidental injury	12 (5.6)
Hypertension	11 (5.1)
Serious adverse events	75 (35)
Treatment-related adverse events	56 (26.2)
Withdrawals due to adverse events	20 (9)

* Values are the number (%) of patients.

Table 3. Adverse events in the present study compared with data from 2 phase III studies*

Adverse events reported in ≥10% of patients	MN301 (n = 60)	MN302 (n = 292)	Extension study (n = 214)
Upper respiratory tract infection	21 (35)	133 (46)	50 (23)
Rash	13 (22)	50 (17)	8 (4)
Diarrhea	10 (17)	80 (27)	18 (8)
Alopecia	8 (13)	57 (20)	4 (2)
Bronchitis	8 (13)	51 (18)	13 (6)
Dyspepsia	8 (13)	27 (9)	9 (4)
Urinary tract infection	8 (13)	23 (8)	7 (3)
Increased cough	8 (13)	23 (8)	6 (3)
Pruritus	8 (13)	23 (8)	5 (2)
Gastrointestinal pain	8 (13)	22 (8)	5 (2)
Nausea	7 (12)	35 (12)	13 (6)
Maculopapular rash	7 (12)	7 (2)	1 (<1)
Tenosynovitis	7 (12)	27 (9)	8 (4)
Hypertension	6 (10)	52 (18)	11 (5)
Back pain	6 (10)	44 (15)	14 (7)
Headache	6 (10)	39 (13)	3 (1)
Arthralgia	6 (10)	18 (6)	0 (0)

* Values are the number (%) of patients. Data for the MN301 and MN302 phase III trials reflect 2 years of study.

study, only 1 adverse event, upper respiratory tract infection (reported in 23% of patients), was reported in >10% of patients, and no new types of adverse events were observed (Table 3).

Most of the serious adverse events represented hospitalizations (surgery, rehabilitation, and intense physiotherapy) associated with the underlying disease or with surgery in the elderly (e.g., hernia, cataract). Seventy-five patients (35%) experienced serious treatment-emergent adverse events, the most common of which were joint disorder (4.7%), osteoarthritis (1.9%), and pneumonia (1.9%). The number of serious adverse events that were considered to be related to the study medication was low (11 events in 9 patients [4.2%]), with some patients experiencing >1 event.

The frequency of primary adverse events that led to discontinuation of the study medication was low, with 13 such events reported in 12 patients (5.6%). Five deaths occurred during this followup study and were attributable to acute myocardial infarction (MI), MI and subsequent pericardial tamponade, septic shock following surgery, cardiorespiratory insufficiency and suspected coronary embolus, and a car accident with a probable cardiac cause. Only 1 of these deaths (septic shock following surgery) was considered to be possibly treatment-related.

Safety data for laboratory variables. The mean (±SD) systolic and diastolic blood pressure values at baseline were, respectively, 134.7 ± 19.95 mm Hg and 80.5 ± 9.82 mm Hg. At the study end point, these values had increased slightly to 141.0 ± 19.29 mm Hg and 84.3 ± 10.25 mm Hg, respectively. The extension phase is the first time during which clinically relevant increases in blood pressure occurred (11 patients; 5.1%). Seven patients (3.3%) had changes in systolic blood pressure (<170 mm Hg at baseline and >170 mm Hg at any visit during the study), and 4 patients (1.9%) had changes in diastolic blood pressure (<90 mm Hg at baseline and >90 mm Hg at any visit during the study). In most cases, the clinically relevant values were observed only at isolated visits and normalized during ongoing leflunomide treatment. Blood pressure increases at consecutive visits were observed in 3 patients, none of whom had hypertension reported as an adverse event.

Safety data regarding changes in laboratory values were available for only 182 patients in this study because baseline laboratory values were not available for 32 patients. The majority of patients had normal liver enzyme levels at baseline and at the end point. In study MN301 or MN302, increases from normal at baseline to above the upper limit of normal at the end point of the extension period were seen for serum aspartate transaminase (AST) (12 patients; 6.6%), serum alanine transaminase (ALT) (18 patients; 9.9%), alkaline phosphatase (22 patients; 12.1%), and lactate dehydrogenase (15 patients; 8.2%) (Table 4). During the extension period, clinically noteworthy increases (at least 3-fold the upper limit of normal) in AST occurred in 4 patients, and in 1 of these patients, the ALT level was also at least 3 times the upper limit of normal. Although in 2 of these patients, no adverse event was reported in conjunction with these elevated levels, arrhythmia was reported in the third patient, and diarrhea and abnormal liver function was recorded in the fourth. This patient's leflunomide treatment was interrupted on 2 occasions, and was later discontinued because of surgery for carcinoma.

Table 4. Abnormal findings on liver function tests and discontinuation in 182 patients*

	Entire study period	Extension period only
Abnormal shift		
Serum alanine transaminase	12 (6.6)	–
Serum aspartate transaminase	18 (9.9)	–
Alkaline phosphatase	22 (12.1)	–
Lactate dehydrogenase	15 (8.2)	–
Serum alanine transaminase >3 times the upper limit of normal	–	1 (0.5)
Serum aspartate transaminase >3 times the upper limit of normal	–	4 (2.2)
Discontinuation due to liver function abnormalities	–	4 (2.2)

* Values are the no. (%) of patients.

Overall, abnormal findings on liver function tests were reported as a mild or moderate adverse event in 7 patients, including the patient described above. All but 1 of these events were considered by the investigator as being possibly related to the study drug. Four patients withdrew because of these events. Of the 3 patients continuing therapy, 1 recovered, and in the other 2, the abnormal findings on liver function tests did not resolve. However, no dosage adjustments were made in these patients.

Most patients had normal leukocyte counts at baseline and at the end point. High leukocyte counts at baseline were observed in 39 patients (21.4%), but these failed to normalize by the end point in only 11 patients (6.0%). Only 21 patients (11.5%) had a normal leukocyte count at baseline that had changed at the end point. In 11 patients (6.0%), the count changed from normal to high, and in 10 patients (5.5%), it changed from normal to low. In 3 of these 10 patients, leukopenia was reported

as a mild primary adverse event. Two of these events reversed during the study, and 2 were considered related to leflunomide. The majority of patients had normal platelet counts at both baseline and the end point. Seventy-three patients (40.1%) had a high platelet count at baseline, which normalized by the end point in 56 patients (30.8%). Only 1 patient had a low value at the end point.

DISCUSSION

This extension study was conducted to assess the long-term efficacy and safety of leflunomide in patients with RA and to allow patients participating in a clinical study to continue receiving treatment with leflunomide prior to its commercial availability. In this cohort of patients, clinical improvements in the signs and symptoms of RA that were achieved as early as 4 weeks after initiation of therapy were maintained for up to 5 years. Improvements in daily activities and physical function accompanied the clinical improvements. Leflunomide was well tolerated, and no unexpected adverse effects or adverse events different from those observed in the phase III studies emerged. In addition, the adverse events reported in the 2-year phase III studies occurred at lower frequencies during this followup study.

DMARDs have been used to treat RA for the past 20 years, and although they have been effective in relieving the symptoms of RA, a gradual loss of efficacy over time and related toxicities have created a need for the development of novel DMARDs. Leflunomide, which is the first new DMARD to be released in more than a decade, was shown in 3 phase III trials to be superior to placebo and at least equivalent to methotrexate or sulfasalazine in improving the signs and symptoms of RA (9–12,15).

This is the first study of a novel DMARD to report on the long-term efficacy and safety in patients with RA who received the study drug for up to 5 years. The improvements in individual primary efficacy variables and overall ACR response rates observed with leflunomide after 1 year were maintained for up to 5 years (maximum treatment duration 5.8 years), demonstrating that the early efficacy of leflunomide is sustained long-term in a subset of patients with RA. Improvements in functional ability in leflunomide-treated patients, as demonstrated by clinically meaningful improvements in the HAQ score (21), were maintained for the duration of the study.

The safety profile of leflunomide in this extension study is consistent with that reported in the previous phase III studies. The types of adverse events experienced here were similar to those previously reported, and no new or different types of adverse events emerged during continued long-term leflunomide treatment. Furthermore, most adverse events occurred early, such that the frequency of adverse events decreased as the use of leflunomide continued (9,11,13–15). In addition, the most common adverse events reported are consistent with the known side effects of leflunomide.

One concern about the safety of leflunomide that was recently raised is the potential for hepatotoxicity. In the present study, the majority of patients had normal liver enzyme levels at both baseline and the end point, demonstrating the absence of serious liver toxicity. A subset of patients experienced clinically relevant increases in liver enzymes, which was not unexpected based on the phase III safety profile. It is suggested that with routine monitoring of liver enzymes and appropriate dosage adjustments, the potential for hepatotoxicity with leflunomide therapy would be minimal.

Clinically relevant elevations in blood pressure were reported in 11 patients, but these cases were isolated, and blood pressure returned to normal levels in all but 3 of these patients. Increased hypertension with age could be responsible for any slight increases observed in this long-term study. Patients with RA generally have anemia, and worsening of anemia may reflect a flare of the chronic inflammatory disease. Testing of red blood cell variables at baseline and at the end point of this study revealed normal values in the majority of patients, reflecting effective control of RA. The majority of patients in this study had normal leukocyte and platelet counts at baseline and at the end point.

In summary, leflunomide is efficacious and well-tolerated over the long term. In the subset of patients with RA in this extension study, a sustained response was achieved for up to 5.8 years. Compared with data from the 2-year phase III studies, no new or different adverse events were observed. Furthermore, the frequency of adverse events in this followup study was lower than that observed during the first 2 years of treatment. It is important to note that this patient population was highly selective and, as such, may differ from the general population of patients with RA. Postmarketing observational cohort studies would better establish the efficacy and safety of leflunomide in a setting similar to clinical practice. However, the current demonstration of sustained efficacy and safety in this selected RA patient population and the reported rapid onset of action of leflunomide relative to other DMARDs indi-

cate that leflunomide has a valuable place in the treatment armamentarium for rheumatoid arthritis.

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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. Pincus T, Marcum SB, Callahan LF. Longterm drug therapy for rheumatoid arthritis in seven rheumatology private practices: II. Second line drugs and prednisone. J Rheumatol 1992;19:1885–94.
3. Wolfe F. Adverse drug reactions of DMARDs and DC-ARTs in rheumatoid arthritis. Clin Exp Rheumatol 1997;15 Suppl 17: S75–81.
4. Davis JP, Cain GA, Pitts WJ, Magolda RL, Copeland RA. The immunosuppressive metabolite of leflunomide is a potent inhibitor of human dihydroorotate dehydrogenase. Biochemistry 1996;35: 1270–3.
5. Fairbanks LD, Bofill M, Ruckemann K, Simmonds HA. Importance of ribonucleotide availability to proliferating T-lymphocytes from healthy humans: disproportionate expansion of pyrimidine pools and contrasting effects of de novo synthesis inhibitors. J Biol Chem 1995;270:29682–9.
6. Bartlett RR, Anagnostopulos H, Zielinski T, Mattar T, Schleyerbach R. Effects of leflunomide on the immune responses and models of inflammation. Springer Semin Immunopathol 1997;14: 381–94.
7. Fox RJ. Mechanism of action of leflunomide in rheumatoid arthritis. J Rheumatol 1998;25 Suppl 53:20–6.
8. Breedveld FC, Dayer JM. Leflunomide: mode of action in the treatment of rheumatoid arthritis. Ann Rheum Dis 2000;59:841–9.
9. Smolen JS, Kalden JR, Scott DL, Rozman B, Kvien TK, Larsen A, et al. Efficacy and safety of leflunomide compared to placebo and sulphasalazine in active rheumatoid arthritis: a double-blind, randomised, multicentre trial. Lancet 1999;353:259–66.
10. Strand V, Cohen S, Schiff M, Weaver A, Fleischmann R, Cannon G, et al. Treatment of active rheumatoid arthritis with leflunomide compared with placebo and methotrexate. Leflunomide Rheumatoid Arthritis Investigators Group. Arch Intern Med 1999:159: 2542–50.
11. Emery P, Breedveld FC, Lemmel EM, Kaltwasser JP, Dawes PT, Gomor B, et al. A comparison of the efficacy and safety of leflunomide and methotrexate for the treatment of rheumatoid arthritis. Rheumatology 2000;39:1–11.
12. Cohen S, Cannon GW, Schiff M, Weaver A, Fox R, Olson N, et al. Two-year, blinded, randomized, controlled trial of treatment of active rheumatoid arthritis with leflunomide compared with methotrexate. Arthritis Rheum 2001;44:1984–92.
13. Kalden JR, Scott DL, Smolen JS, Schattenkirchner M, Rozman B, Williams BD, et al. Improved functional ability in patients with rheumatoid arthritis: long-term treatment with leflunomide versus sulfasalazine. J Rheumatol 2001;28:1983–91.
14. Larsen A, Kvien TK, Schattenkirchner M, Rau R, Scott DL, Smolen JS, et al. Slowing of disease progression in rheumatoid arthritis patients during long-term treatment with leflunomide or sulfasalazine. Scand J Rheumatol 2001;30:135–42.
15. Scott DL, Smolen JS, Kalden JR, van de Putte LBA, Larsen A, Kvien TK, et al. Treatment of active rheumatoid arthritis with leflunomide: two year follow up of a double blind, placebo controlled trial versus sulfasalazine. Ann Rheum Dis 2001;60: 913–23.
16. Felson DT, Anderson JJ, Boers M, Bombardier C, Furst D, Goldsmith C, et al. American College of Rheumatology preliminary definition of improvement in rheumatoid arthritis. Arthritis Rheum 1995;38:727–35.
17. Fries JF, Spitz PW, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. Arthritis Rheum 1980;23:137–45.
18. Kremer JM, Genovese MC, Cannon GW, Caldwell RJ, Cush JJ, Furst DE, et al. Concomitant leflunomide therapy in patients with active rheumatoid arthritis despite stable doses of methotrexate. Ann Intern Med 2002;137:716–33.
19. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315–24.
20. Steinbrocker O, Traeger CH, Batterman RC. Therapeutic criteria in rheumatoid arthritis. JAMA 1949;140:659–62.
21. Wells GA, Tugwell P, Kraag GR, Baker PR, Groh J, Redelmeier DA. Minimum important difference between patients with rheumatoid arthritis: the patient's perspective. J Rheumatol 1993;20: 557–60.