Efficacy and Safety of Leflunomide and Predisposing Factors for Treatment Response in Patients with Active Rheumatoid Arthritis: RELIEF 6-Month Data

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ABSTRACT. ***Objective.*** The RELIEF investigation was a 48-week, multicenter, international study comprising 2 phases. Results from the first phase, a 24-week open-label cohort study that evaluated the safety and efficacy of leflunomide, as well as predisposing factors to treatment response, are reported here.

Methods. Patients received leflunomide 100 mg once daily for 3 days, followed by 20 mg once daily thereafter. All adverse events were documented. Efficacy variables were the European League Against Rheumatism (EULAR) response criteria using the Disease Activity Score (DAS 28) responder rate and the response rate according to American College of Rheumatology (ACR) criteria. At Week 24, baseline data were analyzed to determine predictive factors for treatment response.

Results. A total of 969 patients were entered in the trial. No adverse events that have not previously been seen with leflunomide were reported. Among 968 evaluable patients, 673 (69.6%) completed 24 weeks of treatment and were responders according to DAS 28 response rate, and 587 (60.6%) completed 24 weeks of treatment and were responders according to ACR 20%. Thus, there was a high correlation between the EULAR and ACR criteria in determining treatment response. In addition, 240 (24.8%) patients had a low DAS 28 (≤ 3.2) and 123 (12.7%) patients fulfilled the disease remission criteria (DAS 28 < 2.6) at the end of the study.

Conclusion. This study demonstrates that leflunomide is well tolerated, with a safety profile similar to that seen previously in Phase III studies, and confirms the efficacy of leflunomide across a range of patient categories. (J Rheumatol 2003;30:2572–9)

Key Indexing Terms:
RHEUMATOID ARTHRITIS LEFLUNOMIDE EFFICACY SAFETY CLINICAL TRIALS

Rheumatoid arthritis (RA) is an inflammatory disease that is characterized by joint inflammation and destruction, progressive disability, and premature death. Many patients with RA are unable to work after 10 years[1–3] and the disease is often associated with depression and other psychological effects[4,5]. RA therefore presents profound health and socioeconomic burdens[6,7]. As there is no cure for RA, the aim of current treatments is to control disease activity, alleviate symptoms, maintain physical function, optimize quality of life, slow the rate of joint damage, and, ideally, induce a complete remission[8].

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Disease modifying antirheumatic drugs (DMARD) have the potential to minimize or prevent joint damage, while preserving joint integrity and physical function. In the past, DMARD use was reserved for patients with severe disease. However, it is now recognized that irreversible joint damage and erosions occur soon after the onset of symptoms, often within the first 2 years[9], and early initiation of DMARD is recommended to control RA before joint damage occurs[8].

Leflunomide, an isoxazole derivative and inhibitor of *de novo* pyrimidine synthesis, represents a novel class of DMARD that is structurally unrelated to other antirheumatic drugs. Its primary mode of action is through the selective inhibition of dihydroorotate dehydrogenase, a key enzyme in *de novo* pyrimidine synthesis and subsequent inhibition of RNA and DNA synthesis[10]. Activated T lymphocytes, which are believed to play an important role in the pathogenesis of RA, predominantly synthesize pyrimidines via the *de novo* pathway[10,11].

The efficacy and safety of leflunomide have been reported in Phase III studies involving patients with active RA for up to 2 years[12–19]. In these studies, leflunomide was shown to be superior to placebo and at least as effective as sulfasalazine or methotrexate with folate in improving individual signs and symptoms of RA[12,13,15]. These responses

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were seen as early as 4 weeks and were maintained for up to 2 years[12–17]. Leflunomide also significantly improved patient functional ability and individual health related quality of life (HRQOL), assessed by the Health Assessment Questionnaire (HAQ)[20], compared with placebo and sulfasalazine[17]. More recently, an open-label extension study in patients who continued taking leflunomide treatment showed that these improvements are maintained in the long term, for up to 5 years in a subset of patients, with no different or unexpected adverse effects emerging compared with the initial Phase III studies[21].

A recent meta-analysis has shown the clinical benefit of initiating DMARD therapy early in patients with RA[22]. However, the question of which treatment approach should be used in patients who are not adequately responding to their first DMARD remains to be established. Studies have indicated that addition of a second disease modifying agent to patients who are responding poorly to their current DMARD treatment results in improved responses compared with patients continuing to take only the ineffective DMARD[23–26]. However, no studies have been published comparing the effects of adding a new DMARD with discontinuing an ineffective DMARD and switching to a new one.

RELIEF (Rheumatoid arthritis Evaluation of Leflunomide further Insights into its EFficacy) is a 48-week, multicenter, international study that consists of 2 phases. The first phase was a 24-week open-label cohort, which aimed to evaluate both the safety and efficacy of leflunomide in a setting close to daily clinical practice. The large database of patients in this study also gives the opportunity to evaluate potential predisposing factors to treatment response. Patients who were good or moderate responders to leflunomide treatment (according to the Disease Activity Score, DAS, 28 response rate) continued receiving leflunomide for a further 24 weeks (second open phase). The aim of the second, double-blind phase of RELIEF was to evaluate the efficacy of adding sulfasalazine to leflunomide compared with switching to sulfasalazine in patients who were not adequately responding to leflunomide after 24 weeks' treatment.

This is the first study of primary therapy with leflunomide and it illustrates the safety and efficacy that may be achieved in daily clinical practice. The results from the first 24-week, open-label phase of the RELIEF study are presented here.

MATERIALS AND METHODS

Patients. The study population consisted of men and women aged 18–75 years with active RA as defined by a DAS 28 > 3.2 and meeting the criteria according to American Rheumatology Association (ARA) functional classification of I, II, or III (i.e., patients of functional class IV were not eligible for inclusion). Women of childbearing potential and men were required to use adequate contraception throughout the study. Women who were pregnant or breastfeeding were excluded.

The protocol required therapy with other DMARD to be discontinued at least 4 weeks before enrollment. Stable doses of nonsteroidal antiinflammatory drugs (NSAID) or oral corticosteroids (maximum daily dose 10 mg prednisone or steroid equivalent) were permitted as concomitant medications. Intraarticular injections of corticosteroids (maximum dose 60 mg prednisone or equivalent) were to be avoided if possible, and were not permitted within the 4 weeks preceding the 24-week assessment. Analgesics were allowed, but were not to be taken in the 6 hours before joint examination.

Study design. This was a 24-week, multicenter, international, open-label cohort study, and was the first phase of the RELIEF 48-week study (Figure 1). RELIEF was carried out in 162 centers in 14 countries across Europe, South America, Australia, and New Zealand. After a 1 to 2-week screening period, patients received a leflunomide loading dose of 100 mg once daily for the first 3 days, followed by a maintenance dose of 20 mg once daily for the remainder of the study (Figure 1).

Safety. Safety was monitored by physical examination, vital signs, electrocardiograms, and chest radiograph data. All adverse events were documented. Measurement of blood pressure was made at 4-week intervals in the supine position after a 5-minute rest, although there was no standardized procedure for monitoring hypertension. Hypertension was defined as diastolic blood pressure > 90 mm Hg or systolic blood pressure > 160 mm Hg on at least 2 consecutive visits during treatment period. Standard laboratory analyses were carried out at 4-week intervals. Patients with liver function test abnormalities, serum alanine aminotransferase (ALT) levels ≥ 5 × upper limit of normal (ULN) were discontinued from treatment. Patients with liver function test abnormalities of 3 × ULN ≤ ALT < 5 × ULN were continued on treatment, and the measurements of these enzymes were repeated within one week; if ALT persisted between 3 and 5 ULN then patients stopped the treatment. No dose adjustments were permitted.

Efficacy. The primary efficacy variable analyzed at 4-week intervals and at endpoint (Week 24) was change in disease activity as measured by European League Against Rheumatism (EULAR) response criteria using the DAS 28 score[27]. The DAS 28 score was calculated using the formula: DAS 28 = 0.56 √TJC + 0.28 √SJC + 0.70ln ESR + 0.014 GH score [where TJC is tender joint count (out of 28 assessed joints), SJC is swollen joint count (out of 28 assessed joints), ESR is erythrocyte sedimentation rate, and GH score is general health score as assessed by the patient on a 100 mm visual analog scale]. Remission according to EULAR criteria was defined as a DAS 28 score < 2.6. A good response was defined as a significant change (> 1.2) and low disease activity (DAS 28 ≤ 3.2). In addition, a moderate response was defined as a significant change (> 1.2) and moderate or high disease activity (DAS 28 > 3.2), or a change ≤ 1.2 and > 0.6, and low or moderate disease activity (DAS 28 ≤ 5.1). The DAS 28 response rate is the sum of the good and moderate responders.

The secondary efficacy variables were response rate according to ACR 20%, ACR 50%, and ACR 70% criteria[28] at 4-week intervals and at endpoint. The ACR 20% responder rate indicates the proportion of patients showing a 20% improvement from baseline levels in tender and swollen joint counts, and a 20% improvement in 3 of the following 5 criteria: investigator's global assessment; patient's global assessment; pain intensity assessment; functional disability index (using the HAQ); and C-reactive protein (CRP) or ESR. ACR 50 and ACR 70 response rates were similarly defined, taking into account 50% and 70% improvements, respectively.

Predictive factors for treatment response. At Week 24, baseline data from patients who were classified as responders were compared with data from nonresponders, and were analyzed to evaluate potential predictive factors for treatment response. Baseline data included age, sex, RA duration, disease activity according to EULAR criteria using the DAS 28 score, ARA functional class, previous treatment with at least one DMARD, concomitant treatment with corticosteroids, TJC, SJC, ESR, and CRP.

Statistical analysis. Before the study it was calculated that 795 patients would need to be enrolled to show significance in the second phase of the study. This was based on an anticipated nonresponder rate of 50% and a

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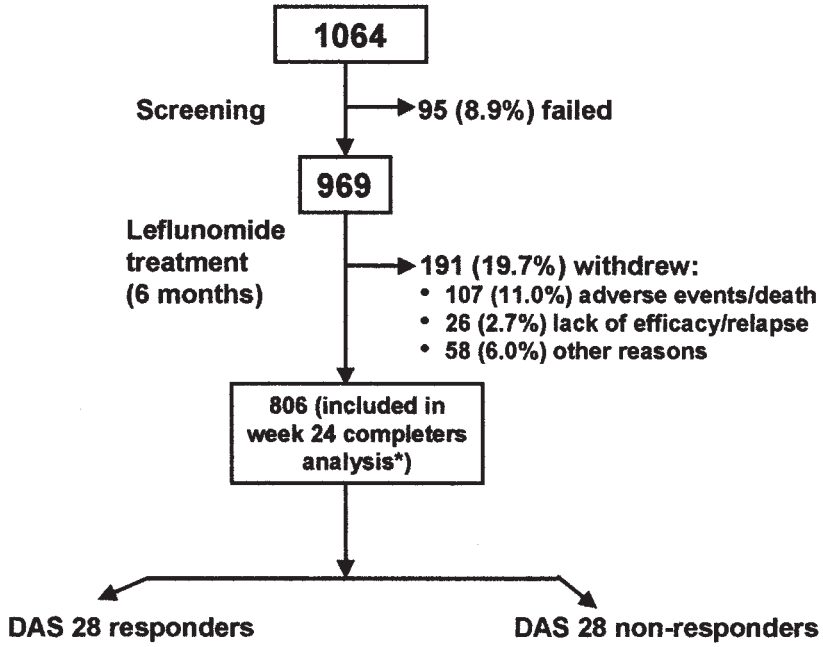

Figure 1. RELIEF study design. *Included patients who completed 24 weeks of therapy and withdrawals who completed 160 days of therapy and who had an evaluation at every time point.

25% withdrawal rate in the first open-label phase, such that 292 evaluable patients would need to enter the second, double-blind phase of the study to enable a difference of 15% (50% response rate in the sulfasalazine plus leflunomide group and 35% response rate in the sulfasalazine-alone group) to be detected at the 5% significance level.

Descriptive statistics were used to describe demographics and baseline characteristics. Safety and efficacy measures were performed on the intent-to-treat (ITT) population (all patients treated).

At each visit during the study (from Week 1 to Week 24) a patient was considered a responder if he/she fulfilled the DAS 28 responder criteria, but also only if this response was sustained during the subsequent visits of the study up to 24 weeks. Moreover, all patients who had to discontinue, whatever the reason, were considered nonresponders.

For the efficacy evaluation, the percentage of patients who improved (responded) according to the DAS 28 criteria (good and moderate) was considered as the main analysis.

A multiple logistic regression analysis was used to identify predictive factors for treatment response. The response variable was DAS 28 responder rate (good and moderate responders) in patients who completed 24 weeks of treatment. The expected treatment response was 50–60% based on previous studies[12–17], with around 60% of patients still remaining in the study at the end of 24 weeks. A stepwise procedure was used to select variables for the multiple logistic regression analysis. The significance level for entering the model was 5%.

RESULTS

Patients and study course. The RELIEF 24-week open-label cohort study screened 1064 patients; a total of 969 patients were included and 806 patients received leflunomide for 24 weeks (Figure 1). One patient was excluded from the ITT analysis as they withdrew from the study after first intake of study medication. Baseline demographics for the ITT population are shown in Table 1.

Previous treatment with at least one DMARD was reported for 72.1% of patients, with the mean number of previous DMARD being 1.8. Methotrexate was the most common previous DMARD and was taken by 75.0% of patients, with 31.3% discontinuing methotrexate therapy due to adverse events. For each of the other DMARD, lack of efficacy was the most frequent reason given for discontinuation.

Table 1. Baseline patient characteristics (n = 969).

Mean age, yrs (range)	55 (19–75)
Female, n (%)	722 (74.5)
Disease duration	
Mean, yrs (range)	7.3 (0–46)
Diagnosed > 2 yrs, n (%)	595 (61.4)
Disease activity	
Mean DAS 28 score (range)	6.3 (3.3–8.9)
High disease activity (DAS 28 > 5.1), n (%)	836 (86.5)
ARA functional class, n (%)	
Class I	119 (12.3)
Class II, III	850 (87.7)
Mean duration of morning stiffness, h	1.8
Rheumatoid factor positive, %	82.7
Pharmacologic therapy	
Previous DMARD therapy, n (%)	699 (72.1)
Mean number of previous DMARD (range)	1.8 (0–10)

There was a high maintenance rate in this study, with 80.3% of patients still receiving leflunomide treatment at 24 weeks. Of the 191 (19.7%) patients who withdrew from the study, 107 (11.0%) withdrew due to new adverse events or worsening of an existing adverse event, 26 (2.7%) due to lack of efficacy, and 58 (6.0%) due to other reasons (i.e., poor compliance, patient did not wish to continue, lost to followup, or administrative reasons).

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Safety. Adverse events were reported in 78.6% of patients of the ITT population, and 56.1% of patients had adverse events that were considered to be possibly treatment related. The most frequent possibly treatment related adverse events were diarrhea (14.6%), hair loss (13.8%), headache (6.1%), nausea (5.8%), hypertension (5.4%), and rash (4.5%) (Table 2). Adverse events leading to treatment discontinuation were reported in 116 (12%) patients and of these, 95 (9.8%) were considered to be possibly related to study medication, as listed in Table 2.

The overall frequency of possibly related serious adverse events was 11.4%, with no event being reported more frequently than another. There were 2 deaths reported during the study: one was a result of left ventricular failure and hypertensive ischemic heart failure, and the other from an acute myocardial infarction. Both deaths were considered unrelated to leflunomide treatment.

Hypertension was reported by the investigator in 76 (7.5%) patients at Week 24 and considered possibly treatment related in 52 (5.4%) patients. In 2 cases, hypertension was reported as a serious adverse event. Of the 721 patients who either had no history of hypertension or no hypertension at screening and baseline, 53 (7.4%) had new-onset hypertension during the study. Of these patients, one (0.1%) discontinued treatment due to hypertension and only 12 (1.7%) were given antihypertensive medication. In contrast, of the 248 patients who had a history of hypertension or hypertension at screening and baseline, 83 (33.5%) had hypertension during the study. Of these patients, 7 (2.8%) discontinued treatment due to hypertension, 11 (4.5%) were given antihypertensive medication, and 34 (13.7%) had their antihypertensive treatment modified.

Table 2. Adverse events possibly treatment related and those leading to treatment discontinuation (n = 969).

Adverse event	Possibly Treatment Related, %	Led to Treatment Discontinuation, %
Diarrhea	14.6	1.3
Hair loss	13.8	0.7
Headache	6.1	0.6
Nausea	5.8	0.6
Hypertention	5.4	0.8
Rash	4.5	0.8
Abdominal pain	3.5	0.9
Liver function test abnormal (increased hepatic enzymes)	2.9	0.7
White blood cell abnormalities	2.6	0.3
Leukopenia	2.1	0.6
ALT increased	1.6	0.4

Table 3. Response at endpoint according to EULAR criteria using DAS 28 score among the 24 completers.

	n (%*)	95 % CI
Das 28 responders	673 (69.6)	66.6–72.4
Low disease activity	240 (24.8)	22.1–27.5
Remission	123 (12.7)	10.6–14.8

* Response rates are given as a percentage of the ITT patient population (n = 968).

The proportion of patients who had liver enzyme elevations of > 1, > 2 and > 3 × ULN were 31.9%, 6.7%, and 2.8%, respectively, for serum ALT, and 20.0%, 2.6%, and 0.9%, respectively, for serum aspartate aminotransferase (AST). Most liver enzyme elevations were mild to moderate (i.e., > 1 and > 2 × ULN) and these usually resolved during continued treatment. Of the 27 (2.8%) patients with ALT elevation > 3 × ULN, 9 patients already had an ALT elevation at baseline of between 1 and 2 × ULN. Thirteen of the 27 patients continued leflunomide and 14 interrupted it. Among the 14 patients who interrupted treatment due to ALT elevations, 7 had normalized values at last observation, 6 improved to < 2 × ULN, and one patient showed an improvement but remained between 2 and 3 × ULN; an ALT elevation was detected in this patient at study entry. Among the 13 patients who continued treatment, ALT levels normalized during the 24-week period in 7 patients and improved to between 1 and 2 × ULN in 2 other patients. For the 4 other patients, the peak of ALT level occurred at the end of the 24-week period and subsequent biological evaluations after 24 weeks showed a decrease in ALT levels in all of these patients; ALT levels remained between 1 and 2 × ULN in 3 patients and between 2 and 3 × ULN in one patient at the last followup visit. ALT abnormalities were noted before treatment initiation in 2 of these 4 patients.

Hepatic adverse events were suspected and reported by the investigator during the 24-week treatment period in 2 patients (suspected hepatitis and liver fatty deposit), but neither was confirmed in the followup.

Leukopenia (white blood cells < 3000/mm^3) and white blood cell abnormalities (neutropenia, low neutrophil count, decrease of neutrophils, and lymphopenia) were each reported in 20 (2.1%) and 25 (2.6%) patients during the study. These were all considered possibly treatment related, and led to treatment discontinuation in 6 (0.6%) and 3 (0.3%) patients, respectively. The main laboratory measure requiring monitoring was neutrophil count, which was < 1500 cells/mm^3 in 25 patients and < 1000 cells/mm^3 in one patient and led to treatment interruption in 5 patients. All of these 25 patients improved with continued treatment or following treatment interruption. At the last observation, a count of < 2000 cells/mm^3 was found in 4 of the 25 patients (range 1390–1990 cells/mm^3). There were no major skin or hematology adverse events and no case of agranulocytosis or pancytopenia was reported.

Efficacy. At study endpoint, 673 (69.6%) patients completed 24 weeks of treatment and were DAS 28 responders — 234 (24.2%) being good responders and 439 (45.4%) moderate responders (Figure 2). During the study, there was a

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progressive increase in the proportion of patients who had a sustained DAS 28 response; that is, they had a response according to EULAR criteria that was maintained at study endpoint (Figure 3). At Week 4, 286 (29.5%) patients were responders and had a sustained response at Week 24. At Week 24, 673 (69.6%) patients were responders according to the EULAR criteria, indicating that an additional 40% of patients became "sustained" responders after 4 weeks.

At study endpoint, 24.8% of patients had low disease activity and 12.7% achieved disease remission (Table 3). The mean DAS 28 score also improved progressively, from 6.3 ± 1.0 at baseline to 4.1 ± 1.4 at endpoint, representing a change of –2.2. Significant improvements in the individual efficacy measures, including pain intensity, SJC, TJC, and CRP, were also seen at study endpoint compared with baseline ($p < 0.001$; Figure 4). Patients' and physicians' overall assessment of disease activity were also improved from baseline.

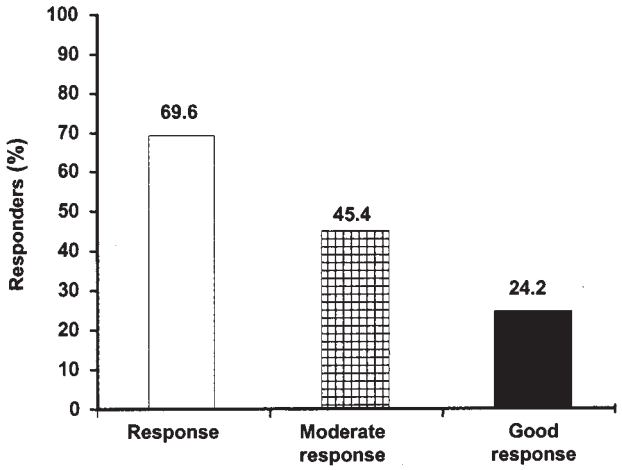

Figure 2. The percentage of responders at study endpoint according to the DAS 28 criteria.

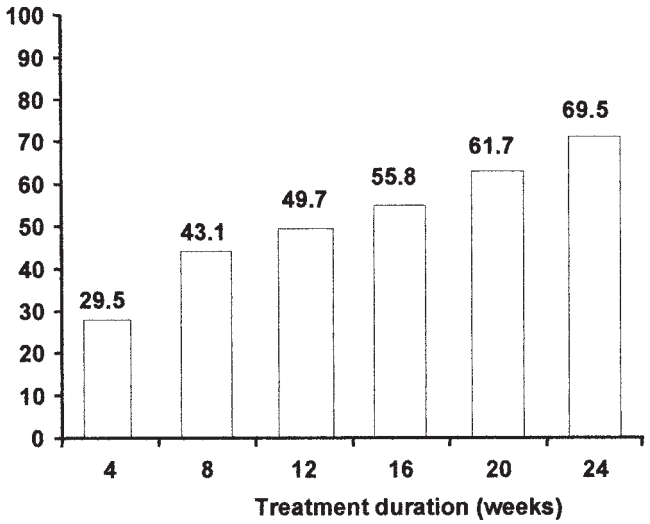

Figure 3. The sustained responder rate (response that is maintained to Week 24) according to the DAS 28 response criteria.

The response rates according to ACR criteria are shown in Figure 5; at study endpoint 60.6%, 33.5%, and 9.6% of patients who completed 24 weeks of treatment achieved ACR 20%, ACR 50%, and ACR 70% response, respectively.

Both DAS 28 and ACR 20% response rates emphasize the early onset of action of leflunomide, with responses being seen as early as 4 weeks. In addition, these efficacy variables reach a plateau at 20–24 weeks, suggesting that this is the optimum time for treatment response.

Overall, 570 (58.8%) patients were defined as responders according to both DAS 28 and ACR 20% response rates, and 278 (28.7%) patients were nonresponders according to either criterion. There was a high correlation between DAS 28 and ACR responder rates, with small discrepancies (1.8% of patients were responders according to ACR 20%, but nonresponders according to DAS 28 criteria, and 10.6% of patients were responders according to DAS 28 but not according to ACR 20%).

Predisposing factors for treatment response. Baseline data from the 69.6% of patients classified as leflunomide responders according to DAS 28 criteria were compared with data from nonresponders (30.5%) and analyzed to determine potential predisposing factors for treatment response.

Neither age (82.8% of patients < 65 years were responders vs 86.0% of patients ≥ 65 years) nor sex (79.7% of male patients were responders vs 84.8% of female patients) were found to affect treatment response. Marginally more patients with RA duration > 2 years (85.6%) responded to leflunomide compared with patients with RA disease duration ≤ 2 years (80.0%; $p = 0.016$, 95% CI for odds ratio 1.1–2.3). In addition, a larger number of patients with ARA class I (90.0%) compared with ARA class II or III (82.6%) responded to treatment ($p = 0.032$, 95% CI for OR 0.2–0.9). However, there were no differences between those patients with a moderate disease activity compared with high disease activity (82.1% 3.2 < DAS 28 ≤ 5.1 vs 83.7% DAS 28 > 5.1). In addition, previous corticosteroid use (81.0% no vs 85.7% yes) did not affect the number of patients who responded to leflunomide. Further, previous treatment with DMARD did not have an effect (84.7% yes vs 80.4% no).

Characteristics of RA severity — TJC, SJC, ESR, and CRP — were also examined. A similar number of patients with < 6 joint counts and ≥ 6 joint counts responded to treatment (81.0% < 6 TJC vs 83.6% ≥ 6 TJC; 79.3% < 6 SJC vs 84.0% ≥ 6 SJC). Patients with an ESR value < 28 mm/h (83.2%) responded to treatment, as did patients with ESR value ≥ 28 mm/h (83.7%). Further, CRP concentrations did not influence patients' response to leflunomide (84.5% < 20 mg/l CRP vs 82.4% ≥ 20 mg/l CRP).

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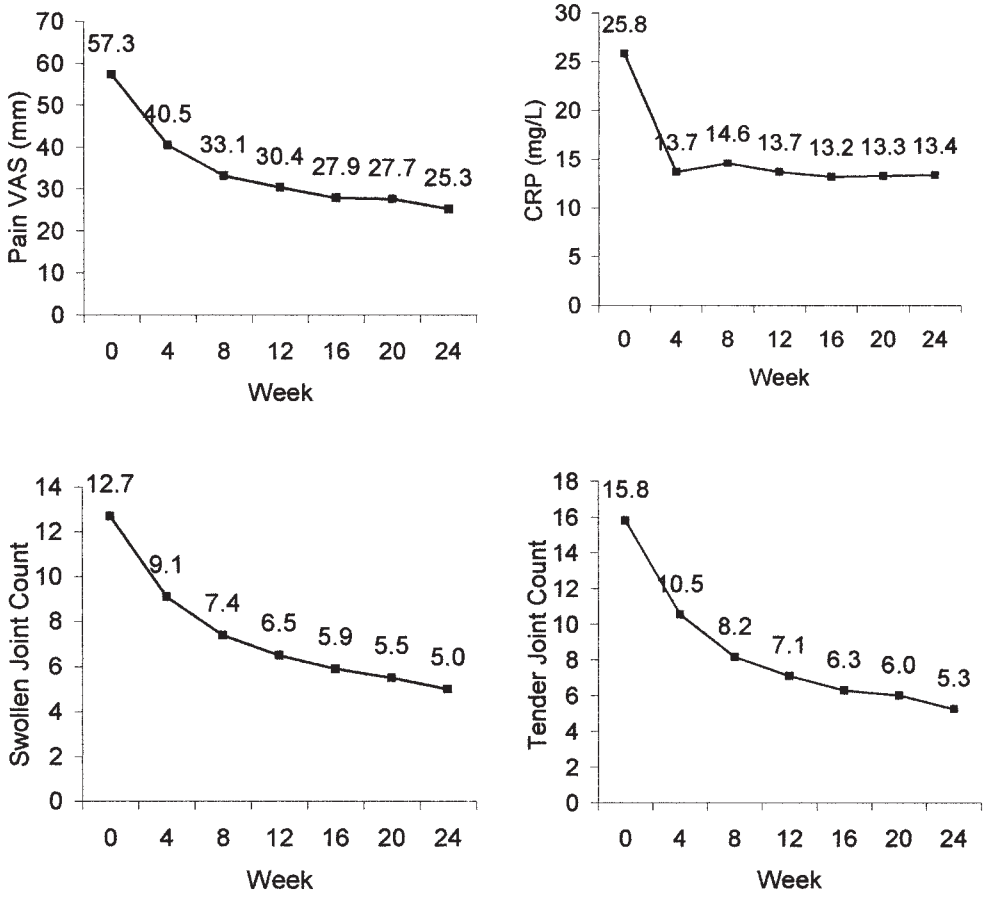

Figure 4. Individual measures of DAS 28 response rate including swollen and tender joint count, pain, and CRP concentrations. VAS: visual analog score; CRP: C-reactive protein.

DISCUSSION

The results from this RELIEF 6-month cohort study confirm the acceptable safety profile and clinical efficacy of leflunomide in patients with active RA. These results suggest that leflunomide is efficacious across the broad range of patient characteristics as there were no clinically significant differences in predisposing factors to treatment response.

Leflunomide was well tolerated with no different or unexpected adverse events that have not previously been reported in Phase III studies of up to 2 years[16–19]. Diarrhea (14.6%), hair loss (13.8 %), and headache (6.1%) were the most frequently reported adverse events that were possibly related to study medication. New-onset hypertension was reported in 7.4% of patients who had either no history of hypertension or no hypertension at screening and baseline, but only 0.1% of patients discontinued study treatment due to hypertension. Further, only 1.7% of patients initiated antihypertensive therapy, confirming that hypertension was mainly mild. In patients with hypertension at baseline or history of hypertension at baseline, 83 (33.5%) had hypertension during the study, with 7 (2.8%) patients discontinuing study treatment due to hypertension. In addition, 4.5% of patients initiated antihypertensive treatment.

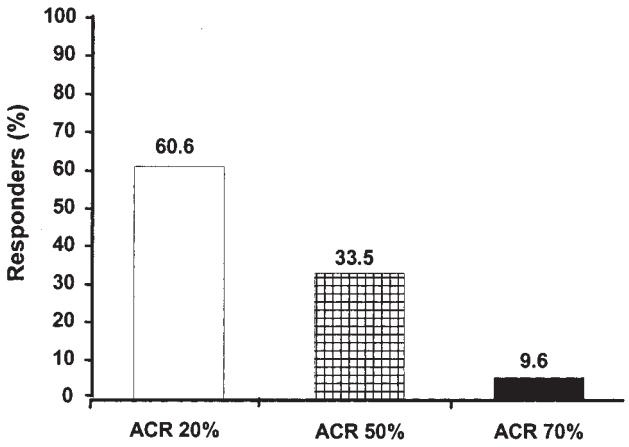

Figure 5. The percentage of responders at study endpoint according to ACR 20%, ACR 50%, and ACR 70% response rates.

The proportion of patients who had liver enzyme elevations > 1, > 2, and > 3 × ULN were 31.9%, 6.7%, and 2.8%, respectively, for serum ALT; and 20.0%, 2.6%, and 0.9%, respectively, for serum AST. These elevations were asymptomatic and reversible with dose reduction or discontinua-

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tion for moderate or marked elevations and often without dose change for milder elevations. Importantly, there was no reported case of jaundice and no liver biopsies were performed.

There was a high maintenance rate in this study, with 80.3% still receiving leflunomide treatment at 24 weeks. The reasons for withdrawal were due to adverse events in 11% of patients, lack of efficacy in 2.7%, and other reasons (i.e., patient did not wish to continue, lost to followup, or administrative reasons) in 6.0% of patients.

Leflunomide treatment was associated with high response rates of 69.6% according to EULAR criteria using the DAS 28 score, and 60.6%, 33.5%, and 9.6% according to ACR 20%, ACR 50%, and ACR 70%, respectively. Further, the response rate reported in this study was higher than previously reported for leflunomide in randomized trials[12,13,16–19] and so was higher than the expected response. This may indicate what may be achieved in daily clinical practice, as the open-label study design and limited inclusion criteria mean that patients can be considered to be treated in a manner closer to clinical practice than might occur during blinded therapy. The major difference between this study design and clinical practice was the need for patients to have withdrawn from preexisting treatments 4 weeks before start of leflunomide.

The efficacy endpoint in this study, response according to the EULAR criteria using the DAS 28 score, classifies patients into groups according to whether they experience a good or moderate or no response to treatment[28]. In addition, the DAS score provides an indication of absolute disease activity. In comparison, the ACR criteria define response in terms of improvement, but do not define absolute disease activity. However, the 2 response rate criteria have been shown to have similar validity[29,30]. The strong correlation between DAS 28 and ACR 20% in this study further confirms the high leflunomide response rate seen with DAS 28.

These results also show that the response to leflunomide is rapid: clinical response determined by the EULAR criteria using the DAS 28 score was observed as early as Week 4 in 29.5% of patients. This response was maintained until Week 24, and an additional 40% of patients were responders by endpoint at 24 weeks.

Our study aimed to examine potential predictive factors for treatment response by evaluating baseline characteristics in patients who responded to leflunomide treatment compared with nonresponders. The analysis did identify 2 potential predictive factors: ARA functional class I and disease duration. Although there was a statistically significant difference for these predictive factors, the clinical relevance of this finding is unclear. In addition, the 2 potential predictive factors are contradictory, with ACR functional class I, indicating earlier disease state, yet longer disease duration, indicating a more progressive disease state as potentially predictive. Age, sex, disease activity, previous DMARD use, and RA severity did not appear to influence treatment response. These findings confirm the efficacy of leflunomide across a broad range of patient categories. Further evaluation may elucidate the clinical relevance of potential predisposing factors for treatment response.

This first open-label phase of the RELIEF study confirms the acceptable and clinically relevant safety and efficacy profile of leflunomide across a range of patient types for RA. Further studies are necessary to evaluate the longterm effect, over several years, of leflunomide therapy.

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