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Two-Year, Blinded, Randomized, Controlled Trial of Treatment of Active Rheumatoid Arthritis With Leflunomide Compared With Methotrexate

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Objective. **Three 6–12-month, double-blind, randomized, controlled trials have shown leflunomide (LEF; 20 mg/day, loading dose 100 mg × 3 days) to be effective and safe for the treatment of rheumatoid arthritis (RA). This analysis of the North American trial assessed whether the clinical benefit evident at month 12 was sustained over 24 months of treatment with LEF as compared with the efficacy and safety of methotrexate (MTX), an equivalent disease-modifying antirheumatic drug, at 24 months.**

Methods. **The year-2 cohort, comprising patients continuing into the second year of treatment with ≥1 dose of study medication and ≥1 followup visit after week 52, consisted of 235 patients (LEF n = 98; placebo n = 36; MTX n = 101). The mean (±SD) maintenance dose of LEF was 19.6 ± 1.99 mg/day in year 2 and that of MTX was 12.6 ± 4.69 mg/week. Statistical analyses used an intent-to-treat (ITT) approach. Statistical comparisons of the active treatments only were prospectively defined in the protocol.**

Results. **In total, 85% and 79% of LEF and MTX patients, respectively, who entered year 2 completed 24 months of treatment. From month 12 to month 24, the American College of Rheumatology improvement response rates of ≥20% (LEF 79% versus MTX 67%; $P = 0.049$), ≥50% (LEF 56% versus MTX 43%; $P = 0.053$), and ≥70% (LEF 26% versus MTX 20%; $P = 0.361$) were sustained in both of the active treatment groups. The mean change in total Sharp radiologic damage scores at year 2 compared with year 1 and baseline (LEF 1.6 versus MTX 1.2) showed statistically equivalent sustained retardation of radiographic progression in the active treatment groups. Maximal improvements evident at 6 months in the Health Assessment Questionnaire (HAQ) disability index (HAQ DI) and the physical component score of the Medical Outcomes Survey 36-item short form were sustained over 12 months and 24 months; improvement in the HAQ DI with LEF (−0.60) was statistically significantly superior to that with MTX (−0.37) at 24 months ($P = 0.005$). Over 24 months in the ITT cohort, serious treatment-related adverse events were reported in 1.6% of the LEF-treated patients and 3.7% of the MTX-treated patients. Frequently reported adverse events included upper respiratory tract infections, diarrhea, nausea and vomiting, rash, reversible alopecia, and transient liver enzyme elevations.**

Conclusion. **The safety and efficacy of LEF and MTX were maintained over the second year of this 2-year trial. Both active treatments retarded radiographic progression over 24 months. LEF was statistically significantly superior to MTX in improving physical function as measured by the HAQ DI over 24**

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months of treatment. Results indicate that LEF is a safe and effective initial treatment for active RA, with clinical benefit sustained over 2 years of treatment without evidence of new or increased toxicity.

Leflunomide (LEF), a pyrimidine synthesis inhibitor (Arava; Aventis Pharmaceuticals, Bridgewater, NJ), is a novel immunomodulatory agent that was first shown to be effective in treating active rheumatoid arthritis (RA) in a placebo-controlled phase II study of 402 patients with active disease (1). Three multinational, randomized, controlled phase III trials demonstrated that LEF is a safe and effective disease-modifying antirheumatic drug (DMARD), equivalent to methotrexate (MTX) and sulfasalazine, for treating the signs and symptoms of RA and retarding disease progression as measured by radiography (2–5).

This report presents the results of the second year of therapy in the 24-month Utilization of Leflunomide in the Treatment of Rheumatoid Arthritis (ULTRA) trial, comparing LEF with MTX and placebo. Initial 12-month data from this trial have previously been published and demonstrated American College of Rheumatology (ACR) response rates of ≥20% with LEF, which were significantly better than the response with placebo and equivalent to the response with MTX (2). Similar results were evident by ACR ≥50% and ACR ≥70% response rates, as well as by mean improvements in individual measures of disease activity and retardation of disease progression as assessed by radiography (2,5). Compared with MTX- and placebo-treated patients, LEF significantly improved physical function and health-related quality of life as measured by the Health Assessment Questionnaire disability index (HAQ DI) at the 12-month followup visit (6,7). The objectives in evaluating the second year of double-blind therapy were to determine if the efficacy and safety observed at 12 months with LEF and MTX were sustained over 24 months of treatment, and to compare the response to the active treatments at 24 months. Sustained therapeutic benefit is important when treating a debilitating chronic disease such as RA.

PATIENTS AND METHODS

Patients. To enroll in the 24-month ULTRA trial, patients had to be 18–75 years of age, to have had RA (by the ACR [formerly, the American Rheumatism Association] criteria [8]) for ≥6 months, and to have not previously received MTX. Active RA was defined by the presence of at least 3 of the following 4 criteria: ≥9 tender joints, ≥6 swollen joints, morning stiffness lasting ≥45 minutes, or Westergren erythrocyte sedimentation rate (ESR) ≥28 mm/hour. Patients could not have been receiving other DMARDs for ≥30 days prior to treatment. Prednisone (≤10 mg/day) and nonsteroidal antiinflammatory drug (NSAID) doses needed to be stable for ≥30 days prior to enrollment and remain so during the protocol treatment. Men and women of childbearing potential were required to use medically approved contraception that had to be continued for ≥6 months after completion of the protocol treatment. This study received approval from the appropriate ethics review boards and was conducted following the principles established by the Declaration of Helsinki.

All patients who continued treatment into the second year and received at least 1 dose of study medication and attended 1 followup visit after week 52 were included in the year-2 cohort, regardless of ACR responder status. Of those continuing into the second year of treatment, 75 LEF-treated patients (77%) and 61 MTX-treated patients (60%) were ACR 20% responders at 12 months.

Study medication and administration. During the second year of treatment, the daily oral dose of LEF was to remain at 20 mg/day, unless problems with tolerability required a dose reduction to 10 mg/day. Weekly doses of MTX could be increased at the discretion of the investigator, from 15 mg to 17.5 mg or 20 mg/week; almost all patients (≥99%) received daily folate at doses of 1–2 mg. As specified in the ACR monitoring guidelines for therapy with MTX, dose adjustments, treatment discontinuation, and/or liver biopsy were mandated for all patients with persistent liver enzyme elevations (9). The protocol mandated dose adjustments for persistent elevations of alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST), defined as >2 but ≤3 times higher than the upper limits of normal values; either a single 7.5 mg/week reduction in the dose of MTX or a single 10 mg/day reduction in the dose of LEF was to occur. If elevations in the ALT and AST persisted after these dose reductions in study medication, the protocol treatment was to be discontinued. For persistent elevations >3 times the upper limit of normal, treatment discontinuation was mandated.

Outcome measures. In treatment year 2, the following components of the ACR response criteria were assessed every 6 weeks, from week 52 to week 100 and at week 104 or at the time of early withdrawal: tender and swollen joint counts (28 joints each), patient and physician global assessments using a visual analog scale (VAS; 0–10 cm), patient assessment of pain on VAS (0–10 cm), modified HAQ score, Westergren ESR, and C-reactive protein level. In addition, the HAQ DI, Problem Elicitation Technique (PET), Medical Outcomes Survey 36-item short form (SF-36), and work productivity index were administered at weeks 76 and 104 or at early withdrawal. Single emulsion radiographs of the hands and feet were obtained at weeks 52 and 104 or at early withdrawal. Films were randomized for sequence and blinded for treatment group and sequence before being scored a second time using the modified Sharp score, in which 34 joints and 36 joints in the hands were assessed for erosions and joint space narrowing, respectively, and 12 joints in the feet (10,11).

At 12 and 24 months, ACR ≥20%, ≥50%, and ≥70% responses and mean changes in each of the individual components of the ACR response criteria were compared between active treatments. The area under the curve (AUC) of the ACR ≥20% responses and the number of weeks a patient

remained an ACR ≥20% responder were compared between the active treatments. Mean changes in the HAQ DI, PET weighted top 5 score, SF-36 scales, and work productivity index were compared over 12 and 24 months of treatment to assess whether improvements in physical function and health-related quality of life were sustained over 2 years within each active treatment group and between active treatments. Radiographic analyses were performed at 12 and 24 months and the results were compared within and between active treatment groups. A correlation analysis of first versus second year Sharp radiologic damage readings was performed to assess within-reader reliability using Pearson's correlation.

Statistical methods. Data from year-2 patients who continued blinded treatment were analyzed to determine if the efficacy and safety observed over 12 months with LEF and MTX would be sustained over 24 months, and to compare their therapeutic effects. Two populations were prospectively defined for analysis: the intent-to-treat (ITT) patient population (all patients enrolled who received ≥1 dose of study drug) and the year-2 cohort (all patients who received ≥1 dose of study medication and had ≥1 followup visit after week 52 and whose data had undergone analysis with the last observation carried forward [LOCF] for those withdrawing early). Results of the 52-week analyses have been published (2,5,6). The year-2 cohort data were analyzed using an ITT approach in which the last observation was carried forward (the LOCF) for those patients discontinuing treatment before week 104; therefore, all patients entering the year-2 cohort were included in the analyses.

Efficacy analyses did not include patients administered alternate therapy on or after 4 months of treatment or the small number of patients receiving placebo who entered the second year of treatment (n = 36) (2,7,12). In the protocol, 2-year comparisons between the active treatments and placebo were performed with exclusions made prospectively; only 14 of the 36 placebo-treated patients completed 2 years of protocol participation, all as ACR responders.

Demographics and disease history were analyzed using a chi-square test for categorical data and analysis of covariance (ANCOVA) for continuous data. Analysis of ACR response criteria for both the ITT population and the year-2 cohort was performed using logistic regression. End-point comparisons of outcome measures between LEF and MTX were performed using ANCOVA. A multivariate analysis of variance, including the HAQ DI, the PET weighted top 5 score, and the 8 domains and physical and mental component scores of the SF-36, was used to characterize overall differences between LEF and MTX at 24 months. When differences were present, analysis of variance was used to compare results on the individual scales between the LEF and MTX treatment groups. Within both active treatment groups, analysis of consistency of effect between month 12 and month 24 was performed using paired *t*-tests. Radiographic data were analyzed using ANCOVA to compare treatment groups, and a Wilcoxon signed-rank test was performed to compare year-1 and year-2 results within the active treatment groups.

Table 1. Patient demographics*

	ITT population		Year-2 cohort	
	LEF (n = 190)	MTX (n = 190)	LEF (n = 98)	MTX (n = 101)
Mean age, years	54	53	55	53
Women, %	73	74	69	68
Mean duration of RA, years	6.9	6.5	5.9	6.7
RA ≤2 years, % patients	39	41	43	44
RA ≥5 years, % patients	44	37	42	37
Past DMARDs, mean no.	0.8	0.9	0.8	0.9
No prior DMARD, % patients	44	44	45	46

* ITT = intent-to-treat; LEF = leflunomide; MTX = methotrexate; RA = rheumatoid arthritis; DMARD = disease-modifying antirheumatic drug.

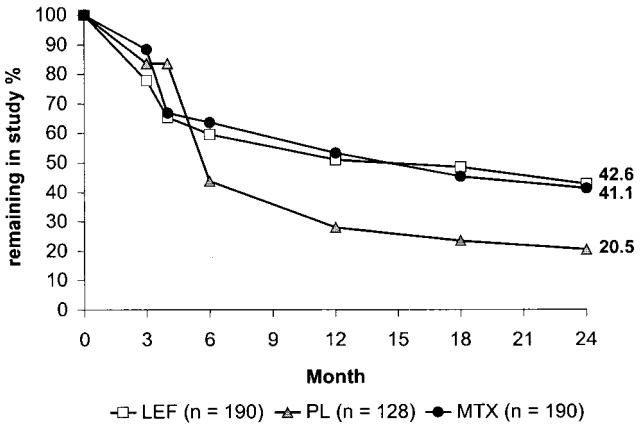

Figure 1. Kaplan-Meier analysis of discontinuations in the intent-to-treat population. LEF = leflunomide; PL = placebo; MTX = methotrexate.

RESULTS

Demographics and patient disposition. Demographic variables in the patient population entering the second year of therapy were similar to the overall ITT population (Table 1). Approximately 40% of patients had a disease duration of ≤2 years, and ~45% of patients were DMARD naive. In all, 508 patients (190 LEF, 128 placebo, 190 MTX) were enrolled in the ULTRA trial (data from 26 patients enrolled in Canada and included here were unavailable for inclusion in the previously reported 1-year results [2]). A total of 199 patients (98 LEF and 101 MTX) continued into the second year of blinded active treatment. Of these 199 patients, 83 patients (85%) receiving LEF and 80 (79%) receiving MTX completed the entire 24 months of therapy (Figure 1). The mean (±SD) maintenance dose of LEF was 19.6 ± 1.99 mg/day during year 2 of treatment (median 20.0 mg/day) compared with 19.7 ± 1.73 mg/day for year 1 (median 20.0 mg/day). The mean

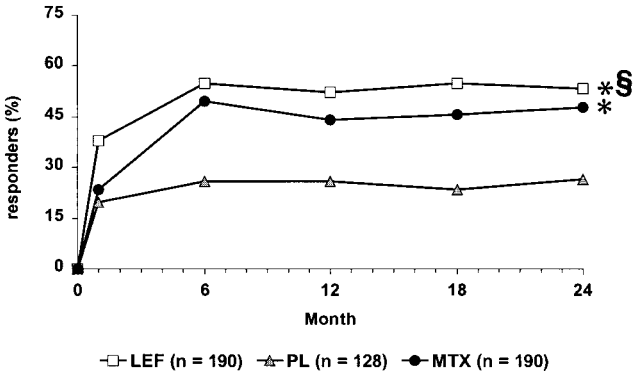

Figure 2. American College of Rheumatology ≥20% improvement response rates over time in the intent-to-treat population. For early withdrawals during year 2, the last observation carried forward is used. * = $P \leq 0.001$ versus PL; § = $P = 0.317$ versus MTX (statistically equivalent; 95% confidence interval −5.0–15.3). See Figure 1 for definitions.

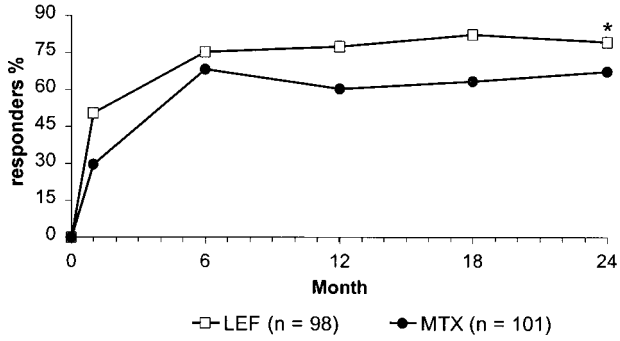

Figure 3. American College of Rheumatology ≥20% improvement response rates over time in the year-2 cohort. For early withdrawals during year 2, the last observation carried forward is used. * = $P = 0.049$ versus MTX (95% confidence interval 0.1–24.4). See Figure 1 for definitions.

maintenance dose of MTX administered during treatment year 2 was 12.6 ± 4.69 mg/week (median 15.0 mg/week) compared with 11.7 ± 3.75 mg/week (median 15.0 mg/week) during year 1. The doses of corticosteroids in the year-2 cohort were decreased after month 12, as allowed per protocol, in 22% of LEF-treated patients (11 of 50) and 24% of MTX-treated patients (9 of 38) (mean decreases of 3.7 mg/day and 3.4 mg/day, respectively).

Table 2. ACR response rates*

	LEF	MTX	95% CI	*P*
ITT population				
No. of patients	190	190		
1-year results				
ACR ≥20%	52	46		
ACR ≥50%	34	23		
ACR ≥70%	20	9		
2-year results				
ACR ≥20%	53	48	−5.0–15.3	0.317
ACR ≥50%	34	28	−2.1–16.6	0.127
ACR ≥70%	17	12	−1.8–12.2	0.143
Mean 2-year AUC, weeks	44	40	−5.3–15.4	0.339
Year-2 cohort				
No. of patients	98	101		
1-year results				
ACR ≥20%	77	60		
ACR ≥50%	57	32		
ACR ≥70%	32	13		
2-year results				
ACR ≥20%	79	67	0.1–24.4	0.049
ACR ≥50%	56	43	−0.2–27.4	0.053
ACR ≥70%	26	20	−6.1–16.8	0.361
Mean 2-year AUC, weeks	78	66	−1.37–23.1	0.082

* Except where otherwise indicated, values are the percentage of patients. For early withdrawals during the trial, the last observation carried forward is used. ACR = American College of Rheumatology; 95% CI = 95% confidence interval; AUC = area under the curve (see Table 1 for other definitions).

Clinical efficacy. Using the LOCF, ACR ≥20% response rates in the LEF and MTX treatment groups were statistically equivalent at 12 months (52% versus 46%, respectively) and 24 months (53% versus 48%; $P = 0.317$, 95% confidence interval [95% CI] −5.0–15.3) in the ITT population (Figure 2). ACR ≥20% response rates showed that the effects of LEF were evident as early as 1 month into therapy. AUC analysis of the weeks of ACR ≥20% responses in the ITT population demonstrated a mean (±SD) of 43.7 ± 42.4 weeks of response with LEF compared with 40.0 ± 37.9 weeks with MTX ($P = 0.339$, 95% CI −5.3–15.4) (Table 2).

In the year-2 cohort, maximal ACR ≥20% response rates were attained on or before 6 months and sustained over 24 months in both active treatment groups (Table 2 and Figure 3). At 24 months, LEF treatment was associated with higher ACR ≥20% response rates than was MTX treatment (79% versus 67%; $P = 0.049$, 95% CI 0.1–24.4). ACR ≥50% response rates for patients at 24 months were numerically greater following treatment with LEF compared with MTX (LEF 56% versus MTX 43%; $P = 0.053$, 95% CI −0.2–27.4). This was also the case for ACR ≥70% response rates (LEF 26% versus MTX 20%; $P = 0.361$, 95% CI −6.1–16.8). Responses were sustained from 12 months to 24 months, reflecting a consistent treatment effect (Table 2). The AUC analysis of weeks of ACR ≥20% response in the year-2 cohort demonstrated a mean (±SD) of 77.6 ± 30.1 weeks (75% of 104 weeks) with LEF administration compared with 66.4 ± 32.0 weeks (64% of 104 weeks) for MTX ($P = 0.082$; 95% CI −1.37–23.1). Mean changes from baseline in individual components of the ACR response criteria over 24

Table 3. Mean changes in individual American College of Rheumatology outcome parameters and morning stiffness in the year-2 cohort*

	Leflunomide (n = 98)	Methotrexate (n = 101)
TJC (28 joints)		
Baseline	13.4 ± 5.6	14.3 ± 6.5
Δ at 12 months	−10.7 ± 6.4	−8.3 ± 7.1
Δ at 24 months	−10.1 ± 6.7†	−8.8 ± 9.0
SJC (28 joints)		
Baseline	13.3 ± 6.3	13.0 ± 5.4
Δ at 12 months	−8.7 ± 5.6	−6.6 ± 5.3
Δ at 24 months	−8.2 ± 6.1	−7.7 ± 6.7
Patient global assessment (VAS)		
Baseline	5.3 ± 2.0	5.1 ± 2.2
Δ at 12 months	−3.4 ± 2.2	−2.4 ± 2.6
Δ at 24 months	−3.3 ± 2.6	−2.4 ± 2.8
Physician global assessment (VAS)		
Baseline	5.9 ± 1.5	5.6 ± 1.7
Δ at 12 months	−4.3 ± 1.9	−3.2 ± 2.2
Δ at 24 months	−4.1 ± 2.4†	−3.4 ± 2.7
MHAQ score		
Baseline	0.7 ± 0.5	0.7 ± 0.5
Δ at 12 months	−0.45 ± 0.5	−0.25 ± 0.5
Δ at 24 months	−0.43 ± 0.5†	−0.28 ± 0.5
Patient assessment of pain (VAS)		
Baseline	5.5 ± 2.2	5.3 ± 2.1
Δ at 12 months	−3.2 ± 2.6	−2.4 ± 2.6
Δ at 24 months	−3.3 ± 2.6†	−2.4 ± 2.8
ESR, mm/hour		
Baseline	38.3 ± 26.0	35.9 ± 25.7
Δ at 12 months	−10.7 ± 24.8	−11.0 ± 22.1
Δ at 24 months	−6.5 ± 27.2	−7.9 ± 23.5
CRP, mg/dl		
Baseline	22.1 ± 27.5	20.2 ± 19.4
Δ at 12 months	−9.6 ± 25.8	−7.8 ± 19.3
Δ at 24 months	−9.8 ± 27.9	−5.4 ± 26.8
Morning stiffness, minutes		
Baseline	191.4 ± 304.8	144.0 ± 215.8
Δ at 12 months	−152.8 ± 260.9	−95.1 ± 226.0
Δ at 24 months	−149.8 ± 321.0†	−90.8 ± 265.5

* Values are the mean ± SD. TJC = tender joint count; SJC = swollen joint count; VAS = visual analog scale (0–10 cm); MHAQ = modified Health Assessment Questionnaire; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein.
† $P \leq 0.05$ versus methotrexate.

months in the year-2 cohort were similar to those observed at 12 months with both active treatments (Table 3).

A total of 137 of 199 patients (69%) in the year-2 cohort had baseline, 12-, and 24-month (or early exit) radiographs. As previously reported, to estimate how rapidly joint destruction occurred between disease onset and study entry, a yearly rate of radiographic progression was estimated by dividing the individual baseline total radiographic score by disease duration for that patient (10). The imputed yearly progression rate for the LEF-treated patients was a 4.03/year increase in total Sharp scores, and for the MTX-treated patients, a 3.75/year increase in total Sharp scores. When comparing the mean changes in total Sharp scores from baseline over 12 months and 24 months of active treatment, both the LEF and MTX treatment groups demonstrated retardation of disease progression (Table 4). In addition, an evaluation of the erosion and joint space narrowing subscores demonstrated retardation of disease progression.

There were no changes from baseline in the median total Sharp scores in both active treatment groups at 12 and 24 months. A high correlation between the duplicate readings of baseline and year-1 radiographs was confirmed when these were reread along with the year-2 films (correlation coefficient 0.971 for year-1 films and 0.972 for baseline films; $P = 0.0001$).

Patients in both treatment groups showed little or no progression of radiographic damage. A total of 88% of LEF-treated patients and 80% of MTX-treated patients in the year-2 cohort had no newly eroded joints during year 2. In addition, 73% of patients in both active treatment groups in the year-2 cohort had no newly eroded joints during 24 months of treatment; 72% of patients in the LEF and 70% in the MTX year-2 cohorts

Table 4. Total Sharp scores and erosion and joint space narrowing (JSN) subscores at 1 and 2 years, and change between year 1 and year 2*

	Leflunomide (n = 71)	Methotrexate (n = 66)	95% CI	P†
Total Sharp score				
Baseline	23.8 ± 38.5	25.1 ± 42.3		
Δ at year 2	1.6 ± 4.2	1.2 ± 3.8	−1.39–2.19	0.659
Δ between year 1 and year 2	0.4 ± 2.7	0.7 ± 2.1		
P, year 1 Δ vs. year 2 Δ‡	0.0172	0.4572		
Erosion subscore				
Baseline	10.3 ± 25.6	10.6 ± 22.9		
Δ at year 2	1.0 ± 3.1	0.6 ± 1.7	−0.67–1.63	0.412
Δ between year 1 and year 2	0.3 ± 1.8	0.3 ± 1.1		
P, year 1 Δ vs. year 2 Δ‡	0.0689	0.8934		
JSN subscore				
Baseline	13.5 ± 17.2	14.5 ± 21.7		
Δ at year 2	0.5 ± 1.7	0.6 ± 2.6	−1.01–0.87	0.878
Δ between year 1 and year 2	0.1 ± 1.31	0.4 ± 1.4		
P, year 1 Δ vs. year 2 Δ‡	0.1621	0.4443		

* Values are the mean ± SD, except where indicated otherwise. 95% CI = 95% confidence interval.
† Relates to comparison between treatment groups.
‡ Relates to change from year 1 to year 2 within treatment groups.

Table 5. Mean change in the HAQ DI, PET top 5, and SF-36 scores in the year-2 cohort*

	Leflunomide (n = 97)	Methotrexate (n = 101)	*P*
HAQ DI			
Baseline	1.2	1.2	
Δ at 12 months	−0.61	−0.38	
Δ at 24 months	−0.60	−0.37	0.005
PET top 5			
Baseline	19.9	18.4	
Δ at 12 months	−9.5	−4.5	
Δ at 24 months	−9.12	−4.34	<0.010
SF-36 PCS			
Baseline	30.9	30.2	
Δ at 12 months	11.88	7.97	
Δ at 24 months	10.8	8.37	0.195
SF-36 MCS			
Baseline	48.5	49.8	
Δ at 12 months	3.57	2.51	
Δ at 24 months	4.65	2.67	0.062

* Negative change indicates improvement for the Health Assessment Questionnaire disability index (HAQ DI) and the Problem Elicitation Technique (PET) weighted top 5 score; positive change indicates improvement for the Medical Outcomes Survey 36-item short form (SF-36) physical and mental component scores (PCS and MCS, respectively).

had no change in erosion scores from baseline to 24 months. During the second year, 81% of LEF-treated patients and 70% of MTX-treated patients had no change in joint space narrowing scores; 73% and 71%, respectively, had no change in joint space narrowing scores from baseline to 24 months.

Analyses of physical function in the year-2 cohort demonstrated that the significant improvements observed at 6–12 months in the HAQ DI, PET top 5 score, and SF-36 scores were maintained over 24 months in both treatment groups (Table 5). Consistent with the data reported following 12 months of treatment (6,7), significantly greater improvements were evident with LEF compared with MTX at 24 months in the HAQ DI (−0.60 versus −0.37; $P = 0.005$), the PET weighted top 5 score (−9.12 versus −4.34; $P = 0.0010$), and 3 of the 8 SF-36 domains: bodily pain (30.13 versus 19.18; $P = 0.0023$), vitality (19.07 versus 12.50; $P = 0.0290$), and emotional role (22.40 versus 6.83; $P = 0.0029$) (Table 5) (6).

Safety. Adverse events were monitored for the entire ITT population over 24 months of treatment (Tables 6 and 7). Adverse events reported in placebo-treated patients (n = 128) were included in the 24-month safety comparison and were used for comparison of event rates per 100 patient-years of exposure (Table 7). During the 24 months of treatment, 27% of LEF-treated, 9.4% of placebo-treated, and 17% of MTX-treated patients withdrew as a result of adverse events.

Serious adverse events were reported in 18.9% of LEF-treated, 9.4% of placebo-treated, and 18.9% of MTX-treated patients over 24 months. Serious adverse events considered by the investigators to be related to study drug administration were reported in 3 LEF-treated (1.6%), 2 placebo-treated (1.6%), and 7 MTX-treated (3.7%) patients. These included asymptomatic liver enzyme elevations (2 LEF, 1 placebo, 4 MTX),

Table 6. Summary of reported serious adverse events (AEs) in the intent-to-treat population*

	First 12 months			24 months		
	LEF (n = 190)	PL (n = 128)	MTX (n = 190)	LEF (n = 190)	PL (n = 128)	MTX (n = 190)
All serious AEs	16.3	8.6	7.4	18.9	9.4	18.9
Treatment-related AEs	1.1	1.6	2.6	1.6	1.6	3.7
AEs leading to withdrawal	3.7	1.6	3.2	4.2	1.6	6.3
Treatment-related AEs leading to withdrawal	0.5	0.8	1.6	1.1	0.8	1.6
Specific AEs						
Diarrhea	32.6	18.8	19.5	36.8	20.3	21.6
URI	28.9	21.1	31.6	37.4	25.0	38.4
Headache	18.4	16.4	20.5	20.0	17.2	23.2
Nausea	16.3	18.0	17.9	18.4	18.8	20.5
Dyspepsia	16.3	14.8	13.2	18.4	16.4	14.2
Rash	14.2	8.6	8.9	17.4	8.6	11.1
Hypertension	11.6	6.3	3.2	18.4	8.6	4.7
New onset	2.1	0.0	1.6	4.7	0.0	2.6
Alopecia	10.0	0.8	5.8	10.5	0.8	5.8
Abdominal pain	8.9	3.1	7.9	11.6	3.9	7.9
Dizziness	7.9	7.0	4.7	8.9	7.0	5.8
UTI	6.8	7.8	1.6	8.4	9.4	5.8
Vomiting	5.8	6.3	2.6	7.4	6.3	3.7
Mouth ulcer	5.8	5.5	9.5	6.8	5.5	10.5
Pruritis	4.7	0.8	2.1	4.7	0.8	3.2

* Values are the percentage of patients. PL = placebo; URI = upper respiratory tract infection; UTI = urinary tract infection (see Table 1 for other definitions).

Table 7. Summary of adverse events in >10 patients per 100 patient-years in any treatment group*

	Leflunomide (n = 190)	Placebo (n = 128)	Methotrexate (n = 190)
Respiratory infection	32.1	32.0	32.3
Diarrhea	31.7	26.0	18.1
Headache	17.2	22.0	19.5
Nausea	15.8	24.0	17.3
Dyspepsia	15.8	21.0	11.9
Hypertension	15.8	11.0	4.0
Rash	14.9	11.0	9.3
LFE elevations	13.1	4.0	9.7
Abdominal pain	10.0	5.0	6.6
Arthralgia	9.5	12.0	8.8
Accidental injury	9.0	11.0	12.4
Asthenia	9.0	12.0	6.2
Sinusitis	9.0	11.0	10.2
UTI	7.2	12.0	4.9
Increased cough	6.3	12.0	7.5

* Values are the number of patients per 100 patient-years of exposure. LFE = liver function enzyme; UTI = urinary tract infection.

pneumonia (1 LEF, 1 MTX), hypertension (1 placebo), sepsis (1 LEF, 1 MTX), and interstitial pneumonitis (1 MTX). Three deaths occurred during the 24-month trial, of which 1 occurred in a placebo-treated patient (cardiac arrest) and 2 in MTX-treated patients (1 from sepsis and pneumonia [treatment related]; 1 from cardiac arrest and pulmonary embolism [not treatment related]).

The most frequently reported adverse events in all groups (placebo and active treatment) included upper respiratory tract infections, diarrhea, headache, nausea, dyspepsia, and rash. The incidence of infections in the active and placebo treatment groups was not significantly different and resulted in treatment withdrawal of 1.0% and 2.1% of the LEF-treated and MTX-treated patients, respectively. No opportunistic infections were reported.

Diarrhea was more prevalent in patients receiving LEF; 9.5% of patients receiving LEF withdrew from treatment because of diarrhea. Oral ulcers were seen more often in patients receiving MTX. Rash and pruritus were observed more frequently with LEF treatment. Reversible alopecia was reported in 10.5%, 0.8%, and 5.8% of patients receiving LEF, placebo, and MTX, respectively. Three LEF-treated, 1 placebo-treated, and 5 MTX-treated patients withdrew early because of alopecia. The commonly reported adverse events in the active treatment groups were comparable when patient-years of exposure were taken into account (Table 7).

Mild-to-moderate hypertension was more frequent in the LEF treatment group after 24 months. However, hypertension was more common in the LEF group at baseline (LEF 13.7%, placebo 8.6%, MTX 2.1%). New-onset hypertension occurred in 4.7% of LEF-treated, 0% of placebo-treated, and 2.6% of MTX-treated patients, all of whom were receiving concomitant NSAIDs. During the 24-month study, mean increases from baseline in the supine systolic and diastolic blood pressures were higher with LEF treatment but remained small in magnitude: 1.61 and 1.31 mm Hg, respectively, with LEF, 0.91 and 0.04 mm Hg, respectively, with placebo, and 0.27 and −0.08 mm Hg, respectively, with MTX treatment.

Mean changes in hematologic parameters were small and not clinically important. No thrombocytopenia (<100,000), leukopenia (<2,000), or pancytopenia was observed. Elevations in the ALT and/or AST levels were observed in all treatment groups. All ALT and/or AST elevations in the LEF-treated patients reversed to ≤2 times the upper limit of normal and/or normalized to ≤1.2 times the upper limit of normal, without a change in dose in approximately half of the LEF-treated patients (13 of 24) (Table 8). Following the ACR guidelines for monitoring liver toxicity (9), 2 liver biopsies performed during the first year of the trial, as previously reported (1 patient receiving LEF [week 10] and 1 patient receiving MTX [week 50]), showed no evidence of fibrosis (2). Three additional biopsies were performed

Table 8. Patients with liver enzyme elevations in the intent-to-treat population*

Measure, outcome	Leflunomide (n = 190)	Placebo (n = 128)	Methotrexate (n = 190)
ALT			
>2× ULN	24	5	19
Reversed to ≤2× ULN	24	5	18
Normalized to ≤1.2× ULN	22	5	15
Normalized without dose change	13	3	8
AST			
>2× ULN	17	4	15
Reversed to ≤2× ULN	17	4	13
Normalized to ≤1.2× ULN	17	4	13

* Elevations defined as >2 times the upper limit of normal (ULN). Values are the number of patients. ALT = alanine aminotransferase; AST = aspartate aminotransferase.

in the second and third year of treatment (including an extension to this trial) in 2 LEF-treated patients at weeks 106 and 135, and in 1 MTX-treated patient at week 156. All liver specimens were classified as Roegnik grades I–IIIA, indicating no significant evidence of fibrosis.

Malignancies were reported in 5 LEF-treated, 3 placebo-treated, and 6 MTX-treated patients. One case of vasculitis was reported in each active treatment group. One case of interstitial pneumonitis and 1 reversible renal failure were reported with MTX treatment.

DISCUSSION

Data from the second 12 months of this randomized, controlled, 24-month trial demonstrate that the beneficial effects observed with LEF and MTX administration over 1 year of treatment are sustained over 2 years. Sustained improvements were observed in the ACR ≥20%, ≥50%, and ≥70% response rates, in the mean changes in individual components of the ACR response criteria (including the MHAQ), in the HAQ DI, PET, and SF-36 scores, and in the modified Sharp scores comparing changes in radiographs from baseline to those observed at 12 and 24 months.

As would be expected, the year-2 cohort included a higher percentage of ACR ≥20% responders than did the ITT population over 12 and 24 months because patients doing well are more likely to continue treatment. In the year-2 cohort, improvements with LEF treatment at 24 months were statistically significant compared with MTX for ACR ≥20% responses, tender joint count, patient-assessed pain, MHAQ scores, physician global assessment, morning stiffness, HAQ DI, PET weighted top 5 score, and 3 of 8 domains of the SF-36.

The mean changes in HAQ-DI scores from baseline to 12 and 24 months in the LEF-treated and MTX-treated patients exceeded the 0.22 units reported to represent minimum clinically important improvement (13–15). This sustained improvement at 24 months is important because previous studies have demonstrated that worsening in the HAQ DI in the first 2 years of disease resulted in significantly greater disability and higher cost at 3 and 8 years of followup (16).

The sustained benefit of both LEF and MTX treatment over 2 years of blinded treatment is further supported by reports from 2 clinical trials conducted in Europe. Kalden et al reported that the therapeutic effect of LEF at 24 months was statistically significant compared with sulfasalazine by ACR ≥20%, ≥50%, and ≥70% responses as well as by patient and physician global assessments and mean HAQ scores (17). Radiographic data at 24 months from this comparative trial demonstrated that the retardation of disease progression initially observed with LEF treatment at 6 months was maintained over 12 and 24 months (3,17,18). Emery et al reported similar 24-month findings in a large, active-controlled trial of LEF and MTX. LEF or MTX treatment resulted in sustained improvement in ACR ≥20% and ≥50% responses, tender and swollen joint counts, and the HAQ DI. ACR ≥20% and ≥50% responses, which were statistically different between treatments at 12 months, were statistically equivalent between LEF and MTX at 24 months (4).

The safety profile after 24 months of treatment with either LEF or MTX was similar to that reported over 1 year of treatment (2). The most commonly reported adverse events following both active treatments included upper respiratory tract infections, which are generally more common in RA subjects than in the general population (19). As reported in the first 12 months of the trial (2), diarrhea, rash, and reversible alopecia were most commonly associated with LEF treatment; oral ulcers, nausea, and headache were more common with MTX. The incidence of adverse events commonly associated with LEF decreased in year 2 when compared with year 1 in the LEF group, as demonstrated by the modest increase in reported adverse events over 24 months compared with the initial 12 months of the study (Table 6). Although alopecia was reported more frequently in LEF-treated patients, more MTX-treated patients withdrew early because of alopecia (5 MTX, 3 LEF). In addition, although diarrhea occurred in 36.8% of LEF-treated patients, only 9.5% of patients discontinued LEF due to the diarrhea.

ALT elevations were most sensitive to treatment with either LEF or MTX. Although regular monitoring of ALT or AST is required with both agents, approximately half of the elevations resolved without dose reductions in either active treatment group. Close followup, as recommended by the protocol guidelines, did not identify any cases of hepatocellular disease. Of 1,339 patients who received LEF in clinical trials, only 3 patients required liver biopsy as recommended by the protocols. In addition, no significant fibrosis or cirrhosis was observed. Although clinical hepatic toxicity was not observed in the patients treated with LEF for 2 years in this study, long-term followup through postmarketing surveillance will be necessary to determine the clinical significance of the elevated liver transaminase levels observed in some LEF-treated patients.

Results in patients receiving LEF or MTX over 2 years of controlled treatment offer compelling evidence that improvements evident at 12 months were sustained

at 24 months. These data are consistent with results from other long-term studies of patients receiving MTX monotherapy (20–23). The change in total Sharp scores was equivalent between the 2 active treatments at 24 months and indicated that both agents retarded radiographic disease progression as compared with baseline and 1-year scores (2,5). These benefits with LEF treatment were equivalent or statistically significantly superior to MTX, the current gold standard for treating RA.

These clinical trial results confirm that LEF is an important first-line treatment for active RA, offering improvement in the signs and symptoms of active disease as early as 1 month into therapy, which is further improved at 12 months and is sustained over 24 months of administration. In addition, LEF also retards the radiographic progression of disease over 24 months of therapy. LEF is significantly more effective than MTX in improving physical function and health-related quality of life.

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