Combination Leflunomide and Methotrexate (MTX) Therapy for Patients with Active Rheumatoid Arthritis Failing MTX Monotherapy: Open-Label Extension of a Randomized, Double-Blind, Placebo Controlled Trial

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ABSTRACT. ***Objective.*** To obtain additional safety and efficacy data on leflunomide (LEF) treatment in combination with methotrexate (MTX) therapy in an open-label extension study in patients with rheumatoid arthritis (RA).

Methods. Following a 24 week, randomized, double-blind trial of adding placebo (PLA) or LEF to stable MTX therapy, patients could enter a 24 week extension. Subjects randomized to LEF and MTX continued treatment [(LEF/LEF) + MTX]. Subjects randomized to PLA and MTX switched to LEF (10 mg/day, no loading dose) and MTX [(PLA/LEF) + MTX]. The double-blind regarding initial randomization was maintained.

Results. For subjects in the extension phase, American College of Rheumatology 20% (ACR20) responder rates for the (LEF/LEF) + MTX group were maintained from Week 24 (57/96, 59.4%) to Week 48 (53/96, 55.2%). ACR20 responder rates improved in patients switched to LEF from PLA at Week 24 [(PLA/LEF) + MTX] from 25.0% (24/96) at Week 24 to 57.3% (55/96) at Week 48. Patients in the extension who switched from PLA to LEF without a loading dose exhibited a lower incidence of elevated transaminases compared to patients initially randomized to LEF. Diarrhea and nausea were less frequent during the open-label extension in patients who did not receive a LEF loading dose.

Conclusion. Response to therapy was maintained to 48 weeks of treatment in patients who continued to receive LEF and MTX during the extension. Importantly, ACR20 response rates after 24 weeks of LEF therapy were similar between patients switched from PLA to LEF without loading dose, and those who received a loading does of LEF (100 mg/day × 2 days) at randomization. Fewer adverse events were reported in patients switched to LEF without a loading dose. (J Rheumatol 2004;31:1521–31)

Key Indexing Terms:
RHEUMATOID ARTHRITIS LEFLUNOMIDE METHOTREXATE OPEN-LABEL TRIAL COMBINATION DISEASE MODIFYING ANTIRHEUMATIC DRUG THERAPY

Rheumatoid arthritis (RA) is a progressive inflammatory disease of unknown etiology that causes severe disability[1,2] and increases mortality[2,3]. Early use of disease modifying antirheumatic drugs (DMARD) has become the standard for treatment of RA; however, an incomplete response to DMARD monotherapy is observed in some patients[4-6].

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Supported by Aventis Pharmaceuticals.

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Submitted March 20, 2003; revision accepted February 4, 2004.

Clinicians now recognize that earlier, more aggressive treatment with DMARD is essential for improving the signs and symptoms of RA, slowing the progression of the disease, and maintaining physical function[7-16]. This approach is supported by the fact that worsening of the physical components of the Health Assessment Questionnaire Disability Index (HAQ DI) was observed with standard-care DMARD monotherapy as well as with some combinations of DMARD[15,17,18].

For the treatment of RA, methotrexate (MTX) is the DMARD most widely used as both monotherapy and in combination therapy[14,18,19]. Because in many patients MTX alone does not adequately control the signs and symptoms of RA at tolerated doses, the practice of combination DMARD therapy has increased[10,13,20] in an attempt to gain efficacy while managing toxicity[20]. A 1997 survey found that 99% of responding rheumatologists prescribed combination DMARD therapy in an estimated 24% of all patients with RA[21].

MTX has been used in combination with many drugs, including sulfasalazine[10,17], sulfasalazine and hydroxychloroquine[12,22], cyclosporine[15,23,24], auranofin[25], azathioprine[26], etanercept[27], infliximab[28,29], and anakinra[30]. Limited data in abstract form are available on combination therapy with leflunomide (LEF) and cyclosporine[31], infliximab[32], and sulfasalazine[33]. In both an open-label trial and a double-blind trial (described below), MTX combined with LEF demonstrated a substantial incremental benefit in patients with RA who had an inadequate response to MTX alone[34-37].

In a 30-patient open-label pilot study of LEF added to MTX in patients with inadequate response to MTX alone, more than half the patients met the American College of Rheumatology 20% (ACR20) response criteria after 36 weeks of therapy, a response rate that was sustained at Week 48[35,36]. This LEF + MTX combination was generally well tolerated, although an increased risk of elevated hepatic enzymes was observed[35,36]. No pharmacokinetic interactions between LEF and MTX were identified[35].

In a randomized, double-blind, placebo controlled trial, LEF was added in patients with active RA despite MTX treatment. Adding LEF provided substantial therapeutic benefit compared with adding placebo (PLA) and it was generally well tolerated[34,37]. Elevations in liver function tests were reversible with discontinuation, dose reduction, or, in mild cases, often with no change in dose[34]. Our objective was to obtain additional descriptive efficacy and safety data on the combination of LEF and MTX in a 24 week, open-label extension of the double-blind, placebo controlled trial[34], in patients taking a stable background dose of MTX.

MATERIALS AND METHODS

Study design. Patients who completed a 24 week, randomized, double-blind trial of adding PLA or LEF to stable MTX therapy[34] were allowed to enter an additional 24 week, open-label, multicenter extension of the study (Figure 1). An institutional review board at each investigative site approved the protocol. The total duration of therapy, including both double-blind and open-label phases, was 48 weeks. All patients who entered the open-label phase received LEF; patients who were initially randomized to receive LEF in the double-blind trial continued LEF in addition to their stable dose of MTX in the open-label phase [termed (LEF/LEF) + MTX], while patients initially randomized to receive PLA in the double-blind phase switched to LEF in the open-label phase in addition to their stable MTX [termed (PLA/LEF) + MTX]. Although this was an open-label extension, the double blind regarding initial randomization to LEF or PLA was maintained.

During the open-label extension, patients were started on LEF 10 mg/day in combination with background MTX, regardless of the final dose of LEF or PLA at the endpoint of the double-blind portion of the trial. At the discretion of the investigator, the dose of LEF could be adjusted to 10 mg every other day for tolerability, or to 20 mg/day if 10 mg/day was tolerated and active disease persisted. Patients receiving PLA in the double-blind phase did not receive a loading dose when beginning LEF at Week 24. In contrast, patients randomized to the LEF + MTX group during the double-blind phase (Weeks 0–24) had been given a loading dose of LEF 100 mg on Days 1 and 2[34].

Patients continuing on LEF in the open-label phase [(LEF/LEF) + MTX] maintained their stable background MTX therapy and were observed for maintenance of effect and any safety issues occurring during the second 24 weeks of combination therapy. Patients switching from PLA in the double-blind phase to LEF in the open-label phase [(PLA/LEF) + MTX] also maintained their stable background MTX therapy and were observed for an incremental therapeutic benefit following initiation of LEF, as well as for additional safety issues during the 24 week open-label phase.

Study population. Patients were male or female (age 18 to 75 years; ≥ 19 years old in Canada) and diagnosed with RA ≥ 6 months prior to enrollment in the initial double-blind study. All patients enrolled in the double-blind study had active RA, determined at 2 separate examinations 7 to 21 days apart, despite MTX treatment for at least 6 months (15–20 mg/week or 10–15 mg/week if this was the maximum tolerated dose for the subject). Active disease was defined by 3 of 4 criteria: ≥ 6 swollen joints, ≥ 9 tender joints, ≥ 45 minutes of morning stiffness, and erythrocyte sedimentation rate (ESR) ≥ 28 mm/h.

Efficacy endpoints. ACR20 response was defined as at least a 20% improvement in tender joint count (TJC) and swollen joint count (SJC), and in 3 of 5 of the following measures: physician global assessment, patient global assessment, pain intensity assessment, HAQ DI, and an acute phase reactant [ESR or C-reactive protein (CRP)]. TJC and SJC were based on 68 and 66-joint assessments, respectively. Physician and patient global assessments of RA disease activity were based on a 0 to 100 mm horizontal visual analog scale (VAS). ACR50 and ACR70 responses were defined by at least 50% and at least 70% improvement, respectively, using the same criteria.

The primary efficacy variable for the intent-to-treat (ITT) population in the 24 week, double-blind phase was ACR20 responder-at-endpoint rate at Week 24, which required both study completion and ACR20 response at Week 24[34]. Patients who discontinued prior to endpoint, or for whom there were insufficient data to assess ACR20, were considered nonresponders for this analysis. In patients entering the open-label extension, the ACR20 responder-at-endpoint rates at Weeks 24 and 48 were assessed to identify trends with continued LEF + MTX combination therapy or following a switch to combination LEF + MTX therapy.

Secondary efficacy variables assessed in the double-blind phase were also assessed in the open-label phase and included the ACR50 and ACR70 responder-at-endpoint rates at Weeks 24 and 48. ACR20, ACR50, and ACR70 response rates at Weeks 24 and 48 were also analyzed using last observation carried forward (LOCF) for patients in the open-label phase who discontinued prior to Week 48. The open-label phase also assessed mean changes from baseline to Weeks 24 and 48 for individual ACR components and rheumatoid factor (RF). Physical function was assessed by change in HAQ DI from baseline to Week 24 and Week 48. Health related quality of life (HRQoL) was assessed by change in the 36 item Medical

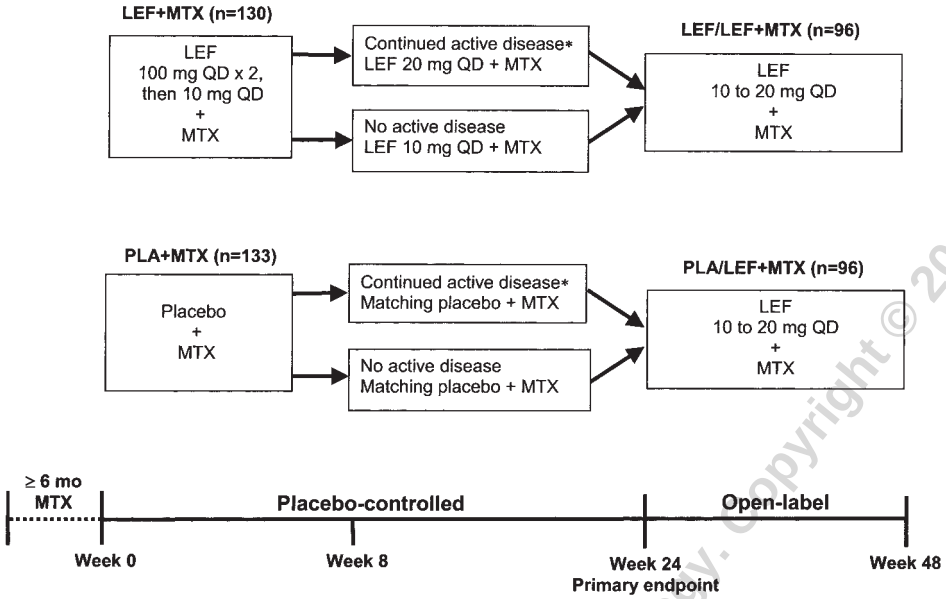

Figure 1. Study design of the double-blind and open-label phases of the trial. *Active disease defined as 3 of the following 4: ≥ 9 tender joints; ≥ 6 swollen joints; ≥ 45 minutes morning stiffness; ESR ≥ 28 mm/h.

Outcome Study Short Form Health Survey (SF–36), including the 8 SF–36 domains and mental (MCS) and physical (PCS) component summary scores from baseline to Week 24 and Week 48[35].

Safety assessment. Safety was assessed by adverse event (AE) reports, physical examinations, and clinical laboratory data. Adverse events were defined as any sign, symptom, syndrome, or illness that appeared or worsened during the open-label extension, and that might have impaired the well being of the subject.

Hematology and blood chemistry tests, including liver function tests (LFT) examining alanine aminotransferase (ALT) and aspartate aminotransferase (AST), were performed at each study visit. Study visits occurred at Weeks 24 and 48 or at early termination and included a followup visit 6 weeks after completion. Clinically significant ALT and AST abnormalities could have resulted in a reduction or discontinuation of LEF, depending on the degree and persistence of the elevation[31]. Occurrence and reversal of the highest elevation of ALT or AST [> 1.2 to ≤ 2 × upper limits of normal (ULN); > 2 to ≤ 3 × ULN; and > 3 × ULN] were summarized.

Statistical analysis. Descriptive statistics were used for all efficacy and safety variables. The treatment groups in the open-label phase are not directly comparable; therefore, no statistical comparisons were made. ACR20, ACR50, and ACR70 response rates based on both responder-at-endpoint and LOCF approaches were provided for each treatment group. McNemar's test was used to compare the ACR20 responder-at-endpoint rates at Weeks 24 and 48 within the (LEF/LEF) + MTX group and the (PLA/LEF) + MTX group. Data for changes from baseline to endpoint for individual ACR criteria are presented as the mean ± standard deviation (SD). Safety variables were summarized on the safety-evaluable population, defined as all patients who received at least one dose of study medication in the open-label extension.

RESULTS

Patient disposition and demographics. Of the 263 patients enrolled in the initial double-blind study, 200 completed the initial 24 weeks of therapy; 192 of 200 (96%) patients eligible to participate in the open-label phase entered the extension. One hundred sixty-eight patients completed the extension study to Week 48 [n = 82, or 85% (PLA/LEF) + MTX; n = 86, or 89% (LEF/LEF) + MTX]. For both groups, the rate of discontinuation appeared to be lower during the open-label phase [14.6% for (PLA/LEF) + MTX and 10.4% for (LEF/LEF) + MTX] compared to the initial double-blind phase (24.8% for PLA + MTX, and 23.1% for LEF + MTX). The most common reason for withdrawal in the open-label phase was the occurrence of AE [2.1% for the (PLA/LEF) + MTX group; 5.2% for the (LEF/LEF) + MTX group].

Clinical and demographic characteristics at baseline for the study population (ITT) have been reported for the double-blind trial[34]. At the beginning of the double-blind study, patients had a mean RA duration of 10.5 and 12.7 years in the LEF + MTX and PLA + MTX groups, respectively. Although radiographic assessment was originally planned as part of the study, not enough radiographs were completed to make any analysis or comparison between groups.

Of the 96 patients who received LEF during the initial double-blind study and continued in the Week 24–48 open-label phase, 60 (62.5%) were taking 20 mg/day, 32 (33.3%) were taking 10 mg/day, and 4 (4.2%) were taking 10 mg every other day at Week 24. Of the 60 patients who were taking LEF 20 mg/day at the endpoint of the double-blind phase, 48 decreased the dosage to 10 mg/day per protocol at the beginning of the open-label phase, and 12 started the open-label phase on the 20 mg/day dosing schedule. During the open-label phase, 25 patients increased their LEF dosage back to 20 mg/day. All 32 LEF + MTX patients who were on a LEF 10 mg/day dosing schedule at the endpoint of the double-blind phase started the open-label phase with 10 mg/day per protocol. Of the 4 LEF + MTX patients who were at 10 mg every other day at the endpoint of the double-

blind phase, 2 started the open-label phase on 10 mg/day, and 2 remained on the same dosing schedule.

Efficacy

For the extension study, efficacy analyses included data from those 192 patients who completed the initial 24 weeks of therapy and continued in the open-label phase of the study. ACR20 completer-at-endpoint responses obtained in the initial double-blind study are included where appropriate for comparison[34]. It should be noted that there are differences in reported results at Week 24 for the double-blind ITT population (n = 263) and the open-label extension population (n = 192). This is not an unexpected finding in an extension study as the analysis from the double-blind study likely includes some patients with lower responses to therapy who chose not to continue in the open-label extension. Additional detail on efficacy results from the double-blind study have been published[34].

(LEF/LEF) + MTX. In the patients who continued LEF therapy on background MTX (n = 96), the ACR20 responder-at-endpoint rate was 59.4% at Week 24 and 55.2% at Week 48, a difference of –4.2% and not statistically different (p = 0.4313) (Table 1, Figure 2). Similar trends were noted for ACR50 and ACR70 responder-at-endpoint rates at Weeks 24 and 48 (Table 1), indicating maintenance of effect across 48 weeks of combination therapy. Changes from baseline in individual ACR criteria and RF are summarized in Table 2. Improvements were observed in TJC and SJC, CRP, RF, and in patient global, physician global and pain intensity assessments.

Table 2 also summarizes the improvements in physical function (HAQ DI) and HRQoL (SF–36 PCS and MCS). The mean change of –0.52 in the HAQ DI at Week 24 was maintained at Week 48 (–0.54). At baseline, 9.6% of (LEF/LEF) + MTX patients had a HAQ DI score ≤ 0.5, the best category, which increased to 41.2% at Week 48. Mean changes in the SF–36 PCS at Week 24 and Week 48 timepoints were 8.5 for both (37% improvement), and those for the SF–36 MCS were 4.5 and 4.2 (12% and 11% improvement), respectively. Although the minimum clinically important difference (MCID) has not yet been formally defined for SF–36, several authors[39-42] have suggested that changes of 5 to 10 points in domains and 2.5 to 5 points in summary scores are associated with meaningful clinical improvements. Therefore, changes in PCS well exceeded the MCID and those for the MCS were within the range associated with clinical improvements.

(PLA/LEF) + MTX. In the patients who switched from PLA to LEF therapy while taking background MTX (n = 96), the ACR20 responder-at-endpoint rate was 25.0% at Week 24, which increased to 57.3% at Week 48, a difference of 32.3%, and was statistically different (p < 0.0001) (Table 1, Figure 2). The 48 week responder rate approximated the ACR20 responder-at-endpoint rate observed for the (LEF/LEF) + MTX patients at the same timepoint. The ACR50 and ACR70 responder-at-endpoint rates for (PLA/LEF) + MTX patients were 28.1% and 11.5% at Week 48, respectively, which were increased from the rates observed at Week 24 on PLA and approached the rates in the (LEF/LEF) + MTX group. Table 2 summarizes changes from baseline in individual ACR criteria and RF, and shows improvements in CRP, TJC, and SJC, as well as in assessments for patient global, physician global, pain intensity, and RF at Week 48 of a magnitude similar to that observed for (LEF/LEF) + MTX patients.

There was a further improvement in the mean change in HAQ DI at Week 48 (–0.33) compared with that seen at Week 24 (–0.15; Table 2) in the (PLA/LEF) + MTX group, although the improvement at Week 48 did not reach that seen in the (LEF/LEF) + MTX patients at Weeks 24 and 48. Patients in the (PLA/LEF) + MTX group obtained a clinically important improvement in SF–36 at 48 weeks, with improvements in the SF–36 PCS exceeding the MCID of 5 points and that for SF–36 MCS not exceeding MCID.

Safety

A detailed safety analysis of the double-blind and open-label studies was performed to assess the longterm safety profile

Table 1. ACR responses in the double-blind phase (ITT population) and in the open-label extension.

	PLA + MTX Week 24*, n = 133	(PLA/LEF) + MTX Week 24, n = 96	(PLA/LEF) + MTX Week 48, n = 96	LEF + MTX Week 24*, n = 130	(LEF/LEF) + MTX Week 24, n = 96	(LEF/LEF) + MTX Week 48, n = 96
Responder-at-endpoint rate						
ACR 20	19.5	25.0	57.3†	46.2	59.4	55.2
ACR 50	6.0	8.3	28.1	25.4	32.3	35.4
ACR 70	2.3	3.1	11.5	9.2	12.5	16.7
Last observation carried forward						
ACR 20	23.3	27.1	58.3†	51.5	59.4	56.3
ACR 50	6.0	8.3	28.1	26.2	33.3	35.4
ACR 70	2.3	3.1	11.5	10.0	13.5	16.7

PLA: placebo, LEF: leflunomide, MTX: methotrexate. * Data for double-blind phase as published[34]. † p < 0.0001 from McNemar's test comparing Week 48 vs Week 24 for the (PLA/LEF) + MTX group.

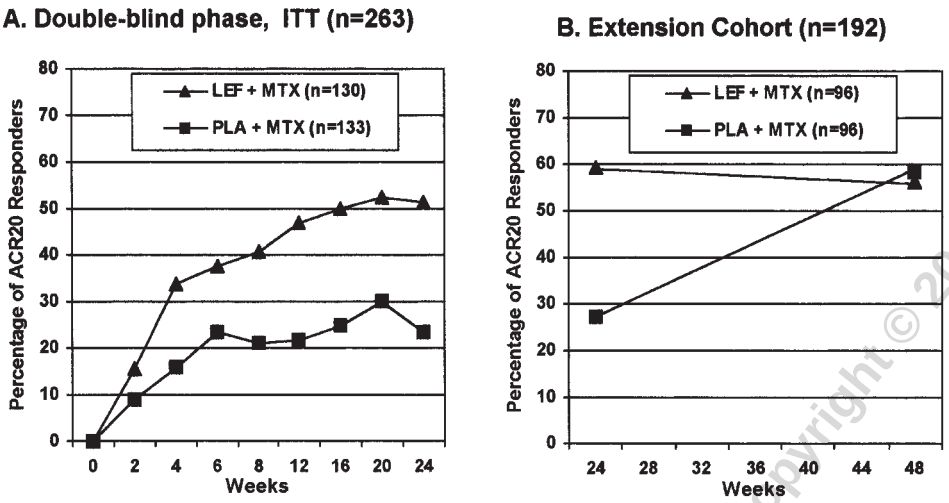

Figure 2. Proportion of ACR20 responders over time (by visit): A. Across Weeks 0–24 in the intent-to-treat population (n = 263) (Kremer, et al 2002). B. Across Weeks 24–48 for subjects who continued in the open-label phase (n = 192).

of combination therapy [(LEF/LEF) + MTX to 48 weeks] and to compare the AE profile between patients initiating LEF therapy with and without a loading dose. Some data from the double-blind study have been published[34].

(LEF/LEF) + MTX. In the first 24 weeks the most commonly reported AE (Table 3) in patients taking LEF + MTX (n = 130) were associated with the digestive system: diarrhea (25.4%) and nausea (16.2%). Rash (7.7%), alopecia (6.2%), and hypertension (4.6%) were also reported. Fewer LEF + MTX patients (40.8%) had infections than PLA + MTX patients (51.9%). No infection was opportunistic, and no patient withdrew from treatment because of infection.

In patients continuing a second 24 weeks of treatment with LEF + MTX (n = 96), diarrhea occurred at a lower rate (3.1%) compared with that in the first 24 weeks of treatment, as did alopecia (1.0%) and hypertension (2.1%); the incidence of rash was similar (7.3%; Table 3). The incidence of all infections combined in the open-label phase (35.4%) was similar to the incidence in the double-blind phase among patients continuing LEF. No increase in toxicity or new type of AE was apparent during the second 24 weeks of combination treatment.

In the first 24 weeks, 11 LEF + MTX patients had 11 serious AE (Table 4); 2 of the 11 serious AE reported for LEF + MTX treated patients (one case of cellulitis and one diagnosis of breast carcinoma) were considered by the investigator to be at least possibly related to study treatment. Events leading to treatment discontinuation in more than one LEF + MTX treated subject were diarrhea (4 patients, 3.1%), abnormal LFT (3 patients, 2.3%), and rash (2 patients, 1.5%).

During the open-label phase, 15 (LEF/LEF) + MTX patients had 21 serious AE: 3 were infections (none opportunistic), 2 were skin carcinoma (one was reported as being related to study treatment). Three patients discontinued study medication due to AE, one each with intestinal perforation/sepsis, gastrointestinal hemorrhage, and atrial fibrillation. No deaths occurred in the open-label phase.

Mild to moderate decreases in leukocyte count and neutrophil count were observed in Weeks 24–48 with (LEF/LEF) + MTX. As in the first 24 weeks, no patient exhibited leukopenia < 2.0 $10^3/mm^3$, neutropenia < 0.5 $10^3/mm^3$, or low platelet count (below normal range of 140.0–440.0 $10^3/mm^3$. The mean change from baseline in hemoglobin was not significant (–0.02); 3.2% of patients had hemoglobin values < 10 g/dl.

The mean increase in liver enzyme concentrations from baseline to Week 48 among patients continuing LEF into the open-label phase (ALT 3.6 U/l; AST 3.7 U/l) was less than that observed for the first 24 weeks of LEF treatment (ALT 9.3 U/l; AST 6.7 U/l). The overall incidence of ALT and AST elevation over the 48 week period in the (LEF/LEF) + MTX group was 33.1% in the first 24 weeks and 19.2% in the final 24 weeks of the study.

The occurrence of various degrees of LFT, based on a subject's highest elevation for the first and second 24 weeks of treatment, is summarized in Table 5. As reported[31], adding LEF in patients tolerating background MTX increased the risk of liver enzyme elevation compared to adding PLA, as seen in the Week 0–24 double-blind phase. The incidence of ALT and AST elevations was lower in the second 24 weeks of combination treatment for patients continuing on combination therapy in the open-label phase, compared with the first 24 weeks of treatment in the LEF + MTX group (ALT 13.7% and 31.5%; AST 6.3% and 16.9%, respectively). During the first 24 weeks, all ALT and AST elevations in LEF + MTX patients normalized with no inter-

Table 2. Changes from baseline in individual efficacy measures at Weeks 24 and 48 (mean ± SD).

Measure	(PLA/LEF) + MTX, n = 96	(LEF/LEF) + MTX, n = 96
Tender joint count		
n*	90	87
Baseline	25.7 ± 12.4	25.2 ± 12.2
Mean change at Week 24	–6.1 ± 13.9	–14.3 ± 11.7
Mean change at Week 48	–14.1 ± 12.4	–15.9 ± 12.3
Swollen joint count		
n*	90	87
Baseline	18.3 ± 8.0	16.6 ± 8.2
Mean change at Week 24	–4.4 ± 8.7	–7.8 ± 7.1
Mean change at Week 48	–9.7 ± 7.0	–8.8 ± 7.5
Patient global assessment, mm		
n*	89	86
Baseline	48.3 ± 21.4	49.5 ± 21.2
Mean change at Week 24	–6.3 ± 25.1	–22.8 ± 28.0
Mean change at Week 48	–20.9 ± 26.1	–22.0 ± 27.2
Physician global assessment, mm		
n*	89	86
Baseline	55.5 ± 15.1	57.9 ± 15.8
Mean change at Week 24	–13.6 ± 22.3	–31.4 ± 21.0
Mean change at Week 48	–29.3 ± 22.9	–33.7 ± 21.0
Pain intensity assessment, mm		
n*	89	86
Baseline	55.3 ± 22.1	58.3 ± 21.4
Mean change at Week 24	–11.6 ± 28.7	–29.4 ± 28.8
Mean change at Week 48	–26.9 ± 26.8	–27.2 ± 26.7
HAQ DI		
n*	91	91
Baseline	1.4 ± 0.56	1.5 ± 0.65
Mean change at Week 24	–0.15 ± 0.45	– 0.52 ± 0.53
Mean change at Week 48	–0.33 ± 0.53	–0.54 ± 0.57
ESR, mm/h		
n*	86	92
Baseline	35.2 ± 25.7	33.8 ± 20.9
Mean change at Week 24	–5.0 ± 19.3	–2.1 ± 20.7
Mean change at Week 48	–4.5 ± 22.7	–2.1 ± 24.2
CRP, mg/l		
n*	90	89
Baseline	22.2 ± 26.8	25.5 ± 31.2
Mean change at Week 24	0.9 ± 25.8	–12.9 ± 38.5
Mean change at Week 48	–8.7 ± 24.5	–13.7 ± 33.0
RF, mU/l		
n*	86	83
Baseline	255.2 ± 409.3	202.0 ± 300.0
Mean change at Week 24	3.7 ± 209.6	–74.9 ± 206.5
Mean change at Week 48	–82.6 ± 255.6	–47.4 ± 194.7
SF-36 PCS		
n*	80	81
Baseline	29.7 ± 8.63	28.6 ± 8.46
Mean change at Week 24	1.09	8.5 ± 10.93
Mean change at Week 48	6.6 ± 10.06	8.5 ± 10.93
Mean % change at Week 24	6	37
Mean % change at Week 48	27	37
SF-36 MCS		
n*	80	81
Baseline	49.5 ± 9.61	48.8 ± 10.46
Mean change at Week 24	1.4 ± 10.88	4.5 ± 11.04
Mean change at Week 48	1.5 ± 10.33	4.2 ± 8.54
Mean % change at Week 24	5	12
Mean % change at Week 48	5	11

Mean change indicates the mean change from baseline. PLA: placebo, LEF: leflunomide, MTX: methotrexate, HAQ DI: Health Assessment Questionnaire Disability Index, PCS: Short-Form 36 physical component summary score, MCS: mental component summary score. *Open-label patients with non-missing values at baseline, double-blind phase endpoint, and open-label phase endpoint.

Table 3. Adverse events across treatment groups in Weeks 0–48.

Adverse Event	Week 0–24 Double-Blind Phase				Week 24–48 Open-Label Phase			
	PLA + MTX, n = 133		LEF + MTX, n = 130		(PLA/LEF) + MTX, n = 96		(LEF/LEF) + MTX, n = 96	
	N	%	N	%	N	%	N	%
Diarrhea	18	13.5	33	25.4	16	16.7	3	3.1
Nausea	15	11.3	21	16.2	4	4.2	3	3.1
Gastroenteritis	3	2.3	10	7.7	2	2.1	2	2.1
Dyspepsia	6	4.5	8	6.2	4	4.2	2	2.1
Gastrointestinal disorder	2	1.5	6	4.6	1	1.0	0	0.0
Liver function test abnormality	2	1.5	5	3.8	1	1.0	2	2.1
Vomiting	5	3.8	3	2.3	1	1.0	0	0.0
Sore mouth	2	1.5	2	1.5	3	3.1	0	0.0
Infection (body as a whole)	7	5.3	14	10.8	10	10.4	4	4.2
Accidental injury	9	6.8	8	6.2	3	3.1	3	3.1
Abdominal pain	9	6.8	8	6.2	5	5.2	1	0.0
Upper respiratory infection	32	24.1	29	22.3	11	11.5	4	14.6
Sinusitis	7	5.3	6	4.6	5	5.2	6	6.3
Bronchitis	5	3.8	2	1.5	5	5.2	3	3.1
Pneumonia	1	0.8	2	1.5	3	3.1	5	5.2
Urinary tract infection	7	5.3	6	4.6	6	6.3	2	2.1
Headache	11	8.3	13	10.0	1	1.0	3	3.1
Dizziness	7	5.3	10	7.7	1	1.0	3	3.1
Rash	11	8.3	10	7.7	6	6.3	7	7.3
Alopecia	5	3.8	8	6.2	8	8.3	1	1.0
Hypertension	4	3.0	6	4.6	3	3.1	2	2.1

vention, or a dose reduction, or discontinuation of study medication at or before the end of the study. Similarly, in the open-label phase, ALT and AST elevations > 2 × ULN normalized after LEF was reduced or discontinued. No patient discontinued due to elevated LFT in the Week 24–48 open-label phase. Mild elevations in ALT or AST (< 2 × ULN) normalized after dose reduction or discontinuation in the Week 24–48 open-label phase.

(PLA/LEF) + MTX. In the first 24 weeks of PLA + MTX treatment (n = 133), commonly reported AE were upper respiratory infection (24.1%), diarrhea (13.5%), nausea (11.3%), headache (8.3%), rash (8.3%), alopecia (3.8%), and hypertension (3.0%). In the open-label, Week 24–48 extension phase (n = 96), when LEF treatment was initiated at Week 24 without a loading dose, diarrhea was the most common gastrointestinal event (16.7%). The incidence of nausea during the first 24 weeks of combination therapy was higher in the LEF + MTX patients in the double-blind study (received a loading dose) compared with patients in the (PLA/LEF) + MTX group who switched to LEF without a loading dose. Other common AE in the (PLA/LEF) + MTX group during the extension included rash (6.3%), alopecia (8.3%), and hypertension (3.1%); incidences of these events were similar to those in the first LEF + MTX group in the double-blind trial. Three (PLA/LEF) + MTX patients discontinued study medication due to AE (maculopapular rash, infection, and joint disorder) during the open-label phase.

During the double-blind phase, 8 patients had 9 serious AE while taking PLA + MTX; 3 of the 9 were considered by the investigator to be treatment related (one case each of pyogenic arthritis, gastritis, and cellulitis). Adverse events leading to discontinuation in more than one PLA + MTX treated patient during the double-blind phase were abnormal LFT (2 patients, 1.5%) and nausea (2 patients, 1.5%). After switching from placebo to LEF in the open-label phase, 13 patients had 18 serious AE. No patient died during the open-label phase. In the first 24 weeks, one subject taking PLA + MTX had an abnormally low platelet count (≥ 100.0 to < 120.0 $10^3/mm^3$), and 6.0% of patients had hemoglobin values < 10 g/dl. No clinically relevant decreases in leukocytes or neutrophils were observed. During the Week 24–48 phase, 5.2% of patients had hemoglobin levels < 10 g/dl.

Table 5 summarizes the number of patients with ALT or AST elevations categorized by the patient's highest value during the first and second 24 weeks of LEF treatment. Patients who switched from PLA to LEF for the second 24 weeks of treatment without a loading dose exhibited an incidence of elevated transaminase enzymes (ALT 14.6%; AST 13.7%) that was lower than in those initially randomized to LEF with a loading dose (ALT 31.5%; AST 16.9%), but higher than in patients initially randomized to PLA (ALT 6.8%; AST 4.6%). All elevations of transaminase enzymes in this group reversed with no intervention, or a dose reduction, or discontinuation of study medication at or before the

Table 4. Serious adverse events across treatment groups in Weeks 0–48.

Adverse Event	Week 0–24 Double-Blind Phase PLA + MTX, n = 133 N	LEF + MTX, n = 130 N	Week 24–48 Open-Label Phase (PLA/LEF) + MTX, n = 96 N	(LEF/LEF) + MTX, n = 96 N
Angina pectoris	1			
Cerebral hemorrhage	1			
Chest pain	1			
Cellulitis*	1*	2		1
Multiorgan failure, lymphoma	1			
Gastritis	1*		1	
Skin carcinoma (basal cell)	1	1		2
Pyogenic arthritis	1*		1	
Intracranial aneurysm		1		
Coronary artery disorder		1		
Atrial fibrillation		1		1
Gastroenteritis		1		
Intestinal obstruction		1		
Breast carcinoma		1*		
Diabetic acidosis		1		
Bone fracture		1	3	2
Arthralgia			1	
Accidental injury				2
Abscess				1
Sepsis				1
Colitis			2	
Gastrointestinal hemorrhage			1	1
Liver carcinoma			1	
Intestinal perforation				1
Stomach atony			1	
Arrhythmia				1
Hypertension				1
Myocardial infarct			1	
Pericarditis				1
Syncope				1
Urinary incontinence				1
Urinary tract infection			1	

* Considered related to study drug. ** One case considered related to study drug. Numbers in each column cannot be summed because a patient may have had more than one serious adverse event in the same body system.

end of the study. No patient initiating LEF at Week 24 discontinued due to elevated LFT during the open-label phase.

DISCUSSION

Our study continues to support the rationale for combined LEF + MTX treatment. The efficacy of LEF + MTX was first reported in an open-label trial in which 57% of patients were ACR20 responders after 36 weeks of therapy — a percentage of improved patients that remained relatively constant for the remainder of the 48 week study[35]. In the 24 week randomized controlled trial preceding this extension study, adding LEF in patients with active disease despite MTX treatment provided significant benefit compared with adding placebo. The benefits were documented by significant improvement in ACR20, ACR50, and ACR70 response rates, as well as in quality of life measures[34] (Table 2). Individual components of the ACR response criteria also followed a pattern of maintained or further improvement during the second 24 weeks of combination therapy, with the exception of ESR. Baseline ESR was only mildly elevated in these subjects who were taking background MTX therapy, which may in part explain the lack of improvement despite clinical improvement in other ACR components measured.

The ACR20 response rate was significantly lower in the PLA + MTX group (27.1%) compared with the LEF + MTX group (59.4%) in the initial 24 weeks. When patients receiving placebo had LEF added at Week 24, they achieved an ACR20 response rate at Week 48 of the same magnitude (58.3%) as that attained by patients originally randomized to LEF + MTX. This is especially interesting, as the patients who switched from PLA to LEF did so without a loading dose. The finding cannot be attributed to the fact that all patients knew they were receiving open-label combination therapy, because the double blind regarding their initial treatment arm was maintained.

Table 5. Highest liver enzyme elevations and normalization during the first and second 24 weeks of treatment.

	Weeks 0–24 (Double-Blind Phase)					
	PLA + MTX, n = 133			LEF + MTX, n = 130		
	> 1.2 to ≤ 2 × ULN	> 2 to ≤ 3 × ULN	> 3 × ULN	> 1.2 to ≤ 2 × ULN	> 2 to ≤ 3 × ULN	> 3 × ULN
ALT						
Patients, n (%)	6 (4.5)	2 (1.5)	1 (0.8)	28 (21.5)	8 (6.2)	5 (3.8)
Normalized to ≤ 1.2 × ULN*	5	1	0	28	8	5
After dose reduction	1	0	—	5	5	2
After no change in dose	4	1	—	22	2	0
After discontinuation**	0	0	—	1	1	3
Discontinuation due to LFT§, †	0	1	1	0	0	3
AST						
Patients, n (%)	5 (3.8)	0	1 (0.8)	16 (12.3)	4 (3.1)	2 (1.5)
Normalized to ≤ 1.2 × ULN*	5	—	0	16	4	2
After dose reduction	1	—	—	1	2	0
After no change in dose	3	—	—	13	0	0
After discontinuation**	1	—	—	2	2	2
Discontinuation due to LFT§, †	1	—	1	0	2	1

	Weeks 24–48 (Open-Label Phase)					
	(PLA/LEF) + MTX, n = 96			(LEF/LEF) + MTX, n = 95		
	> 1.2 to ≤ 2 × ULN	> 2 to ≤ 3 × ULN	> 3 × ULN	> 1.2 to ≤ 2 × ULN	> 2 to ≤ 3 × ULN	> 3 × ULN
ALT						
Patients, n (%)	10 (10.4)	2 (2.1)	2 (2.1)	10 (10.5)	3 (3.2)	0
Normalization to ≤ 1.2 × ULN	9	1	1	7	3	—
After dose reduction	0	0	0	0	1	—
After no change in dose	6	1	1	5	0	—
After discontinuation**	3	0	0	2	2	—
Discontinuation due to LFT¶	0	0	0	0	0	—
AST						
Patients, n (%)	11 (11.5)	1 (1.0)	1 (1.0)	4 (4.2)	1 (1.1)	1 (1.1)
Normalization to ≤ 1.2 × ULN	10	1	0	3	1	1
After dose reduction	1	0	—	1	0	0
After no change in dose	6	1	—	2	0	0
After discontinuation**	3	0	—	0	1	1
Discontinuation due to LFT#	0	0	0	0	0	0

ULN: upper limit of normal, ALT: alanine aminotransferase, LFT: liver function tests, AST: aspartate aminotransferase. * In the PLA + MTX group, 3 of 9 patients with ALT elevations and 1 of 6 patients with AST elevations did not normalize to ≤ 1.2 × ULN prior to or at the final study visit. ** Resolved after termination of study. § Discontinuations due to AE of abnormal LFT: 3 LEF + MTX patients discontinued in Weeks 0–24 due to elevations of ALT and AST, which normalized by the followup visit. † Two PLA + MTX patients discontinued due to elevations of ALT and AST, which remained elevated at the followup visit but normalized several months later. ¶ No (LEF/LEF) + MTX patient in Weeks 24–48 discontinued due to an AE of abnormal LFT. # No patient switching from PLA to LEF [(PLA/LEF) + MTX] discontinued in Weeks 24–48 due to an AE of abnormal LFT.

The improvement seen in HAQ DI at Week 48 for patients switching from PLA to LEF at Week 24 did not reach the magnitude seen in the group originally randomized to combination therapy for the first 24 weeks (Table 2); nonetheless, HAQ DI improved by –0.33, a clinically important improvement. Failure to achieve the same magnitude of improvement in HAQ DI level may possibly have been related to the delay of 24 weeks prior to the addition of LEF.

For patients in the (LEF/LEF) + MTX group, the mean change of –0.52 in the HAQ DI at Week 24, which was maintained at Week 48 (–0.54) (Table 2), exceeded the MCID of –0.22 points for HAQ DI[39]. The distribution of HAQ DI scores at baseline and at Weeks 24 and 48 showed the ability of combined LEF and MTX therapy to greatly reduce functional impairment and disability over time.

A safety concern of combining LEF and MTX is potential hepatotoxicity. Liver enzyme elevations that occurred in patients receiving combination LEF + MTX during Weeks 24–48 normalized after a reduction or discontinuation of LEF, as seen in the earlier double-blind trial. Three patients whose elevations normalized had a reelevation to > 1.2 to ≤ 2 × ULN. After initiating LEF at Week 24 without a loading dose, fewer patients had elevated LFT in a 24 week period than did those who added LEF with a loading dose at the beginning of the double-blind phase. Similarly, the incidence of both diarrhea and nausea was less during the open-

label phase when LEF was added without a loading dose, compared with that seen during the first 24 weeks of LEF + MTX when a loading dose of LEF was given.

Although the reversibility of mild liver enzyme elevations in a clinical trial setting is reassuring, the potential for increased hepatic toxicity with the use of LEF and MTX combination should be recognized, confirming the need for regular liver enzyme monitoring. We recommend monitoring monthly for the first 6 months, and then every 4 to 8 weeks, as described in the guidelines for monitoring MTX[43]. It should be noted that LEF was initiated at lower dose in the study than that recommended for monotherapy. It is important to use proper selection to avoid the combination in patients with known hepatic disease and/or other hepatic risk factors. In addition, there should be a higher level of vigilance for adverse effects, with regular hepatic enzyme and hematologic monitoring.

Given the progressive nature of RA, most double-blind placebo controlled studies in RA are of limited duration (6 months or less), as prolonged treatment with placebo is considered unethical in patients with active RA. While extension studies provide clinicians with valuable longterm safety and efficacy information on RA therapies, it should be recognized that there are inherent weaknesses in such trials. Since extension studies usually exclude patients who do not complete the initial trial, efficacy responses in the extension may be biased, as patients with a good response to therapy are more likely to continue in the extension study (and subjects with a poorer response more likely to drop out). In addition, it is not clear if outcome measures reported in the initial trial are the most appropriate measures to be used in an extension trial. A review by Landewe and van der Heijde discusses in depth the role and limitations of extension studies in RA[44]. Thus, it is important that this extension study provides new insight and information regarding safety of LEF combination therapy, as well as information regarding the safety and efficacy of LEF given in the absence of a loading dose.

In summary, the therapeutic benefit of combination LEF + MTX for the treatment of RA in patients with active disease taking MTX alone, including improvements in the signs and symptoms (ACR response), physical function (HAQ DI), and HRQoL (SF–36), was maintained to 48 weeks. Adverse events after adding LEF were similar to those reported in the LEF monotherapy studies. Elevated liver enzymes, diarrhea, and nausea were less frequent in the 24 weeks after adding LEF without a loading dose than they were after adding LEF with a loading dose. While the time required to achieve an ACR20 response without a loading dose is uncertain, it appears that a useful strategy to lessen toxicity would be to decrease or omit a loading dose of LEF 100 mg on Days 1 and 2 when LEF is added to MTX. Our findings support the more recent paradigm of combined DMARD therapy for RA treatment when control on monotherapy is inadequate[45], and provides further insight on how to lessen toxicity when LEF is added to MTX.

ACKNOWLEDGMENT

The authors thank Marilyn Stearns, MD, for editorial assistance in the development of this report.

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