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Original article

Efficacy and safety of leflunomide in DMARD-naïve patients with early rheumatoid arthritis: comparison of a loading and a fixed-dose regimen

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Abstract

Objective. To assess the efficacy of LEF administered with or without a loading dose in DMARD-naïve patients with early RA.

Methods. This multicentre, double-blind, randomized clinical trial included adults with RA diagnosed within 6 months (ACR criteria). Patients were randomly selected to receive either a 100 mg loading dose or a 20 mg fixed dose of LEF for 3 days, followed by a 3-month open-label maintenance period of 20 mg LEF qd. The primary outcome criterion was ACR20 response rate at study end in the intent-to-treat population. Secondary criteria were ACR20, ACR50, ACR70 and DAS28 response rates at 1 and 3 months and safety.

Results. The intent-to-treat population included 120 patients (median time since diagnosis 0.95 months). The ACR20 response rate at study end was 69.0% (95%CI 60.5%, 77.4%). Response rates were significantly lower ($P = 0.025$) in the loading-dose group [58.5% (45.2%, 71.8%)] than in the fixed-dose group [77.8% (67.5%, 88.0%)]. Three-month ACR50, ACR70 and DAS28 response rates were 41.4%, 17.7% and 81.7%, respectively, with no significant differences between groups. Adverse events occurred in 53.7% (loading-dose group) and 49.3% (fixed-dose group) of patients, most frequently diarrhoea and elevated hepatic enzymes; these occurred more frequently and earlier in treatment when the loading dose was used.

Conclusion. LEF was effective in DMARD-naïve patients with early disease. No incremental benefit was observed with the use of a loading dose, which may be associated with an increased initial rate of adverse events. The advantage of LEF initiation with a loading dose is not confirmed in this population.

Trial Registration. ClinicalTrials.gov, http://clinicaltrials.gov/, NCT00596206.

Key words: early rheumatoid arthritis, leflunomide, loading dose, efficacy, safety.

CLINICAL SCIENCE

Introduction

The goal of RA therapy is to control disease activity, retard the progression of joint damage, decrease pain and prevent or delay the emergence of functional disability [1, 2]. This may be achieved by the use of DMARDs, which have the potential to reduce or prevent joint damage and to preserve joint integrity and function. The most recent European League Against Rheumatism (EULAR) guidelines (2010) recommend that newly diagnosed RA patients should be started on DMARD therapy as soon as possible after diagnosis with the aim of achieving remission, and to adapt treatment as necessary if this target is not reached [3].

LEF is a DMARD whose clinical benefit has been well characterized in established RA [4]. A recent systematic review conducted for the purposes of informing the 2010 EULAR guidelines for the management of RA concluded that LEF was as effective as MTX in the treatment of established RA [5]. Its pluripotential mechanism of action [6–12] makes it a promising candidate for the treatment

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of early RA [13]. However, no dedicated study of its potential benefit has yet been performed. Nonetheless, the use of LEF in early RA is supported by subgroup analysis of phase III trials showing rapid efficacy in early RA patients [14]. In addition, a prospective open-label study of 334 patients with early RA reported a response rate of 85% and a remission rate of 25% 6 months after starting LEF [15]. Current EULAR recommendations for early RA management identify LEF as a first-line treatment option in patients with recently diagnosed disease in whom MTX is contraindicated or poorly tolerated [3, 16].

When LEF was first introduced, it was recommended to initiate treatment with a loading dose of 100 mg qd for 3 days followed by a maintenance dose of 20 mg qd. The rationale for this was to achieve steady-state plasma levels as rapidly as possible [13]. However, loading doses have been reported to be associated with a higher incidence of side effects [17], particularly nausea and diarrhoea, and consequently treatment discontinuation [18]. For this reason, many rheumatologists do not use a loading dose in everyday practice. For example, a survey conducted in the USA showed that around one-third of patients did not receive a loading dose [18]. The necessity of systematic use of a loading dose has thus been questioned [19] and further research is required to determine the pertinence of this strategy, particularly in the management of DMARD-naïve patients with early RA, where ensuring adherence to a potentially long-term treatment regimen is important.

We have thus undertaken a multicentre randomized clinical trial of LEF in early RA. The primary objective was to assess the efficacy of LEF in patients with early RA, as determined by the ACR20 response rate at 3 months. Secondary objectives were to compare outcome between two different initial dosing regimens with and without a 100 mg loading dose, to assess complementary efficacy criteria at 1 and 3 months and to evaluate biological and clinical safety.

Methods

This multinational, double-blind, randomized, double-dummy, parallel-group study was performed between December 2007 and October 2009 at 24 centres in the Czech Republic, Italy, Korea, Portugal and Romania. It consisted of a 3-day double-blind period followed by a 3-month open-label maintenance phase. This study was conducted in line with the Declaration of Helsinki and pertinent national legal and regulatory requirements. Written informed consent was obtained from each patient. The study was approved by the appropriate ethics committees or institutional review boards in each participating country. Patient confidentiality was ensured by assigning to each patient a study code that was used in the case report form in lieu of the patient's name.

Patients

The study included patients aged $\geqslant$18 years with a diagnosis of active RA according to the ACR criteria [20], assigned in the previous 6 months, with current active disease demonstrated by clinical and biological criteria [1], who were starting DMARD treatment for the first time. Exclusion criteria included initiation or change in NSAID or oral glucocorticoid treatment in the month preceding inclusion, a history of other inflammatory joint disease, contraindications to LEF, previous DMARD treatment (other than glucocorticoids) and any medical condition that could interfere with the implementation or interpretation of the study. Both men and women were expected to use an adequate means of contraception during the study. Women who were pregnant or breastfeeding were excluded from the study.

Study procedures

Patients fulfilling the entry criteria underwent a full clinical and biological evaluation at the inclusion visit and were then randomized by centre and by blocks of four to receive either LEF 20 mg qd (fixed dose group: FD) or LEF 100 mg qd (loading dose group: LD), with matching placebos, for 3 days. Thereafter all patients received LEF at a dose of 20 mg qd for up to 3 months. The total duration of the treatment evaluation period was 90 days. At the end of the study treatment period, the investigator could choose whether to continue or stop the study medication. All patients were re-evaluated at follow-up visits at 1 and 3 months.

Outcome measures

The primary outcome measure was the ACR20 response rate at study end (3-month follow-up visit or last observation). This has been used as a primary outcome measure in a previous phase III pivotal trial of LEF in established RA [21], as well as in a pivotal trial of etanercept [22], and is consistent with current guidance from the European Medicines Agency, which states that validated composite clinical endpoints such as the ACR should be used to document efficacy, and specifically that the ACR20 or ACR50 should be used to document signs and symptoms after 3–6 months [23, 24]. Data were collected using the Patient Assessment Form and the Physician Assessment Form published by the ACR. Patient global pain and global health were determined using a 10-point visual analogue scale and patient function using an adaptation of the multidimensional HAQ, scored on a scale ranging from 0 to 10. Secondary outcome measures were the ACR20 response rate at 1 month, ACR50, ACR70 and DAS28 [25] response rates at 1 and 3 months, the duration of morning stiffness, changes in concomitant RA treatments (glucocorticoids, analgesics and NSAIDs), and quality of life, determined with the Medical Outcomes Study Short Form (36) Health Survey (SF-36) [26]. The safety evaluation consisted of reporting of adverse events and systematic monitoring of haematology, blood chemistry and vital signs. Compliance was evaluated by counting tablets returned by the patient at visits 2 (30 days) and 3 (90 days).

Statistical methods

The target sample size was determined from *a priori* power calculations and was based on an estimated ACR20 response rate at 3 months of 65%, as observed in previous trials of DMARD monotherapy in early RA trials [22, 27–29]. In order to estimate this response rate in each treatment group with a precision of 10% using a two-sided 95% CI, it would be necessary to include 88 patients per arm. Assuming a drop-out rate of 11%, 100 patients would be required in each treatment group. It should be noted that the study was powered in order to determine response rates precisely but not to identify small differences between the two treatment arms or to demonstrate non-inferiority of one treatment regimen with respect to the other.

Three populations of patients are considered: the safety analysis (SA) population, defined as all randomized patients with at least one intake of study medication; the intent-to-treat (ITT) population, defined as those members of the SA population who had been evaluated at least once following inclusion; and the per protocol (PP) population, defined as those members of the ITT population without major protocol violations.

For the primary efficacy variable (ACR20 response rates), the responder rate was determined in the total study population, as well as separately in each treatment group, together with its 95% CI. The between-group hazard ratio was determined together with its 95% CI, and the two groups were compared using the χ^2 or Fisher's exact test. As a supportive analysis, the primary efficacy variable was evaluated in an identical way in the PP population. A similar procedure was followed for the ACR50, ACR70 and DAS28 responder rates. Protocol-specified subgroup analyses were performed to compare ACR20 responder rates at endpoint according to the presence of anti-CCP antibodies and according to the presence of radiographic changes in or adjacent to an involved joint. The safety analysis was conducted on the SA population. The time-course of the appearance of adverse events in the two treatment groups was compared using Kaplan–Meier survival analysis.

A probability threshold of 0.05 was taken as statistically significant and two-tailed tests were used throughout. All statistical analyses were performed using SAS version 9.1.3 (Cary, NC, USA).

Role of the funding source

This study was initiated and funded by Sanofi, manufacturer of LEF. The sponsor co-opted a scientific advisory committee, who advised on study design, interpretation of data, writing and publication of this report. Operational management of the study and data management were assured by Altizem (Nanterre, France), a contract research organization. Statistical analyses were performed by Altizem under the responsibility of Sanofi, based on a statistical analysis plan validated by the study steering committee. The authors have reviewed and take full responsibility for the results of this analysis.

Results

Study population

Twenty-four centres agreed to participate in the study, of whom 19 actively recruited 124 patients. The flow of the patients through the study is presented in Fig. 1. The SA population consisted of 121 patients, the ITT population 120 patients and the PP population 116 patients. Overall, 109 randomized patients (87.9%) completed the study as planned and 15 patients discontinued the study prematurely (8 in the LD group and 7 in the FD group). The most frequent reason for study discontinuation was the occurrence of an adverse event (three in the LD group and four in the FD group). The mean time in the study was 112 days in the LD group and 115 days in the FD group. Four major protocol violations were identified: two patients in the LD group who did not meet the specified criteria for early RA and two in the FD group for whom the 3-month follow-up visit was not performed at the right time. Patient characteristics at baseline are presented in Table 1. The two groups were well balanced with respect to age and RA-related clinical variables. However, men and glucocorticoid users were overrepresented in the FD group. The between-group difference in glucocorticoid use was not statistically significant, but the difference in gender reached statistical significance for the PP population ($P = 0.04$).

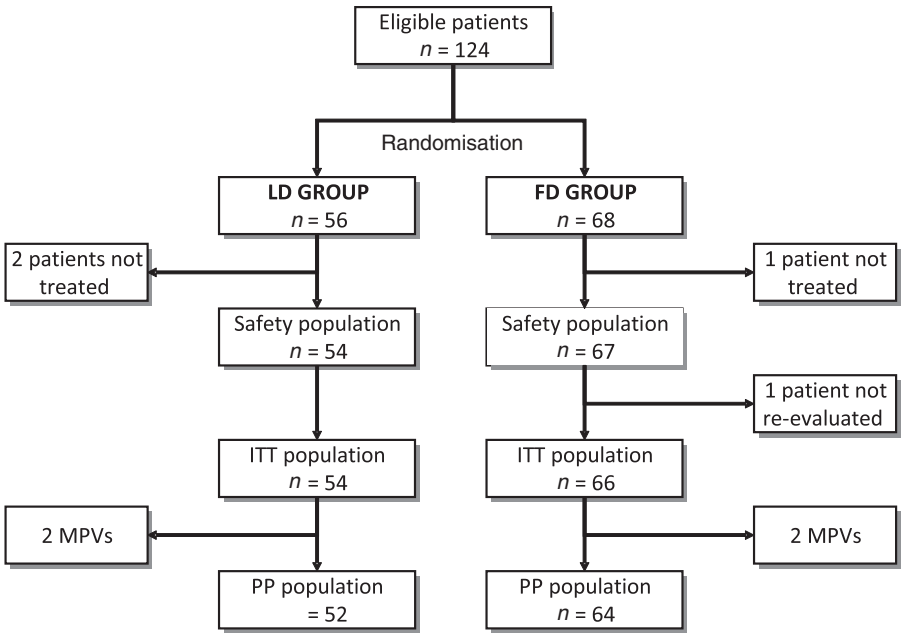
Efficacy

The primary efficacy variable was the ACR20 response rate at study end in the ITT population. The overall response rate was 69.0% (95% CI 60.5%, 77.4%). The response rate was significantly lower ($P = 0.025$; χ^2 test) in the LD group [58.5% (45.2%, 71.8%)] compared with the FD group [77.8% (67.5%, 88.0%)]. The between-group difference was −19.3% (95% CI −36.1%, −2.5%), corresponding to a risk ratio of 0.752 (95% CI 0.578, 0.978). A similar difference was observed in the PP population (Table 2). Overall response rates were similar in subgroups of patients who were anti-CPP seropositive (50/71; 70.4%) and seronegative (28/43; 65.1%) and in patients with (30/46; 65.2%) or without (50/70; 71.4%) radiological change.

The ACR20 response rate at 1 month was 58.6%. ACR50 and ACR70 response rates were 24.8 and 7.7%, respectively, at 1 month and 42.2 and 17.8% at 3 months. The DAS28 response rate was 69.6% at 1 month and 81.5% at 3 months. At study end, 8 patients in the LD group (14.8%) and 10 in the FD group (15.6%) were considered to be in remission (DAS28 score <2.6). No significant between-group differences were observed for any of these secondary outcome variables (Table 2). Significant improvements were observed for all ACR items between baseline and inclusion (Table 3). Mean morning stiffness duration decreased over the course of the study (Table 3), with no between-group difference.

Since there was a suggestion of an imbalance in groups in terms of gender, an exploratory *post hoc* analysis was performed to evaluate a possible interaction between

FIG. 1 Patient flow diagram indicating the interrelationship of the study populations.



MPV: major protocol violation; LD: 100 mg initial dose; FD: 20 mg initial dose.

TABLE 1 Baseline characteristics of patients in the ITT population at the inclusion visit

Baseline variable	LD group ($n = 54$)	FD group ($n = 66$)	Total ($n = 120$)
Gender			
Women, *n* (%)	47 (87.0)	48 (72.7)	95 (79.2)
Men, *n* (%)	7 (13.0)	18 (27.3)	25 (20.8)
Age, years			
Mean (S.D.)	52.4 (12.4)	54.2 (14.0)	53.4 (13.3)
Median (range)	54.0 (24–78)	55.0 (28–79)	54.0 (24–79)
Time since first symptoms, months			
Mean (S.D.)	9.93 (13.38)	13.48 (24.56)	11.89 (20.31)
Median (range)	5.09 (1.4–73.9)	6.65 (1.3–175.6)	6.09 (1.3–175.6)
Time since diagnosis, months			
Mean (S.D.)	1.26 (1.41)	1.51 (1.67)	1.40 (1.56)
Median (range)	0.94 (0–5.7)	0.97 (0–6.8)	0.95 (0–6.8)
Swollen joint count		$n = 64$	$n = 118$
Mean (S.D.)	8.9 (4.9)	9.5 (5.7)	9.2 (5.3)
Median (range)	8 (1–22)	8 (1–24)	8 (1–24)
Tender joint count		$n = 64$	$n = 118$
Mean (S.D.)	11.7 (6.0)	12.3 (6.6)	12.0 (6.3)
Median (range)	11 (1–26)	11 (2–28)	11 (1–28)
DAS28 score			
Mean (S.D.)	6.02 (1.03)	6.10 (0.96)	6.09 (0.99)
Median (range)	6.09 (3.6–8.1)	6.14 (4.0–8.7)	6.5 (3.6–8.7)
HAQ score, mean (S.D.)	0.91 (0.59)	1.01 (0.53)	9.63 (0.53)
Anti-CPP antibodies, *n* (%)	$n = 53$	$n = 65$	$n = 118$
	33 (62.3)	41 (63.1)	74 (61.7)
Radiographic changes, *n* (%)	21 (38.9)	27 (40.9)	48 (40.0)
Glucocorticoid use, *n* (%)	19 (35.2)	31 (47.0)	50 (41.7)
Mean dose (S.D.), mg/day	6.3 (2.9)	6.2 (2.8)	6.3 (2.8)

TABLE 2 Response rates

Endpoint	LD group	FD group	Between-group difference	Risk ratio	*P*
ACR20 response rate at study end (ITT), %	31 [58.5 (45.2, 71.8)]	49 [77.8 (67.5, 88.0)]	−19.3 (−36.1, −2.5)	0.752 (0.578, 0.978)	0.025
ACR20 response rate at study end (PP), %	30 [58.8 (45.3, 72.3)]	48 [78.7 (68.4, 89.0)]	−19.9 (−36.8, −2.9)	0.748 (0.574, 0.974)	0.023
ACR20 response rate at 1 month (ITT), %	33 [62.3 (49.2, 75.3)]	35 [55.6 (43.3, 67.8)]	6.7 (−11.2, 24.6)	1.121 (0.827, 1.520)	0.465
ACR20 response rate at 3 months (ITT), %	30 [58.8 (45.3, 72.3)]	45 [76.3 (65.4, 87.1)]	−17.4 (−34.8, −0.1)	0.771 (0.589, 1.010)	0.050
ACR50 response rate at 1 month (ITT), %	14 [27.5 (15.2, 39.7)]	14 [22.6 (12.2, 33.0)]	4.9 (−11.2, 20.9)	1.216 (0.640, 2.309)	0.551
ACR50 response rate at 3 months (ITT), %	22 [43.1 (29.5, 56.7)]	24 [41.4 (28.7, 54.1)]	−1.8 (−16.8, 20.3)	1.042 (0.672, 1.618)	0.853
ACR70 response rate at 1 month (ITT), %	2 [3.8 (0, 8.9)]	7 [10.9 (3.3, 18.6)]	−7.2 (−16.4, 2.0)	0.345 (0.075, 1.591)	0.180
ACR70 response rate at 3 months (ITT), %	9 [18.0 (7.4, 28.6)]	10 [17.5 (7.7, 27.4)]	0.5 (−14.1, 15.0)	1.026 (0.453, 2.322)	0.951
DAS28 response rate at 1 month (ITT), %	37 [71.2 (58.8, 83.5)]	41 [68.3 (56.6, 80.1)]	−2.8 (−14.2, 19.9)	1.041 (0.816, 1.329)	0.746
DAS28 response rate at 3 months (ITT), %	40 [78.4 (67.1, 89.7)]	48 [84.2 (74.7, 93.7)]	−5.8 (−20.5, 9.0)	0.931 (0.776, 1.118)	0.440

Data are presented as percentages with their 95% CIs. Due to missing data, it was not possible to assign a response status to certain patients (see legend to Table 3). The number of patients concerned varied between endpoints, but was never higher than nine in either patient group.

gender and ACR20 response at 3 months. This analysis did not support the hypothesis that the difference in primary outcome between the groups could be explained by this imbalance.

Concomitant treatments

Concomitant medication for the treatment of RA (glucocorticoids, analgesics or NSAIDs) was taken by 71 patients (59.2%). Glucocorticoids, analgesics and NSAIDs were used by 50, 9 and 55 patients, respectively. The mean daily dose of glucocorticoids prescribed at baseline was 6.3 (S.D. 2.8) mg. The initial dose remained unchanged throughout the study in 42 patients (84.0%), was reduced in 5 patients (10.0%) and needed to be increased in 3 patients (6.0%).

Safety

Treatment-emergent adverse events were reported by the physician in 53.7% of patients in the LD group and in 49.3% in the FD group (Table 4). The most commonly reported individual adverse event was diarrhoea. Diarrhoea and elevated hepatic enzymes were reported more frequently in the LD group, although the difference was not significant ($P = 0.13$ and $P = 0.09$, respectively). Serious adverse events were reported by three patients in each group, none of which was considered to be possibly related to treatment. An analysis of the appearance of adverse events over time revealed that these accrued earlier in the LD group than in the FD group (Fig. 2).

Haematology and blood chemistry were monitored throughout. One case of thrombocytopenia (<100 000/mm^3) in the LD group and one case of elevated transaminases (>3× ULN) in the FD group were identified. In addition, no relevant changes in mean blood pressure were observed over the course of the study. Five patients in the LD group and three in the FD group presented potentially clinically abnormal blood pressure measurements at some stage during the study.

Discussion

The primary objective of the study was to assess the clinical efficacy response rate in patients with early RA treated with LEF using the ACR20 criteria evaluated at 3 months. The proportion of patients fulfilling this response criterion was 69%. All three ACR thresholds evaluated in the study (ACR20, ACR50 and ACR70) evolved in a coherent way over the course of the study. The proportion of patients fulfilling the ACR70 criterion at 3 months was 18%.

Other secondary efficacy outcome measures were consistent with a beneficial treatment effect of LEF, with, for example, a DAS28 response rate of 81.7%. Mean tender and swollen joint counts were reduced by more than 60% and the mean duration of morning stiffness by a factor of five. These findings are in agreement with those from previous exploratory studies [14, 15] and provide further support for the EULAR guidelines that recommend LEF as an alternative first-line therapy for patients with early RA [3, 16].

Table 3 Change in individual components of the ACR score and in morning stiffness

ACR component	Baseline	Study end	Mean change in value from baseline to study end (95% CI)	*P*
Tender joint count[a]	12.0 (6.3)	4.5 (4.9)	−7.6 (−8.8, −6.3)	<0.0001
Swollen joint count[a]	9.2 (5.3)	2.9 (3.4)	−6.4 (−7.5, −5.3)	<0.0001
Patient global health	57.2 (20.3)	31.7 (19.6)	−25.6 (−29.9, −21.2)	<0.0001
Patient global pain	60.7 (20.2)	30.8 (20.7)	−34.5 (−34.2, −25.7)	<0.0001
Physician global disease	55.3 (17.0)	25.8 (17.5)	−29.5 (−33.3, −25.6)	<0.0001
Patient function score[b]	3.21 (1.76)	1.80 (1.45)	−1.40 (−1.75, −1.04)	<0.0001
Patient pain scale score	3.06 (1.92)	2.26 (1.86)	−0.80 (−1.20, −0.39)	0.0012
CRP, mg/l[c]	17.9 (20.0)	8.6 (12. 7)	−9.5 (−12.7, −6.3)	<0.0001
ESR, mm/h[d]	45.8 (24.2)	30.3 (22.8)	−15.6 (−19.5, −11.6)	<0.0001
Morning stiffness duration, h:min	2:26 (3:40)	0:34 (0:54)	−1:52 (−2:33, −1:11)	<0.0001

Values are mean (S.D.), unless otherwise indicated. Data are presented for the entire ITT study population of 120 patients. [a]Data were missing for two patients at baseline for these variables. [b]Data were missing for two patients at baseline and for one patient at study end. [c]Data were missing for 10 patients at baseline and for 14 patients at study end. [d]Data were missing for one patient at baseline and for two patients at study end.

Table 4 Treatment-emergent adverse events reported in the study and laboratory safety variables

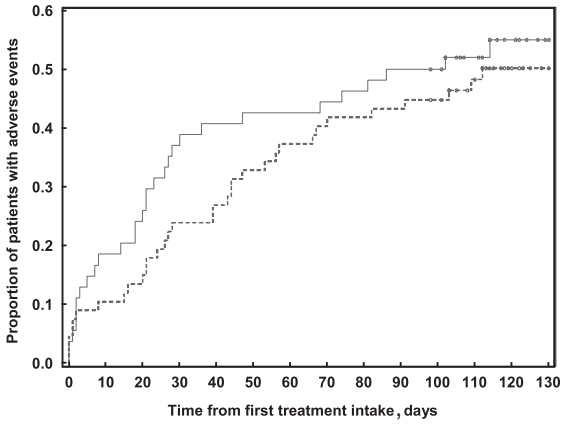
Adverse event	LD group (*n* = 54)		FD group (*n* = 67)	
	Events	Patients, *n* (%)	Events	Patients, *n* (%)
Any treatment-emergent adverse event	58	29 (53.7)		33 (49.3)
Diarrhoea	8	8 (14.8)	5	4 (6.0)
Vomiting	3	3 (5.6)		None
Hepatic enzyme increased	6	5 (9.3)	1	1 (1.5)
Alanine aminotransferase increased	4	4 (7.4)	1	1 (1.5)
Alopecia	3	3 (5.6)		None
Headache	3	3 (5.6)		None
Serious adverse events	3	3 (5.6)	3	3 (4.5)
All deaths		None		None
Adverse events leading to treatment discontinuation[a]	10	7 (13.0)	9	8 (11.9)
Adverse events possibly related to treatment	30	18 (33.3)	26	19 (28.4)

Only individual events reported in more than two patients in either group are listed. [a]Includes both permanent and temporary treatment discontinuation.

It was not possible to determine the absolute treatment effect size in the absence of a placebo group. Nonetheless, it is possible to address indirectly the treatment effect size for LEF in early RA observed here by comparison with effect sizes reported in other studies. For example, ACR response rates observed in the present study (58.6%) are somewhat, but systematically, higher than those observed in the phase III pivotal trials of LEF in established RA [21, 30, 31], in which ACR20 response rates ranged from 51% to 55%. This is consistent with data collected from a number of previous studies with other DMARDs which show that early treatment of RA provides better disease control than delayed treatment [32–34].

Moreover, the effect size for LEF may be compared with data from randomized clinical trials of other DMARDs in early RA. For example, ACR response rates for LEF observed at 3 months are quite comparable with those reported for MTX monotherapy [22, 27–29] trials, and for monotherapy with etanercept [22] or adalimumab [28], although it should be noted that the treatment duration in these trials is not identical. Response and remission rates may be expected to increase over time with a longer treatment duration, as demonstrated in the Combination of Methotrexate and Etanercept in early RA (COMET) trial [29]. On the other hand, response rates of combination therapy with biologic agents and MTX [27–29] were generally superior to those observed with LEF monotherapy in the present trial, as well as to the internal monotherapy treatment arms of these studies. The remission rate obtained with LEF was also somewhat lower than that observed after a similar duration of treatment with MTX in the Swedish Pharmacotherapy (SWEFOT) study, in which

Fig. 2 Kaplan–Meier survival curves for the emergence of adverse events in the two treatment arms.



Solid line: LD group; broken line: FD group.

treatment was initiated more rapidly after symptom onset (mean delay 6 months) than was the case in our LEF study (mean delay 12 months) and in many other earlier studies of DMARDs in early RA.

The treatment response to LEF occurred as early as 30 days in the present study, with response rates at this time being 58.6% for ACR20 and 69.6% for the DAS28. Response rates then increased slightly over time until the end of the study period at 3 months. In this relatively short trial, it is not possible to address long-term treatment outcome.

With respect to safety, the adverse events observed were consistent with the known safety profile of LEF [35], and no unanticipated safety issues were identified. The frequency of serious adverse events (5.0%) and of adverse events leading to treatment discontinuation (12.4%) were both low, considering that the occurrence of adverse events was actively sought after by the investigator at each study visit.

A secondary objective of the study was to compare the efficacy and safety of the FD and LD groups. No additional benefit was demonstrated with the use of the LD regimen on any of the efficacy outcomes and indeed, on the primary outcome measure, the response rate obtained in the FD group was significantly higher than in the LD group. With respect to safety, the incidence of gastrointestinal side effects and of elevated liver enzymes reported as adverse events was higher in the LD group, and patients in this group experienced adverse events earlier than did patients in the FD group.

The finding of a superior efficacy in the FD group with respect to the primary outcome measure was unanticipated. We have no explanation for this finding, although it cannot be excluded that imbalance between the two groups with respect to glucocorticoid use may contribute to the observed difference. Indeed, the findings of the Better Antirheumatic Pharmacotherapy (BARFOT) study indicated that patients with early RA treated with DMARDs and glucocorticoids had a better outcome than those receiving DMARDs alone [36]. It should be noted, however, that the between-group difference in glucocorticoid use was not statistically significant and that glucocorticoid use had been stable for the month preceding inclusion (as specified in the eligibility criteria) and remained stable throughout the follow-up period for the majority of patients. In addition, the higher occurrence of gastrointestinal side effects in the LD group may in some way compromise efficacy, or its measurement.

The statistical power of the study was insufficient to assess non-inferiority of the FD regimen compared with the LD regimen at the earlier time point of 1 month. Although use of a loading dose of LEF seems pertinent from a theoretical perspective, and indeed is currently recommended in the prescribing information for this drug, up until now the potential benefits of treatment regimens with and without a loading dose have not been compared formally in a randomized clinical trial. Our study addresses this issue for the first time and does not confirm the anticipated benefit of the use of a loading dose within the first 3 months of treatment in DMARD-naïve patients with early RA. The implication of this finding is that current practice may need to be revised to offer more flexibility in how LEF treatment is initiated, with the option to forego the use of a loading dose if this is deemed necessary. This may be particularly relevant in early RA, where concerns about tolerability may be a barrier to initiating treatment and remaining adherent through the early phase of therapy.

The study has several strengths and limitations. Among the strengths, the high proportion of randomized patients who completed the study without protocol violations indicates that the findings should be reliable. Secondly, the included patients were representative of early RA in terms of age, gender and biological markers, although tender and swollen joint counts and the extent of radiographic changes tended to be lower than in several other clinical trials of early RA [27–29, 37] in which the disease duration eligibility criterion was less stringent than in the present study. Finally, consistent improvements over the study period were observed for all outcome measures, suggesting that the findings are robust. With respect to limitations, the absence of a placebo group has already been alluded to. Secondly, the study enrolled fewer patients than anticipated (124 rather than 200), which may have led to some underpowering of the study, in particular for comparing the LD and FD groups. Nonetheless, the targeted precision for the primary outcome measure (95% CI $<10\%$) was achieved, and there was no suggestion on any of the outcome measures for a trend towards superior efficacy of the loading dose that could have been established in a larger patient cohort. In addition, there was some imbalance in randomization, which can probably be explained by the relatively large number of participating centres, several of whom only used a single block of four randomization numbers that were not all attributed. It should also be noted that the study was performed before publication of the 2010 EULAR guidelines [3]; in the light of these guidelines, future trials may consider

other designs, for example using remission as a primary endpoint, as more appropriate. In addition, we have no information on potential structural effects of treatment, since data on radiological outcome were not collected. This needs to be addressed in future studies in order to provide a clearer picture of the overall treatment benefit conferred by LEF in early RA, and in particular when used over the long term.

In conclusion, the treatment of DMARD-naïve patients with early RA with LEF over a 3-month period provides a response rate that compares favourably with that observed with this drug in established RA. However, no incremental overall benefit was observed with the use of an LD regimen compared with a fixed dose of 20 mg/day from the beginning; on the contrary, the ACR20 response rate was significantly higher in the FD group. Moreover, the LD regimen appeared to be associated with more tolerability issues in the early phase of treatment. The benefit of the current practice of initiating LEF treatment with a loading dose in this population is not confirmed in the present study.

Rheumatology key messages

- This study confirms earlier results regarding the efficacy of LEF in early RA.
- No additional benefit was observed from initiating treatment of RA with a loading dose of LEF.

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