

Leflunomide in psoriatic arthritis: a retrospective study of discontinuation rate in daily clinical practice compared with methotrexate

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Received on January 24, 2007; accepted in revised form on May 29, 2007.

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Key words: Psoriatic arthritis, safety, leflunomide, methotrexate.

ABSTRACT

Objective. To assess the safety profile of leflunomide (LEF) in a two-year retrospective analysis of psoriatic arthritis (PsA) patients (pts) treated in daily clinical practice compared with methotrexate (MTX).

Patients. Forty-two PsA patients with polyarticular involvement or asymmetrical oligoarticular arthritis, satisfying ESSG criteria for the spondyloarthropathies, treated with LEF monotherapy (10-20mg/die without loading dose) between September, 2004 and August, 2006 were reviewed. They were compared with MTX (7.5-15mg/week) users (44 cases). The adverse events (AEs) and the causes of withdrawal were evaluated.

Results. At 24 months, cumulative survival rate of pts remaining on drugs was 54.9% in LEF users and 57.0% in MTX users ($p > 0.05$). The discontinuation rate (DR) for toxicity was higher in LEF group (29.2%) than in MTX group (10.8%) ($p = 0.07$). The occurrence of AEs was more frequently registered in the first year in both groups. LEF monotherapy showed a significant higher crude incidence for any AEs (38.7 events x100 person-years) compared to MTX (14.3 events x100 person-years) ($p < 0.001$). The cumulative DR for inefficacy was greater but not statistically significant in MTX group than LEF (28.6% vs. 12.6% respectively; $p = 0.056$). Finally, DR for other causes accounted for 8.7% vs. 11.0% respectively ($p > 0.05$).

Conclusions. Our data showed, in a setting of clinical practice, that the rate of PsA pts remaining on drug was comparable between LEF and MTX, and a manageable LEF safety profile during a 24 months of follow-up, even if a greater incidence of DR for AEs was registered than in MTX users.

Introduction

Leflunomide (LEF) is an isoxazole derivate that has immunomodulatory effects for the inhibition of the de novo pyrimidine synthesis, by its active metabolite (A77-1726) (1). It has been demonstrated in randomized clinical trials (RCTs) its efficacy and safety as disease-modifying antirheumatic drug

(DMARD), in rheumatoid arthritis (RA) (2) and in psoriatic arthritis (PsA) (3).

Nevertheless, recent post-marketing observational studies have pointed out that LEF has a higher discontinuation rate (DR) for toxicity than expected (4, 5). Moreover, there is a lack of long-term evaluation of safety and efficacy of LEF in RCTs of PsA, such as in practice care.

In this retrospective cohort study of PsA patients, we investigated the safety profile of LEF and compared it with that of methotrexate (MTX) in a setting of rheumatology practice.

Patients and methods

Patients

Clinical charts of consecutive outpatients with PsA, seen at the Rheumatology Unit of Second University of Naples between September 2004 and August 2006, were reviewed. All patients satisfied the ESSG criteria for spondyloarthropathies (6) and had polyarticular involvement or asymmetrical oligoarticular arthritis. They were treated with LEF or MTX according to a flexible protocol that takes into account their efficacy and safety.

Safety protocol

All patients attending our clinic followed a program of drug surveillance including the collection of clinical and laboratory data as follows: a)- physical examination at baseline visit and during the follow up every 3 months; b)-evaluation of biochemical tests (*i.e.*, liver function tests, blood cell count and platelets, creatininemia and urinalysis) every 6-8 weeks; c)-instrumental investigations (*i.e.*, chest x-ray and liver echography every 12 months or when appropriate).

Biochemical abnormalities were evaluated according to the respective normal ranges. In particular, were considered, as abnormal, the changes of the transaminases levels > 2 times ULN; white cell count $< 3.500\text{mmc}$; platelet count $< 100.000\text{mmc}$; creatininemia $> 1.4\text{mg/dl}$.

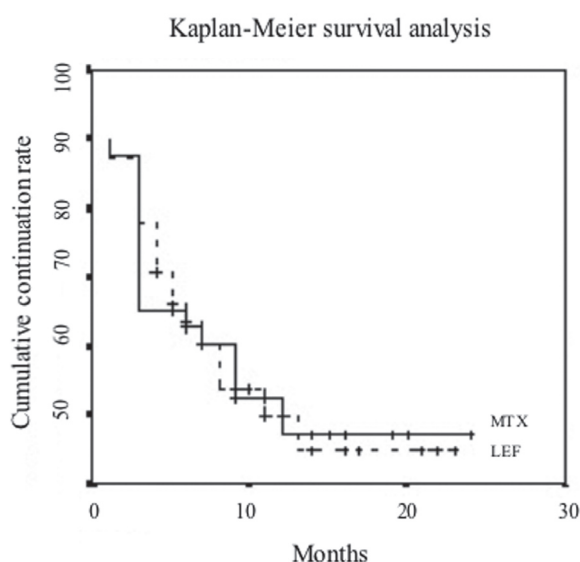
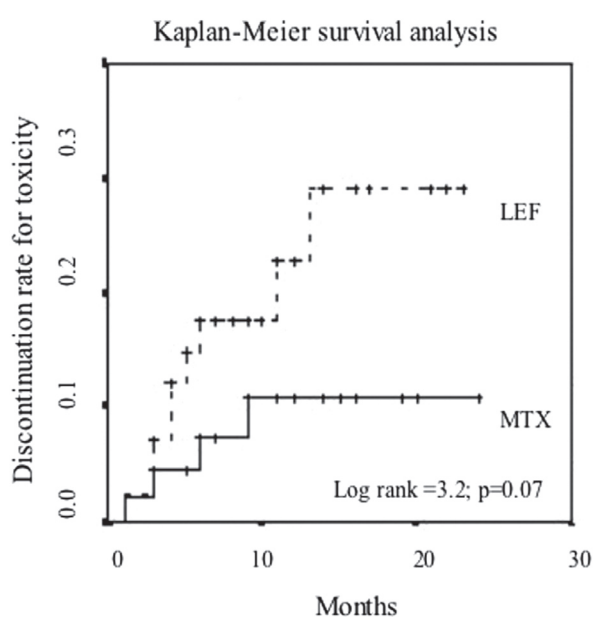
The adverse events (AEs) were defined as new medical condition or worsening of a pre-existing medical condition occurring during the treatment period.

Competing interests: none declared.

Table I. Epidemiological and clinical characteristics of 86 patients with psoriatic arthritis.

	LEF group No. 42	MTX group No. 44
Age (years), mean $\pm$ SD	46.4 $\pm$ 12.1	48.9 $\pm$ 10.6
Sex, female:male ratio	1.6:1	1.1:1
Disease duration (years), mean $\pm$ SD	3.9 $\pm$ 2.9	7.4 $\pm$ 5.7
No of previous DMARDs, mean $\pm$ SD	1.6 $\pm$ 0.60	1.5 $\pm$ 0.9
Number of naive, n (%)	26 (61.9)	26 (59.1)
Concomitant NSAIDs (%)	11/42 (26.2)	9/44 (20.5)
Corticosteroids (%)	12/42 (28.6)	7/44 (15.9)
Concomitant disease (%)	19.0	29.5
Diabetes mellitus, n. cases	1	4
Hypertension, n. cases	3	8
Hypothyroidism, n. cases	3	0
Lipid disorders, n. cases	1	1

LEF: leflunomide; MTX: methotrexate.

**Fig. 1.** Cumulative continuation rate of treatment with leflunomide (LEF) or methotrexate (MTX) in psoriatic arthritis patients.**Fig. 2.** Cumulative discontinuation rate of treatment for toxicity with leflunomide (LEF) or methotrexate (MTX) in psoriatic arthritis patients.

They were divided into minor or major events, if hospitalization occurred.

The reasons for DR were classified as discontinuation due to AEs, inefficacy, or other reasons.

Statistical analysis

Data were expressed as mean $\pm$ standard deviation (SD) or 95% confidence interval (CI), when appropriate. All statistical calculations were performed using SPSS software for PC. The differences in the frequencies of AEs between the groups of treatment were compared using Fisher's exact probability test. Mann-Whitney for independent samples was used to compare ordinal data. Cumulative survival rates were analyzed according to Kaplan-Meier method and Log-rank test. Cox regression was used to compare toxicity DR of the LEF or MTX, controlling for potential confounders as age, disease duration, or comorbidities. Statistical significance was set as $p < 0.05$.

Results

According to the safety end point, out of the 91 pts reviewed, we included in this study only 86 with monotherapy courses of LEF (42 pts) or MTX (44 pts), excluding the courses of combination therapy with other DMARDs (4 courses), or biological agents (one course) prescribed in patients who did not respond to monotherapy during the follow-up.

Table I shows the epidemiological and clinical characteristics of our PsA patients divided according to drug exposure. They were comparable for age and sex, whereas disease duration was higher in MTX users than LEF, with statistical significant difference ($p < 0.001$). Almost half of the patients were DMARD naive at study entry. The remaining patients had received prior treatment with almost one DMARD (*i.e.* sulfasalazine 1-2g/die, cyclosporine A 100-200mg/die, methotrexate 7.5-15mg/week). Two out of 42 LEF patients had been previously treated with MTX, whereas none of MTX group had received LEF.

They contributed 85.0 person-years of total follow-up, with a mean time of drug exposure of 11.9 months.

Forty-two patients had received a pre-prescription of LEF 20mg/die without loading dose. At the last visit, the daily dose was 10mg in 2 patients. LEF monotherapy exposure accounted for 36.2 person-years of follow-up, with a mean time of 10.3 months.

Forty-four patients used MTX 7.5-15mg/week; at the last visit, the weekly dose was 10 mg in 2 pts. MTX monotherapy exposure accounted for 48.8 person-years of follow-up, with a mean time of 13.3 months. The MTX exposure was longer than that of LEF, but not significantly different.

Nineteen out of 86 (22.1%) patients used a low dose of glucocorticoids (median dose of prednisone equivalent 7.5mg/die) and/or 20 out of 86 (23.3%) pts NSAIDs/Cox2-inhibitors to standard daily dosage. All MTX patients used drug supplementation with folic acid at 5 mg/week.

The relevant comorbidity registered in our cohort are listed in Table I. Patients were using drugs for concomitant hypertension (Ca-antagonists, 6 cases; ACE-inhibitors, 3; Beta-blockers, 2); for diabetes mellitus, oral hypoglycemic drugs, (5 cases); for dislipidemia, statins (2 cases); for hypothyroidism, L-tiroxine (3 cases).

The cumulative survival rate of continuation treatment was 54.9% in LEF users and 57.0% in MTX users at 24 months. No significant difference between the two groups emerged (Fig. 1). Thus, the cumulative DR for all causes was 45.1% and 43.0%, respectively. It was caused by toxicity in 29.2% of LEF group and 10.8% of MTX group (Log rank 3.2; $p = 0.07$), and their occurrence was above all more frequently registered in the first year of follow-up (Fig. 2). In particular, that frequency of DR was due to the occurrence of 7/11 AEs in LEF patients vs. 3/5 in MTX pts at 6 months, and 10/11 AEs vs. 5/5, at 12 months, respectively. Controlling for potential confounders, such as age, disease duration, and comorbidities, multivariate analysis (Cox regression) with stepwise procedure showed that age and disease duration were the only significant predictors for toxicity discontinuation.

LEF monotherapy had a higher crude incidence rate for any AEs (38.7 events

x100 person-years) compared to MTX monotherapy (14.3 events x 100 person-years) ($p < 0.001$).

The AEs are listed in Table II. No major events were observed. Of the 11 LEF users who discontinued because of AEs, 3 cases were for hypertransaminasemia, 2 for diarrhea, 2 for nausea, 2 for hypertension, 2 for leucopenia. Of the 5 patients who discontinued MTX, 4 cases were for hypertransaminasemia and one for nausea. In 2 out of 4 patients in which hypertension was registered, a Ca-antagonist co-medication was added and the treatment continued reducing LEF dosage to 10 mg/die. Similarly 2 out of 3 patients with nausea or dyspepsia, continued MTX reducing dosage from 15mg/week to 10 mg/week.

The cumulative DR for inefficacy at 24 months of follow up resulted higher, but not statistically significant, in MTX (28.6%) than in LEF (12.6%) (Log rank 3.7, $p = 0.056$). Finally, cumulative DR for other causes accounted only for 8.7% vs. 11.0%, respectively ($p > 0.05$).

Discussion

To our knowledge, this is the first study that analyzes the safety of LEF 20 mg/die without loading dose in the treatment of PsA over 2 years in a setting of practice care on unselected patients.

A significantly higher crude incidence rate for all AEs was registered in patients using LEF than those with MTX. This finding is in contrast with the results reported by Cannon *et al.* in a large retrospective cohort of RA patients (7). This discrepancy might be due to epidemiological and clinical differences between the two populations,

to different cohort size, and or to study design that analyzed claims database.

As expected, laboratory abnormalities, such as hypertransaminasemia, and dyspepsia were more frequently registered. Nevertheless, according to Cohen *et al.* (8) we were not able to demonstrate statistically significant differences on their frequency between LEF and MTX users during the 24 months of follow-up. On the contrary, occurrence of hypertension in patients at risk was registered only in those using LEF (12.5 events x100 person-years), confirming its great frequency even in other databases (8, 9).

In the LEF group, an abnormal level of transaminases was the most common cause of discontinuation, as reported by Emery *et al.* (9). Almost 50% of the AEs were detected during the first 24 weeks of treatment, such as in the MTX group. On the whole, the AEs occurred more frequently during the first year of follow-up, as reported in both observational studies of clinical practice and RCTs on RA (4, 5, 8, 9). However, our results showed a lower DR for LEF toxicity than that reported by Kaltwasser *et al.* in a study of 24 weeks (3), as observed also in some clinical care studies on RA during a 1-year follow-up (4, 5). Therefore, we confirm that the reduction of LEF dose could avoid the discontinuation of treatment. Moreover, our data indicate that even if the total DR of LEF is comparable with that of MTX (45.1% vs. 43.0%, respectively), LEF shows both a higher DR for toxicity (29.2%) and a lower DR for inefficacy (12.6%) than that of MTX (10.8% and 28.6%, respectively).

Table II. Adverse events registered during the follow-up in 86 patients with psoriatic arthritis treated with leflunomide (LEF) or methotrexate (MTX).

Adverse Events	LEF users n. 42	MTX users n. 44
Cases (%)	14 (33.3)	7 (15.9)
Nausea	2 (4.8)	3 (6.8)
Diarrhea	2 (4.8)	-
Hypertransaminasemia (>2ULN)	4 (9.5)	4 (9.1)
Hypertension*	4 (9.5)	-
Leucopenia	2 (4.8)	-

*WHO criteria

Finally, we confirm previous data on lower efficacy of MTX than LEF in PsA patients (10).

Our study has the limitations of a retrospective analysis and included a relatively small number of patients.

The patients treated with MTX received a low dose (7.5-15mg weekly), since it is considered an effective dosage in PsA, as demonstrated in 2 RCTs (11, 12). In addition, a meta-analysis detected a higher risk of liver toxicity from long-term administration of MTX in PsA than in RA patients (13).

In our cohort of PsA, 22% of the patients used steroids. This frequency is not different from that reported in a multicenter study on clinical practice (24%) (14), and in a clinical trial (3). The frequent use of steroids by rheumatologists in PsA patients has been confirmed in a recent review (10).

In conclusion, our study indicates that, during two years of follow-up, LEF 20 mg/die showed a manageable safety profile in PsA, even if, a higher incidence of DR for AEs was registered than for MTX. A prospective follow-up on those patients might give useful indications on longer-term safety of LEF.

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