Clinical and Experimental Rheumatology 2006; 24: 168-171.

Leflunomide in rheumatoid arthritis in daily practice: treatment discontinuation rates in comparison with other DMARDs

I. Bettembourg-Brault, L. Gossec, T. Pham, J.-E. Gottenberg, J. Damiano, M. Dougados

Rheumatology B Department, Cochin Hospital, AP-HP, Rene Descartes University, Paris, France

Isabelle Bettembourg-Brault, MD: Service de Rhumatologie B, Nancy-Brabois Hospital, Vandoeuvre les Nancy, France. Laure Gossec, MD, Joel Damiano, MD, Maxime Dougados, MD: Rheumatology B Department, Cochin Hospital, AP-HP, Rene Descartes University, Paris, France. Thao Pham, MD: Service de Rhumatologie Sud, Conception Hospital, AP-HM, Marseille, France.
Jacques-Eric Gottenberg, MD: Service de Rhumatologie, Kremlin-Bicetre Hospital, AP-HP, Kremlin-Bicetre, France.

Address correspondence to Laure Gossec, MD (laure.gossec@cch.aphp.fr) and reprint requests to Pr. Maxime Dougados, at Service de Rhumatologie B, Hardy B2, hôpital Cochin, 27, rue du faubourg St Jacques, 75014 Paris, France.

Received on January 10, 2005; accepted in revised form on October 6, 2005.

Keys words: Leflunomide, termination rate, rheumatoid arthritis, continuation, clinical practice, retrospective, DMARDs, efficacy, tolerance.

ABSTRACT

Objective. *To evaluate the treatment discontinuation rate of leflunomide in rheumatoid arthritis (RA) in comparison with the discontinuation of other disease modifying anti-rheumatic drugs (DMARDs), in daily practice, in a single center and during the same period of time.*

Methods. *Study design: 3-year, retrospective, monocenter. Patients: RA patients for whom leflunomide or another DMARD was initiated between 1998 and 2001 (several DMARDs could be initiated for a given patient during this period). Collected data: For each patient, demographic and disease data. For each treatment course, date of initiation, if relevant date of discontinuation and reason for discontinuation. Analysis: Percentage of patients discontinuing treatment over time (life table method; Kaplan-Meier), comparison between leflunomide and the "any other DMARD" or methotrexate groups using the Log-Rank test.*

Results. *During the study period, 515 DMARDs were initiated in 285 patients. Leflunomide was initiated in 161 patients who were older and had a longer disease duration than the other treated patients (59 ± 13 years and 14 ± 9 years versus 54 ± 15 years and 11 ± 10 years in the leflunomide group and other DMARDs group respectively). Discontinuation rate of leflunomide after 1 year was 56.7%, mainly because of adverse drug reactions (41.6%). The discontinuation rate whatever the reason and for toxicity was higher for leflunomide than for other DMARDs studied. However discontinuation for inefficacy was similar in both groups.*

Conclusion. *This study conducted in conditions of daily practice when leflunomide was first available suggests a higher discontinuation rate of leflunomide because of adverse events when compared to other DMARDs.*

Introduction

Leflunomide represents a novel class of disease modifying anti-rheumatic drugs (DMARD), the isoxazole derivatives. Efficacy and safety of leflunomide for the treatment of rheumatoid arthritis (RA) have been demonstrated in randomized controlled trials that included over 1000 patients treated with leflunomide (1-7). These trials indicated a relatively high treatment continuation rate (after 1 year, 50%). However, by inclusion of patients based on selection criteria and strict follow-up, the trial setting is different from daily clinical practice in rheumatology, which may limit the extrapolation of data from trials to RA patients in clinical practice. Thus observational studies are important in daily practice notably with newly approved therapies (8).

The percentage of patients still on treatment over time has been proposed as a relevant tool to evaluate the different aspects of effectiveness of a treatment (9). Lack of efficacy and adverse effects can be evaluated by the rate of discontinuation due to these 2 aspects. However, if discontinuation rates are to have optimal clinical relevance, they have to be compared to those of other drugs, in the same setting (same physician, same period of time).

In this study we evaluated the discontinuation rates of leflunomide in comparison with other DMARDs, introduced during the same period, in the same department, and we compared the causes of treatment interruption (inefficacy or toxicity).

Material and methods

Patients

All outpatients of our rheumatology tertiary-referral department fulfilling the diagnosis of RA according to the 1987 ACR criteria, and for whom leflunomide was initiated between September 1, 1998 and June 30, 2001, were included. In France, leflunomide was first available on September 1, 1998 and we wished to study the period following initial availability of the drug. A sample of other RA patients followed-up in our department were also screened [in common with another study selecting RA patients on the basis of availability of HLA-typing (10)], to obtain data on other DMARD treatment courses initiated during the same period of time. DMARD initiations studied were either leflunomide or one of the following: methotrexate, gold salts, sulfasalazine, TNF alpha inhibitors, or

hydroxychloroquine. Patients for whom several DMARDs were initiated (including or not leflunomide) between September 1998 and June 2001 were thus analyzed several times.

Data collection

Data was collected retrospectively based on perusal of the whole medical records and if necessary by contacting patients by telephone. A standard dataset consisted of patients' and disease characteristics, and for each course of DMARDs initiated during the target time-frame, we collected the date of initiation, the date of the last visit, if relevant the date of discontinuation and the reason for discontinuation. This reason could be inefficacy, toxicity, both, or other and was determined by expert physicians, based on clinical and biological data. For leflunomide, treatment in mono-therapy or in combination with other DMARDs was noted.

Statistical analysis

Descriptive statistics were used to compare patients at initiation of a DMARD. Treatment discontinuation rates were analyzed using survival by the Kaplan-Meier life-table method, showing the cumulative percentage of patients stopping a treatment regimen function of time. The life-table curves of leflunomide versus the other DMARDs were compared using the Log-rank test with a validity control. To avoid multiple testing, leflunomide was compared only to the group "any other DMARD" and to the group "methotrexate". There was a secondary analysis concerning cause of withdrawal: intolerance or inefficacy.

Results

Patients and treatment courses

Of the 456 screened patients, 285 were eligible for the study since they fulfilled the ACR criteria for RA and since in all of them at least one course of DMARDs was initiated during the study period. During the 34-month period, 515 DMARDs were initiated in 285 patients (Table I). Leflunomide was initiated in 161 patients. Leflunomide was given as mono-therapy in 109 patients and in combination in 52 (second drug was: methotrexate n = 26, hydroxychloroquine n = 15, gold salts n = 10, sulfasalazine n = 1). The other most frequently prescribed drugs were methotrexate (n = 114), hydroxychloroquine (n = 83) and gold salts (n = 65). These drugs are often prescribed as part of combination therapies in our department.

The characteristics of the 285 patients at the time of initiation of each course of DMARD are summarized in Table I. Patients receiving leflunomide were significantly older (59±13 years versus 54±15 years, p=0.005) and had a longer disease duration (14 ± 9 years versus 11 ± 10 years, p = 0.012) than the group initiated with any other DMARD.

Leflunomide and other DMARD discontinuation rates after one year of follow-up (Table II)

Whatever the reason for discontinuation. Discontinuation rate of leflunomide after 1 year was 56.7%, versus 31.6% for methotrexate, 45.9% for hydroxychloroquine and 53.3% for gold salts. The discontinuation rate whatever the reason was higher for leflunomide than for the pooled group of other studied DMARDs (p = 0.005) and was also higher than for methotrexate (p < 0.0001).

Discontinuation for inefficacy (Fig. 1). Discontinuation rate of leflunomide after 1 year for inefficacy was 33.3%, versus 18.2% for methotrexate. The discontinuation rate for inefficacy was not higher for leflunomide than for the

Table I. Baseline characteristics of patients (N = 285) with regard to the DMARD initiated (number of treatment courses = 515). Note that some patients appear several times, when several treatments were initiated during the study period.

	Leflunomide	Methotrexate	Hydroxychloroquine	Gold salts	Sulfasalazine	Anti-TNFα	p-value*
Number of patients	161	114	83	65	40	42	
Age (years), mean ± SD	59 ± 13	54 ± 15	52 ± 14	53 ± 15	51 ± 12	51 ± 14	0.005
Sex, % females	78	83	72	81	75	78	NS
Disease duration (years), mean ± SD	14.0 ± 9.2	9.6 ± 8.0	8.5 ± 7.7	8.6 ± 6.7	11.3 ± 7.2	7.7 ± 5.4	0.012
Number of previous DMARDs, mean ± SD	4.5 ± 1.7	4.0 ± 0.9	3.5 ± 1.1	3.9 ± 1.3	5.3 ± 1.9	4.3 ± 1.4	NS
% rheumatoid factor positive	78	72	87	71	88	67	NS

DMARD: disease modifying drug. SD: standard deviation. NS = non significant.
* Statistical significance concerns comparison of leflunomide initiation patients with any other DMARD initiation patients.

Table II. Treatment discontinuation rates after 1 year of treatment with regard to the DMARD (% standard deviation).

	Leflunomide	Methotrexate	Hydroxychloroquine	Gold salts	Sulfasalazine	Anti-TNF	p-value*
Discontinuation whatever the reason	56.7 ± 0.1	31.6 ± 0.1	45.9 ± 0.1	53.3 ± 0.1	59.3 ± 0.2	38.0 ± 0.2	0.005
Discontinuation for inefficacy	33.3 ± 0.1	18.2 ± 0.1	28.8 ± 0.1	37.9 ± 0.1	39.9 ± 0.2	35.8 ± 0.2	NS
Discontinuation for toxicity	41.6 ± 0.1	10.4 ± 0.1	15.3 ± 0.1	17.2 ± 0.1	22.3 ± 0.1	0	0.005

*Statistical significance (Log-Rank test) comparing the leflunomide group with the "any other DMARD" group.

pooled group of other studied DMARDs; however, it was higher than for methotrexate (p = 0.008).

Discontinuation for adverse effects (Fig. 2). Discontinuation rate of leflunomide after 1 year for adverse effects was 41.6%, versus 10.4% for methotrexate. The discontinuation rate for inefficacy was significantly higher for leflunomide than for the pooled group of other studied DMARDs (p = 0.005) and was also higher than for methotrexate (p < 0.0001).

Discontinuation for both inefficacy and adverse effects. 16 patients (10%) taking leflunomide discontinued treatment for both inefficacy and adverse effects.

Leflunomide in monotherapy versus in combination with other DMARDs. There were no statistically significant differences between the discontinuation rates of the two sub-groups (data not shown).

Adverse drug reactions leading to discontinuation of leflunomide

Intolerance resulted in the withdrawal of leflunomide in 57 patients of which 14 suffering from 2 or more undesirable effects. Side-effects were as follows: 19% digestive side-effects, 19% skin side-effects, 18% hypertension, 12% significant weight loss, 10% hepatic intolerance (liver enzymes above twice upper limit of the norm), 2% leucopenia, 21% other side effects (4 patients dyspnoea, 2 anaemia, 2 thoracic pain, 1 chronic cough, 1 severe infection, 1 headache, 1 gingivitis). No death was noted over the study period.

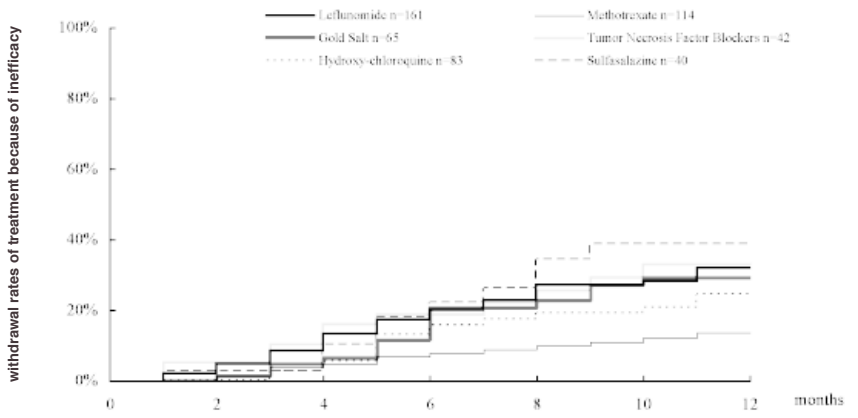

Fig. 1. Discontinuation rates for leflunomide and other DMARDs over time due to inefficacy (Kaplan-Meier life table method).

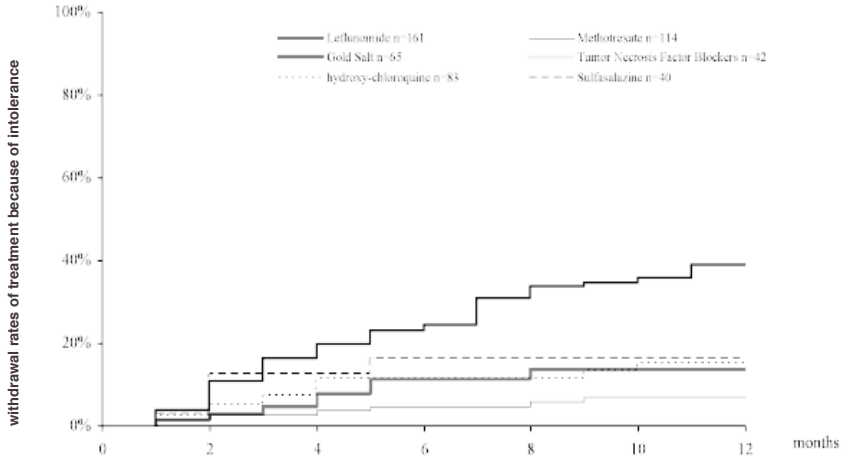

Fig. 2. Discontinuation rates for leflunomide and other DMARDs over time due to toxicity. (Kaplan-Meier life table method).

Discussion

Studies of patient populations outside the setting of randomized controlled trials are important to learn about drug efficacy and safety in daily clinical practice (11, 12). This study offers a picture of the use of leflunomide in a French department in the first 3 years of its availability.

Some remarks should be made on the limitations of the present study. One question is the representativity of the leflunomide patients and "controls" (other DMARDs patients) included, versus RA patients followed-up in our department. Indeed, although every consecutive patient receiving leflunomide during the target period was included, not every patient initiating a DMARD during the same period was included, due to the impossibility of selecting directly through a computer search the correct charts; however, it is estimated that the 285 patients represent ~ 50% of all treatments initiated during the time-frame. Furthermore, the selection of "other DMARD" patients can be considered close to a random selection, since the selection was based only on availability of HLA-typing for these patients (10). External validity can also be limited because patients treated with leflunomide were older and had a longer duration of disease. This indicates that leflunomide was given to more severe RA patients, patients who had often run out of other treatment options, possible also "poor responders", which could of course influence results, but also reflects frequent treatment algorithms for RA (13).

This study suggests that leflunomide had a higher discontinuation rate than other DMARDs [notably methotrexate (14, 15)], which is not the result observed in controlled trials, but was however noted in another study in daily practice (16). Tolerance often seems, as here, to be the main reason for discontinuation (13, 16); the side effects observed here are similar to those described in the literature (3, 7).

Some possible reasons for the high discontinuation rates observed for leflunomide during the period immediately following its licensing for the treatment of RA include factors such as patients' subjectivity in regard to a new drug, physicians' prescription habits, worries about toxicity (e.g. for leflunomide,

liver toxicity which was an initial concern) (17). Furthermore, anti-TNF drugs became available at the same period, which may have encouraged physicians to switch therapeutics rather "easily". These elements may also partly explain the high discontinuation rates noted for anti-TNF therapies. Another element is that in our study, leflunomide dosage was classic, 20 mg/d after a loading dose, whereas it has been recently recommended to reduce leflunomide dosage or to avoid the loading dose to reduce adverse events (18).

In our study, the combination of leflunomide with other DMARDs seemed to be well tolerated, which confirms the possibility of using leflunomide in combination therapy (19).

Leflunomide offers an efficacious treatment option, although discontinuation rates in the present study were high. More experience with this drug should help physicians determine the optimal place of leflunomide for the management of RA.

References

1. STRAND V, COHEN S, SCHIFF M *et al.*: Treatment of active rheumatoid arthritis with leflunomide compared with placebo and methotrexate. *Arch Intern Med* 1999; 159: 2542-50.
2. SMOLEN J, KALDEN J, SCOTT D *et al.*: Efficacy and safety of leflunomide compared with placebo and sulphasalazine in active rheumatoid arthritis: a double-blind, randomised, multicentre trial. *Lancet* 1999; 353: 259-66.
3. SHARP J, STAND V, LEUNG H *et al.*: on behalf of the LEFLUNOMIDE ARTHRITIS INVESTIGATORS GROUP: Treatment with Leflunomide slows radiographic progression of rheumatoid arthritis. *Arthritis Rheum* 2000; 43: 495-505.
4. EMERY P, BREEDVELD C, LEMMEL E *et al.*: A comparison of the efficacy and safety of Leflunomide and methotrexate for the treatment of rheumatoid arthritis. *Rheumatology* 2000; 39: 655-65.
5. COHEN S, CANNON G, SCHIFF M *et al.*: Two-year, blinded, randomized, controlled trial of treatment of active rheumatoid arthritis with leflunomide compared with methotrexate. *Arthritis Rheum* 2001; 44: 1984-92.
6. DOUGADOS M, EMERY P, LEMMEL EM *et al.*: Efficacy and safety of Leflunomide and predisposing factors for treatment response in patients with active rheumatoid arthritis: RELIEF 6-month data. *J Rheumatol* 2003; 30: 2572-9.
7. KALDEN JR, SCHATTENKIRCHNER M, SORENSEN H *et al.*: The efficacy and safety of Leflunomide in patients with active rheumatoid arthritis: a five-year followup study. *Arthritis Rheum* 2003; 48: 1513-20.
8. PINCUS T, STEIN CM: Why randomized controlled clinical trials do not depict accurately long-term outcomes in rheumatoid arthritis: some explanations and suggestions for future studies. *Clin Exp Rheumatol* 1997; 15 (Suppl. 17): S27-38.
9. DOUGADOS M, NGUYEN M, DUCHESNE L, BENJELLOUN M, AMOR B: Evaluation of the usefulness of delayed-action preparations in the treatment of rheumatoid polyarthritis by analyzing the therapeutic maintenance dose. *Rev Rhum Mal Osteoartic* 1989; 56: 89-92.
10. GOSSEC L, BETTEMBOURG-BRAULT I, PHAM T, DOUGADOS M: HLA DR phenotyping does not predict the need for joint surgery in rheumatoid arthritis. A retrospective quantitative evaluation of 300 French patients. *Clin Exp Rheumatol* 2004; 22: 462-4.
11. SOKKA T, PINCUS T: Most patients receiving routine care for rheumatoid arthritis in 2001 did not meet inclusion criteria for most recent clinical trials or American College of Rheumatology criteria for remission. *J Rheumatol* 2003; 30: 1138-46.
12. SOKKA T, PINCUS T: Eligibility of patients in routine care for major clinical trials of anti-tumor necrosis factor alpha agents in rheumatoid arthritis. *Arthritis Rheum* 2003; 48: 313-8.
13. VAN ROON EN, JANSEN TL, MOURAD L *et al.*: Leflunomide in active rheumatoid arthritis: a prospective study in daily practice.
14. WOLFE F, HAWLEY DJ, CATHEY MA: Termination of slow acting antirheumatic therapy in rheumatoid arthritis: a 14-year prospective evaluation of 1017 consecutive starts. *J Rheumatol* 1990; 17: 994-1002.
15. PINCUS T, MARCUM SB, CALLAHAN LF: Longterm drug therapy for rheumatoid arthritis in seven rheumatology private practices: II. Second line drugs and prednisone. *J Rheumatol* 1992; 19: 1885-94.
16. ALETAHA D, STAMM T, KAPRAL T *et al.*: Survival and effectiveness of Leflunomide compared with methotrexate and sulfasalazine in rheumatoid arthritis: a matched observational study. *Ann Rheum Dis* 2003; 62: 944-51.
17. WEINBLATT M, DIXON J, FALCHUK K: Serious liver disease in a patient receiving methotrexate and Leflunomide. *Arthritis Rheum* 2000; 43: 2609-13.
18. MADDISON P, KIELY P, KIRKHAM B *et al.*: Leflunomide in rheumatoid arthritis: recommendations through a process of consensus. *Rheumatology* (*Oxford*) 2005; 30: 5001.
19. DOUGADOS M, EMERY P, LEMMEL EM *et al.*: When a DMARD fails, should patients switch to sulfasalazine or add sulfasalazine to continuing leflunomide? *Ann Rheum Dis* 2005; 64: 44-51.