

Effectiveness and safety profile of leflunomide in rheumatoid arthritis: actual practice compared with clinical trials

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Abstract

Objective

Leflunomide, an immunosuppressant agent for treating rheumatoid arthritis, was first marketed in France in 2000. Three years after its launch, we sought to assess its prescription patterns in the real world of prescription and use, and to see if its efficacy and safety profiles observed during clinical trials were confirmed.

Methods

All patients treated with leflunomide from May 2000 to April 2003 in the Department of Rheumatology of the Bordeaux University Hospital were identified, and their treatment patterns and outcome ascertained. This was compared to data from clinical trials.

Results

116 were included (mean age = 55 years, 70% women). Almost 21.7% stopped treatment for lack of efficacy (after a mean delay of 3.6 months), 16% for secondary loss of efficacy (median = 7 months), and 32% for the occurrence of an adverse event (half within 4 months). Over a similar time frame in clinical trials, in patients of about the same age and sex but with less severe disease, the corresponding figures were 7-17% for lack or loss of efficacy, and 14-22% for adverse effects. At one year of follow-up, the discontinuation rate was 70% in the cohort compared to 28-47% in clinical trials.

Discussion

The differences between the two populations confirm the need to conduct post-marketing studies in order to obtain better knowledge on the effectiveness and safety of a new drug. In many cases, a simple drug utilization study can provide relevant information on the degree of shift between populations included in clinical trials and those treated in real life.

Key words

Leflunomide, clinical trials, drug utilization, effectiveness, drug safety.

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Introduction

Rheumatoid arthritis (RA) is a progressive disease that is characterized by chronic synovial inflammation leading to destruction of the joints and functional disability. Treatment may be symptomatic with non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids, or may attempt to minimize joint damage and to postpone disease progression by using disease-modifying antirheumatic drugs (DMARDs) such as gold salts or immunosuppressives. However, long-term use of DMARDs often results in poor therapeutic response, secondary loss of efficacy or occurrence of adverse effects (1,2).

Leflunomide, a novel DMARD active on RA, was first marketed in France in 2000. This anti-rheumatic drug inhibits *de novo* pyrimidine synthesis by *reversible* selective inhibition of dihydroorotate dehydrogenase (DHODH). Nevertheless, due to its immunosuppressive activity, it is prone to induce various adverse effects. This cumulative toxicity is reinforced by the chronic nature of RA which requires long-term treatment. During clinical trials (3-5), the clinical response with leflunomide was considered to be equivalent to methotrexate or sulphasalazine. During follow-up, varying between 6 to 12 months, 14.3 to 22% of patients stopped the treatment because of adverse events and 7 to 17% because of lack or loss of efficacy; therefore, 53 to 72% completed the trials.

In clinical trials efficacy and safety were assessed under realistic conditions, but we thought it would be interesting to assess its prescription patterns in the real world of prescription and use, and to see if its efficacy and safety profiles observed during clinical trials were confirmed.

The objective of this study was to describe the prescription patterns and the effectiveness and safety of leflunomide and to compare them with data from clinical trials.

Patients and methods

First, to describe the use of leflunomide, we identified a cohort of all patients treated with leflunomide between

May 1, 2000 and March 31, 2003 and followed up in the Rheumatology Department of the Bordeaux University Hospital. Because of the observational character of the study, there were no exclusion criteria. Patients were followed up from treatment onset to treatment withdrawal for whatever reason. The following data were obtained from the clinical charts: (i) demographic characteristics: age, gender; (ii) disease characteristics (RA duration) and severity of the disease (percentage of RF, previous DMARD treatment, concomitant NSAIDs and corticosteroid); (iii) concurrently prescribed drugs, and (iv) duration of treatment with leflunomide. Second, the three clinical trials taken into consideration by the French government during the drug approval process (3-5) were used to compare the prescription patterns, efficacy and safety of this immunosuppressive agent between the two populations, *i.e.*, clinical trials and routine practice. The data extracted from the two populations were expressed as qualitative (percentages) or quantitative values (*e.g.* average durations, in months or years). For comparison, clinical trials were considered as the "gold standard". As several clinical trials have been considered for approval, and in order to avoid a too restrictive definition of the target population, the extreme percentages for each item in the clinical trials were considered to define the range of the reference variable, even if it corresponded to very few patients. For example, if one clinical trial had included 60% women and another 72%, the percentage of women in the clinical trials used as the reference was considered to range from 60 to 72%. We used the indicator "anti-hypertensive drugs" as a proxy in order to compute the percentage of patients with systemic hypertension.

Data concerning effectiveness were assessed using the percentage of patients presenting with a lack or secondary loss of efficacy and data concerning safety were evaluated based on the percentage of adverse events leading to withdrawal.

Based on the criteria of the American College of Rheumatology (ACR20) (6), lack of efficacy was defined as patients

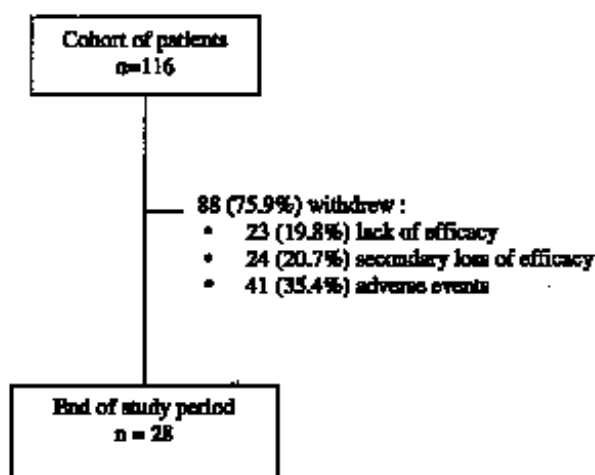


Fig. 1. Flowchart of outcome in the cohort treated with leflunomide.

not showing a 20% improvement in tender and swollen joint counts nor a 20% improvement in 3 of the 5 remaining ACR score set measures: patient and physician global assessments, pain, disability, or an acute phase reactant within 12 weeks after the beginning of treatment with leflunomide. Secondary loss of efficacy was defined as a secondary lack of efficacy after a primary response to treatment. Kaplan-Meier life table analysis was used to estimate the percentage of treatment withdrawals due to lack of efficacy or adverse events according to time of follow-up. Statistical analysis was performed using STATA 8.0 (Texas, USA) for Macintosh.

Results

Description of the cohort

One hundred and sixteen patients were treated with leflunomide during the study period, most of them with a daily dose of 20 mg. All patients had previously received a 100 mg loading dose over 3 days and had a Disease Activity Score (DAS) score greater than 3.2 at the start of leflunomide treatment. The mean duration of treatment was 9.7 months (median: 6 months, range: 2 weeks - 31 months). The mean age at the start of the treatment was 55.6 years (range: 27-81). The M/F sex ratio was 0.45. The mean duration of the disease at treatment onset was 10.2 years (median=8 years, range: 0.5-55). The aver-

age number of prior DMARD treatments was 3.4 (range: 0-7). None of the patients was being concomitantly treated with another DMARD such as methotrexate or sulfasalazine. Indications were: rheumatoid arthritis (93%), psoriatic arthritis (6%), and ankylosing spondylitis with peripheral involvement (1%). Concomitant prescriptions were corticosteroids (83%) with a daily dose higher than 10 mg of prednisone-equivalent in 26.7%, NSAIDs (77.6%), and non-NSAID analgesics (47.4%). Anti-ulcer drugs were co-prescribed in 73.3% in patients treated with NSAIDs.

During the study period, treatment was stopped in 88 patients (75.9%) (Fig. 1). This was for lack of efficacy in 23 patients (mean delay: 3.6 months, range: 2-6 months); for secondary loss of efficacy, after a mean delay of 11.4 months, in 24 patients (median: 8.5 months, range: 3-31 months); and for the occurrence of an adverse event (AE) in 41 patients (50% within 4 months, delay of onset: 2 weeks to 26 months). The most frequent AEs involved the skin (17.7%), blood (12.6%), gastrointestinal tract, peripheral nervous system (9.5%) and liver (3.4%). Considering all the treated patients, the treatment was stopped for adverse events in 35.1%, which led to a probability of being under treatment at the end of the follow up of 43% (Fig. 2). The treatment was also stopped for lack of efficacy in

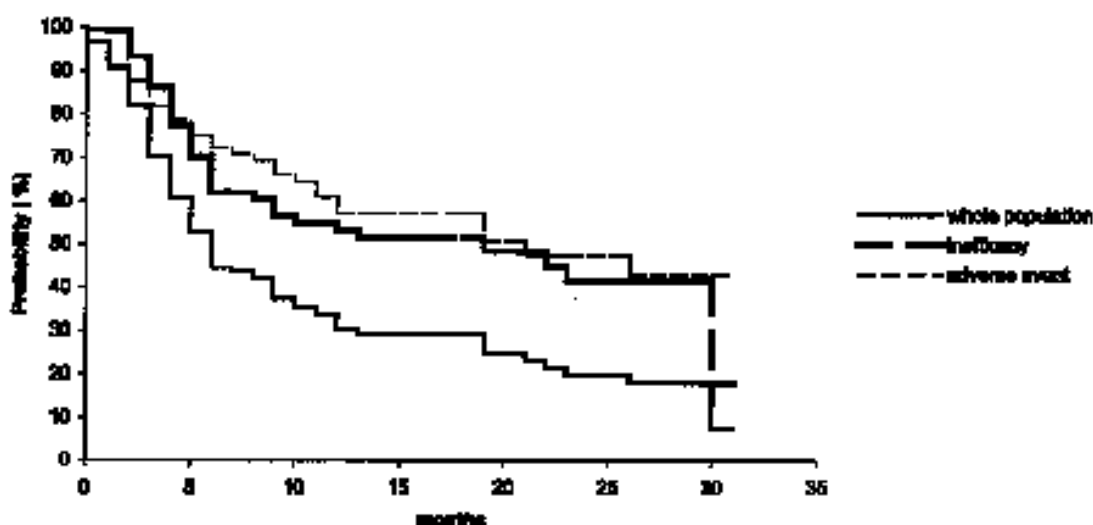


Fig. 2. Discontinuation of leflunomide due to adverse events and inefficacy according to duration of treatment in months (time): Kaplan-Meier survival analysis.

19.8%, and for secondary loss of efficacy in 20.7% (probability of being under treatment at the end of the follow up: 18%). In 24.1%, the treatment had not been discontinued until the end of follow-up (median: 6 months, range: 3-31).

Comparison with population included in clinical trials

Table I summarizes data from clinical trials and compares them with data on patients included in the cohort.

Demographic characteristics between the two populations were roughly the same. Nevertheless, the percentage of positive rheumatoid factor was higher and the diagnosis of RA was made at a more advanced age in the cohort study. Consequently, the percentage of patients with previous DMARD treatment was higher in this population. The same conclusion was obtained regarding the higher percentage of co-prescribed corticosteroids in the cohort. Finally, the treated patients seemed to suffer more frequently from systemic hypertension, at least if we considered treatment with "antihypertensive drugs" as a good proxy for this pathology.

At one year of follow-up, which corresponds to the maximal duration of treatment in the clinical trials, 32% of the patients of the cohort had stopped treatment due to the occurrence of an adverse event *versus* less than a quarter in clinical trials. The delay before stopping the treatment because of safety concerns ranged from 1 to 27 months. Thirty-eight percent stopped the treatment for inefficacy *versus* 7-17% in clinical trials. At one year, the global discontinuation rate was 70% in the cohort compared to 28-47% in clinical trials. At two years, 78% of the patients had stopped the treatment, whatever the reason.

Discussion

Since leflunomide was put on the market, very few studies have assessed its effectiveness and safety in a real-life setting. The extent and duration of the initial clinical trials (7-10), from 24 months to 5 years, does not reflect actual use in clinical practice. Our results showed that the patient profile is heterogeneous, leading to a wide range in the age, prior duration of disease and number of prior treatments.

Most of the patients were concomitantly treated with NSAIDs and corticosteroids. Nevertheless, the population treated with leflunomide in routine practice differed from the population included in clinical trials. Patients had the same age and gender but the characteristics of the disease differed markedly: duration of the disease and severity were higher in the cohort and only 1% of the patients were naive. Thus the average number with prior DMARD treatment was also higher. Moreover, patients had more concomitant diseases in the cohort.

Differences concerning the age of the disease between the two populations could be easily explained by the fact that in real practice, a new antirheumatic agent is rarely prescribed as a first line drug, but rather to patients with secondary loss of efficacy or in whom other drugs marketed for a longer time were contraindicated. Thus, the average number of previous treatments with DMARDs and the percentages of naive patients were extremely different across the two populations. The higher percentage of co-prescribed corticosteroids could be due to the fact that in clinical trials the severity of the disease is generally lower than in actual practice. The same explanation could be advanced for the number of concomitant diseases, which along with concomitant treatment are often constitute exclusion criteria in clinical trials.

Concerning adverse events leading to treatment withdrawal, these did not differ qualitatively as they were of expected types, but they did differ quantitatively. The percentage of withdrawals due to adverse events was much higher in the cohort than in clinical trials: 32% *versus* 14.3-22% at one year of follow-up. The majority of adverse events leading to withdrawal occurred during the first year and a half within the first 4 months of treatment. This difference could be due to the fact that in clinical trials with strict protocols, non-serious adverse events lead less frequently to treatment withdrawal than in actual practice.

The treatment withdrawals due to lack of efficacy and secondary loss of efficacy were also more frequent than ex-

Table I. Differences in leflunomide use between clinical trials and clinical practice.

| | Clinical trials (3-5) n = 482 | Cohort study n = 116 |
|--|----------------------------------|-------------------------|
| Maximal duration of follow up (months) | 6 to 12 | 31 |
| Mean age (years) | 54 to 58.3 | 55.5 |
| Women (%) | 71 to 76 | 71 |
| Rheumatoid arthritis duration (years) | 3.7 to 7.6 | 10.2 |
| Positive rheumatoid factor (%) | 65 to 79 | 88 |
| Prior treatment with DMARDs (%) | 55 to 66 | 99 |
| Average number of prior DMARD treatment | 0.8 to 1.2 | 3.4 |
| Naive patients (%) | 34 to 44 | 1 |
| Concomitant NSAIDs (%) | 75 to 85 | 77.6 |
| Concomitant corticosteroids (%) | 29 to 54 | 83 |
| Concomitant disease (%) | | |
| Hypertension | 21.4 to 25.7 | 35 |
| Hypothyroidism | 4.6 to 8.9 | 4.3 |
| Lipid disorders | 2.8 to 6.0 | - |
| Diabetes mellitus | 5.1 to 5.2 | 6 |
| Reason for withdrawal | | |
| Adverse event | 14.3 to 22 | 32 |
| Lack or loss of efficacy | 7 to 17 | 38 |
| Adverse events leading to withdrawal (%) | | |
| Skin rash | 10.8 to 12.4 | 17.7 |
| Diarrhoea | 22.2 to 33.5 | 12.6 |
| Rise of aminotransferases | 5.8 to 10.2 | 3.4 |
| Arterial hypertension | 8.9 to 11 | 3.4 |
| Peripheral neuropathy or paresthesia | 3.2 to 3.6 | 9.5 |

pected from clinical trials. Secondary loss of efficacy was not mentioned in the clinical trials, although 27% of patients were concerned in our cohort. Several reasons could explain such a difference: as previously mentioned, the disease was more severe in the cohort than in clinical trials with a higher activity (higher percentage of rheumatoid factor, higher concurrent prescription of corticosteroids). Moreover, compared to clinical trials, most of the patients included in the cohort had previously been unsuccessfully treated with multiple DMARDs before leflunomide and therefore could be, on average, more refractory than the patients included in clinical trials. Nevertheless, these last two findings remained consistent with previous studies concerning leflunomide use in daily practice (11-14), despite the fact that their duration of follow-up was shorter (approximately one year).

The discontinuation rates after approximately one year varied between 36.4% to 41.6% because of toxicity and 17% to 33.3% because of inefficacy, resulting in a discontinuation rate varying between 38% to 62%. In the postmarketing surveillance study published by Geborek *et al.* (15), the discontinuation rate was 78% after 20 months of follow-up, which is also consistent with the results of the present study. On the other hand, our results are less positive than those of a large national cohort study of veterans (14) where the treatment was discontinued in only 42% of patients after 33 months of follow-up. This was also the case in the study of Aletaha *et al.* in which the discontinuation rate was approximately 55% after two years of follow-up (16). These discrepancies could reflect differences in patient characteristics or in therapeutic management. In addition, it is understandable that the definition of lack or secondary loss of efficacy differed in these three studies. In any case, like the other published studies, our results show that the percentage of treatment withdrawal is higher during the first year of treatment.

In the present study, we did not have the opportunity to compare the discontinuation rate of leflunomide with another DMARD. Nevertheless, the discontinuation rate of leflunomide methotrexate and sulfasalazine in clinical practice was roughly the same in the study by Aletaha *et al.* (16). However, in our study, the discontinuation rate with methotrexate was lower than under leflunomide. Discontinuation for adverse events occurred earlier with leflunomide and sulfasalazine than with methotrexate. One possible explanation for the early occurrence of adverse effects with leflunomide could be the loading dose used in some therapeutic protocols (17).

Conclusion

This study shows that the prescription patterns, effectiveness and safety of leflunomide in clinical practice differ from those expected from clinical trials. A high percentage of patients stopped the treatment due to lack of efficacy. The differences between the two populations studied confirm the need to conduct early post-marketing studies such as the present one in order to obtain better knowledge of the effectiveness and safety of recently marketed new drugs. In many cases, a simple drug utilization study can provide relevant information on the degree of shift between the populations included in clinical trials and the populations treated in real practice.

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