ОРИГИНАЛНИ СТАТИИ
ORIGINAL ARTICLES

LEFLUNOMIDE IN RHEUMATOID ARTHRITIS: FACTORS ASSOCIATED WITH THERAPEUTIC MAINTENANCE

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Abstract. Introduction. *Leflunomide is an immunomodulator indicated for the treatment of rheumatoid arthritis (RA). Its advent coincided with the arrival of biologics, limiting the scientific community interest in analyzing its efficacy. Our study aimed to evaluate the therapeutic maintenance of leflunomide during the treatment of RA and to analyze the possible associated factors.* ***Methods.*** *We conducted a single-center retrospective study at a rheumatology department, including all patients with RA, according to ACR/EULAR criteria, who received leflunomide for one month and more. RA activity parameters and reports of adverse events were collected.* ***Results.*** *We studied 73 patients including into 70 women and 3 men. The average age at the time of introduction of leflunomide was 49.77 years [23-73]. The mean duration of treatment was 12.45 ± 11.75 months. The rate of leflunomide maintenance was 96%, 73%, 27%, 15%, 10% and 4% at three months, six months, twelve months, eighteen months, 24 months, 36 months and 48 months, respectively. The incidence rate for leflunomide discontinuation was 109 per 100 patient-years with a 95% confidence interval of 101 to 116 per 100 patient-years. Reasons for discontinuation of leflunomide were mainly the occurrence of adverse events (52%) and ineffectiveness of treatment (42%). In multivariate analysis, the factors associated with leflunomide maintenance were: age less than 50 years (p = 0.027; HR = 1.806; 95% CI [1.071; 3.048]) and use of systemic corticosteroids at leflunomide initiation (p = 0.001; HR = 2.713; 95% CI [1.480; 4.978]).* ***Conclusion.*** *Our study confirmed the efficacy of leflunomide prescribed in RA. A strict control of patients is recommended to avoid adverse events leading to drug discontinuation.*

Key words: *rheumatoid arthritis, leflunomide, therapeutic maintenance, efficacy, adverse drug effect, tolerance*

Introduction

Rheumatoid arthritis (RA) is the most common chronic inflammatory rheumatism with a prevalence of 0.3% in the Tunisian adult population [1]. The pathophysiology of this disease is multifactorial. There are immunological, genetic and environmental factors [2, 3].

Thanks to the scientific advances in the pathogenesis of RA and the advances in the pharmaceutical industry, effective treatment is currently available [4]. The rheumatologist's principal real in the treatment of RA is to obtain remission while avoiding drug toxicity [5]. Methotrexate represents the cornerstone of the management of RA. Leflunomide (Arava®) is the latest synthetic conventional disease-modifying antirheumatic drug (csDMARD) developed for the treatment of RA. Food and Drug Administration approved it in the 1990s for its use to treat RA [6]. The efficacy of this immunomodulator in the treatment of RA [7] as well as in the treatment of other autoimmune diseases [8-10] was proven.

The arrival of leflunomide coincided unfortunately with the concomitant arrival of the first biotherapies [11]. Anti-TNF agents represented a therapeutic revolution in the management of RA by improving the functional and vital prognosis and providing an optimal control of RA [12].

However, the high cost of the treatment compared to csDMARDs may represent a limit to their use [13]. RA is the most prevalent chronic rheumatic disease, the evaluation of the treatment cost is necessary and should be taken into consideration.

Given its cost-effectiveness and demonstrated efficacy, leflunomide reemerges as a crucial treatment for RA, especially in regions where medication affordability is a significant public health challenge.

The principal objective in managing this chronic pathology is to recommend a treatment that not only demonstrates proven efficacy and acceptable tolerance but also comes at an affordable cost. Regrettably, there is a scarcity of studies examining both the effectiveness and the long-term therapeutic maintenance of such treatments. Given the insufficient data from Tunisia regarding the study of therapeutic maintenance of leflunomide in the treatment of RA, in the present study we aimed to evaluate leflunomide survival and efficacy during the treatment of RA and to analyze the associated factors.

Methods

Study design

A retrospective cohort study was conducted in a rheumatology department. The study was carried out on patients treated with leflunomide and followed up in the department from January 1, 2000 to January 1, 2021.

All patients were diagnosed with RA according to ACR/EULAR criteria; they were treated with leflunomide for at least one month and have stopped it at the moment of the study. Patients treated with leflunomide for other inflammatory rheumatic diseases were not included. The patients who were lost to follow-up before the switching from leflunomide to another treatment and those who were lost to follow-up for more than six months were excluded.

Data sources and outcome measurements

Data was collected as part of routine clinical practice. For each patient, the following variables were collected from the medical record: baseline characteristics (age, sex, body mass index, medical history, family history of RA), disease characteristics (duration of RA, positivity of rheumatoid factor (RF) and anticitrullinated protein antibodies (ACPA), presence of erosion, prior treatments, and concomitant treatments), clinical data (number of nocturnal awakenings (NNA), morning stiffness duration (MSD), pain Visual Analogue Scale (VAS-pain), patient global assessment (PGA), disease activity score in 28 joints using erythrocyte sedimentation rate (DAS28), number of swollen joints (NSJ), number of tender joints (NTJ), biological data (sedimentation rate (ESR), C-reactive protein (CRP)) and adverse drug effects (type, time of appearance). Medical records were reviewed from initiation of leflunomide to discontinuation, follow-up loss, or the study end. Information on treatment duration, the interruption of leflunomide, and the reasons of this interruption was collected. Therapeutic maintenance is defined as “the length of time that treatment and instructions are continued by the patient” [14]. The therapeutic maintenance level is represented by the calculation of the percentage of patients who have continued treatment as a function of time.

We assessed the therapeutic maintenance level from the start of leflunomide treatment, at months 3, 6, 12, 24, 36 and 48, at year 4 of follow-up or at its interruption.

Response to leflunomide was assessed using the EULAR cut-off [15]. EULAR responses are summarized in Table 1.

Table 1. Classification of patients according to EULAR response

Improvement in DAS28 compared with To*			
DAS 28 at T6**	≥ 1,2	> 0,6 et < 1,2	≤ 0,6
≤ 3,2	Good responder		
> 3,2 et < 5,1		Moderate responder	
≥ 5,1			No responder

*T0: initiation of leflunomide; **T6: six months of leflunomide treatment, DAS28: Disease Activity Score 28 joints.

Statistical Analysis

Data were managed and analyzed with the IBM SPSS Statistics software version 25.0.

Quantitative variables were expressed as mean values ± standard deviation minimum and maximum. Categorical variables were indicated as frequencies and percentages.

Comparisons between variables were made with the chi-square test (categorical variables) and the Mann-Whitney test (continuous variables). Missing data were not replaced.

The drug survival rates were assessed according to a Kaplan-Meier survival curve. A univariate Cox proportional hazards regression model was used to estimate the potential factors of leflunomide maintenance, followed by a multivariate Cox model to identify significant predictors of this maintenance therapy. Variables, whose degree of significance in univariate analysis that was ≤ 0.50, were introduced into a multivariate Cox model.

The level of statistical significance was set at $p < 0.05$ in all tests.

Results

Demographic and RA characteristics of RA patients

During the study period, a cohort of 73 patients was selected. The average age at diagnosis was 43.55 ± 11.23 years. Females constituted a majority, comprising 96% of the participants. The mean body mass index (BMI) was 24.75 ± 4.28 kg/m^2. RA manifested as immunopositive in 89% of the cases and erosive in 84% of our study population. Prior to initiating leflunomide, all patients underwent conventional treatment, with methotrexate being the most frequently prescribed background treatment (59%).

Table 2 summarizes the epidemiological, clinical characteristics and the activity of RA at the initiation of leflunomide.

Table 2. The epidemiological, clinical characteristics and the activity of RA at the initiation of leflunomide.

Characteristics	Mean value ± SD
Age ± SD (years)	49,77 ± 10,64
Ratio-Sex	0,04
Disease duration (years)	7,09 ans ± 6,17
Duration of treatment (month)	12,45 ± 11,75
Therapeutic compliance (%)	88
Analgesics associtiated to leflunomide(%)	10
NSAIDs (%)	7
Corticosteroids (%)	79
Mean dose of corticosteroids (mg/day)	9,52 ± 4,99
NNA (per night)	1,15 ± 1,1
MSD (minutes)	17,48 ± 17,9
TJC	7,72 ± 7,2
SJC	3,44 ± 3,8
VAS-pain	56,16 ± 28,2
PGA	50,28 ± 22,6
CRP (mg/l)	19,48 ± 25,8
ESR	46,25 ± 25,8
HAQ	1,24 ± 0,8
DAS28	5,04 ± 1,3

RA: Rheumatoid arthritis, VAS-Pain: Pain Visual Analog Scale, PGA: Patient global assessment, MSD: Morning stiffness duration, NNA: Number of night awakenings, TJC: Tender joint count, SJC: Swollen joint count, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, DAS28: Disease Activity Score in 28 joints, HAQ: Health Assessment Questionnaire, SD: standard deviation, NSAIDS: non-steroidal antiinflammatory drugs.

Leflunomide maintenance

Among the 73 patients who received leflunomide, treatment was discontinued entirely in 70 cases (96%). The average leflunomide maintenance rate was calculated to be 13%, with a 95% confidence interval ranging from 10.27% to 16.04%. The median leflunomide maintenance rate was determined to be 8% [6.15-9.85]. The median treatment duration was 12.45 ± 11.75 months.

The following therapeutic maintenance levels were observed: 96% at the third month, 73% at the sixth month, 44% at one year, 27% at the eighteenth month, 15% at two years, and 10% at the thirty-sixth month. Notably, only three patients persisted with the treatment beyond 48 months, resulting in a maintenance therapy rate of 4% (Fig. 1).

The incidence rate of leflunomide discontinuation was 24 per 100 patient-years, with a 95% confidence interval of 22 to 25. The reasons for discontinuation were adverse events in 52% of cases, ineffectiveness – in 42% of patients, and pregnancy – in one case.

Predictive factors of leflunomide maintenance

Our univariate analysis uncovered statistically significant associations between leflunomide maintenance and specific factors, namely, age under 50 years (p = 0.049), overweight (p = 0.022), and the initiation of corticosteroids alongside leflunomide (p = 0.0001). No other demographic, clinical, or paraclinical characteristics demonstrated a significant association with drug maintenance. Refer to Table 3 for a comprehensive summary of factors related to leflunomide maintenance as identified through multivariate analysis.

Table 3. Factors associated with leflunomide maintenance in multivariate analysis

		Lower 95%	Upper 95%	p-
Parameters	HR	CI	CI	Value
Age < 50 years	**1,806**	**1,071**	**3,048**	**0,027**
Overweight	1,546	0,881	2,714	0,129
Biological inflammatory syndrome at initiation of leflunomide	0,742	0,456	1,210	0,232
Concomitant corticosteroid therapy	**2,713**	**1,480**	**4,978**	**0,001**
Symptomatic treatment associated with leflunomide	0,775	0,484	1,240	0,288

HR: hazard ratio, CI: confidence interval, p: statistical significance level

Efficacy of leflunomide

According to EULAR response criteria, a good response was observed in 19% of patients after six months of treatment. The distribution of moderate responders and non-responders was 38% and 43%,

respectively. In our study, a consistent reduction in all parameters reflecting rheumatoid arthritis (RA) activity was observed in patients maintaining leflunomide treatment. Specifically, the mean scores for VAS-pain and PGA exhibited significant decreases up to 24 months of treatment, while joint count showed a significant reduction up to 12 months.

The mean erythrocyte sedimentation rate (ESR) exhibited a significant decrease up to 6 months of treatment. However, a noteworthy increase was observed at 12 months, followed by a significant decrease at 18 months. Subsequently, there was a significant increase again at 24 and 36 months of treatment, with a subsequent significant decrease at 48 months.

Regarding C-reactive protein (CRP), a significant reduction was noted up to 24 months of treatment, with a subsequent rise at 36 months. Patients on leflunomide demonstrated a decrease in Health Assessment Questionnaire (HAQ) scores.

The Disease Activity Score 28 (DAS28) exhibited a significant decrease in patients remaining on leflunomide for up to 48 months, with the exception of a significant rise at 18 months.

Assessment of adverse effects of leflunomide

All adverse events experienced by patients during leflunomide treatment were systematically documented. The medical imputability of these adverse events was predominantly verified by a pharmacovigilance center in the majority of cases or, alternatively, by the attending physician. A comprehensive record of eleven distinct types of adverse effects was maintained throughout the study.

Approximately fifty-seven percent of patients encountered at least one adverse event during the course of treatment. It is noteworthy that none of these patients manifested a severe adverse effect necessitating urgent hospitalization.

Table 4 summarizes the adverse effects of leflunomide.

Discussion

In our study, the leflunomide maintenance rate was 96% at three months and 73% at six months. In the literature, the leflunomide maintenance rate at six months of RA treatment ranged from 76.2% to 80.3% [16, 17]. This result was by the rate found in our series.

In the 12th month, the rate of leflunomide maintenance was 44%. The evaluation of 12-month leflunomide maintenance in RA was the main objective of several studies. Indeed, the rate of patients who maintained this treatment during the follow-up period varied from 44% to 45% [18-20]. Siva et al. (2003) evaluated leflunomide maintenance in 1086 patients with RA. Among these patients, 59% maintained treatment at three months and 37% at six months [21]. The results are similar to our results.

However, in the study by Martin et al. (2005) this rate was lower at 24.2% [22]. Differences in the epidemiologic and therapeutic characteristics of the population could explain this. A longer duration of RA progression could lead to shorter therapeutic maintenance. On the other hand, in our study, the duration of RA progression at leflunomide initiation was not associated with longer maintenance ($p = 0.918$). Previous csDMARDs' failure was also considered a factor associated with less prolonged maintenance in RA patients treated with leflunomide [22].

Table 4. The adverse effects of leflunomide

Type of the adverse effect	Number of patients (%)	Discontinuation (average in days)	Appearance time (average in months)
Cytolysis hepatitis (n,%)	12 (16)	PD	4,8
Diarrhea (n,%)	7 (10)	TD (15)	5,8
Aphthae (n,%)	1 (1)	-	12
High blood pressure (n,%)	6 (8)	PD	5
Peripheral neuropathy (n,%)	4 (5)	PD	NP
Leukopenia (n,%)	4 (5)	TD (30)	3,8
Anemia (n,%)	1 (1)	-	6
Thrombocytopenia (n,%)	1 (1)	PD	12
Mucocutaneous infections (n,%)	3 (4)	TD (45)	12
Pulmonary infections (n,%)	1 (1)	TD (21)	5
Depressive disorder (n,%)	2 (3)	-	NS

PD: permanent discontinuation, TD: temprary discontinuation, NS: not specified

In our study, the drug survival at 24 months was 15%. In the literature, this rate at 24 months varied from 36.8% to 53% [23-25]. We could explain this difference by our small-sized population. Our study's retention rate at 36 months of treatment was 10%. Van Roon et al. (2004) evaluated leflunomide maintenance in 279 patients over a follow-up period of 38.9 months. The maintenance rate was 38% [26]. Rodriguez-Rodriguez et al. (2013) evaluated leflunomide maintenance over the same period as our study in 306 patients [27]. At the end of the follow-up period, 57.09% of the patients were maintaining leflunomide. Only 4% of patients in our study maintained treatment at 48 months.

Young age (< 50 years) was a factor associated with therapeutic maintenance of leflunomide in RA ($p = 0.027$; HR (95% CI) = 1.806 [1.071; 3.048]) in our study. The factors associated with leflunomide maintenance in a study conducted by Siva et al. (2003) [21] were: young age (< 44 years), age greater than 75 years, family income less than $ 60,000 per year and starting the treatment with a loading dose of 100 mg per day for three days. In our study, the use of corticosteroids concomitant with leflunomide initiation was associated with more prolonged maintenance ($p = 0.001$; HR (95% CI) = 2.713 [1.480; 4.978]). Our results are in line with those reported in the literature. In the study conducted by van Roon et al. (2005) [18], concomitant use of systemic corticosteroids ($p = 0.006$; HR (95% CI) = 1.58 [1.14; 2.21]) and ESR < 35 mm ($p = 0.03$; HR (95% CI) = 1.42 [1.03; 1.96]) at treatment initiation were the factors associated with leflunomide maintenance. The concurrent use of corticosteroids with leflunomide may result in synergistic therapeutic effects, effectively improving the management of inflammation and symptoms associated with RA. Furthermore, the swift anti-inflammatory action of corticosteroids is widely recognized for delivering rapid relief from symptoms. This immediate alleviation could enhance patient satisfaction and foster adherence to the comprehensive treatment regimen, including leflunomide.

We found an incidence rate for discontinuation of leflunomide 24 per 100 patient-years, with a 95% confidence interval of 22 to 25. This result aligns with the incidence rate of leflunomide discontinuation found in the Rodriguez-Rodriguez et al. (2013) study, which was 27 per 100 patient-years [27]. In other study, one hundred and seventy-three of the 279 patients discontinued leflunomide for a follow-up period of 42 months [28]. However, this rate differed from the rates found in other studies, which ranged from 55.5 to 56.2 per 100 patient-years [28, 29]. The observed difference can be explained by the relatively small size of our population and the decreasing number of patients monitored over time. The total population at each follow-up interval during the four-year monitoring period is reflected in the count of patients who remained on leflunomide. As our follow-up progressed, some patients ceased leflunomide, resulting in an overall reduction in the number of patients under observation.

During the 48-month follow-up period, 70 patients discontinued leflunomide. The reason for discontinuation was the appearance of adverse effects in 52% of the cases and treatment ineffectiveness in 42%. In the literature, the most common reasons for discontinuation were adverse effects and ineffectiveness, with frequencies ranging from 22% to 73.05% and 4% to 53%, respectively.

In the prospective study of Van Roon et al. (2004), 76 of 136 patients (56%) discontinued leflunomide during the 30-month follow-up period. The main reason for discontinuation was the appearance of adverse effects in 29% of patients, followed by ineffectiveness in 13% [26]. However, discontinuation due to adverse events was not the main reason in the study by Martin et al. (2005) [22]. The discontinuation rate for leflunomide was 75.8% over 12 months. Discontinuation for adverse effects was noted in 46.6% of patients and for ineffectiveness in 53%. Rodriguez-Rodriguez et al. (2013) showed a discontinuation rate related to adverse events of 73.05% and ineffectiveness in only 6.38% of patients [27]. In this study, the assessment of leflunomide efficacy was based only on the physician's judgment. There needs to be objective criteria for evaluating therapeutic response to bias the results. Although the efficacy of leflunomide in RA has been clearly explained, it is not devoid of adverse effects.

Admittedly, adverse events induced by leflunomide during the treatment of RA are frequent, but the safety profile of this treatment remains acceptable. Withal, no serious adverse effects have been described in the studies [30-32]. The reported impacts were considered manageable by the experts [32]. Table 5 summarizes the principal adverse events of leflunomide in previous studies during the treatment of RA.

Our study represents the first national investigation into the drug survival and adverse effects of leflunomide. We evaluated the therapeutic maintenance of leflunomide over a 48-month treatment period for rheumatoid arthritis, implementing rigorous follow-up intervals.

Table 5. Principal adverse events of leflunomide in previous studies during treatement of RA

Authors (Reference)	Adverse effects rates (%)	Hepatic events (%)	Digestive events (%)	High blood hypertension (%)
Prakash et al. [33]	60	10	27	-
Emery et al. [23]	71,4	8,1	29,1	6,8
Smolen et al. [34]	14	-	17	6
White DH et al. [24]	50,6	10,5	49,1	7
Strand et al. [35]	22	14,8	60,4	2,1
Edmund et al. [36]	-	15	17	-
Dougados et al. [37]	56,1	20,4	2,9	1,8
Kellner et al. [38]	9,6	5,4	6,6	1,8
Ishaq et al. [39]	-	-	-	41
Our study	60	10	16	6,8

However, several limitations were identified. The modest size of the population hindered a comprehensive statistical analysis, and the single-center design introduced a potential selection bias, limiting the generalizability of our results to a broader population.

Given the retrospective nature of the study and reliance on medical records, some data were missing, rendering certain statistical analyses unfeasible. To corroborate our findings, it is recommended to conduct multicenter studies involving rheumatoid arthritis patients treated with leflunomide.

Furthermore, prospective research initiatives should delve into elucidating the precise mechanisms and long-term implications associated with the concurrent use of corticosteroid therapy to enhance the therapeutic sustainability of leflunomide in treating RA. It is essential to conduct studies aimed at determining the optimal duration and minimum effective dose based on patient demographics and the therapeutic characteristics of rheumatoid arthritis.

Conclusion

The therapeutic maintenance level of leflunomide observed in our study was proven to be satisfactory, aligning with comparable findings in other series and influenced by various factors. Furthermore, this study affirmed that the response and tolerance profile of leflunomide in real-life scenarios for patients with rheumatoid arthritis (RA) could be deemed to be acceptable.

To enhance the therapeutic maintenance of leflunomide, it is recommended to take into account factors such as the patient's age and any corticosteroid therapy received. Leflunomide, being economically viable, reinstates its pivotal role as a fundamental treatment for RA, particularly in regions where the cost of medication remains a pivotal consideration in the decision-making process for pharmacological interventions.

The exploration of comparative multicenter longitudinal studies involving RA patients who maintained leflunomide and those who discontinued it could yield valuable insights for future research and clinical practice.

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