EJR European Journal of Rheumatology

DOI: 10.5152/eurjrheum.2020.20113

Original Article

Treating rheumatoid arthritis with leflunomide monotherapy versus combination therapy with methotrexate

Daniel Ampessan Guadagnin[1], Leonardo Vinicius Mazzali[1], Thelma Larocca Skare[2], Bárbara Stadler Kahlow[2, 3]

Abstract

Objective: Combination therapies have been proposed as a strategy to control inflammation more effectively in patients with rheumatoid arthritis (RA). Few studies examine the combined effect of methotrexate (MTX) and leflunomide (LFN). This study evaluated the symptom control and side effects of the combination of MTX and LFN compared with LFN monotherapy.

Methods: We conducted a retrospective analysis of 113 patients with RA treated with either LFN alone (n=22) or in combination with MTX (n=91). Data on disease activity score 28 erythrocyte sedimentation rate (DAS-28 ESR), DAS-28 C-reactive protein (DAS-28 CRP), blood cell count, liver enzymes, and creatinine levels were determined. Samples were collected on day 0 (initiation of LFN) and at 6 and 12 months.

Results: We found no differences between the 2 groups in DAS-28 on day 0 and at 6 and 12 months (p=0.89, p=0.42, and p=0.09, respectively, for DAS-28 ESR; p=0.97, p=0.27, and p=0.63, respectively, for DAS-28 CRP). In addition, we observed no differences in the blood cell count, liver enzymes, and creatinine levels between the treatment groups at any of the time points (all p>0.05).

Conclusion: Our results suggest that the efficacy of the combined treatment with MTX and LFN is similar to that of LFN alone. No increase in toxicity was observed with the combination therapy.

Keywords: Rheumatoid arthritis, methotrexate, leflunomide, inflammation

Introduction

Despite recent progress in rheumatoid arthritis (RA) therapies, with the advent of biologic and small-molecule treatments, methotrexate (MTX) is still considered an anchor drug, because it is effective and well tolerated (1). The first study to describe its therapeutic efficacy for RA was published in 1984 by Weinblatt et al. (2). Almost 40 years later, this drug is still considered to play a central role in the treatment of RA (3). A combination treatment with MTX and a low-dose glucocorticoid leads to remission or low disease activity in 30%-50% of patients with early RA (4). In situations in which patients do not achieve symptom control with MTX, it may be necessary to change medications or add a new form of treatment. Achieving proper control of inflammation is important, because it reduces the radiographic damage and avoids deformities (5).

The 2017 Brazilian guidelines for RA treatment (6) suggest that if MTX treatment fails, the therapeutic options include combining MTX with leflunomide (LFN) or hydroxychloroquine and sulfasalazine, substituting MTX for LFN, or sulfasalazine alone. The combination of MTX and LFN is widely used in Brazil, although few studies address the benefits of this combination over the use of LFN alone. Thus, we conducted a retrospective study of patients with RA treated either with LFN and MTX or with LFN alone to compare the inflammation control and risk of toxicity.

Methods

After obtaining approval from the Committee of Ethics in Research (Faculdade Evangélica Mackenzie; Approval Date: November 19, 2019; Approval Number: 3.713.726), we conducted a retrospective analysis of the charts of 129 patients with RA from a single rheumatology unit. Informed consent was waived, because this was a retrospective study. To be included in the study, the patients needed to fulfill at least 6 points in the American College of Rheumatology/European League Against Rheumatism classification criteria for RA (7). This sample represents all patients treated with either LFN alone or MTX and LFN who came for regular consultation during the 12-month period. Furthermore, 3 patients using LFN alone and 2 using MTX and LFN stopped using medication on their own during the observation period; data in 11 of the patient charts

Cite this article as: Guadagnin DA, Mazzali LV, Skare TL, Kahlow BS. Treating rheumatoid arthritis with leflunomide monotherapy versus combination therapy with methotrexate. Eur J Rheumatol 2021; 8(1): 12-5.

[1] Mackenzie Evangelical College of Parana, Curitiba, PR, Brazil
[2] Unit of Rheumatology, Hospital Evangélico Mackenzie, Curitiba, PR, Brazil
[3] Pontifical Catholic University of Parana, Curitiba, PR, Brazil

Address for Correspondence: Bárbara Stadler Kahlow; Unit of Rheumatology, Hospital Evangélico Mackenzie, Curitiba, PR, Brazil; Pontifical Catholic University of Parana, Curitiba, PR, Brazil

E-mail: bazinha_st@yahoo.com.br

Submitted: June 09, 2020
Accepted: August 16, 2020
Available Online Date: November 5, 2020

Table 1. Descriptive analysis of the studied sample (118 patients with rheumatoid arthritis).

	Total, N=113	Using LFN, n=22	Using LFN+MTX, n=91	p*
Female sex	99 (87.6%)	19 (86.3%)	80 (87.9%)	1.0
Mean age, years (±SD)	57.8±9.6	61.05±11.9	56.7±9.15	0.07
Median disease duration, years (IQR)	9 (5.7-14.2)	10 (5.5-15.5)	9 (5.5-14)	0.33
Using prednisone	103/113 (91.1%)	17/22 (77.2%)	86/91 (94.5%)	0.02
Median prednisone dose (mg/day) (IQR)	10 (10-20)	10 (10-20)	10 (10-15)	0.27

*p values refer to the comparison of LFN versus LFN+MTX.
LFN: leflunomide; MTX: methotrexate; N: number; IQR: interquartile range; SD: standard deviation.

Table 2. Comparison of inflammatory parameters in patients with RA treated with MTX+LFN versus monotherapy with LFN on day 0 and after 6 and 12 months.

	Day 0			6 months			12 months		
	LFN	MTX+LFN	p	LFN	MTX+LFN	p	LFN	MTX+LFN	p
Median DAS-28 ESR (IQR)	5.49 (3.64-6.01)	5.30 (3.69-6.05)	0.86	4.32 (3.19-6.13)	4.09 (2.84-5.24)	0.42	4.73 (4.43-5.26)	4.31 (2.7-5.4)	0.09
Mean DAS-28 CRP (SD)	4.19±1.85	4.13±1.35	0.97	2.77±1.24	3.36±1.56	0.27	3.95±1.39	3.64±1.57	0.63
Median ESR (mm) (IQR)	41 (22.5-54.5)	36 (19.5-61.5)	0.6	38 (20-55)	31 (15-50.7)	0.46	41 (21.5-56.5)	32.5 (18-58)	0.67
Median CRP mg/dL (IQR)	11.9 (4-28.6)	5 (2.6-15.7)	0.08	5.5 (2.5-21.5)	6 (3.74-15)	0.90	12 (3.9-21.5)	5 (2.61-12)	0.90

RA: rheumatoid arthritis; LFN: leflunomide; MTX: methotrexate; DAS: disease activity score; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; IQR: interquartile range; SD: standard deviation.

were incomplete. These patients were excluded; thus, the final sample number was 113.

Data on C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), disease activity score (DAS)-28 ESR, DAS-28 CRP, complete blood cell count, serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, creatinine, and transaminase levels were collected on day 0 and at 6 and 12 months after the LFN treatment was initiated.

Statistical analysis

Data were registered in Microsoft Excel sheets, and data analysis was performed using GraphPad Prism (GraphPad; San Diego, CA, USA). To judge the data distribution, we used the Shapiro-Wilk test. Central tendency was expressed as mean and standard deviation when the sample was parametric and as median and interquartile range (IQR) when the sample was nonparametric. We used the unpaired t-test and Mann-Whitney U test to compare age, disease duration, daily doses of prednisone, blood cell count, transaminase and creatinine levels, and DAS-28 ESR, DAS-28 CRP, ESR, and CRP values between patients treated with LFN alone and those using LFN and MTX. We used the Fisher's exact test to compare sex and the number of patients using prednisone. The accepted statistical significance was 5%.

Main Points

- To study the effectiveness of the combination of leflunomide and methotrexate.
- To study the toxicity of the combination of leflunomide and methotrexate leflunomide.
- Leflunomide monotherapy is a good treatment option for rheumatoid arthritis.

Results

In our sample, 22 of 113 (19.4%) individuals were treated with LFN alone and 91 of 113 (80.5%) used a combination of LFN and MTX. Table 1 lists the main characteristics of these individuals. None of the patients received any other treatments except glucocorticoids. The use of glucocorticoids was common in patients receiving combination therapy and the dose was similar (Table 1). In the combination therapy group, the median dose of MTX was 25 mg/week (IQR=20-25 mg/week). The combination group first received MTX, but because of the failure of disease control by MTX alone, LFN was added later. The group that received LFN monotherapy was treated with MTX, but because of intolerance to MTX, the treatment was changed to LFN monotherapy.

In patients treated with LFN as a monotherapy, the reasons for stopping MTX treatment were gastrointestinal intolerance in 11 (50%) of 22 patients, hepatotoxicity in 3 (13.6%), renal failure in 1 (4.5%), pulmonary fibrosis in 1 (4.5%), nodulosis in 1 (4.5%), and unspecified in 5 (22.7%). Patients who stopped using MTX because of liver or renal dysfunction began using LFN after 2 months, when their exam results became normal.

Table 2 shows the results of our comparative analysis of disease activity for the 2 groups. As shown in Table 2, we found no differences between the 2 treatment groups. Table 3 shows the comparison of the blood cell count, hepatic enzymes, and creatinine levels for the groups. Moreover, 7 patients, 1 (1/22, 4.5%) in the LFN group and 6 (6/91, 6.5%) in the LFN and MTX group achieved symptom control and were able to stop using prednisone (p=1.0).

Discussion

Our results indicated that there was no advantage obtained from the combination therapy of MTX and LFN compared with LFN monotherapy. We also showed that this drug combination is no more toxic than the use of LFN alone. A study in 60 Belgian patients with RA compared the treatment survival of MTX and LFN with LFN alone and found no differences in the groups after 30 months with 65% and 55% survival, respectively (8). They also did not find any differences in the occurrence of side effects, similar to our findings. Another study by Mroczkowski et al. (9) analyzed the combi-

Table 3. Comparison of the blood cell count, hepatic enzymes, and creatinine levels in patients with RA treated with MTX+LFN versus monotherapy with LFN on day 0 and after 6 and 12 months.

	Day 0			6 months			12 months		
	LFN	LFN+MTX	p	LFN	LFN+MTX	p	LFN	LFN+MTX	p
Median hemoglobin g/dL (IQR)	13.1 (11.9-14)	13.1 (12.4-13.9)	0.91	13.1 (11.6-14)	13 (12.4-13.8)	0.98	13.2 (12.3-14.4)	13 (12-13.9)	0.64
Median leukocytes (n/mm^3) (IQR)	7,175 (5,238-9,888)	7,510 (6,400-9,140)	0.65	6,400 (5,230-8,100)	7,030 (5,270-8,620)	0.61	7,120 (5,370-9,960)	6,830 (5,380-8,820)	0.91
Median platelets (n/mm^3) (IQR)	2,47,000 (220,500-306,500)	2,61,000 (2,24,000-3,10,000)	0.64	2,95,000 (1,98,000-2,44,000)	2,48,000 (2,02,750-2,76,000)	0.052	2,95,000 (1,92,000-2,34,000)	240,500 (1,97,000-3,09,000)	0.28
Median SGOT (UI/L) (IQR)	24 (18.6-32)	23 (19-28)	0.36	30 (19.5-36.4)	23.3 (19.8-35)	0.62	29 (23-31)	23.8 (19.2-30)	0.16
Median SGPT (UI/L) (IQR)	24 (15.6-32)	23 (19-28)	0.36	30 (19.5-36.4)	23.3 (19.8-35)	0.62	29 (23-31)	23.9 (16.9-33)	0.92
Median creatinine (mg/dL) (IQR)	0.85 (0.73-0.98)	0.77 (0.61-0.86)	0.01	0.74 (0.6-0.9)	0.8 (0.64-0.9)	0.72	0.79 (0.65-0.88)	0.79 (0.68-0.88)	0.77

RA: rheumatoid arthritis; LFN: leflunomide; MTX: methotrexate; IQR: interquartile range; n: number; SGOT: serum glutamic oxaloacetic transaminase; SGPT: serum glutamic pyruvic transaminase.

nation of MTX and LFN in patients who did not achieve symptom control with MTX alone, and they found that the combination treatment was effective. Lee et al. (10) observed the same result in their evaluation of 75 patients with RA. However, in the latter 2 studies, they did not compare the use of the combination therapy with the use of LFN alone. Lee et al. (10) also found that the liver enzymes were altered in 21.6% of the participants.

MTX and LFN are effective medications for the treatment of RA when used as monotherapies. MTX is frequently coprescribed with biologics and more recently with tofacitinib; combinations of MTX with conventional RA treatments are more controversial, especially with LFN (11). Combination drugs that have different biochemical mechanisms underlying the therapeutic effect could help to control RA disease, because their effects may be additive or synergic (5). LFN is an inhibitor of pyrimidine nucleotide synthesis that arrests the proliferation of T lymphocytes and thereby decreases the autoimmune responses (11). MTX has several mechanisms of action. It inhibits the synthesis of purine and polyamines, modulates cytokine activity (interleukins 1 and 6 and tumor necrosis factor-α), and increases the release of adenosine, which is a potent anti-inflammatory molecule (11). Thus, it is expected that a combination of LFN and MTX would be more effective than the use of either drug alone; however, this hypothesis was not corroborated by our findings. Our results showed that the inflammatory activity indices of the 2 groups were equivalent, despite the fact that more patients used prednisone in the combination group than in the LFN monotherapy group. A possible explanation is that LFN was given to MTX nonresponders, so the contribution of MTX in the combination could have been minimal. If the combination was used as a primary option, the results may have been different.

This study has several limitations, including its retrospective design and the number of patients available, particularly those using LFN as monotherapy. There was an absence of patients treated with LFN monotherapy or MTX and LFN as a first-line treatment rather than in response to MTX monotherapy failure, because in the public health system in Brazil, LFN is used only after MTX failure or intolerance. We also did not have any data on the radiographical outcomes. However, our results reveal that the use of the combination therapy (MTX and LFN) may not be more effective than LFN alone in patients who do not respond to MTX alone. Future prospective studies with a larger sample size are needed to confirm this possibility. In conclusion, our results suggest that the combination therapy of MTX and LFN is neither more effective nor more toxic than the use of LFN alone.

Ethics Committee Approval: Ethics committee approval was received for this study from the Committee of Ethics in Research of Faculdade Evangélica Mackenzie de Medicina (Approval Date: November 19, 2019; Approval Number: 3.713.726).

Informed Consent: Informed consent was not obtained due to the nature of this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - B.S.K.; Design - B.S.K.; Supervision - B.S.K.; Materials - T.L.S.; Data Collection and/ or Processing - D.A.G., L.V.M.; Analysis and/or Interpretation - T.L.S.; Literature Search - D.A.G., L.V.M.; Writing Manuscript - B.S.K.; Critical Review - T.L.S.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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