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Is combining methotrexate and leflunomide a safe option for treating rheumatoid arthritis?

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Abstract

Rheumatoid arthritis (RA) is a chronic immune-mediated disease marked by synovial inflammation and systemic features. Early management typically relies on conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), with methotrexate (Mtx) serving as the primary therapeutic agent. When Mtx is contraindicated, leflunomide (Lef) can be used as a treatment strategy. There are concerns about hepatotoxicity, cytopenia, pneumonia, and increased risk of infection when these therapies are combined. In this study, we aimed to evaluate the side effects and treatment duration of the Mtx/Lef combination in patients with RA. All patients admitted to the Rheumatology clinic between 2016 and 2023 and diagnosed with RA were retrospectively reviewed. Patients who received Mtx/Lef combination therapy during this period were identified. The data for patients who continued Mtx/Lef combination therapy were recorded at the last visit, and those who discontinued the combination therapy were recorded at the visit of discontinuation. Adverse effects associated with Mtx/Lef combination therapy were assessed through retrospective review of clinical follow-up notes, laboratory test results, and drug safety monitoring forms. Adverse events leading to treatment discontinuation were classified as either due to side effects or lack of therapeutic response. This study was conducted with a total of 222 participants, comprising 184 females (82.9%) and 38 males (17.1%). No side effects were observed in 141 (63.5%) patients after Mtx/Lef use. Gastrointestinal system side effects were observed in 16.7% of the participants, followed by elevated liver function tests in 11.3%. It was determined that 55% of the participants were unable to continue treatment due to treatment ineffectiveness or side effects. Our study results offer a good safety profile and long-term drug survival. Survival in long-term treatment may contribute to reducing treatment costs.

Keywords: Methotrexate, leflunomide, side effects, drug survival, rheumatoid arthritis

Introduction

Rheumatoid arthritis (RA) is a chronic and disabling autoimmune disease associated with systemic inflammation that affects 1% of the global population [1]. The use of conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), primarily methotrexate (Mtx), is the first step in the treatment of RA. If Mtx monotherapy is insufficient, combination treatment can be applied, but if it is contraindicated, other csDMARDs are preferred instead of the combination. When Mtx is contraindicated, Lef or sulfasalazine should be part of the treatment strategy [2,3].

For patients with RA who cannot tolerate csDMARDs or whose RA cannot be adequately controlled with csDMARDs, therapies such as tumour necrosis inhibitors, T-cell stimulation inhibitors, CD20 inhibitors, IL-6 inhibitors and JAK inhibitors are increasingly recommended. However, biologics are known to be significantly more costly than csDMARDs. Studies are being conducted to determine whether csDMARD combinations are more cost-effective [4].

A combination of Mtx and Lef may be preferred as an option before starting biologic disease-modifying antirheumatic

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drugs (bDMARDs) or targeted synthetic disease-modifying antirheumatic drugs (tsDMARDs). Mtx and Lef, as conventional synthetic DMARDs, exert their therapeutic effects through different biochemical pathways; Mtx primarily disrupts purine metabolism and influences 5-Aminoimidazole-4-carboxamide ribonucleotide (AICAR) activity, while Lef targets the inhibition of pyrimidine biosynthesis. There are concerns about hepatotoxicity, cytopenia, pneumonia, and increased risk of infection with the combined use of Mtx and Lef [5]. In this study, we aimed to evaluate the side effects of the Mtx/Lef combination and the treatment survival rate.

Material and Methods

A total of 222 patients diagnosed with AR according to the 1987 American College of Rheumatology (ACR) criteria or the 2010 European League Against Rheumatism/ACR criteria were included in the study [6,7]. Ethical approval was obtained for this study by Malatya Clinical Research Ethics Committee on 28.11.2023 (Ethics committee approval number: 5281). The study was conducted in accordance with the Declaration of Helsinki.

All patients (1810 patients) admitted to the Inönü University Faculty of Medicine, Rheumatology Clinic between 2016 and 2023 and diagnosed with RA were retrospectively reviewed. Patients who received the Mtx/Lef combination therapy during this period were identified. The data of the patients who continued the Mtx/Lef combination at the last visit were recorded in the case report form. In cases in which the patient discontinued the Mtx/Lef combination, the data of the discontinued visit were recorded.

Patients with another inflammatory rheumatic disease in addition to RA and those who visited our clinic only once were excluded from the study. The presence of diabetes mellitus (DM), hypertension (HT), coronary artery disease (CAD), malignancy and hepatitis were analysed. In terms of additional medications, antidiabetic (anti-DM), antihypertensive (anti-HT), steroid, nonsteroidal anti-inflammatory drug (NSAID), and hepatitis antiviral agents were analysed. Regardless of whether patients continued the Mtx/Lef combination, duration of use, the reason for discontinuation and side effects were recorded. Adverse effects related to Mtx and Lef use were evaluated by retrospectively reviewing patient files. Clinical follow-up notes, laboratory test results, and drug safety monitoring forms were reviewed. In particular, liver function tests (ALT, AST), renal function tests (serum creatinine), haematological parameters (leukocyte, haemoglobin, platelet count), and gastrointestinal complaints reported by patients during visits were used to determine potential adverse effects. Reasons for discontinuation of MTX and/or Lef treatment were classified as adverse effects or unresponsiveness to treatment. Documented adverse effects such as liver enzyme elevation, cytopenia, gastrointestinal intolerance, infection development, or dermatological reactions were recorded in the case record form. All drug-related adverse effects that led to discontinuation of treatment were included in the study.

Laboratory values of anti-cyclic citrullinated peptide (anti-CCP), rheumatoid factor (RF), alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine, albumin, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), white blood count (WBC), haemoglobin and platelet values were recorded.

As a general approach, drug doses were increased gradually. Lef 10 mg 1x1/day was added to the treatment of patients who were taking Mtx 15 mg/week and did not respond adequately. Meanwhile, Mtx 10 mg/week was added to the treatment of patients receiving Lef 20 mg 1x1/day. If patients could tolerate it, treatment doses were adjusted to Mtx 15 mg/week and Lef 20 mg/day.

Statistical Analysis

The minimum sample size required for the study was determined to be 199 patients according to a theoretical power analysis using a one-sample t-test with a type I error (alpha) of 0.05, a power of the test (1-beta) of 0.8, and an effect size of 0.2 [8].

The data were statistically analysed using Statistical Program for the Social Sciences (SPSS) 17.0. Data related to quantitative variables are given as mean±standard deviation and minimums and maximums, while data related to qualitative variables are given as numbers and percentages. Normal distribution of data was investigated with the Kolmogorov–Smirnov normality test. Patients with and without side effects due to the Mtx/Lef combination therapy were divided into two groups. These two groups were compared in terms of age, gender, presence of comorbidities, RF positivity and CCP positivity. Fisher's Chi-Square test was used for the analysis of qualitative variables, while an independent samples t-test was used for the analysis of quantitative variables. Values of $p<0.05$ were accepted as statistically significant.

Results

A total of 222 participants joined the study, with 184 (82.9%) females and 38 (17.1%) males. The mean age of the participants was 57.83±10.17 years. The mean duration of Mtx/Lef combination use was 18.19±16.14 months. One hundred and forty-one (63.5%) patients had no side effects after using Mtx/Lef, while 81 (36.5%) participants had side effects. The study evaluated the participants' underlying health conditions, their medication for these conditions, the specific medications they were taking, whether they continued using Mtx/Lef, reasons for discontinuing Mtx/Lef, and the seropositivity status of the patients. These details are presented in Table 1. Laboratory data (AST, ALT, BUN, creatinine, ESR, WBC, Hb and platelet) of the participants were recorded and are presented in Table 2. The types of side effects attributed to the Mtx/Lef combination are shown in Table 3.

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Table 1. Descriptive characteristics of the patients

Features	n	%
Gender		
Woman	184	82.9
Male	38	17.1
Presence of comorbidities		
Yes	113	50.9
No	109	49.1
Comorbidities		
Diabetes	13	11.5
Hypertension	49	43.4
CAD	8	7.1
Malignancy	3	2.6
Hepatitis	3	2.6
2 or more	37	32.8
Medication use		
Yes	164	73.9
No	58	26.1
Medicines used		
Anti DM	8	4.9
Anti HT	24	14.6
Steroid	34	20.7
NSAID	7	4.3
Hepatitis	2	1.2
2 or more	89	54.3
Mtx/Lef continuation status		
Yes	100	45.0
No	122	55.0
Reason for leaving Mtx/Lef		
Ineffectiveness	41	18.5
Side effect	75	33.8
Two of them	6	2.7
Continue	100	45.0
Mtx/Lef side effect presence		
Yes	81	36.5
No	141	63,5
RF or anti-CCP positivity		
Negative	51	23.0
Positive	171	77.0
	Mean (SD)	**Min-Max**
Mean age	57.83±10.17	29-78
Mtx/Lef usage period (month)	18.19±16.14	3-76

Mtx: methotrexate, Lef: leflunomide, CAD: coronary artery disease, NSAID: non-steroidal anti-inflammatory drug, RF: rheumatoid factor, Anti-CCP: anti-cyclic citrullinated peptide, Anti-DM: anti-diabetic medication, Anti-HT: anti-hypertensive medication

Table 2. Mean laboratory values of the patients

	Mean±SD	Min-Max
ALT	29.10±29.00	6-317
AST	24.47±12.98	6-93
BUN	16.25±7.38	2-39
Creatinine	0.78±0.17	0.4-1.60
Albumin	3.93±0.43	0.3-5.30
ESR	3.93±0.43	1-89
WBC	7751.05±2419.77	1052-15620
Haemoglobin	12.99±1.45	9.6-16.7
Platelet	286.10±78.35	101-627
CRP	1.04±1.39	0.30-15.00

ALT: alanine Aminotransferase, AST: aspartate Aminotransferase, BUN: blood urea nitrogen, ESR: erythrocyte sedimentation rate, WBC: white blood cell count, CRP: C-reactive protein

Table 3. Types of side effects associated with Mtx/Lef use

Features	n	%
Mtx/Lef side effect		
GIS	37	16.7
LFT	25	11.3
Creatinine	5	2.3
Cytopenia	1	0.5
Headache - dizziness	1	0.5
Hair loss	3	1.4
Other	9	4.1
No side effects	141	63.5

Mtx: methotrexate, Lef: leflunomide, GIS: gastrointestinal system, LFT: liver function tests

The mean age of patients who developed side effects due to Mtx/Lef use was 58.24±10.50 years, while the mean age of patients who did not develop side effects was 57.11±9.61 years. There was no statistically significant difference in age between the two groups. Of the 38 male patients who received the Mtx/Lef combination, 29 (76.3%) had no side effects, while 9 (23.7%) had side effects. Of the 184 female patients receiving the Mtx/Lef combination, 112 (60.9%) had no side effects, while 72 (39.1%) had side effects. Comparing the side effects of Mtx/Lef use based on gender, no statistically significant difference was found between men and women. Additionally, the groups with and without side effects were compared in terms of the presence of comorbidities, RF or anti-CCP positivity. No statistically significant difference was found between the groups (Table 4).

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Table 4. Statistical comparison of those with and without Mtx/Lef side effects

		Patients without Mtx/Lef-related side effects n (%)	Patients with Mtx/Lef-related side effects n (%)	X^2	p[a]
Gender	**Male**	29 (76.3)	9 (23.7)	3.24	0.95
	Female	112 (60.9)	72 (39.1)		
Additional disease	**No**	71 (65.1)	38 (34.9)	0.24	0.67
	Yes	70 (61.9)	43 (38.1)		
RF	**Negative**	41 (61.2)	26 (38.8)	0.22	0.65
	Positive	100 (64.5)	55 (35.5)		
Anti-CCP	**Negative**	52 (57.8)	38 (42.2)	2.14	0.15
	Positive	89 (67.4)	43 (32.6)		
		Mean±SD	**Mean±SD**	**F**	**p[b]**
Age		58.24±10.50	57.11±9.61	1.45	0.42

Mtx: methotrexate, Lef: leflunomide, RF: rheumatoid factor, anti-CCP: anti-cyclic citrullinated peptide

Discussion

This study investigated the side effects and drug duration of the Mtx/Lef combination. In our study, 100 of 222 patients continued treatment, and the mean duration of treatment was approximately 1.5 years. Gastrointestinal intolerance and liver function tests (LFTs) abnormalities were the most common side effects. However, no fatal side effects were encountered in any of the patients.

Cost, as well as efficacy, is an essential consideration in RA treatment. Many years ago, Mtx was recognised as the 'anchor' drug for RA treatment, meaning that it can be used alone or in combination with synthetic and biological DMARDs at any stage of RA. This drug shows well-established efficacy in patients who are new to DMARDs [9]. Lef has been shown to be comparable to Mtx in controlling the signs and symptoms of RA in many studies for its efficacy. It has also been associated with slowing the progression of joint damage [10]. As outlined in the latest recommendations of the European Alliance of Associations for Rheumatology (EULAR), in cases of inadequate response to Mtx—particularly in the presence of poor prognostic factors—treatment should be intensified either by combining csDMARDs (commonly referred to as triple therapy, such as Mtx with Lef or with sulfasalazine and hydroxychloroquine) or by introducing a bDMARD or tsDMARD [2]. Studies on the efficacy of Mtx/Lef are available [11,12] and have shown that the combination is effective in patients for whom other synthetic DMARD combinations have failed. The Mtx/Lef combination is more cost-effective than biological DMARDs [5].

In RA treatment, the sustainability of treatment, as well as its efficacy, is essential. Many studies on treatment survival have reported short-term follow-up results compared to ours. They do not reveal longer-term drug survival results [5,13-15]. There are few studies with long-term data [16-18]. In a study reporting 10-year data, higher drug survival rates were reported for a Lef/Mtx combination compared to a Mtx plus sulfasalazine combination [16].

In contrast, in another study, no statistically significant difference in terms of drug survival was found between a Mtx/Lef combination and Mtx plus hydroxychloroquine plus sulfasalazine [19]. In a study by Kaul et al., Mtx/Lef treatment survival rate was 51%, and the mean treatment survival time was 32.8 months [17]. In our study, the treatment survival rate was 45%, with a mean survival time of approximately 18 months. The prolonged survival time in the study by Kaul et al. may be due to the exclusion of use for less than six months. This is likely due to primary nonresponse and intolerance in the first six months. These studies suggest that Mtx/Lef combinations may be a good option in terms of survival.

One of the most critical factors affecting drug survival is side effects. In a study conducted by Bredemeier et al., side effect events were reported to be 26.5 per 100 patient-years. This study reported that the Mtx/Lef treatment offered an excellent safety profile compared with the Mtx/Ssz combination and advanced combinations [16]. In another database-based study by Cannon et al., the incidence of side effects in patients using Mtx/Lef was reported as 43 per 1000 patient-years, which is generally lower or similar to the rates of side effects seen with Mtx and other agents [18]. In our study, 141 (63.5%) patients did not develop any side effects, while 24.16% of the side effects were observed per year. Our results are similar to those of Bredemeier et al. However, more side effects were observed in our study compared to a study by Cannon et al. This may be because the most common gastrointestinal system (GIS) side effects in our study were not evaluated in the study of Cannon et al.

Kaul et al. reported GIS side effects as the most common set of side effects related to the Mtx/Lef combination [17], which

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is similar to what we observed in our study. Due to GIS side effects, 16.7% of our patients could not continue the combination treatment. The participants' complaints disappeared with the discontinuation of the treatment. In this context, our study results are parallel with those of the mentioned study. Ding et al. reported GIS side effects related to the Mtx/Lef combination as one of the common side effects, although they were not the most common [15]. However, the follow-up period for the patients in this study was 12 weeks, which is considerably shorter than ours.

Elevated LFT has been reported as a significant side effect in Mtx/Lef combination therapy studies in general [13,15,17,18,20,21]. In our study, the second most common side effect was elevated LFT (11.3%). The LFT of patients with elevated LFTs returned to normal when treatment was interrupted or discontinued. Our study results are generally parallel with those of previous studies. However, in a study by Hodkinson et al., 39 of 194 patients discontinued treatment due to side effects, and hepatotoxicity was reported in only 3 (1.5%) of them. One possible reason for the low rate of hepatotoxicity in this study is that Mtx-related liver toxicity is less common in black Africans, and this is probably related to the rarity of MTHFR gene polymorphism, which has been shown to be associated with Mtx in whites [5]. These studies show that LFT values are one of the most critical follow-up parameters in side effect follow-up.

Treatment discontinuation due to renal failure has not been reported among the common side effects in other studies [5,15,17,18,22,23]. In our study, treatment was discontinued in 5 (2.3%) patients due to renal failure. Three of these patients received combination therapy for less than three months. The reason for this may be that renal failure due to Mtx/Lef combinations occurs in the early period.

These studies show that side effects other than GIS and liver side effects are rare. GIS and liver side effects are mild and usually resolve with interruption or discontinuation of the drug.

Our study has several strengths. Our study is the largest patient series evaluating the side effect profile of the combination of mtx/lef in Türkiye. The fact that this is one of the few studies showing long-term drug survival and long-term use-related side effects is an important advantage. The applicability of the findings of the study to both theoretical frameworks and practical applications is another important element that increases the contribution of the research to the field.

This study has several limitations. First, due to its retrospective design, there may have been potential biases in patient selection and data recording. Disease activity scores (such as DAS28) were not systematically assessed, thus limiting a comprehensive evaluation of treatment responses. The assessment of adverse events relied primarily on clinical observations and laboratory parameters (e.g., AST, ALT, WBC and Hb), and imaging methods were not consistently performed across all participants. This may have led to an underestimation of subclinical adverse events.

Additionally, Mtx and Lef dosages were adjusted individually based on patient tolerance rather than following a standardised protocol. In addition, since some of the patients had started using Mtx or Lef years before applying to us, the average duration of patients' separate use of Mtx and Lef could not be calculated exactly. Finally, the single-centre design and the relatively homogeneous patient population may limit the generalisability of the findings to broader and more diverse populations.

Conclusion

In conclusion, although bDMARD and tsDMARD treatments have good efficacy, their high costs impose a serious burden on the country's healthcare system's economies. Our study results provide a good safety profile and long-term drug survival. Studies in different clinical and sociodemographic settings are needed to confirm these findings.

Conflict of Interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
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Ethical Approval
Ethical approval was obtained for this study by Malatya Clinical Research Ethics Committee on 28.11.2023 (Ethics committee approval number: 5281).

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