



Evaluation of The Efficacy, Side Effects, and Drug Survival Data with Methotrexate-leflunomide Combination Therapy in Patients with Inflammatory Arthritis

Enflamatuvar Artritli Hastalarda, Metotreksat-leflünomid Kombinasyon Tedavisi ile Etkinlik, Yan Etki ve İlaçta Kalım Verilerinin Değerlendirilmesi

© Pınar Talu Erten

İzmir Medicana International Hospital, Clinic of Internal Medicine, Division of Rheumatology, İzmir, Turkey

Abstract

Objective: Conventional synthetic disease-modifying antirheumatic drugs are used alone or in combination to treat inflammatory arthritis. The risk of serious side effects may also increase with the combination of methotrexate and leflunomide (MTX + LEF), which is used for better clinical response.

Materials and Methods: The data of 107 patients who received MTX + LEF treatment for inflammatory arthritis were retrospectively reviewed.

Results: The mean age was 50 (± 13), and the median disease duration was five years. Three months after the initiation of MTX + LEF treatment, 76.6% of patients continued treatment in remission. The mean duration of drug survival for these patients was 30 months. The most important reasons for drug discontinuation in the first three months after treatment initiation were primary inefficacy and >2 -fold increase in transaminases, whereas remission, patient decision, or secondary non-response were found in long-term follow-up. The frequency of transaminase elevations was 9.3% (10/107), and 70% of these were observed in the first three months of treatment, and all resolved after drug discontinuation. The incidence of serious infections was 6.5% (7/107), and mortality was not observed; the incidence of serious infections was higher in the elderly ($p=0.002$). The MTX + LEF continuation rate was 45% at the last visit of the patients included in the study.

Conclusion: The MTX + LEF combination is a safe and effective option for achieving remission when used considering old age and comorbidities; It is important to closely monitor transaminase levels, especially in the first three months.

Keywords: Arthritis, methotrexate, leflunomide combination, efficacy, side effects

Öz

Amaç: Enflamatuvar artrit tedavisinde konvansiyonel sentetik hastalık modifiye edici antiromatizmal ilaçlar tek başına veya kombinasyon halinde kullanılmaktadır. Daha iyi klinik yanıt için kullanılan metotreksat ve leflunomid (MTX + LEF) kombinasyonu ile ciddi yan etki riski de artabilir.

Gereç ve Yöntemler: Çalışmamızda enflamatuvar artrit nedeniyle MTX + LEF tedavisi alan 107 hastanın verileri retrospektif olarak incelendi.

Bulgular: Ortalama yaş 50 (± 13), ortalama hastalık süresi 5 yıldır. MTX + LEF tedavisi başladıktan 3 ay sonra hastaların %76,6'sı remisyonda tedaviye devam etti. Bu hastalar için ortalama ilaç kullanım süresi 30 ay saptandı. Tedavi başlangıcından sonraki dönemde ilk üç ay içinde ilaç kesilmesinin en önemli nedenleri birincil etkisizlik ve transaminazlarda >2 kat artış iken, uzun dönem takiplerde ilaç kesilmesinin nedenleri ise remisyon, hasta kararı veya sekonder yanıtızlık olarak saptandı. Transaminaz yükselmelerinin sıklığı %9,3 (10/107) idi ve bunların %70'i tedavinin ilk üç ayında gözlemlendi ve tümü ilaç kesildikten sonra düzeldi. Ciddi enfeksiyon sıklığı %6,5 (7/107) olup, mortalite gözlemlenmedi, ciddi enfeksiyon sıklığı yaşlılıkta daha fazlaydı ($p=0,002$). Hiçbir hastamızda tedaviye bağlı mortalite görülmedi. Çalışmaya alınan hastaların son vizitte MTX + LEF devam oranı %45 bulundu.

Address for Correspondence/Yazışma Adresi: Pınar Talu Erten MD, İzmir Medicana International Hospital, Clinic of Internal Medicine, Division of Rheumatology, İzmir, Turkey

Phone: +90 533 225 54 14 **E-mail:** doktortalu@yahoo.com

ORCID ID: orcid.org/0000-0002-0697-360X

Received/Geliş Tarihi: 30.05.2023

Accepted/Kabul Tarihi: 01.08.2023



Sonuç: MTX + LEF kombinasyonu yaşlılık ve komorbiditeler dikkate alınarak kullanıldığında remisyon sağlamada güvenli ve etkili bir seçenektir; özellikle ilk 3 ay transaminaz düzeylerinin yakından izlenmesi önemlidir.

Anahtar Kelimeler: Artrit, metotreksat, leflunomid kombinasyon, etkinlik, yan etki

Introduction

Most treatment guidelines and recommendations recommend methotrexate (MTX) and conventional disease-modifying antirheumatic drugs (csDMARDs) alone or in combination as first-line treatment for inflammatory arthritis. These drugs are advantageous treatment options due to their low risk, cost profile, and mostly oral use.

MTX, a structural analog of folic acid, acts by suppressing inflammation mediated by adenosine increases. Although most of the common side effects with MTX are mild and do not require discontinuation of the drug, serious side effects such as hepatotoxicity, pulmonary toxicity, infections, and myelosuppression can be seen rarely as treatment complications (1). Risk factors for pulmonary toxicity are the presence of diabetes, advanced age, rheumatoid lung involvement, and hypoalbuminemia (2-5). Risk factors for hepatotoxicity are untreated hepatitis B and C infection, not using folic acid, obesity, hyperlipidemia, hepatosteatorosis, alcohol consumption, and high doses of MTX (2-6). Risk factors for hematological side effects are MTX overdose, inadvertent daily use of the drug, renal failure, hypoalbuminemia, and concomitant use of trimethoprim/sulfamethoxazole (3,4). Despite these infrequent serious side effects, MTX has a very good safety profile with appropriate patient selection, education, and follow-up.

Leflunomide (LEF) is an immunomodulatory agent which works by blocking T-cell proliferation by inhibiting pyrimidine synthesis. The most common side effects are gastrointestinal symptoms (cramps and diarrhea) and hepatotoxicity (1). Interstitial lung disease with LEF is a rare but serious pulmonary complication with high mortality. Concomitant use of LEF and MTX raises concerns about hepatotoxicity, bone marrow suppression, pneumonitis, and risk of infection (1,6-9).

In this study, we aim to retrospectively evaluate patients treated with MTX + LEF in clinical practice and to obtain real-world data regarding efficacy, safety, and adverse events.

Materials and Methods

This is a single-center, retrospective, and observational study. This study was approved by the Bakırçay University Faculty of Medicine Research Ethics Committee after reviewing the ethical issues (decision no: 1044, date: 17.05.2023). Between January 2011 and October 2022, 107 patients who received combination MTX + LEF treatment for inflammatory peripheral arthritis in İzmir University of Economics Medical Point Hospital Rheumatology Clinic were included in the study. The patients included

in the study were selected from patients over 18 years of age with rheumatoid arthritis (RA), psoriatic arthritis (PsA), undifferentiated spondylarthritis (uSPA), and undifferentiated connective tissue disease (uCTD). None of the patients had regular alcohol use, known interstitial lung disease, or hepatitis B and C infections. Patients with drug incompatibility and not attending follow-up were excluded from the study. Of the patients included in the study, 75 were diagnosed with RA according to the 2010 RA classification criteria (10), and 23 were diagnosed with PsA according to the classification of psoriatic arthritis criteria (11). Of the other patients with inflammatory arthritis included in the study, five were diagnosed with uSPA and four with uCTD.

The data of the patients were obtained from computer records. These records included patient complaints, tender and swollen joint counts, physical examination findings, acute phase responses, routine complete blood counts and biochemical parameters, and, if any, other detailed additional tests required at that visit.

Statistical Analysis

IBM SPSS 21.0 program was used for statistical analysis. Descriptive statistical methods were used to evaluate the data. Pearson correlation test in determining the linear relationship of quantitative variables; Spearman's correlation test was used to evaluate ordinal variables. The chi-square test was used when comparing the qualitative variables of two independent groups. The statistical significance value was taken as $p < 0.05$.

Results

Demographic data of 107 patients included in the study is given in Table 1. 70% of patients were women. (male/female: 30/77) The mean age of the patients was 50 (± 13) years, and 44% of the patients had additional diseases such as hypertension, diabetes mellitus, thyroid disease, chronic obstructive pulmonary disease, coronary artery disease, and insulin resistance. The median duration of the disease was five years (1-39 years). 70% of the patients included in the study were diagnosed with RA, 21% were diagnosed with PsA, and the remaining patients were diagnosed with uCTD and uSPA.

Patients who were followed up for at least three months after initiating the MTX + LEF combination were included in the study. The median time to initiate the MTX + LEF combination in our patients was 24 months.

Remission was defined as no tender or swollen joints on examination of 51 joints (12) and normal acute phase

responses. The presence of active arthritis was evaluated as a clinical ineffectiveness.

Survival in MTX + LEF combination therapy:

Although the follow-up processes of the patients were different, drug survival rates were evaluated considering the drugs used at the last visit.

In the 3rd month of MTX + LEF treatment, 76.6% of the patients (82/107 patients) were able to continue the treatment in remission. These patients' mean duration of drug survival at follow-up was 30 months. The rate of patients who were continuing MTX + LEF treatment at their last visit at the time of the study analyses was 45% (Table 1).

MTX + LEF combination discontinuation:

After MTX + LEF treatment was started, combination therapy was discontinued in 55% (59 patients) of the patients for

various reasons. 42% of drug discontinuations occurred within the first three months.

In these patients whose treatment was discontinued within the first three months (25/107), the reasons for discontinuation were adverse events in 16 patients and primary clinical ineffectiveness in 9 patients (Table 2).

The main reasons for discontinuing the treatment during the follow-up period in patients who are in remission and continue their medication as of the third-month visits (82/107) are; secondary ineffectiveness or patients left on their own because of their well-being or concerns (Table 2).

Side effects of MTX + LEF combination therapy:

Side effects that led to drug discontinuation in the first three months were found to be >2 times higher transaminases in 7 of the patients, serious infection in 3, and diarrhea, alopecia, and skin rash in 6 of them.

While the frequency of transaminase elevation >2 times higher in the whole group was 9.3% (10/107), this side effect occurred in 70% of the patients in the first three months of treatment, and advanced age did not have a negative effect in this regard ($p > 0.05$).

The rate of serious infection in the whole group was found to be 6.5% (7/107). Three of these infections were seen in the first three months. Of the seven serious infections in our patients, 4 were pneumonia, 1 was intra-abdominal and 2 were urinary tract infections. Hospitalization was required in 3 patients, and all patients recovered with treatment. A significant correlation was found between advanced age and serious infection (r spearman=0.299 $p=0.002$). Comorbidity was present in 5 of 7 patients with severe infection.

Clinical efficacy:

MTX + LEF combination therapy was discontinued in 19 (17%) of patients due to ineffectiveness. While 9 of these patients were primary unresponsive, 10 were secondary non-responders.

In our study, no correlation was found between rheumatoid factor and anti-cyclic citrullinated peptide (CCP) antibody (anti-CCP) positivity and the effectiveness of combination therapy (r pearson=-0.031 $p=0.07$ and r pearson=-0.006 $p=0.96$ respectively). Drug discontinuation rates did not differ according to the diagnosis of the patients ($p > 0.05$).

Total (n)	107
Female/male (n)	77/30
Mean age (years)	50 (\pm 13)
Disease duration (years)	median: 5 (1-39)
Diagnosis (number of patients)	
RA	75
PsA	23
uCTD	5
uSPA	4
Drug survival at the last visit (number of patients)	48(44.5%)
Comorbidities (number of patients) (DM, HT, COPD, thyroid, CAD)	48(44.5%)
RA: Rheumatoid arthritis, PSA: Psoriatic arthritis, uCTD: Undifferentiated connective tissue disease, uSPA: Undifferentiated spondyloarthritis, DM: Diabetes mellitus, HT: Hypertension, COPD: Chronic obstructive pulmonary disease, CAD: Coronary artery disease	

	>2x transaminase elevation	Severe infections (n)	Intolerant (n)	Quit by their own decision	Non-responders
Discontinued in the first 3 months (n=25) 42%	7	3	6	-	9 (primary ineffectiveness)
Discontinued in the follow-up period (n=34) 58%	3	4	6	11	10 (secondary loss of response)
Total (n=59)	10	7	12	11	19
MTX: Methotrexate, LEF: Leflunomide					

Discussion

This is a study examining the efficacy and safety of the MTX + LEF combination in inflammatory arthritis based on real-life data. In our study, the data of 107 patients who were followed up by our rheumatology outpatient clinic and received combination therapy for a period of 10 years were analyzed retrospectively. In our results, the rate of >2 times transaminase elevation, which is one of the important treatment-related side effects, was found to be 9.5%, and 70% were recorded within the first three months. As of the 3rd month of the treatment, the rate of patients who tolerated the treatment and were in remission was 76%, and the median drug survival was 30 months in these patients. The frequency of serious infection was 6.5%, and a significantly increased correlation was found between advanced age and the risk of serious infection. No treatment-related mortality was observed in our patients. During the long-term follow-up, the main factors for discontinuation of combination therapy were secondary loss of response or the patient's desire to discontinue one of the drugs while in remission.

Although the rates of transaminase elevations observed with MTX and LEF were reported to be between 5.4-16.3% in randomized controlled studies, the rate of transaminase elevation was found to be 31% in patients with PsA, alcohol use, and higher doses of MTX, in the study of Curtis et al. (3,8,13-15). Alves et al. (16), in a series of 71 RA patients, showed that there was no difference between MTX monotherapy and MTX + LEF combination in terms of transaminase elevation. In our study, the frequency of >2 -fold elevation of transaminases was found to be 9.5%, and 70% was observed within the first three months. In our study, transaminase elevation did not differ in patients with RA or PsA. Patients with alcohol use or chronic liver disease were not already given combination therapy, and MTX doses were not included in our analyses.

In a series of 194 patients examining the data of the MTX + LEF combination, six patients had serious infections, and 2 of these infections resulted in death, while other infections were reported as sepsis in 3 patients and tuberculosis in 1 patient (17). In our patients, 3 of 7 serious infections required hospitalization, and all patients recovered with treatment. Patients who developed serious infections were predominantly elderly patients, and this relationship between increasing age and infection was found to be statistically significant.

In a multicenter study, data from 1671 RA patients were analyzed. Patients were grouped according to treatments as follows: MTF + LEF combination; MTX alone; LEF alone; or MTX/LEF + biological DMARD/Janus kinase inhibitor (JAKi). While the side effects seen with the MTF + LEF combination were similar to the patients who received MTX or LEF alone, the risk of serious side effects and risk of infection was found to be lower than those who received biological DMARD/JAKi + MTX/LEF (18).

In a study of 120 RA patients, the group receiving MTX + LEF combination was compared with the group receiving only MTX, adverse reaction rates were found to be similar, while both clinical and acute phase responses were found to be better in the group receiving MTX + LEF. Interleukin-1 and tumor necrosis factor-alpha levels were also found to be lower in this group (19). In another study retrospectively examining the data of 91 patients receiving the MTX + LEF combination and 22 patients receiving LEF alone, the efficacy of the MTX + LEF combination was not found to be superior to those who received LEF alone. In this study, no difference was found in terms of side effects (20).

In a study of RA patients with inadequate response to MTX monotherapy in China, patients were randomized into two groups, either MTX + LEF or MTX + hydroxychloroquine (HQ). MTX + HQ group was found to be superior in this cohort of two years of real-world data (21). The safety profiles were not of concern, and there were no significant differences between the two groups.

In another study, the results of 45 PsA patients who were unresponsive to MTX monotherapy and switched to the MTX + LEF combination was evaluated, and it was found that only 7 of these patients had to switch to biological DMARDs during follow-up. The reasons for the treatment change in these seven patients were determined as MTX + LEF ineffectiveness and hepatotoxicity. The authors reported that this combination was well tolerated, and drug survival was very good. 84% of patients were continuing with MTX + LEF at the time the study ended (22). In our study, the rate of patients continuing MTX + LEF treatment at the last visit was 45%, and the median drug survival was 30 months.

Most of the studies in the literature are observational and retrospective. Factors such as the short follow-up period of the patients, the heterogeneity of the doses of MTX and LEF used in combination therapy, the comorbidities and the lack of data on other concomitant drugs are the main limitations of these studies. The COMPLETE-PsA trial was a randomized, placebo-controlled, double-blind clinical trial. This study will provide important information for treatment strategies and recommendations (23).

In our study, the lack of a control group and drug doses were limiting factors. On the other hand, it is valuable in terms of having the longest follow-up period compared to other studies, the effect of additional diseases on side effects, and comparing the results in different disease groups.

Conclusion

In conclusion, the combination of MTX + LEF appears to be an effective and safe treatment option in patients with both RA, PsA, uSpa, and uCTD. These results are important in reassuring physicians and patients, especially in low-budget countries, when the transition to bDMARD needs to be postponed to the next steps due to the health system policies of countries or various conditions.

Our study suggests that patients with advanced age and additional disease should be more careful in terms of infection risk and that patients should be followed more frequently in terms of hepatotoxicity, especially in the first three months.

Ethics

Ethics Committee Approval: This study was approved by the Bakırçay University Faculty of Medicine Research Ethics Committee after reviewing the ethical issues (decision no: 1044, date: 17.05.2023).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Conflict of Interest: No conflict of interest was declared by the author.

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

References

- Mueller A, Weinblatt ME, Methotrexate. *Rheumatology*, Eighth edition Copyright © 2023, Chapter:63 pp 501-508
- Salliot C, van der Heijde D. Long-term safety of methotrexate monotherapy in patients with rheumatoid arthritis: a systematic literature research. *Ann Rheum Dis* 2009; 68: 1100-4.
- Emery P, Breedveld FC, Lemmel EM, Kaltwasser JP, Dawes PT, Gömör B, et al. A comparison of the efficacy and safety of leflunomide and methotrexate for the treatment of rheumatoid arthritis. *Rheumatology (Oxford)* 2000; 39: 655-65.
- Kent PD, Luthra HS, Michet C Jr. Risk factors for methotrexate-induced abnormal laboratory monitoring results in patients with rheumatoid arthritis. *J Rheumatol* 2004; 31: 1727-31.
- Alarcón GS, Kremer JM, Macaluso M, Weinblatt ME, Cannon GW, Palmer WR, et al. Risk factors for methotrexate-induced lung injury in patients with rheumatoid arthritis. A multicenter, case-control study. *Methotrexate-Lung Study Group. Ann Intern Med* 1997; 127: 356-64.
- Suissa S, Hudson M, Ernst P. Leflunomide use and the risk of interstitial lung disease in rheumatoid arthritis. *Arthritis Rheum* 2006; 54: 1435-9.
- Jenks KA, Stamp LK, O'Donnell JL, Savage RL, Chapman PT. Leflunomide-associated infections in rheumatoid arthritis. *J Rheumatol* 2007; 34: 2201-3.
- Curtis JR, Beukelman T, Onofrei A, Cassell S, Greenberg JD, Kavanaugh A, et al. Elevated liver enzyme tests among patients with rheumatoid arthritis or psoriatic arthritis treated with methotrexate and/or leflunomide. *Ann Rheum Dis* 2010; 69: 43-7.
- Rutanan J, Kononoff A, Arstila L, Elfving P, Koskela H, Kaipainen-Seppänen O. Five cases of interstitial lung disease after leflunomide was combined with methotrexate therapy. *Scand J Rheumatol* 2014; 43: 254-6.
- Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO 3rd, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis Rheum* 2010; 62: 2569-81.
- Taylor W, Gladman D, Helliwell P, Marchesoni A, Mease P, Mielants H; CASPAR Study Group. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. *Arthritis Rheum* 2006; 54: 2665-73.
- Cook MJ, Diffin J, Scirè CA, Lunt M, MacGregor AJ, Symmons DP, et al. Predictors and outcomes of sustained, intermittent or never achieving remission in patients with recent onset inflammatory polyarthritis: results from the Norfolk Arthritis Register. *Rheumatology (Oxford)* 2016; 55: 1601-9.
- Toth P, Bernd R. Severe leukopenia in a rheumatoid arthritis patient treated with a methotrexate/leflunomide combination. *Rev Bras Reumatol* 2014; 54: 152-4.
- Kremer J, Genovese M, Cannon GW, Caldwell J, Cush J, Furst DE, et al. Combination leflunomide and methotrexate (MTX) therapy for patients with active rheumatoid arthritis failing MTX monotherapy: open-label extension of a randomized, double-blind, placebo controlled trial. *J Rheumatol* 2004; 31: 1521-31.
- Strand V, Cohen S, Schiff M, Weaver A, Fleischmann R, Cannon G, et al. Treatment of active rheumatoid arthritis with leflunomide compared with placebo and methotrexate. *Leflunomide Rheumatoid Arthritis Investigators Group. Arch Intern Med* 1999; 159: 2542-50.
- Alves JA, Fialho SC, Morato EF, Castro GR, Zimmermann AF, Ribeiro GG, et al. Liver toxicity is rare in rheumatoid arthritis patients using combination therapy with leflunomide and methotrexate. *Rev Bras Reumatol* 2011; 51: 141-4.
- Hodkinson B, Magomero KR, Tikly M. Combination leflunomide and methotrexate in refractory rheumatoid arthritis: a biologic sparing approach. *Ther Adv Musculoskelet Dis* 2016; 8: 172-9.
- Bredemeier M, Ranza R, Kakehasi AM, Ranzolin A, da Silveira IG, Ribeiro ACM, et al. Safety of the Methotrexate-leflunomide Combination in Rheumatoid Arthritis: Results of a Multicentric, Registry-based, Cohort Study (BiobadaBrasil). *J Rheumatol* 2021; 48: 1519-27.
- Chen F, Wang Y, Wang L, Du H, He S. Combination of Methotrexate and Leflunomide Is Efficient and Safe for 60 Patients with Rheumatoid Arthritis. *Comput Math Methods Med* 2022; 2022: 6829358.
- Guadagnin DA, Mazzali LV, Skare TL, Kahlow BS. Treating rheumatoid arthritis with leflunomide monotherapy versus combination therapy with methotrexate. *Eur J Rheumatol* 2021; 8: 12-5.
- Zhang L, Chen F, Geng S, Wang X, Gu L, Lang Y, et al. Methotrexate (MTX) Plus Hydroxychloroquine versus MTX Plus Leflunomide in Patients with MTX-Resistant Active Rheumatoid Arthritis: A 2-Year Cohort Study in Real World. *J Inflamm Res* 2020; 13: 1141-50.
- Haroon M, Batool S, Asif S, Hashmi F, Ullah S. Combination of Methotrexate and Leflunomide Is Safe and Has Good Drug Retention Among Patients With Psoriatic Arthritis. *J Rheumatol* 2021; 48: 1624-6.
- Mulder MLM, Vriezekolk JE, den Broeder N, Mahler EAM, Helliwell PS, van den Hoogen FHJ, et al. Comparing methotrexate monotherapy with methotrexate plus leflunomide combination therapy in psoriatic arthritis: protocol of a randomized, placebo-controlled, double-blind clinical trial (COMPLETE-PSA). *Trials* 2020; 21: 155.