e-ISSN: 0976-822X, p-ISSN:2961-6042

Available online on http://www.ijcpr.com/

International Journal of Current Pharmaceutical Review and Research 2025; 17(8); 1568-1574

Original Research Article

Clinical and Functional Outcomes of Methotrexate and Leflunomide Combination Therapy for Anti-CCP and Anti-RA Positive Rheumatoid Arthritis Patients Refractory to Monotherapy: A Retrospective Study

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Received: 27-06-2025 / Revised: 25-07-2025 / Accepted: 27-08-2025
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Conflict of interest: Nil

Abstract:

Background: About one-third of RA patients who receive synthetic disease-modifying antirheumatic medications (sDMARDs), such as methotrexate (MTX), chloroquine (CQ), and sulfasalazine (SSZ), either as a monotherapy or combination therapy, experience adequate control of disease activity.

Objectives: With a focus on identifying methotrexate resistance and its effect on disease control, the study aimed to compare the safety profile, treatment response, and clinical outcomes of methotrexate plus leflunomide combination therapy to methotrexate monotherapy in patients with RA.

Materials and Methods: It was a retrospective, observational study. The study was carried out at a tertiary care centre. The study data that was retrieved was for one year. Data from 234 participants were retrieved for the study. The study included all patients with RA identified by the 2010 ACR/EULAR diagnostic criteria, aged 18–65, receiving either methotrexate monotherapy or methotrexate + leflunomide combination therapy.

Results: The study population was 47.2 ± 11.1 years old on average. Eighty-three percent of the 176 participants were female. 5.4 years was the median duration of the disorder (IQR: 3.2–7.6 years). With a mean DAS28 reduction of -2.7 ± 0.8 versus -1.9 ± 0.9 in the MTX group, patients in the MTX+LEF group demonstrated a substantially higher reduction in disease activity (p-value <0.001). 45 (36.3%) patients on MTX+LEF and 25 (22.7%) on MTX alone experienced remission (DAS28 <2.6), with a p-value of 0.01.

Conclusion: Although the differences were not statistically significant, the study found that methotrexate and leflunomide combination therapy was linked to a somewhat higher frequency of adverse events than methotrexate only.

Recommendations: Patients with RA who do not respond well to methotrexate alone may be candidates for combination therapy that combines leflunomide and methotrexate.

Keywords: Rheumatoid Arthritis, Methotrexate, Leflunomide, RA, Anti-RA, sDMARD.

Introduction

About one-third of RA patients who receive synthetic disease-modifying antirheumatic medications (sDMARDs), such as methotrexate (MTX), chloroquine (CQ), and sulfasalazine (SSZ), either as a monotherapy or combination therapy, experience adequate control of disease activity [1, 2]. Biologic medication access is restricted in resource-constrained environments, which poses a significant management issue for refractory RA.

Combining MTX and leflunomide (LEF) is one strategy for patients who have not responded to triple combination therapy (MTX, CQ, and SSZ). The mechanisms of action of these two sDMARDs differ: LEF inhibits pyrimidine synthesis, while MTX inhibits purine synthesis and 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR) [3].

LEF was first approved as a monotherapy to treat active RA. Numerous observational studies and clinical trials have shown that it is just as effective and tolerable as other sDMARDs, controlling disease activity, improving functional disability, and slowing the progression of radiography [4, 5].

According to recommendations from the European League Against Rheumatism (EULAR), patients who do not respond to one sDMARD and have poor prognostic factors (such as seropositivity, high

disease activity, and early radiographic damage) should be switched to a biologic DMARD (bDMARD) instead of combination sDMARDs [6].

In animal models of autoimmune illness, leflunomide, an isoxazole immunomodulatory drug, has shown both preventative and therapeutic benefits [7]. After leflunomide is taken orally, the isoxazole ring is quickly broken down to produce the active metabolite, which attaches itself to the enzyme dihydroorotate dehydrogenase and prevents the creation of new pyrimidines [8].

This causes cell cycle arrest in rapidly dividing cell types, including activated lymphocytes, which can be reversed in vitro and in vivo by uridine injection [9, 10].

For patients for whom there are no contraindications to its administration, methotrexate (MTX) should always be the first line of treatment. About 50% of patients who begin using MTX are able to control their condition, according to several studies [11, 12, 13].

With a focus on identifying methotrexate resistance and its effect on disease control, the study aimed to compare the safety profile, treatment response, and clinical outcomes of methotrexate plus leflunomide combination therapy to methotrexate monotherapy in patients with RA.

Methodology

Study Design: It was a retrospective, observational study.

Study Settings: The study was carried out at a tertiary care centre. The study data that was retrieved was for one year.

Study Population: Data of 234 participants were retrieved for the study. The study included all patients with RA identified by the 2010 ACR/EULAR diagnostic criteria, aged 18–65, receiving either methotrexate monotherapy or methotrexate + leflunomide combination therapy. Patients were deemed resistant if they needed to be escalated to combination therapy because they continued to exhibit disease activity (DAS28 > 3.2) even after receiving a sufficient dose and duration of methotrexate monotherapy (at least 6 months with a minimum dose of 15 mg/week). Patients were deemed eligible only if they consented to the use of their clinical data and had a minimum follow-up of six months with sufficient treatment records.

Individuals having a history of alcohol or drug misuse, chronic liver disease, renal impairment, severe lung disease, or other autoimmune connective tissue diseases such psoriatic arthritis or systemic lupus erythematosus were not included. The analysis further excluded patients with inadequate records or lost to follow-up, patients on biologic DMARDs or JAK inhibitors during the research period, and pregnant or lactating women.

Data Collection: The following demographic information was systematically documented: age, sex, smoking status, BMI, clinical features (disease duration, comorbidities, baseline severity, treatment regimens (MTX + LEF or MTX only), and outcomes (treatment response, adverse events, discontinuation rates). Results such as radiographic progression, CRP/ESR trends, HAQ score, ACR response, and DAS28 were also recorded.

Study Procedure: According to the records, eligible participants were split into two groups according to the type of treatment they got. For example, Group A (MTX + LEF) consisted of patients who received methotrexate and leflunomide together, whereas Group B (MTX Alone) consisted of patients who received methotrexate alone. At the time of recruitment, baseline demographic information was recorded, including age, sex, smoking status, BMI, and disease characteristics, including baseline activity, concomitant diseases, and disease duration.

In accordance with conventional treatment practice, patients were monitored at regular intervals. Using disease activity scores, clinical response was evaluated and classified as good, moderate, or nonexistent. During the course of the trial, adverse events like infections, hepatotoxicity, cytopenia, and gastrointestinal intolerance were tracked and documented.

Statistical Analysis: SPSS version 26.0 was used for statistical analysis. Data were initially entered in Microsoft Excel. The data have been presented as either the number of participants (n) with percentages (%), or mean±SD, or median with inter-quartile range.

The independent t-test was used for statistical analysis. Statistical significance was defined as a p-value of less than 0.05.

Results

The study population was 47.2 ± 11.1 years old on average. Eighty-three percent of the 176 participants were female. 5.4 years was the median duration of the disorder (IQR: 3.2–7.6 years). Every patient tested 100% positive for RF and 100% positive for anti-CCP. The average CDAI score was 28.7 ± 7.2 and the average DAS28-CRP score was 5.9 ± 0.8. The baseline characteristics of the individuals are shown in Table 1.

Table 1: Characteristics of Participants at Baseline

Parameters	Value
Age (in years)	47.2 ± 11.1
Female Participants	176 (83%)
Smoking Status	62 (29.2%)
Disease Duration (in years)	5.4 (3.2–7.6)
Anti-CCP Positive	234 (100%)
RF Positive	234 (100%)
DAS28-CRP	5.9 ± 0.8
CDAI	28.7 ± 7.2
HAQ-DI	1.7 ± 0.5
Prior MTX monotherapy	152 (71.7%)
Prior LEF monotherapy	60 (28.3%)

With 34 cases in the MTX+LEF group and 32 cases in the MTX alone group, the bulk of patients were between the ages of 40 and 49. The 50–59 age group came next, with 30 and 28 instances, respectively. Twenty-eight patients in the MTX+LEF group and twenty-four in the MTX alone group were between the ages of thirty and thirty-nine. The age distribution of research participants is displayed in Figure 1.

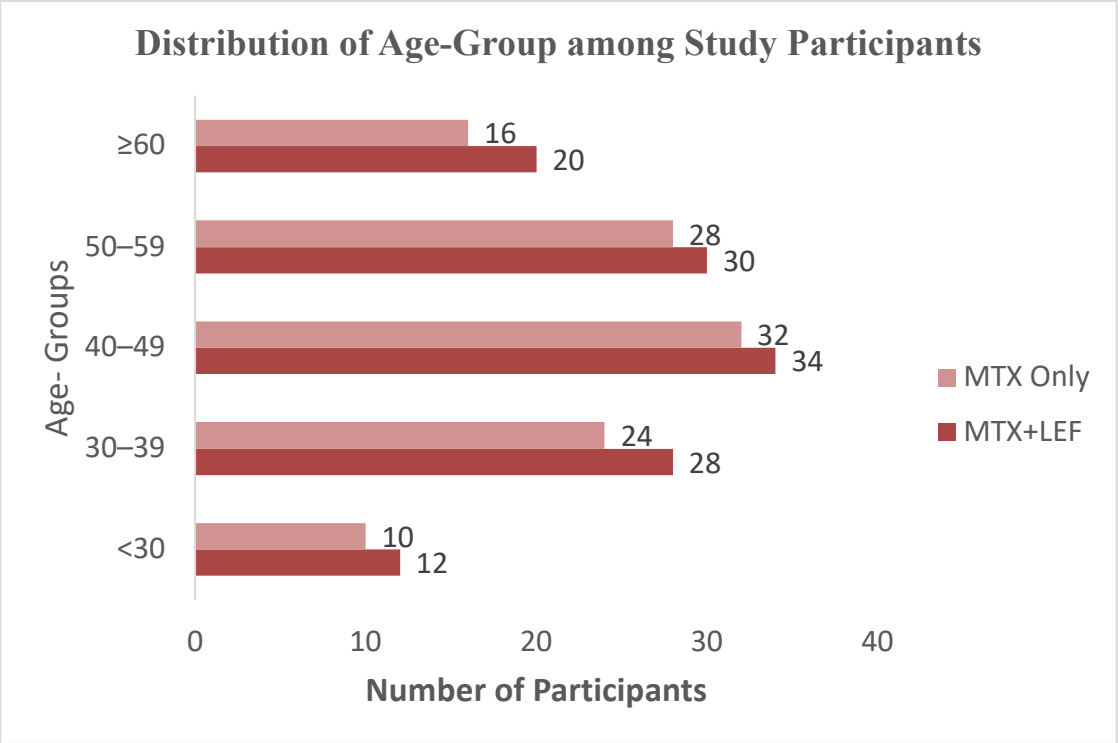

Figure 1: Distribution of Age-Groups among Study Participants

Compared to 56 patients in the MTX alone group, 62 patients in the MTX+LEF group did not have any comorbidities. Thirty patients in the MTX+LEF group and twenty-eight individuals in the MTX monotherapy group had hypertension, the most prevalent comorbidity. Thyroid problems were detected in 12 and 10 patients, respectively, while diabetes mellitus was noted in 20 and 16 patients. The distribution of comorbidities across research participants is displayed in Figure 2.

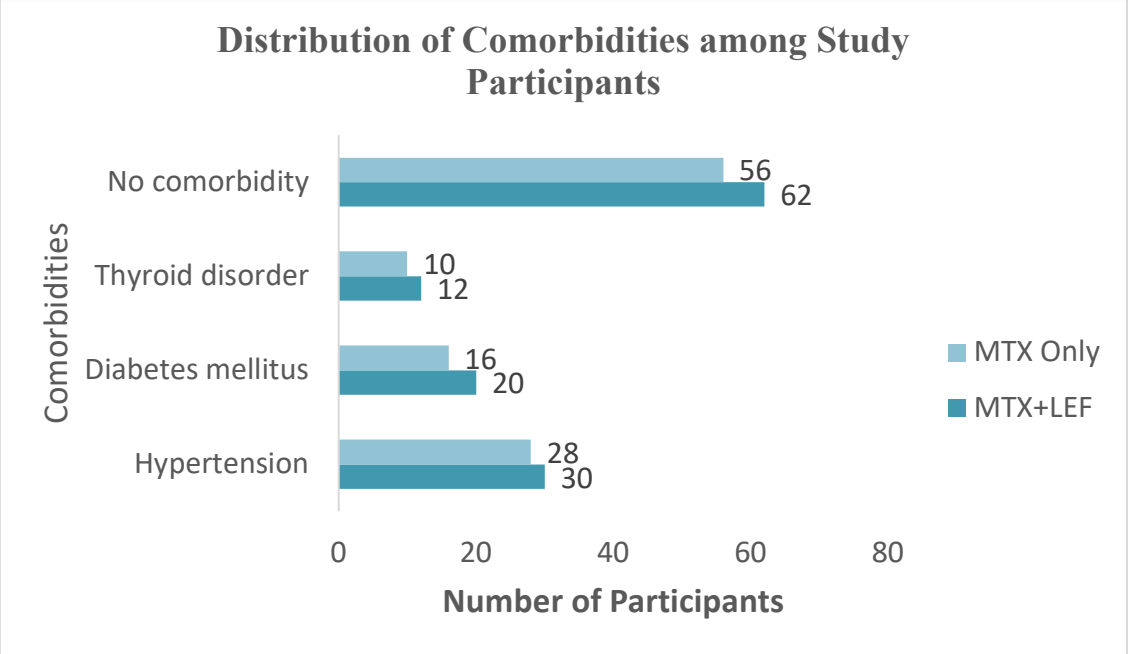

Figure 2: Distribution of Comorbidities among Study Participants

With a mean DAS28 reduction of -2.7 ± 0.8 versus -1.9 ± 0.9 in the MTX group, patients in the MTX+LEF group demonstrated a substantially higher reduction in disease activity (p-value <0.001). 45 (36.3%) patients on MTX+LEF and 25 (22.7%) on MTX alone experienced remission (DAS28 <2.6), with a p-value of 0.01. Similarly, with a p-value of 0.02, 76 (61.3%) of the MTX+LEF group achieved modest disease activity, compared to 50 (45.5%) in the MTX group.

Table 2: Comparative Outcomes Between the Treatments

Outcome	MTX+LEF (n=124)	MTX Only (n=110)	p-value
DAS28 reduction	-2.7 ± 0.8	-1.9 ± 0.9	**<0.001**
Remission (DAS28 <2.6)	45 (36.3%)	25 (22.7%)	**0.01**
Low disease activity	76 (61.3%)	50 (45.5%)	**0.02**
Mean HAQ-DI improvement	-0.58 ± 0.21	-0.39 ± 0.19	**<0.001**
Patients achieving MCID in HAQ-DI	89 (72%)	60 (54.5%)	**0.003**
ACR20 response	97 (78.2%)	68 (61.8%)	**0.004**
ACR50 response	70 (56.4%)	42 (38.2%)	**0.002**
ACR70 response	35 (28.6%)	17 (15.5%)	**0.01**
CRP reduction (mg/L)	-15.4 ± 6.8	-9.7 ± 5.9	**<0.001**
ESR reduction (mm/hr)	-24.6 ± 10.2	-16.3 ± 9.7	**<0.001**
Radiographic progression at 12 months	18 (14.5%)	30 (27.3%)	**0.008**

There were 18 patients (16.1%) in Class I, 45 (40.3%) in Class II, 41 (36.6%) in Class III, and 14 (12.9%) in Class IV in the MTX+LEF group. In contrast, 18 patients (16.4%) were in Class I, 40 patients (36.4%) were in Class II, 42 patients (38.0%) were in Class III, and 18 patients (16.4%) were in Class IV in the MTX alone group. The distribution of ACR classes among study participants was displayed in Figure 3.

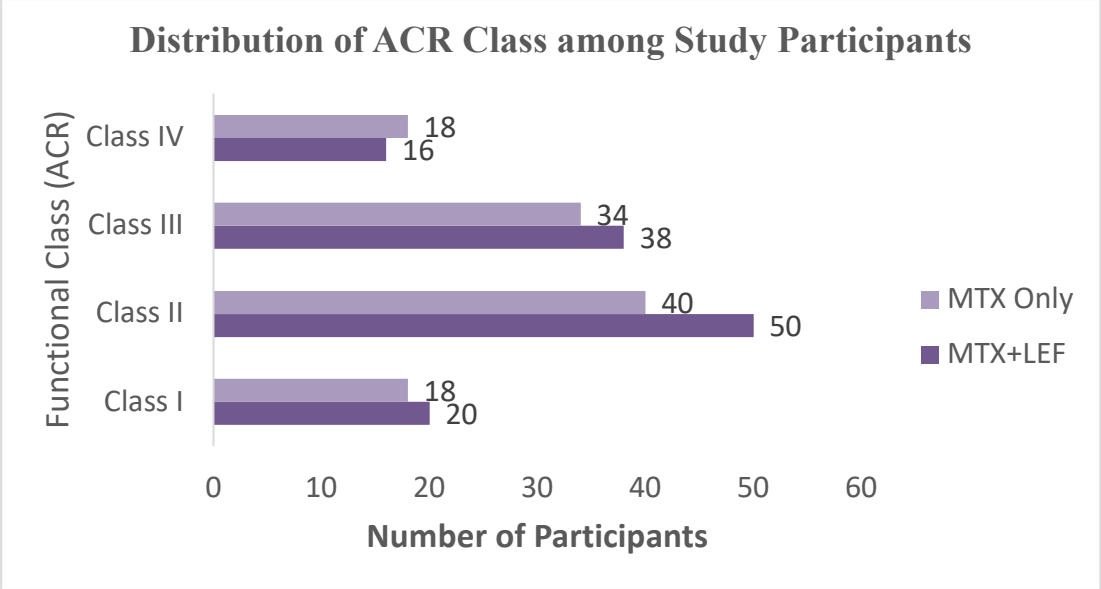

Figure 3: Functional Class of ACR at Baseline

With a p-value of less than 0.001, 60 patients (48.7%) receiving MTX+LEF showed good response, compared to 35 patients (31.9%) in the MTX alone group. 44 patients (39.5%) on MTX alone and 43 patients (34.6%) on MTX+LEF had moderate responses, which were not statistically significant (p-value = 0.24). The study participants' EULAR responses are shown in Table 3.

Table 3: Response of EULAR among Study Participants

Response	MTX+LEF (n=124)	MTX Alone (n=110)	p-value
Good	60 (48.7%)	35 (31.9%)	**<0.001**
Moderate	43 (34.6%)	44 (39.5%)	0.24
No response	21 (16.7%)	31 (28.6%)	**0.002**

There was no significant difference in the incidence of gastrointestinal intolerance between the MTX+LEF group, which included 19 patients (15.4%), and the MTX only group, which included 14 patients (12.7%) (p = 0.62). Ten patients (8.1%) on MTX+LEF and five patients (4.5%) on MTX alone had elevated liver enzymes; however, this difference was not statistically significant (p = 0.23). Compared to 3 patients (2.7%) on MTX alone, 6 patients (4.8%) on MTX+LEF experienced hepatotoxicity (p = 0.38). Adverse occurrences among study participants are displayed in Table 4.

Table 4: Adverse Events among Study Participants

Adverse Event	MTX+LEF (n=124)	MTX Only (n=110)	p-value
GI intolerance	19 (15.4%)	14 (12.7%)	0.62
Elevated liver enzymes	10 (8.1%)	05 (4.5%)	0.23
Hepatotoxicity	06 (4.8%)	03 (2.7%)	0.38
Cytopenia	05 (4.0%)	03 (2.7%)	0.59
Serious infections	03 (2.4%)	03 (2.7%)	0.89
Discontinuation due to AE	07 (5.6%)	05 (4.5%)	0.71

Discussion

In patients with refractory RA, the current study contrasted the safety and effectiveness of MTX monotherapy with MTX + LEF combination therapy. When compared to MTX alone, the results showed that combination therapy improved clinical outcomes and disease control more effectively without significantly increasing side effects.

According to a number of earlier studies, MTX is still the mainstay of treatment for RA; however, a significant percentage of patients have unsatisfactory response, which calls for either dose increase or the inclusion of other DMARDs [14]. The combination of MTX with LEF, an inhibitor of pyrimidine production, is a logical treatment approach because of their complimentary actions [15]. Accordingly, the current study found that the MTX+LEF group had a better clinical response than the MTX monotherapy group.

There were similar adverse effects in the two groups. Although they did not differ significantly between

groups, the most frequent adverse events were increased liver enzymes and gastrointestinal discomfort. This is in line with past clinical trials where the most common toxicities observed were gastrointestinal intolerance and hepatotoxicity, although these were not appreciably more common in the combination group [16, 17]. Cytopenias and serious infections were uncommon in both groups, confirming the regimen's general tolerability.

Although not statistically significant, the rate of discontinuation due to adverse events was marginally higher in the MTX+LEF group, which is consistent with earlier research showing that patients undergoing combination therapy experienced somewhat higher withdrawal rates [18]. Significantly, it was discovered that smoking status had a detrimental effect on treatment response, which is in line with other research that indicated smoking to be a predictor of poor RA outcomes and decreased DMARD efficacy [19, 20].

The study highlights that, particularly for patients who are resistant to MTX monotherapy, MTX+LEF can be a financially advantageous substitute in areas with low resources where biologics may not be easily available. Hematological markers and liver function must still be closely monitored, though.

Conclusion

Although the differences were not statistically significant, the study found that methotrexate and leflunomide combination therapy was linked to a somewhat higher frequency of adverse events than methotrexate only. When methotrexate and leflunomide were used together, the rate of side effects was marginally greater but still controllable. Given the general safety of both regimens, the combination is a good choice for treating methotrexate-resistant rheumatoid arthritis under careful observation.

Limitations

Since this study was conducted in a single urban tertiary care facility, it may not be feasible to extrapolate the findings to the broader population. Additionally, the study's sample size was too small to draw conclusions and extrapolate findings.

Recommendations

Patients with RA who do not respond well to methotrexate alone may be candidates for combination therapy that combines leflunomide and methotrexate. To guarantee safety and maximize therapeutic results, it is highly advised to carefully identify patients, check liver function and hematological parameters on a regular basis, and provide counseling regarding side effects.

List of Abbreviations

RA- Rheumatoid Arthritis

sDMARDS- Synthetic disease-modifying antirheumatic medications

DMARDS- Disease Modifying Anti-Rheumatic Drugs

MTX- Methotrexate

CQ- Chloroquine

SSZ- Sulfasalazine

LEF- Leflunomide

ACR- American College of Rheumatology

EULAR- European League Against Rheumatism

IQR- Intra-quartile Range

RF- Rheumatoid Factor

ACPA- Anti-Citrullinated Protein Antibody

NSAIDS- Non-Steroidal Anti-Inflammatory Drugs

CRP- C-Reactive Protein

ESR- Erythrocyte Sedimentation Rate

DAS28- Disease Activity Score-28

Anti-CCP- Anti-Cyclic Citrullinated Peptide

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