ORIGINAL ARTICLE

Efficacy and Safety of Methotrexate Plus Leflunomide in Patients of Rheumatoid Arthritis not Responding to Methotrexate Alone

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ABSTRACT

Introduction: Rheumatoid Arthritis (RA) is a chronic inflammatory disease affecting approximately 0.24% of the global population and can lead to joint destruction, functional decline, disability, and decreased quality of life. According to ACR and EULAR guidelines, patients with RA should initiate treatment with conventional synthetic Disease-Modifying Antirheumatic Drugs (csDMARDs), such as Methotrexate (MTX). In patients with an inadequate response to csDMARDs, it is recommended to add a targeted synthetic DMARD, such leflunomide or a biologic DMARD (bDMARD), such as tumor necrosis factor inhibitor (TNFi). **Objectives:** To study the efficacy and safety of methotrexate and leflunomide in patients of Rheumatoid arthritis not responding to methotrexate alone. **Materials and Methods:** It was a single centre, observational study in 50 patients of Rheumatoid Arthritis taking methotrexate plus leflunomide after inadequate response to methotrexate monotherapy (15mg/week) for 12 weeks. Patients were included in the study after meeting inclusion and exclusion criteria. Patients were taking leflunomide in a dose of 10 mg/day and methotrexate in a dose of 15 mg/week with Folic acid 5 mg/week. Efficacy outcomes; ACR 20/50/70 and DAS-28 CRP based remission/low disease activity were assessed at 12 weeks and 24 weeks. Statistical analysis was done using Jamovi (V2.3.18) software. **Results:** Improvement from baseline to weeks 12 and 24 was observed for all efficacy outcomes (including ACR 20/50 and DAS-28 CRP based low disease activity/remission) in patients taking methotrexate plus leflunomide. At 24 week 64% achieved ACR-20, 44% patients achieved ACR-50, 24% patients achieved Low Disease activity (LDA) and 6% patients achieved remission. The most common adverse effect was nausea and vomiting at 24 weeks. No deaths were reported. **Conclusion:** In our study methotrexate and leflunomide conferred improvement in disease activity measures and functional outcomes after 24 weeks of treatment.

Keywords: Rheumatoid arthritis, RA, Methotrexate, Leflunomide.

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INTRODUCTION

Rheumatoid Arthritis (RA) is a chronic inflammatory disease affecting approximately 0.24% of the global population[1] and can lead to joint destruction, functional decline, disability, and decreased quality of life.[2,3] The American College of Rheumatology (ACR) and European Alliance of Associations for Rheumatology (EULAR) recommend using a treat to-target approach with the aim of achieving remission or, at least, Low Disease Activity (LDA),[5,6] so that progression to joint damage can be prevented.[4]

According to ACR and EULAR guidelines, patients with RA should initiate treatment with conventional synthetic Disease-Modifying Antirheumatic Drugs

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(csDMARDs), such as Methotrexate (MTX). In patients with an inadequate response to csDMARDs, it is recommended to add a targeted synthetic DMARD followed by biologic DMARD (bDMARD), such as a Tumor Necrosis Factor inhibitor (TNFi) if inadequate response is seen.[5,6]

In a randomized, double-blind, placebo controlled trial; leflunomide was added in patients with active RA despite MTX treatment. Adding leflunomide provided substantial therapeutic benefit compared with adding Placebo (PLA) and it was generally well tolerated.[7,8] Elevations in liver function tests were reversible with discontinuation, dose reduction, or, in mild cases, often with no change in dose.[7]

This study was done to evaluate efficacy and safety of methotrexate plus leflunomide in patients of rheumatoid arthritis not responding to methotrexate alone.

AIMS AND OBJECTIVES

1. To study the efficacy and safety of methotrexate and leflunomidein patients of Rheumatoid Arthritis not responding to methotrexate alone.
2. To determine the proportion of patients who reached 20%, 50%, and 70% improvement in activity of Rheumatoid Arthritis According to ACR (2010) criteria in 12, 24 weeks after start of therapy.
3. To determine the proportion of patients who reached remission and low disease activity according to DAS28-CRP criteria in 12, 24 weeks after start of therapy.
4. To determine the range, frequency and severity of adverse events with administration of methotrexate and leflunomidein patients with rheumatoid arthritis

MATERIALS AND METHODS

Study design

It was a Single centre, Observational study carried out in KPS Post Graduate Institute of Medicine, G.S.V.M. Medical College, Kanpur from January 2022 to October 2022.

Patients

50 patients of Rheumatoid Arthritis taking methotrexate plus leflunomide after no response to methotrexate monotherapy (15mg/week) for 12 weeks were included in the study.

Inclusion criteria

- Patients willing to give written signed informed consent to participate in the study.
- Patients 18-65 years of age.
- Patient of either sex (Male/Female).
- Patient diagnosed with RA (according to ACR/EULAR criteria 2010) for at least 6 months.
- Patients with moderate to severe disease activity defined as DAS-28 score >3.2 despite methotrexate therapy for 12 weeks.
- Patients receiving methotrexate in a stable dose for at least 4 weeks prior to the inclusion to the study. (15-25 mg/week).
- Steroids and NSAIDs doses need to be stable for at least 4 weeks prior to inclusion to study.
- Patients of child bearing potential must agree to use medically approved contraception that had to be continued for >6 months after completion of the treatment protocol.

Exclusion criteria

- Patients with low activity of rheumatoid arthritis (DAS28-CRP index <3.2 points).
- Patients receiving other DMARDs within 4 weeks prior to inclusion to the study.
- Presence or history of any other joint disease, recent fracture, systemic autoimmune disease or demyelinating disease.
- Patients of active tuberculosis, HIV, syphilis, HBV and active Hepatitis C.
- Patients with organ transplantation history or malignancy.
- Present or history of alcoholism or drug abuse.
- Pregnant or planning pregnancy within 6 months after the end of study and lactating women.
- Patients with clinically significant neurological, metabolic, hepatic, renal, cardiovascular or pulmonary dysfunction.
- Determined hypersensitivity to any components of study drugs.

Follow up

Patients were taking leflunomide in a dose of 10 mg/day and methotrexate in a dose of 15 mg/week with Folic acid 5 mg/week.

Following scales were used for tracking disease status and for documenting treatment response.

1. The ACR 20, 50, and 70 improvement criteria.
2. The Disease Activity Score 28 (DAS-28) CRP Score.

Statistical analysis

Statistical analysis of the obtained data was performed using Jamovi (v2.3.18) software. p value <0.05 was taken as statistically significant.

Observations

Table 1: Demographics and baseline disease characteristics of patients.

Age in years (mean ± SD)	39.42 ±10
Male	8%
Female	92%
Disease duration in years	2.78 ±1.67
Swollen joint count (28)	14.4 ±3.04
Tender joint count (28)	9.16 ±3.09
Patient global assessment score (10)	5.94 ±1.05
Serum CRP level (mg/dl)	9.61 ± 6.26
DAS28-(CRP) score	4.6± 0.58
Disease activity based on DAS28-(CRP) score	
Moderate (3.3 - 5.1)	72%
High (>5.1)	28%

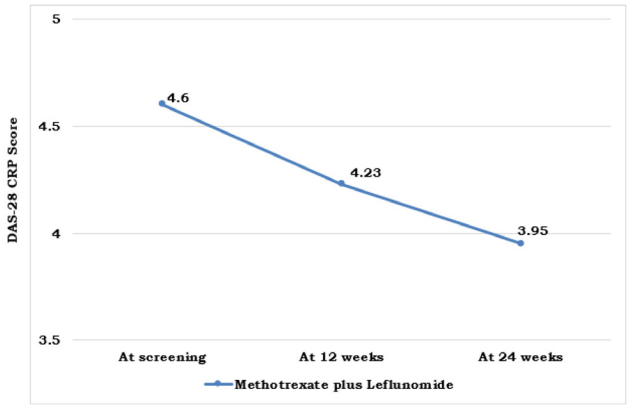

Figure 1: Comparison of DAS-28 CRP score from baseline to follow-up (*n* = 50).

RESULTS

Efficacy

There was significant reduction in swollen joint count, tender joint count, Patient Global Assessment score, serum CRP level (mg/dl) and DAS-28 CRP score (Figure 1) progressively at 12 weeks and 24 weeks. 6% patients achieved remission at 24 weeks. (Figure 2). 6% and 24% patients achieved low Disease activity at 12 weeks and 24 weeks respectively. (Figure 2). 42% and 64% patients achieved ACR-20 at 12 weeks and 24 weeksrespectively. 2% and 44% patients achieved ACR-50 at 12 weeks and 24 weeksrespectively. No patient achieved ACR-70 at 12 week and 24 weeks. (Figure 3).

Safety

The most common adverse effect was nausea and vomiting at 12 weeks and 24 weeks. Mild Liver enzyme (SGOT/SGPT) elevations occurred in patients

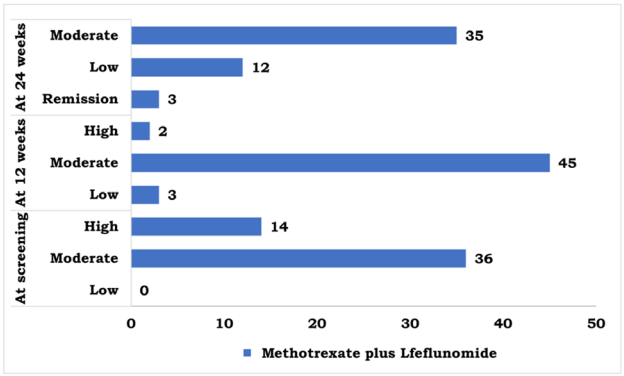

Figure 2: Distribution of cases according to severity (based on DAS-28 CRP score). (*n* = 50).

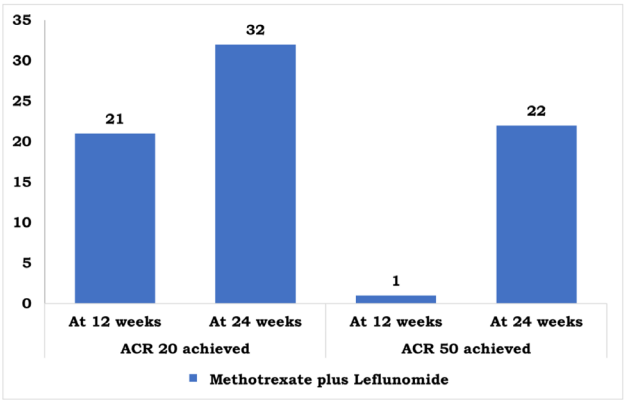

Figure 3: Distribution of cases according to achievement of ACR 20/50 from baseline to follow-up. (*n* = 50).

receiving Methotrexate plus Leflunomide during 24 weeks period which normalized after a discontinuation of Methotrexate plus Leflunomide.

Clinical and demographic characteristics

Clinical and demographic characteristics of the study population at baseline were: Age in years (mean + SD) 39.42 + 10, Male 8%, Female 92%, Disease duration in years 2.78 + 1.67, Swollen joint count (28) 14.4 + 3.04, Tender joint count (28) 9.16 + 3.09, Patient global assessment score (10) 5.94 + 1.05, Serum CRP level (mg/dl) 9.61 + 6.26, DAS28-(CRP) score 4.6 + 0.58, Disease activity based on DAS28-(CRP) score Moderate (3.3 - 5.1) 72%, High (>5.1) 28%. (Table 1)

DISCUSSION

To study the efficacy and safety of methotrexate and leflunomidein patients of Rheumatoid Arthritis (RA) not responding to methotrexate alone, we followed up 50 patients of RA taking methotrexate plus leflunomide for 24 weeks.

Methotrexate plus leflunomide conferred significant improvements in disease activity measures with 64% patients achieving ACR-20 and 44% patients achieving ACR-50 after 24 weeks as seen in earlier studies Joel Kremer *et al*.[7] and 6% patients achieving remission and 24% patients achieving low disease activity after 24 weeks of treatment as seen in earlier studies Joel Kremer *et al*.[7]

Mild Liver enzyme (SGOT/SGPT) elevations that occurred in patients receiving Methotrexate plus Leflunomide during 24 weeks period, normalized after a reduction or discontinuation of Methotrexate plus Leflunomide, as seen in earlier studies Joel Kremer *et al*.[7]

In our study, clinical and functional responses in patients of RA taking Methotrexate plus Leflunomide were assessed at 12 weeks and 24 weeks. There were statistically significant improvements in clinical and functional outcome measures like swollen joint count, tender joint count, DAS-28 CRP score and ACR20/50 response rate at 12 weeks and 24 weeks.

CONCLUSION

It was concluded that there was statistically significant improvement in swollen joint count, tender joint count, Patient Global Assessment score, serum CRP level (mg/dl), DAS-28 CRP score and ACR-20/50 response rates in patients of RA taking methotrexate plus leflunomideat 12 weeks and 24 weeks.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

Ethical Approval

Institutional ethics committee.

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