ejpmr, 2022,9(12), 61-64

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

THE EFFICACY OF COMBINATION LEFLUNOMIDE AND METHOTREXATE (MTX) THERAPY FOR PATIENTS WITH ACTIVE RHEUMATOID ARTHRITIS

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Article Received on 13/10/2022 **Article Revised on 03/11/2022** **Article Accepted on 24/11/2022**

ABSTRACT

Background: Rheumatoid arthritis (RA) is a progressive inflammatory disease of unknown etiology that causes mortality. In recent days it was found that, methotrexate (MTX) combined with leflunomide (LEF) demonstrated a substantial incremental benefit in patients with RA. **Objective:** In the study our main aim is to evaluate the Outcome of Combination leflunomide and methotrexate (MTX) therapy for patients with active rheumatoid arthritis. **Method:** This cross sectional study was carried out at tertiary medical hospital from February 2021 to February 2022. Where a total of 200 patients of Rheumatoid Arthritis were attended OPD were included as a sample size. During the study patients were divided into two group, placebo + MTX, n=100, whereas patients randomized to LEF and MTX continued treatment [(LEF/LEF) + MTX], n=100, were used as another group. **Results:** During the study, majority were belonging to 45-55 years age group, 65% and 85% were male. In the patients who switched from PLA to LEF therapy while taking background MTX, the ACR20 responder-at-endpoint rate was 25.0% at Week 24, which increased to 59.4% at Week 48, and was statistically different ($p < 0.0001$). in addition, there was a further improvement in the mean change in HAQ DI at Week 48 (–0.33) compared with that seen at Week 24. In Placebo+MTX group events like diarrhea, nausea, gastroenteritis, vomiting, sore mouth, UTI, hypotension were higher than LEF+MTX. **Conclusion:** The therapeutic advantage of combination LEF + MTX for the treatment of RA in patients with active illness receiving MTX alone was maintained for 48 weeks, including improvements in signs and symptoms (ACR response), physical function (HAQ DI).

KEYWORDS: Rheumatoid arthritis (RA), meth'otrexate (MTX), leflunomide (LEF).

INTRODUCTION

Rheumatoid arthritis is a painful, disabling joint condition characterized by synovium growth and progressive cartilage and bone loss. Early use of disease-modifying antirheumatic medications (DMARD) has become the gold standard for treating RA; nevertheless, some patients show an inadequate response to DMARD monotherapy.[1-2]

For the treatment of RA, methotrexate (MTX) is the DMARD most widely used as both monotherapy and in combination therapy. Because in many patients MTX alone does not adequately control the signs and symptoms of RA at tolerated doses, the practice of combination DMARD therapy has increased in an attempt to gain efficacy while managing toxicity. A 1997 survey found that 99% of responding rheumatologists prescribed combination DMARD therapy in an estimated 24% of all patients with RA.[3-5]

MTX has been used in combination with many drugs, including sulfasalazine, sulfasalazine and hydroxy chloroquine, cyclosporine, auranofin, azathioprine, etanercept, infliximab, and anakinra. Limited data in abstract form are available on combination therapy with leflunomide (LEF) and cyclosporine, infliximа, and sulfasalazine. In both an open-label trial and a doubleblind trial MTX combined with LEF demonstrated a substantial incremental benefit in patients with RA.[6-8]

In the study our main aim is to evaluate the Outcome of Combination leflunomide and methotrexate (MTX) therapy for patients with active rheumatoid arthritis.

OBJECTIVE

- To asses the efficacy of Combination leflunomide and methotrexate (MTX) therapy for patients with active rheumatoid arthritis.

METHODOLOGY

This cross sectional study was carried out at tertiary medical hospital from February 2021 to February 2022. Where a total of 200 patients of Rheumatoid Arthritis were attended OPD were included as a sample size. During the study patients were divided into two group, placebo + MTX, n=100, whereas patients randomized to

LEF and MTX continued treatment [(LEF/LEF) + MTX], n=100, were identified as another group.

All relevant information from history, clinical examination and investigations were collected in a semi-structured data collection sheet. Collected data were processed and analyzed by using computer based software, statistical package for Social Science (SPSS).

RESULTS

In table-1 shows age distribution of the study group where majority were belonging to 45-55 years age group, 65%. The following table is given below in detail:

Table 1: Age distribution of the patients.

Age group	%
34-44 years	10%
45-55 years	65%
>55 years	25%

In figure-1 shows gender distribution of the patients where 85% were female. The following figure is given below in detail:

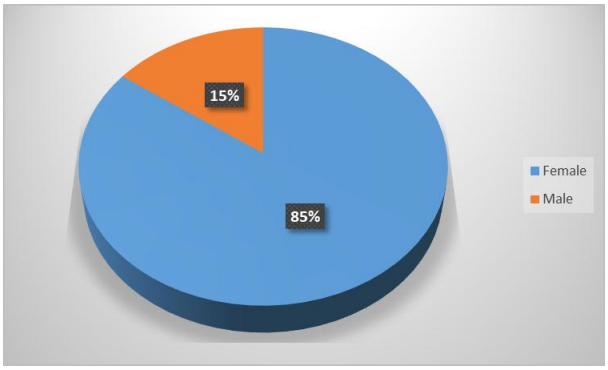

Figure-1: Gender distribution of the patients.

In table-2 shows ACR responses in the double-blind phase (ITT population) and in the open-label extension. Where PLA/LEF) + MTX, in the patients who switched from PLA to LEF therapy while taking background MTX, the ACR20 responder-at-endpoint rate was 25.0% at Week 24, which increased to 59.4% at Week 48, and was statistically different ($p < 0.0001$). The following table is given below in detail:

Table 2: ACR responses in the double-blind phase (ITT population) and in the open-label extension.

Responder-at-endpoint rate	Placebo+MTX, week 24, %	Placebo+MTX, week 48, %	LEF+MTX, week 24, %	LEF + MTX, week 48, %
ACR-20	19.5	25.0	59.4	55.2
ACR-50	6.0	8.3	32.3	35.4
ACR-70	2.3	3.1	12.5	16.7
Last observation carried forward				
ACR-20	23.3	27.2	59.4	56.3
ACR-50	6.0	8.3	33.3	35.4
ACR-70	2.4	3.2	13.5	16.7

In table-3 shows changes from baseline in individual efficacy measures at Weeks 24 and 48 (mean ± SD) where there was a further improvement in the mean change in HAQ DI at Week 48 (–0.33) compared with that seen at Week 24. The following table is given below in detail:

Table-3: Changes from baseline in individual efficacy measures at Weeks 24 and 48 (mean ± SD)

Baseline changes	Placebo+MTX, %	LEF+MTX, %
Tender joint count:		
Mean change at Week 24	–6.1 ± 13.9	–14.3 ± 11.7
Mean change at Week 48	–14.1 ± 12.4	–15.9 ± 12.3
Swollen joint count:		
Mean change at Week 24	–4.4 ± 8.7	–7.8 ± 7.1
Mean change at Week 48	–9.7 ± 7.0	–8.8 ± 7.2
Patient global assessment, mm		
Mean change at Week 24	–6.3 ± 25.1	–22.8 ± 28.0
Mean change at Week 48	–20.9 ± 26.1	–20.9 ± 26.1
Physician global assessment, mm		
Mean change at Week 24	–13.6 ± 22.3	–31.4 ± 21.0
Mean change at Week 48	–29.3 ± 22.9	–33.7 ± 21.0
Pain intensity assessment, mm		
Mean change at Week 24	–11.6 ± 28.7	–29.4 ± 28.8
Mean change at Week 48	–26.9 ± 26.8	–27.2 ± 26.7
HAQ DI		
Mean change at Week 24	-0.15 ± 0.45	-0.52 ± 0.53

Mean change at Week 48	–0.33 ± 0.53	–0.54 ± 0.57
ESR, mm/h		
Mean change at Week 24	–5.0 ± 19.3	–2.1 ± 20.7
Mean change at Week 48	–4.5 ± 22.7	–2.1 ± 24.2

In table-4 shows Adverse events across treatment groups in Weeks 0–48 where in Placebo+MTX group events like diarrhea, nausea, gastroenteritis, vomiting, sore mouth, UTI, hypotension were higher than LEF+MTX. The following table is given below in detail:

Table 4: Adverse events across treatment groups in Weeks 0–48.

Adverse events	Placebo+MTX, %	LEF+MTX, %
Diarrhea	15%	3%
Nausea	12%	2.5%
Gastroenteritis	12%	1.1%
Dyspepsia	9%	2.1%
Gastrointestinal disorder	5%	1.1%
Vomiting	3%	1.2%
Sore mouth	2%	1.1%
Infection	3%	1%
Accidental injury	2%	.1%
Pneumonia	2%	1%
Urinary tract infection	1%	.5%
Hypertension	5%	1%

DISCUSSION

In our study, individual components of the ACR response criteria also followed a pattern of maintained or further improvement uring the second 24 weeks of combination therapy, with the exception of ESR. Baseline ESR was only mildly elevated in these subjects who were taking background MTX therapy, which may in part explain the lack of improvement despite clinical improvement in other ACR components measured.

The ACR20 response rate was significantly lower in the PLA + MTX group compared with the LEF + MTX group in the initial 24 weeks. When patients receiving placebo had LEF added at Week 24, they achieved an ACR20 response rate at Week 48 of the same magnitude as that attained by patients originally randomized to LEF + MTX.

The improvement seen in HAQ DI at Week 48 for patients switching from PLA to LEF at Week 24 did not reach the magnitude seen in the group originally randomized to combination therapy for the first 24 weeks ; nonetheless, HAQ DI improved by –0.33, a clinically important improvement. Failure to achieve the same magnitude of improvement in HAQ DI level may possibly have been related to the delayof 24 weeks prior to the addition of LEF. Which was supported by many studies.[9-11]

For patients in the (LEF/LEF) + MTX group, the mean change of –0.52 in the HAQ DI at Week 24, which was maintained at Week 48 (–0.54), exceeded the MCID of –0.22 points for HAQ DI.

A safety concern of combining LEF and MTX is potential hepatotoxicity. Liver enzyme elevations that occurred in patients receiving combination LEF + MTX during Weeks 24–48 normalized after a reduction or discontinuation of LEF, as seen in the earlier double-blind trial. Where it was found that, in Placebo+MTX group events like diarrhea, nausea, gastroenteritis, vomiting, sore mouth, UTI, hypotension were higher than LEF+MTX. Which are similar to other studies.[12-13]

In fact, other study recommended that, It should be noted that LEF was initiated at lower dose in the study than that recommended for monotherapy. It is important to use proper selection to avoid the combination in patients with known hepatic disease and/or other hepatic risk factors. In addition, there should be a higher level of vigilance for adverse effects, with regular hepatic enzyme and hematologic monitoring.[14]

CONCLUSION

The therapeutic advantage of combination LEF + MTX for the treatment of RA in patients with active illness receiving MTX alone was maintained for 48 weeks, including improvements in signs and symptoms (ACR response), physical function (HAQ DI), and HRQoL (SF-36).

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