Original Article

Comparison of Leflunomide Monotherapy with Combination of Methotrexate and Hydroxychloroquine in Active Rheumatoid Arthritis

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ABSTRACT

Objective: We compared the clinical outcomes of Leflunomide (LEF) monotherapy with combination therapy of methotrexate (MTX) plus hydroxychloroquine for managing moderate to severe rheumatoid arthritis (RA).

Study Design: Comparative study

Place and Duration of Study: This study was conducted at the rheumatology clinic of Pakistan Institute of Medical Sciences (PIMS) Islamabad from June-2020 to July-2021.

Methods: Patients were divided in two groups as per the given treatment, either in group L or group MH. In group L, 20 mg LEF per day was given for 3 months. In group MH, 200 mg hydroxychloroquine was given for 3 months, along with hydroxychloroquine, in these patients 7.5 mg/week MTX was given for first week after that the dose was increased 2.5mg/week until it reached 25 mg/week. Patients' follow-up was done for 3 months, data of biochemical markers and clinical outcomes was noted at each follow-up.

Results: The mean age was 42.94±10.7 years in group L and 43.15±10.2 years in group MH. Majority of studied patients were females; 27 (67.5%) in group L and 29 (72.5%) in group MH (p-value 0.62). DAS-28 after 3 months of treatment was 4.36±1.5 in group L and 4.24±1.3 in group MH (p-value 0.70). The ESR and SJC scores after 3 months of treatment was 27.3±14.5 in group L versus 26.1±11.4 and 5.1±4.9 in group L versus 5.05±4.2 in group MH. The SJC score, DAS-28 score and ESR levels reduced at each follow- up post- treatment with statistically significant difference with $P < 0.001$.

Conclusion: Leflunomide (LEF) monotherapy has similar efficacy in comparison to combination of methotrexate and hydroxychloroquine for managing moderate to severe RA.

Key Words: Rheumatoid arthritis, Leflunomide, methotrexate, Hydroxychloroquine

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INTRODUCTION

Rheumatoid arthritis (RA) is one the commonest auto-immune disease. RA cause inflammation in synovial joints resulting in joints erosion[1] These patients presents with painful swelling of synovial joints limiting physical functioning and reduction in quality of life (QOL). The prevalence of RA is 0.5% to 1.0%, with 2 to 3 times higher incidence in females.[2, 3]

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The pathogenesis of RA is still under clear, therefore still no definitive treatment exists. The aim of RA treatment is mainly to stop and reduce the disease severity.[4] Disease modifying anti-rheumatic drugs (DMARD/s) are the mainstay for management of RA. The commonly used drugs for RA are methotrexate (MTX), sulfasalazine (SSZ) and hydroxychloroquine (HCQ). While the steroids and nonsteroidal anti-inflammatory drugs (NSAIDs) can be used as adjuvants.[4, 5]

Leflunomide (LEF) is gaining popularity among rheumatologists for treating RA. LEF is well-tolerated and has rapid onset of action (about 4 weeks) and has reported to be effective for early and advanced stages of RA.[6] Studies have reported that LEF is beneficial in decreasing the levels of erythrocyte sedimentation rate (ESR), c-reactive proteins (CRPs) and significant improvements in severity and signs of RA, QOL and minimize the joint damage.[7] Kaldan et al. conducted a long follow-up study regarding long term (5 years) efficacy of LEF, reported that LEF efficacy achieved in

early periods is maintained over longer periods of time.[8]

To our knowledge, there is no study available that reported the efficacy of LEF monotherapy with combination therapy of MTX plus hydroxychloroquine for RA patients in Pakistani population. Keeping in view the existing literature we aimed to compare the efficacy and safety of LEF monotherapy with combination therapy of MTX plus hydroxychloroquine for managing RA.

METHODS

In this quasi-experimental study, a total of 80 patients of RA (DAS28 >5.1 and CDAI >22) who presented in the rheumatology clinic of PIMS Islamabad were included from June-2020 to July-2021. The patients were recruited by non- probability convenient sampling. Patients having co-morbidities such as renal disease, liver disease, uncontrolled diabetes and hypertension, or pregnant females were excluded. Hospital IRB approval was obtained for study protocol (Approval Number; ECPIMS/02/01). Written consent was obtained from each patient by first counselling them about study protocol and benefits. Non-probability consecutive sampling was used for data collection.

Detailed history and clinical examination of patients was done and all related investigations such as CBC, serum creatinine, and radiologic investigations were advised. Patients were divided in two equals half's. In group L, 20 mg LEF per day was given for 3 months. In group MH, 200 mg hydroxychloroquine was given for 3 months, along with hydroxychloroquine, in these patients 7.5 mg/week MTX was given for first week after that the dose was increased 2.5mg/week until it reached 25 mg/week. Patients follow-up was done for 3 months. Disease activity score (DAS) using DAS28 questionnaire was calculated at baseline, 6 weeks and 3 months follow-up. There was no lost in follow-up period. At follow-up, the side effects of each drug and biochemical markers of recovery were noted. For data analysis we used SPSS version 25. Independent sample t-test and chi-square test were applied to compare quantitative variables and qualitative variables respectively between the groups. P-value ≤0.05 was taken as significant difference.

RESULTS

In this study of 80 patients, 40 patients received LEF and 40 patients received methotrexate plus hydroxychloroquine. Mean age was 42.94±10.7 years in group L and 43.15±10.2 years in group MH (p-value 0.92). Majority of studied patients were females; 27 (67.5%) in group L and 29 (72.5%) in group MH (p-value 0.62). Baseline DAS-28 score was 6.5±0.8 in group L and 6.6±1.0 in group MH (p-value 0.62). Mean baseline SJC score was 11.9±8.3 in group L and 12.19±8.1 in group MH (p-value 0.87). Mean baseline ESR levels were 45.7±18 in group L and 43.8±20 in group MH (p-value 0.65) (Table 1).

The mean DAS-28 score at 6 weeks of treatment was 5.19±1.2 in group L and 5.14±1.1 in group MH (p-value 0.84). DAS-28 after 3 months of treatment was 4.36±1.5 in group L and 4.24±1.3 in group MH (p-value 0.70). ESR at 6 weeks of treatment was 36.18±17.4 in group L versus 34.7±14.3 in group MH (p-value 0.84). ESR at 3 months treatment was 27.3±14.5 in group L versus 26.1±11.4 (p-value 0.68). SJC score at 6 weeks treatment 6.4±5.8 in group L versus 6.5±6.1 in group MH (p-value 0.94). SJC at 3 months of treatment was 5.1±4.9 in group L versus 5.05±4.2 in group MH (p-value 0.96) [Table 2].

On repeated measures ANOVA we found significant reduction in DAS score, SJC score and ESR within the group at 6 weeks and 3 months from baseline, for both patients receiving LEF alone plus hydroxychloroquine group with p-value 0f <0.0001 and <0.0001 respectively.

Table No.1. Baseline study variables.

	Group L	Group MH	P-value
Age (Years)	42.94±10.7	43.15±10.2	0.92
Male	13 (32.5%)	11 (27.5%)	0.62
Female	27 (67.5%)	29 (72.5%)	
RA Duration	2.71±1.2	2.94±1.3	0.41
Swollen Joints count (SJC)	11.9±8.3	12.19±8.1	0.87
DAS-28	6.5±0.8	6.6±1.0	0.62
ESR	45.7±18	43.8±20	0.65

Table No. 2. Comparison of Study Outcomes.

	Group L	Group MH	P-value
DAS-28 at 6 weeks	5.19±1.2	5.14±1.1	0.84
DAS-28 at 3 months	4.36±1.5	4.24±1.3	0.70
ESR at 6 weeks	36.18±17.4	34.7±14.3	0.67
ESR at 3 months	27.3±14.5	26.1±11.4	0.68
SJC at 6 weeks	6.4±5.8	6.5±6.1	0.94
SJC at 3 months	5.1±4.9	5.05±4.2	0.96

DISCUSSION

The early aggressive treatment is the current recommended treatment for RA.[9] the updated EULAR guidelines recommended that the treatment of RA should be based on severity of disease and associated co-morbidities keeping in view the safety concerns of drugs with ultimate goal to relief patient symptoms of

RA.[10] MTX is the initial standard treatment for RA.[11] In patients with inadequate response to MTX, combination of drugs is advised in comparison to single. Hydroxychloroquine is the commonly prescribed drug along with MTX. Recently, LEF has gained popularity as standalone treatment for severe cases of RA. In this study, we compared the outcomes of MTX plus hydroxychloroquine treatment with LEF for managing RA and overall treatment cost.

LEF suppresses the immune cell reactions and therefore is effective in treating RA. Smolen et al. determined the efficacy of LEF in a placebo controlled trial and reported significantly better clinical outcomes at 3 months follow-up using LEF. the recommended dose of LEF is 20 mg/day. However, a recent study has suggested that lower dose of LEF can also be adopted the study did not report any significant difference in 3 months outcomes using 10/day LEF and 20 mg/days LEF. In this study we used only recommended dose of 20 mg/day.

El-Sayed in a non-randomized observational study on effects of LEF alone reported that LEF is an effective treatment option for patients with resistant RA, and how get inappropriate treatment response using other DMARDs.[12]

Deng et al. in a large trial observing different treatment options of RA; including LEF+MTX, LEF+hydroxychloroquine,

LEF+MTX+hydroxychloroquine and LEF alone reported no significant difference in DAS-28 scores, ESR, CRP, TJC and QOL scores between the groups and reported that LEF monotherapy is no inferior to combination therapy so LEF alone can be prescribed for severe RA.[13] Mathur et al. in another study of 12 weeks follow-up including patients of moderate to severe RA, on efficacy of LEF monotherapy in comparison to combination of MTX+hydroxyl-chloroquine reported no significant difference in DAS-28 scores at 12 weeks follow-up. [14] The results of present study were similar to above mentioned studies. However, a study by Zhang et al. conducted in China reported that combination of MTX+LEF is inferior to MTX+ hydroxychloroquine group. The results of these studies are contrary to above mentioned studies.[15]

The shorter follow-up period is the major limitation of present study, we followed the patients only for 3 months. Studies with larger sample sizes and longer follow-up are needed to determine the safety profile and sustained efficacy of LEF in moderate to severe RA patients.

CONCLUSION

Leflunomide (LEF) monotherapy has similar efficacy in comparison to combination of methotrexate and hydroxychloroquine for managing moderate to severe RA. So it can be considered for initial sole therapy in RA patients instead of combination drugs.

Author's Contribution:

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