Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/jptcp.v30i18.3217

THE SHORT-TERM EFFECTIVENESS OF LEFLUNOMIDE IN PATIENTS WITH ACTIVE RHEUMATOID ARTHRITIS

Salma Zeb[1], Zafar Mehmood[2], Sumaira Bakhtiar[3*], Muhammad Bilal Awan[4], Yaseen Khan[5], Zia ullah Chamkani[6]

[1]Assistant professor Department of Internal Medicine, MTI Lady Reading Hospital, Peshawar, Pakistan
[2]Assistant professor Department of neurology, MTI Lady Reading Hospital, Peshawar, Pakistan
[3*]Assistant professor Department of Internal Medicine, MTI Lady Reading Hospital, Peshawar, Pakistan
[4]Assistant professor Department of Internal Medicine, MTI Lady Reading Hospital, Peshawar, Pakistan
[5]Assistant professor Department of Internal Medicine, MTI Lady Reading Hospital, Peshawar, Pakistan
[6]Assistant professor Department of Internal Medicine, MTI Lady Reading Hospital, Peshawar, Pakistan

***Corresponding Author:** Sumaira Bakhtiar
*Assistant professor Department of Internal Medicine, MTI Lady Reading Hospital, Peshawar, Pakistan. Email: drsumaira@gmail.com

Abstract
Objective: To assess leflunomide's short-term effectiveness in patients with active rheumatoid arthritis.

Study design: A Descriptive Cross Sectional Study

Duration and place of study: Department of Medical B Unit Lady Reading's hospital Peshawar. from 1st June 2022 to 31st May 2023

Methodology: The Medical B Unit of MTI Lady Readings Hospital in Peshawar hosted this descriptive cross-sectional research, Over a period of one year from June 1, 2022, to May 31, 2023. This research comprised 147 individuals with active RA (DAS28>5.1). Patients enrolled in the trial were administered 20 mg of leflunomide daily. Using the European League against Rheumatisms (EULAR) standards, the effectiveness of both medications was evaluated after six months of therapy in terms of DAS 28 scores.

Results: Following a 6-month course of therapy with leflunomide, 47 patients saw no response, while 100 patients (68.02%) showed a moderate response. Leflunomide caused a mean change in DAS 28 score of 1.79 ±0.75.

Conclusion: Based on EULAR response criteria, leflunomide showed a considerable short-term effectiveness in RA patients.

Key Words: (Leflunomide), (DMARD) Disease Modifying Anti-Rheumatic Drugs)

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic, inflammatory, chronic illness with an uncertain aetiology that, if left untreated, may erode bone and cartilage, causing deformity and loss of joints. The frequency of it is 1%. Early pharmacological intervention is necessary for successful care in order to halt the course of the illness and induce remission shortly after diagnosis. 1.

Non-steroidal anti-inflammatory medicines (NSAIDs), steroids, and medications that modify anti-rheumatic disease (DMARDs) in relation to biological and non-biological disorders are among the pharmacologic therapies for RA. DMARDs slow the damaging erosive process, while NSAIDs are used to manage discomfort. 2.

For more than 20 years, DMARDs have been the mainstay of RA therapy and have been used extensively. The reason for their extensive usage is because they not only manage the disease's symptoms and signs but also delay radiographically-assessed joint deterioration, which is a hallmark of rheumatoid arthritis. Synthetic DMARD methotrexate is regarded as the main anchor medication for the treatment of RA. It is often administered as the first line DMARD3 because to its well-established effectiveness both as a monotherapy and in conjunction with other DMARDs. Another synthetic first-line DMARD that has received approval in the USA and Europe is leflunomide4. Both medications' side-effect profiles and clinical and radiographic effectiveness have been evaluated, and the results indicate that they are identical5–6.

Leflunomide's effectiveness as a combination treatment with biological DMARD is shown to be similar to that of methotrexate7. Leflunomide's advantages and disadvantages have been evaluated, and recommendations have been made on the drug's potential efficacy as a RA therapy 8. Leflunomide's effectiveness in treating newly diagnosed RA was evaluated, and the results revealed an 81.7% improvement in DAS 28 score 9.

Similar to this, the short-term efficacy of leflunomide was evaluated in a local research. Of the approximately 88.3% of patients who responded, 46.6% had an excellent response and 41.7% had a moderate response10. Leflunomide and methotrexate's effectiveness in treating RA patients from lower socioeconomic groups was evaluated in a different local trial. The study's findings demonstrated that both medications were equally effective in controlling RA over the long term11. Leflunomide has been on the market for a while, but it has received the least research attention of all the DMARDs in Pakistan. Because of worries about its effectiveness and safety, doctors are reluctant to recommend Leflunomide as a first-line treatment. As a result, it is customary to use methotrexate as the first-line DMARD and to stay away from leflunomide. Our study's objectives were to evaluate Leflunomide's effectiveness in our patients and provide evidence in favour of Leflunomide as a first-line DMARD if it performed as well as Methothrexate, the most often used first-line DMARD.

METHODOLOGY

The research was conducted in the Medical B Unit Lady Readings Hospital in Peshawar, Pakistan, from June 1st, 2022, to May 31st, 2023. The research comprised consecutive participants with active rheumatoid arthritis (RA; disease activity score DAS>5.1) who met the 2010 ACR/EULAR classifications/criteria for RA12. Inclusion criteria also included patients older than 16 years old and of both genders. Pregnancy or intending to become pregnant, nursing mothers, liver illness (including hepatitis B, C, and chronic liver disease), chronic infections such as TB, etc., and previously identified immunodeficiency syndromes or blood dyscrasias, as documented in the medical file, were among the exclusion criteria.

Out of the 147 patients that fulfilled the inclusion criteria, 18 were eliminated based on the exclusion criteria, and 20 patients were not found. One hundred and five (105) participants were added to the

study from the total of 105 individuals who were involved in it. The research was approved by the ethics committees of PGMI Lady Reading Hospitals, and all participants provided written permission. Every patient was questioned. The medical and historical records of the patients were used to compile the clinical (disease duration, prior treatments) and demographic (age, gender) data.

The hospital's laboratory was consulted for the evaluation of each patient's erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). The hospital laboratory assessed the RA factor using dilution agglutination titers, whereas the anti-CCP titers were submitted to a different reference laboratory since this study was not available at our hospital. Patients were given the 2010 ACR/EULAR classification criteria for rheumatoid arthritis, and those who met the criteria were considered to be instances of RA. DAS 28 baseline scoring was carried out. We recruited patients Every patient received 20 mg of leflunomide daily. Initially, steroids and non-steroidal anti-inflammatory medications (NSAIDS) were used to treat the symptoms. Patients were checked on again six months later. They had a clinical evaluation to see if the quantity of tenderness and swollen joints had improved, and blood samples were taken to measure CRP and ESR levels. The response was evaluated using EULAR response criteria13, and DAS 28 scoring was carried out. Every lab experiment was carried out from the aforementioned lab. Pre-designed Performa had all of the aforementioned data, including name, age, gender, and hospital number.

The proportion of patients who, after six months of therapy with the individual medicine, achieved the desired decreases in disease activity score (DAS 28) was used to assess the efficacy of the treatment. According to EULAR response criteria13, the aim was a good to moderate response, and it was dependent on each individual's baseline DAS 28. Since all patients' initial DAS 28 scores were more than 5.1 in our research samples, any improvement in DAS 28 of more than 1.2 was deemed to be a moderate response, while any change in DAS 28 scores below this threshold was deemed to be a no response. Version 23 of the SPSS programme was used to analyse the data. All variables had their descriptive statistics computed and shown as mean and SD. Both the Fisher Exact t-test and the independent sample t-test were used to compare the means changes of the effectiveness end-points. Every statistical test used a two-tailed design, with a probability (P) of less than 0.05 deemed significant.

RESULTS

Table 1 displays the clinical features and demographics of the RA patients. The aforementioned groups were matched at baseline in terms of demographic and clinical features, as shown. Table 1 illustrates this, however after 6 months of therapy, the mean change in DAS 28 with leflunamide in our research was somewhat less than that of methotrexate in previous studies (1.79±0.75). In a similar vein, according to EULAR criteria, 68.02 percent of patients receiving leflunamide compared to methotrexate had a moderate response.

DISCUSSION

Our research evaluated leflunomide's short-term therapeutic effectiveness in terms of DAS 28 score improvement. Table 1 displays the demographic information, including the number of patients, age, gender, and clinical features (Baseline DAS28). Leflunomide's effectiveness was shown to have improved (moderate response according to EULAR criteria) in a sizable percentage of patients in our research; nevertheless, when we compared this to earlier methotrexate studies, the difference was not statistically significant. Strand et al. (2014) reported similar outcomes, demonstrating that there was no significant difference in the number of sore and swollen joints or in the overall evaluation ratings between patients and doctors treated with leflunomide or methotrexate. The effectiveness of both medications was compared in a sizable prospective multicentric trial. According to the study's findings, 26% of the patients in the methotrexate group and 20% of the patients on leflonomide had remission 15. Our results are contradicted by a head-to-head trial 16 that compared the effectiveness of methotrexate and leflunomide. The trial revealed that, following a year of treatment, the

Methotrexate group's clinical improvement in terms of ACR 20 response was significantly greater than Leflunomide's (64.8 vs. 50.5%). However, both groups' side effect profiles and radiological disease progression were similar. Leflunomide's clinical and radiographic effectiveness was shown to be similar to methotrexate 17 in the 2010 Cochrane review of Leflunomide and meta-analysis, which included 33 studies, 11 of which compared Leflunomide with Methotrexate.

A meta-analysis of seven research, including four randomised controlled trials comparing leflunomide monotherapy versus methotrexate, added support to the Cochrane review's results. The two medications have comparable efficacies18,19. Our findings that leflonomide and methotrexate are almost equally effective are therefore supported by the results of the Cochrane review and the subsequent meta-analyses. The short-term follow-up and lack of cost and side-effects consideration as co-factors were the weaknesses of our research. Likewise, only those with very active RA (DAS28>5.1) were taken into account. Future local research should take these issues into account.

CONCLUSION

Leflunomide may be used as a first-line DMARD in patients with active RA unless it is contraindicated, particularly in those with high baseline DAS 28 scores. It has a comparably strong short-term effectiveness in treating individuals with active RA.

REFERENCES

1. Hellmann DB, Imboden JB. Musculoskeleton and Immunological disorders. In: Papadakis MA, McPhee SJ. Current medical diagnosis and treatment.52 ed. New York: McGraw Hill Medical; 2013.809-69.
2. Moreland LW, Russell AS, Paulus HE. Management of rheumatoid arthritis: the historical context. J rheumatol 2001; 28:1431-522.
3. Taqweem A, Ahmed I, Alam I, Ali Z, Nowsherawan, Mehboob A. Short-term effectiveness of methotrexate in the treatment of active rheumatoid arthritis. J Postgrad Med Inst 2010; 24:252.
4. Li EK1, Tam LS, Tomlinson B. Leflunomide in the treatment of rheumatoid arthritis. Clin Ther 2004; 26:447-59.
5. 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.
6. Baig S, Humail M, Zaidi IS, Noor S, Anwar S, Rehman S. Toxicity profiles of disease modifying anti-rheumatoid drugs(DMARDS) in rheumatoid arthritis patients in Karachi. Pak Orthop Assoc 2009; 21:38-43.
7. Behrens F, Koehm M, Burkhardt H. Update 2011: leflunomide in rheumatoid arthritis - strengths and weaknesses. Curr Opin Rheumatol 2011; 23:282-7.
8. Smolen JS, Landewé R, Breedveld FC, Dougados M, Emery P, Gaujoux-Viala C, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biologic disease modifying antirheumatic drugs. Ann Rheum Dis 2010; 69:964–75.
9. Cutolo M, Bolosiu H, Perdriset G, LEADER Study Group. Efficacy and safety of leflunomide in DMARD-naive patients with early rheumatoid arthritis: comparison of a loading and a fixed-dose regimen. Rheumatology (Oxford) 2013; 52:1132-40.
10. Taqweem A, Ahmad I, Nowsherawan, Ali Z, Mehboob A. Short-term effectiveness of leflunomide in treatment of active rheumatoid arthritis. J Postgrad Med Inst 2010; 24:153-9
11. Ishaq M, Muhammad J, Hameed K, Mirza I A. Leflunomide or Methotrexate? Comparison of clinical efficacy and safety in low socio-economic rheumatoid arthritis patients. Mod Rheumatol2011; 21:375-80.
12. 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. Ann Rheum Dis 2010; 69:1580–8.

13. Fransen J, van Riel. PL. The Disease Activity Score and the EULAR response criteria. Rheum Dis Clin North Am. 2009 2009; 35:745-57.
14. Strand V, Cohen S, Schiff M, Weaver A, Fleischmann R, Cannon G, et al. Treatment of active Rheumatoid Arthritis with Lelunamide compared to Placebo and Methotrexate, Lelunomide Rheumatoid Arthritis Investigator group. Arch Intern Med 1999; 159: 2542-50.
15. Singer O, Gibofsky A. Methotrexate versus leflunomide in rheumatoid arthritis: what is new in 2011? Curr Opin Rheumatol 2011; 23:288-92.
16. Favalli EG, Bugatti S, Biggioggero M, Caporali R. Treatment comparison in RA: Head to Head trials and innovative study designs. Bio Med Res Int 2014; 2014:831603.
17. Osiri M, Shea B, Robinson V, Suarez-Almazor M, Strand V, Tugwell P, et al. Leflonamide for the treatment of RA. Cochrane Database Syst Rev 2003:CD002047.
18. Gaujoux-Viala C, Dougados M, Smolen JS. Leflunomide appears efficacious and as efficacious as methotrexate on signs and symptoms, function and structure in RA: a mata-analysis of randomized controlled trials. Ann Rheum Dis 2009; 69:214.
19. Fedorenko E, Lukina GV, Sigidin YA. Effects of 4 different treatment regimens on radiographic progression in early RA. Ann Rheum Dis 2010; 69: 214.f prospective non interventional study. Clin Rheum Dis 2010; 29:913-20.

Authors Contribution

SZ and ZM conceived the idea, planned the study, and drafted the manuscript. ZM, LZ and AB helped acquisition of data and did statistical analysis. MBA, YK supervised the study and critically revised the manuscript. All authors contributed significantly to the submitted manuscript