

Original Article

Comparison of Liver Injury in Patients Taking Methotrexate and Leflunamide in Rheumatoid Arthritis

Maheen Zahid¹, Adnan Manzar², Waqas Qureshi¹, Javed Iqbal³, Fizza Khursheed¹, Asma Saeed¹, Sahar Abdul Rauf¹, Ishfaq Ahmed⁴, Muhammad Farrukh Habib^{5*}

¹Resident Medicine, CMH Lahore, Pakistan.

²Consultant Rheumatology, CMH Lahore, Pakistan.

³Consultant Medical Specialist, CMH Lahore, Pakistan.

⁴Resident Medicine, CMH Quetta, Pakistan.

⁵Department of Management Sciences, Shifa Tameer-E-Millat University Islamabad, Pakistan.

*Corresponding Author: Muhammad Farrukh Habib; Email: muhammadfarrukhh Habib@gmail.com

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ABSTRACT

Background: Rheumatoid arthritis (RA) is a chronic autoimmune disease that primarily affects the joints, leading to inflammation and potential joint damage. Methotrexate (MTX) and Leflunomide (LEF) are commonly used disease-modifying antirheumatic drugs (DMARDs) for RA, but their hepatotoxic effects require careful monitoring.

Objective: This study aimed to compare the incidence of liver injury in RA patients treated with Methotrexate versus Leflunomide.

Methods: This prospective study was conducted from January 2023 to June 2023 and included 80 RA patients aged 20 years or older, who reported to the Medicine Department at Combined Military Hospital (CMH) Lahore. Patients were divided into two groups: Group A received 20 mg/day Methotrexate (n=40), and Group B received 20 mg/day Leflunomide (n=40). Exclusion criteria included pregnant females, patients with hepatitis B or C, those with known allergies to Methotrexate or Leflunomide, and alcoholics. Baseline investigations, including liver enzyme levels (ALT/AST), were performed, and patients were monitored every three months. Hepatotoxicity was defined as an increase in ALT/AST levels to at least twice the upper limit of normal (ULN). Data were analyzed using SPSS version 25.0, with mean and standard deviation for quantitative data and frequency and percentage for qualitative data. The Chi-square test was used to compare variables, with p<0.05 considered statistically significant.

Results: Out of 80 patients, 43 (53.75%) were female, and 37 (46.25%) were male. In Group A, 7 patients (17.5%) had elevated ALT/AST levels, while 6 patients (15%) in Group B exhibited elevated liver enzymes. The mean age was 52.4 ± 8.3 years in Group A and 50.6 ± 9.1 years in Group B. The mean BMI was 26.7 ± 3.5 kg/m² in Group A and 27.1 ± 3.8 kg/m² in Group B. No statistically significant difference in hepatotoxicity was observed between the two groups (p>0.05).

Conclusion: Methotrexate and Leflunomide were equally effective in treating RA, with no significant difference in liver toxicity observed between the two groups. Both medications have comparable risks for hepatotoxicity, necessitating regular liver function monitoring during treatment.

Keywords: Rheumatoid arthritis, Methotrexate, Leflunomide, DMARDs, hepatotoxicity, liver injury, ALT, AST, autoimmune disease, liver function monitoring.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, symmetrical inflammatory autoimmune disease that primarily affects small joints before progressing to larger joints and potentially involving the skin, eyes, heart, kidneys, and lungs. Joint bone and cartilage are frequently damaged, and ligaments and tendons can deteriorate (1). RA affects 0.5% to 1% of the global population, with women being three times more likely to develop the disease compared to men (2). Research indicates that the incidence of RA varies within different regions of Pakistan, ranging from 5.5% in the north to 0.142% in the south. The American College of Rheumatology advocates for the early initiation of disease-modifying antirheumatic drugs (DMARDs) to prevent further joint destruction, despite the absence of a definitive cure for RA (3). Methotrexate (MTX) is the most frequently prescribed DMARD for RA. Additionally, to prevent the

development of neutralizing antibodies that may reduce treatment efficacy, new biological agents such as TNF- α blockers and anti-CD20 monoclonal antibodies often require combination therapy with MTX (4).

In the realm of DMARDs, Methotrexate (MTX) is recommended as the first-line medication according to the European League Against Rheumatism (EULAR). Introduced in 1951, MTX is a structural analog of folic acid. The EULAR also currently recommends Leflunomide (LEF), an inhibitor of pyrimidine synthesis, as a first-line medication for RA treatment. LEF is as effective as MTX in halting joint damage progression and reducing T cell proliferation (5). Consequently, most RA patients receive MTX, either alone or in combination with other DMARDs, unless contraindicated by systemic conditions such as liver or interstitial lung disease (6) (7). Despite its efficacy, long-term use of MTX can lead to significant side effects, including hepatitis (8). These adverse effects are less common with non-steroidal anti-inflammatory drugs (NSAIDs) or other DMARDs. However, Leflunomide, a newer drug often used in conjunction with MTX, has been associated with a significant risk of liver toxicity, which can manifest as elevated liver enzymes or more severe conditions like liver fibrosis (9).

Randomized control trials have shown that both MTX and LEF monotherapy can elevate ALT/AST levels, indicating a risk of hepatotoxicity (10). A study by P. Bird et al. reported liver enzyme abnormalities in 12% of the MTX group and 16% of the LEF group (11). Despite the widespread use of MTX and LEF by medical professionals, the hepatotoxicity associated with these drugs is not well-documented in Pakistan. This study aims to compare the incidence of liver injury in patients with RA who are treated with Methotrexate versus Leflunomide.

MATERIAL AND METHODS

This prospective study was conducted on 80 patients from January 2023 to June 2023, using the WHO calculator with a prevalence rate of rheumatoid arthritis set at 5.5%. Patients aged 20 years or older with rheumatoid arthritis, who reported to the Medicine Department at Combined Military Hospital (CMH) Lahore, were included. The study utilized convenience sampling. Ethical approval for the methodology and study concept was obtained from the Ethical Committee of CMH Lahore, Pakistan, and ethical clearance was granted. Written informed consent was obtained from all patients and their next of kin in accordance with the Declaration of Helsinki.

Patients included in the study met the following criteria: aged 20 years or above, diagnosed with rheumatoid arthritis according to ACR criteria, had active disease, and had diabetes or hypertension without end-organ damage. Exclusion criteria were pregnant females, patients previously diagnosed with hepatitis B and C, those with allergic reactions to Methotrexate or Leflunomide, and individuals with a history of alcoholism.

The patients were divided into two groups, with 40 patients in each group. Group A received 20 mg/day of Methotrexate, while Group B received 20 mg/day of Leflunomide. A comprehensive examination, medical history, baseline investigations, and ultrasound of the abdomen were performed. Follow-up assessments were conducted every twelve weeks for all enrolled patients. Laboratory variables analyzed included aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels. Liver enzyme levels were checked every three months and one month after the initiation of Methotrexate and Leflunomide treatment. Hepatotoxicity was defined as AST or ALT levels rising to at least twice the upper limit of normal (ULN).

Data collection was meticulously recorded and entered into SPSS version 25.0 for analysis. Quantitative data were expressed as mean \pm standard deviation (SD), while qualitative data were presented as frequencies and percentages. The Chi-square test was applied to assess the association between variables, with a p-value of less than 0.05 considered statistically significant.

RESULTS

Table 1: Demographic Characteristics

Characteristic	Group A (Methotrexate)	Group B (Leflunomide)	Total
Age (Mean \pm SD)	52.4 \pm 8.3	50.6 \pm 9.1	51.5 \pm 8.7
BMI (Mean \pm SD)	26.7 \pm 3.5	27.1 \pm 3.8	26.9 \pm 3.6
Gender – Male	18 (45%)	19 (47.5%)	37 (46.25%)
Gender - Female	22 (55%)	21 (52.5%)	43 (53.75%)

Table 2: Study Characteristics

Characteristic	Group A (Methotrexate)	Group B (Leflunomide)
Duration of RA (Mean \pm SD, years)	6.2 \pm 2.4	5.8 \pm 2.6
DAS-28 Score (Mean \pm SD)	5.6 \pm 1.1	5.4 \pm 1.2

Characteristic	Group A (Methotrexate)	Group B (Leflunomide)
Comorbid Conditions		
- Diabetes	8 (20%)	7 (17.5%)
- Hypertension	10 (25%)	11 (27.5%)
- Both Diabetes and Hypertension	4 (10%)	5 (12.5%)
- None	18 (45%)	17 (42.5%)
Previous Treatments		
- Other DMARDs	12 (30%)	13 (32.5%)
- NSAIDs	28 (70%)	27 (67.5%)
Elevated ALT/AST Levels	7 (17.5%)	6 (15%)
Symptoms of Hepatotoxicity		
- Jaundice	2	3
- Fatigue	5	4
- Abdominal Pain	3	2
- None	30	31
Medication Tolerability (Mean \pm SD)	7.8 \pm 1.5	8.1 \pm 1.4

The study included 80 patients, with 40 in the Methotrexate group (Group A) and 40 in the Leflunomide group (Group B). The gender distribution revealed a slightly higher proportion of females, with 43 (53.75%) female patients and 37 (46.25%) male patients across both groups. In Group A, 22 (55%) were female and 18 (45%) were male, whereas Group B had 21 (52.5%) female and 19 (47.5%) male patients (Table 1).

The mean age of patients in Group A was 52.4 years with a standard deviation (SD) of 8.3 years, while in Group B, the mean age was slightly lower at 50.6 years with an SD of 9.1 years. The overall mean age for all patients was 51.5 years with an SD of 8.7 years (Table 1). The body mass index (BMI) of patients showed a mean of 26.7 kg/m² (SD 3.5) in Group A and 27.1 kg/m² (SD 3.8) in Group B, reflecting a similar distribution across the groups with an overall mean BMI of 26.9 kg/m² (SD 3.6) (Table 1).

Clinical characteristics indicated that the mean duration of rheumatoid arthritis was 6.2 years (SD 2.4) in Group A and 5.8 years (SD 2.6) in Group B. The severity of the disease, measured by the DAS-28 score, averaged 5.6 (SD 1.1) in the Methotrexate group and 5.4 (SD 1.2) in the Leflunomide group, showing comparable disease activity levels between the groups (Table 2).

Comorbid conditions were common among the study population. In Group A, 8 patients (20%) had diabetes, 10 (25%) had hypertension, and 4 (10%) had both diabetes and hypertension. Group B had 7 patients (17.5%) with diabetes, 11 (27.5%) with hypertension, and 5 (12.5%) with both conditions. A significant portion of patients in both groups had no comorbid conditions, with 18 (45%) in Group A and 17 (42.5%) in Group B (Table 2).

Regarding previous treatments, 12 patients (30%) in the Methotrexate group and 13 patients (32.5%) in the Leflunomide group had been treated with other DMARDs. The majority of patients in both groups had used NSAIDs, with 28 (70%) in Group A and 27 (67.5%) in Group B (Table 2).

The incidence of elevated liver enzymes was closely monitored, with 7 patients (17.5%) in Group A and 6 patients (15%) in Group B showing elevated ALT/AST levels, indicating hepatotoxicity. Symptoms of hepatotoxicity included jaundice in 2 patients in Group A and 3 in Group B, fatigue in 5 patients in Group A and 4 in Group B, and abdominal pain in 3 patients in Group A and 2 in Group B. Notably, 30 patients in Group A and 31 in Group B did not exhibit any symptoms of hepatotoxicity (Table 2).

Medication tolerability was assessed, and patients in Group A reported a mean tolerability score of 7.8 (SD 1.5), while those in Group B reported a slightly higher mean score of 8.1 (SD 1.4), suggesting good tolerability for both medications overall (Table 2).

The results highlight that while both Methotrexate and Leflunomide are generally well-tolerated, there is a notable incidence of hepatotoxicity that warrants close monitoring. The similarity in the distribution of demographic and clinical characteristics between the two groups ensures that the comparisons made are robust and reliable, reflecting real-world patient experiences with these DMARDs in treating rheumatoid arthritis.

DISCUSSION

The study included 80 patients with rheumatoid arthritis, divided into two groups: one treated with methotrexate and the other with leflunomide. The investigation revealed no statistically significant difference in liver injury between the two groups. These findings align with the study conducted by Anila Nisar et al., which demonstrated the efficacy of both methotrexate and leflunomide

in treating rheumatoid arthritis. However, our study provides additional insights by specifically focusing on the hepatotoxic effects of these drugs (12).

In our study, 7 patients (17.5%) in the methotrexate group exhibited elevated ALT/AST levels, compared to 6 patients (15%) in the leflunomide group. This result contrasts with the findings of Saima Riaz et al., who reported a statistically significant difference in hepatotoxicity between these groups, potentially due to the inclusion of steroids in their treatment protocol (13). Furthermore, a meta-analysis by Alfaro-Lara R. et al. suggested that leflunomide is associated with higher hepatotoxicity and fewer gastrointestinal complaints, which was not observed in our study (14). Similarly, Choi SR reported minimal hepatotoxicity associated with methotrexate, a finding that our study supports (15).

Our results differed from those of Jorge Augusto Nunes Rodrigues Alves et al., who found no statistical difference in hepatotoxicity between patients taking methotrexate alone and those taking it in combination with leflunomide (16). Conversely, the findings of Tamseela Mumtaz et al., which indicated that methotrexate is less hepatotoxic than leflunomide, were not consistent with our results (17). Additionally, J. Avouac et al. found methotrexate to be superior to leflunomide in terms of efficacy and lower risk of liver fibrosis, a finding not corroborated by our study (18).

The study's strengths included a well-defined patient population and a clear focus on comparing the hepatotoxic effects of methotrexate and leflunomide. However, several limitations must be acknowledged. The lack of a control group and the exclusion of female patients limited the generalizability of the findings. The observational design and small sample size further restricted the robustness of the conclusions. Additionally, the study excluded individuals with normal liver enzyme results and did not consider potential risk factors for hepatotoxicity.

Future research should address these limitations by including a control group, expanding the sample size, and considering both genders. Studies should also explore the long-term effects of these medications on liver health and incorporate a broader range of risk factors. Comprehensive randomized controlled trials would provide more definitive evidence regarding the comparative hepatotoxicity of methotrexate and leflunomide in rheumatoid arthritis treatment.

CONCLUSION

In conclusion, methotrexate and leflunomide were equally effective in treating rheumatoid arthritis, with no significant difference in liver toxicity observed between the groups. Both medications present comparable risks for hepatotoxicity, emphasizing the need for regular monitoring of liver function during treatment.

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