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# SAFETY PROFILE OF METHOTREXATE ALONE VS COMBINATION METHOTREXATE PLUS LEFLUNOMIDE IN PATIENTS WITH RHEUMATOID ARTHRITIS

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**Abstract**

**Background**: Rheumatoid arthritis (RA) is a chronic inflammatory disorder causing significant morbidity and impaired quality of life. Methotrexate (MTX) is a cornerstone treatment for RA, but combination therapy with other disease-modifying antirheumatic drugs (DMARDs) like leflunomide (LEF) is often used for better disease control. Despite its widespread use, the safety profile of this combination needs thorough assessment.

**Objective**: This study aims to evaluate the safety profiles of MTX alone versus MTX plus LEF in patients with RA, focusing on liver and renal function tests, hematological disturbances, gastrointestinal side effects, and infections.

**Methods**: This prospective cohort study was conducted at the Department of Rheumatology, Lady Reading Hospital, Peshawar, from April, 2024 to Sep, 2024. A total of 303 participants were enrolled and divided into two groups one receiving MTX alone (n=151) and the other receiving MTX plus LEF (n=152). Baseline characteristics, adverse events, and laboratory results were collected and analyzed using SPSS version 25, with a p-value of <0.05 considered significant.

**Results**: The combination therapy group (MTX+LEF) exhibited a higher incidence of elevated liver function tests (26.3% vs. 18.5%,p=0.034).Elevated renal function tests were more common in the MTX+LEF group (14.5% vs. 11.3%,p= 0.219), as was anemia (29.6% vs. 22.5%, p=0.099). Gastrointestinal side effects were reported more frequently in the combination group (22.4% vs. 15.2%, p=0.075), along with infections (14.5% vs. 9.9%, p= 0.188). While these differences were not

statistically significant for renal function, anemia, gastrointestinal side effects, and infections, they are clinically relevant.

**Conclusion:** The combination of MTX and LEF in RA patients is associated with a higher incidence of elevated liver function tests and other adverse events compared to MTX alone. These findings underscore the importance of vigilant monitoring and patient education in managing RA with DMARD therapy.

**Keywords**: Rheumatoid arthritis, Methotrexate, Leflunomide, Safety profile, Adverse events, Liver function, Renal function, DMARDs.

## Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disorder primarily affecting joints, leading to significant morbidity and impaired quality of life (1). Methotrexate (MTX) remains the cornerstone of RA treatment due to its efficacy and safety profile (2). However, for patients who do not achieve adequate disease control with MTX alone, combination therapy with other disease-modifying anti-rheumatic drugs (DMARDs) is often considered (3). Leflunomide (LEF), another DMARD, is frequently used in combination with MTX to enhance therapeutic outcomes (4). Despite the widespread use of MTX and LEF in combination, there is a need to thoroughly assess the safety profile of this regimen. Previous studies have provided mixed results regarding the adverse effects of combination therapy compared to MTX monotherapy (5). This study aims to fill this gap by providing a comprehensive evaluation of the safety profile of MTX alone versus MTX plus LEF in patients with RA.

The primary objective of this study is to compare the incidence of adverse events, including liver function abnormalities, renal function changes, and hematological disturbances, between the two treatment groups. Secondary objectives include assessing the frequency of gastrointestinal side effects, infections, and other adverse events.

The significance of this study lies in its potential to inform clinical practice by identifying any additional risks associated with combination therapy. Given the prevalence of RA in Pakistan, which stands at 26.9%, understanding these safety profiles is crucial for optimizing treatment strategies (6).

## Methods

### Study Design

This prospective cohort study was conducted at the Department of Rheumatology, Lady Reading Hospital, Peshawar, from April, 2024 to Sep, 2024. We aimed to compare the safety of methotrexate (MTX) alone versus MTX plus leflunomide (LEF).

### Sample Size Calculation

We calculated the sample size using the WHO calculator. The prevalence of rheumatoid arthritis in Pakistan is 26.9% as per Rehan et al. (6). We needed 303 participants for adequate power.

### Setting and Participants

The study took place at the Department of Rheumatology, Lady Reading Hospital, Peshawar. Inclusion criteria were a diagnosis of rheumatoid arthritis, age 18 or older, and consent. We excluded those with liver or kidney disease, those on other DMARDs, or those allergic to MTX or LEF.

### Intervention

Participants were split into two groups. Group 1 received MTX alone, 15-25 mg weekly. Group 2 received MTX (15-25 mg weekly) plus LEF (20 mg daily). Standard clinical protocols guided their treatment.

### Outcomes

Primary outcomes were adverse events related to LFTs, RFTs, and CBC. Secondary outcomes included gastrointestinal side effects, infections, and other adverse events.

**Data Collection**

We collected data through interviews, records, and lab reports. Baseline data included age, gender, disease duration, and prior treatments. We performed LFTs, RFTs, and CBC at baseline and regularly during the study. We recorded and categorized adverse events by severity and treatment relation.

**Statistical Analysis**

We used SPSS version 25 for analysis. We expressed continuous variables as mean ± SD or median (IQR). Categorical variables were in frequencies and percentages. We used the chi-square test for categorical variables and t-test or Mann-Whitney U test for continuous variables. A p-value of <0.05 indicated significance.

**Results**

The study included a total of 303 participants; they were divided into two groups: 151 received methotrexate (MTX) alone, and 152 received a combination of MTX and leflunomide (LEF).

**Table 1: Baseline Characteristics of Study Population**

| **Characteristic** | **MTX Group (n=151)** | **MTX + Leflunomide Group** $(n = 152)$ |
|---|---|---|
| Mean Age (years) | 54.3±11.2 | 55.1±10.8 |
| Female(%) | 75 | 75.7 |
| Male(%) | 25 | 24.3 |
| Median Disease Duration (years) | 7(5-9) | 7(5-9) |

Baseline characteristics of the participants are detailed in Table 1. The mean age of participants was 54.3 years (SD=11.2) for the MTX group and 55.1 years (SD = 10.8) for the MTX+LEF group. The female-to-male ratio was 3:1, with 227 females and 76 males. The median disease duration was 7 years (IQR: 5-9 years) for both groups.

**Table 2: Primary Outcomes**

| **Parameter** | **MTX Group (n=151)** | **MTX + Leflunomide Group** $(n = 152)$ | **p-value** |
|---|---|---|---|
| Elevated LFTs (%) | 18.5 | 26.3 | 0.034 |
| Elevated RFTs (%) | 11.3 | 14.5 | 0.219 |
| Anemia (%) | 22.5 | 29.6 | 0.099 |

The primary outcomes focused on the safety profile, including liver function tests (LFTs), renal function tests (RFTs), and complete blood counts (CBC). The results are summarized in Table 2.

**Table 3: Secondary Outcomes**

| Adverse Event | MTX Group (n=151) | MTX+LEF Group (n=152) | p- value |
|---|---|---|---|
| Gastrointestinal Side Effects (%) | 15.2 | 22.4 | 0.075 |
| Frequency of Infections (%) | 9.9 | 14.5 | 0.188 |
| Other Adverse Events (%) | 12.6 | 18.4 | 0.103 |

Secondary outcomes included the evaluation of gastrointestinal side effects, frequency of infections, and other adverse events. These results are detailed in Table 3.

The combination therapy group experienced a higher, though not statistically significant, frequency of gastrointestinal side effects (22.4% vs 15.2%, p=0.075) and infections (14.5% vs 9.9%, p=0.188). The combination of MTX and LEF demonstrated a higher incidence of elevated liver function tests compared to MTX alone. Other adverse events, including gastrointestinal side effects and infections, were more frequent in the combination therapy group but did not reach statistical significance.

**Discussion:**

The study evaluated the safety profiles of methotrexate (MTX) alone versus MTX plus leflunomide (LEF) in patients with rheumatoid arthritis (RA). This research provides crucial insights into the comparative safety of these treatments, given the high prevalence of RA in Pakistan and the common use of these medications in clinical practice.

Key findings indicated that the combination therapy group (MTX+LEF) experienced a higher incidence of elevated liver function tests compared to the MTX alone group. Specifically, elevated liver function tests were observed in 26.3% of the combination group versus 18.5% in the MTX group, with a statistically significant difference (p=0.034). This finding aligns with prior research indicating potential hepatotoxicity risks associated with combination DMARD therapy (7).

Elevated renal function tests were more common in the MTX+LEF group (14.5% vs. 11.3% in the MTX group), though this difference was not statistically significant. Similarly, the incidence of anemia was higher in the combination therapy group (29.6% vs. 22.5%), but again, the difference was not statistically significant. These results suggest that while the combination therapy may pose additional risks, these are not uniformly statistically significant across all measured parameters.

In terms of secondary outcomes, gastrointestinal side effects were reported more frequently in the MTX+LEF group (22.4% vs. 15.2%), and infections were also more common in this group (14.5%vs. 9.9%). Although these differences were not statistically significant, they are clinically relevant and warrant further attention. Previous studies have reported similar trends, emphasizing the need for careful monitoring of patients on combination DMARD therapy (8,9).

These findings are consistent with existing literature that highlights the increased risk of adverse events with combination DMARD therapy. For instance, Salliot and van der Heijde demonstrated that patients on combination therapy exhibited higher rates of liver enzyme elevations and gastrointestinal symptoms compared to those on monotherapy (7). Similarly, Weinblatt et al. reported higher infection rates in patients receiving combination therapy (8). Moreover, Maini et al. found that combining infliximab with methotrexate significantly improved therapeutic outcomes but also increased adverse events (9). Emery et al. supported this finding by showing a higher incidence of side effects in combination therapy groups (10). Strand et al. noted increased gastrointestinal and liver-related side effects with combination therapies (11). Klareskog et al. found that combining etanercept with methotrexate significantly improved therapeutic outcomes but also increased adverse events (12). Kremer et al. supported this finding by showing a higher incidence of side effects in combination therapy groups (13). Bathon et al. also noted increased gastrointestinal and liver-related side effects with combination therapies (14). Van Vollenhoven et al. recommended long-term studies to better understand these safety profiles (15). Moreland et al. highlighted the effectiveness of etanercept but also pointed out its associated risks, including infections (16). These findings suggest a consistent trend across different studies and therapeutic combinations.

The implications for clinical practice are significant. Physicians must weigh the benefits of improved disease control against the potential for increased adverse events when considering combination therapy. Regular monitoring of liver and renal function, as well as blood counts, is essential for patients receiving these treatments. Additionally, patients should be educated about the signs of potential adverse effects and encouraged to report any symptoms promptly. Future research should focus on larger, multi-center studies to confirm these findings and explore the underlying mechanisms of these adverse events. Investigating alternative combination therapies with potentially lower toxicity profiles may also be beneficial. Furthermore, long-term studies assessing the cumulative effects of these treatments over extended periods would provide valuable insights.

**Limitations**: While this study provides valuable information, it has certain limitations. The sample size, while adequate for initial comparisons, may not be sufficient to detect all potential differences in adverse event rates. Additionally, the study's observational design limits the ability to establish causality. Future randomized controlled trials are needed to validate these findings and provide more robust evidence.

## Conclusion

In conclusion, the combination of MTX and LEF in patients with RA is associated with a higher incidence of elevated liver function tests and other adverse events compared to MTX alone. These findings underscore the importance of vigilant monitoring and patient education in managing RA with DMARD therapy.

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