Pakistan Journal of Intensive Care Medicine
eISSN: 2708-2261; pISSN: 2958-4728
www.pjicm.com
DOI: https://doi.org/10.54112/pjicm.v5i01.61
Pak. J. Inten. Care Med., volume 2025: 61
Original Research Article

FREQUENCY OF METHOTREXATE INDUCED HEPATOTOXICITY IN PATIENTS WITH RHEUMATOID ARTHRITIS

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(Received, 25th March 2025, Revised 20th April 2025, Accepted 22nd April, Published 24th April 2025)

ABSTRACT

Background: *Methotrexate (MTX) is a cornerstone drug in the management of rheumatoid arthritis (RA), but its use is associated with potential adverse effects, notably hepatotoxicity. Identifying the frequency and contributing factors to MTX-induced liver toxicity is essential for optimizing therapeutic safety in RA patients.* ***Objective****: To evaluate the frequency and associated risk factors of methotrexate-induced hepatotoxicity among patients with rheumatoid arthritis.* ***Study Design:*** *Descriptive cross-sectional study.* ***Setting****: This study was conducted at the Department of Medicine at Lady Reading Hospital, Peshawar.* ***Duration of Study:*** *The study was conducted over six months* [11-September-2024 to 11-March-2025]. ***Methods:*** *A total of 78 patients diagnosed with RA and undergoing MTX therapy, irrespective of age and gender, were enrolled. Hepatotoxicity was defined as serum alanine aminotransferase (ALT) levels exceeding twice the standard upper limit. Data regarding age, gender, MTX dosage, and liver function tests were recorded. Statistical analysis was performed using SPSS version 24. Chi-square and t-tests were used to assess associations, with a p-value ≤ 0.05 considered statistically significant.* ***Results:*** *The mean age of participants was 45.29 ± 12.38 years. Most were female (56.4%), while males accounted for 43.6%. Hepatotoxicity was observed in 19.2% of patients. A significant association was found between hepatotoxicity and higher MTX dosage (25 mg/week) (p = 0.01). No significant correlations were identified with age (p = 0.39) or gender (p = 0.39).* ***Conclusion:*** *Methotrexate-induced hepatotoxicity was found in nearly one-fifth of RA patients, with higher MTX doses significantly associated with liver enzyme elevation. These findings highlight the importance of regular liver function monitoring, particularly in patients receiving higher MTX dosages.*

Keywords: Methotrexate, Hepatotoxicity, Rheumatoid Arthritis, Dose-Dependent Liver Enzymes

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic autoimmune disorder marked by inflammatory arthritis that extends beyond the joints. This chronic inflammatory disorder is often the result of interactions between genetic predispositions and environmental factors, such as tobacco, and primarily affects synovial joints. It usually starts within small peripheral joints, exhibits symmetry, and advances to affect proximal joints if not treated (1-3)—chronic inflammation results in joint destruction, including cartilage loss and bone erosions. RA with a manifestation duration of less than six months is classified as early RA. In contrast, symptoms persisting for six months are categorized as established RA (4). The Global Burden of Disease 2010 Study indicates that the global incidence of RA is approximately 0.24% (5). Methotrexate is frequently used as the initial treatment for rheumatoid arthritis, managed in weekly doses at medical centers. It is regarded as the primary effective medication for patients affected by rheumatoid arthritis (6,7). Due to its success rate and cost-effectiveness, methotrexate is frequently used to treat rheumatoid arthritis. Although generally well tolerated, prolonged administration of methotrexate at recommended dosages may be responsible for toxic effects, affecting the liver, as well as the gastrointestinal system. Seven to nine Methotrexate improves adenosine concentration and decreases cytokine levels (8, 9).

Hepatotoxicity associated with methotrexate in patients with rheumatoid arthritis is established and may result in hepatic fibrosis as well as cirrhosis. Oral folic acid supplementation at doses is linked to a decreased incidence of hepatotoxicity (10, 11). The effects of methotrexate may raise the risk factors associated with liver fibrosis and cirrhosis. A study recorded the frequency of hepatotoxicity with methotrexate in rheumatoid arthritis, 27% (12-14).

Although considerable work has been done on this internationally, there is a remarkable paucity of data locally. Therefore, this study is designed to highlight the magnitude of hepatotoxicity in rheumatoid arthritis patients taking methotrexate in our population. The results of this study will be used to guide future recommendations for the importance of diagnosis of this complication and guide treatment strategies in the management of RA patients, because the significant frequency of hepatotoxicity warrants early diagnosis and management of this prognostically life-threatening, yet silent, complication of methotrexate.

METHODOLOGY

After taking ethical approval from the institute, we initiated this descriptive cross-sectional study in the Department of Medicine at Lady Reading Hospital, Peshawar [11-September-2024—11-March-2025]. We enrolled 78 patients, selected through consecutive sampling, with a confidence level of 95%, an absolute precision of 10%, and a frequency of hepatotoxicity of 27% as derived from previous studies (12-14). The study included patients diagnosed with rheumatoid arthritis who had been using methotrexate for six months to one year, regardless of their age and gender. Patients with conditions as rheumatic heart disease or dilated cardiomyopathy confirmed via echocardiography, prior history of chronic liver disease, liver transplantation, physical liver trauma, or alcohol dependency were not involved. Hepatotoxicity was defined in our study as ALT > 2-fold that of ULN (2N) or an ALT/AP ratio ≥ 5. The purpose of the research was explained to participants or their relatives in a clear and comprehensible manner, and consent was secured. All diagnostic procedures were performed by a consultant gastroenterologist or a general medicine consultant who was an Associate Professor and Fellow of the College of Physicians and Surgeons of Pakistan, with

experience managing such cases. The investigator assisted during the assessments and recorded all relevant data onto a pre-designed proforma.

Data analysis was carried out using SPSS 20. Variables like age were presented as means and standard deviations, while frequencies and percentages were assessed for gender, number of doses, and hepatotoxicity. Hepatotoxicity was stratified with gender, number of doses, and age using the Chi Square test, where the P value was kept notable at < 0.05.

RESULTS

The study included 78 participants who had a mean age of 45.29±12.39 years. The cohort consisted of 34 males (43.6%) and 44 females (56.4%) (Figure 1). Regarding the dosage, 22 patients (28.2%) received 10 mg/week, while 29 (37.2%) received 15 mg/week, and 27 (34.6%) received 25 mg/week (Table 1). Hepatotoxicity was observed in around 15 patients (19.2%) (Table 2). Age distribution analysis showed that 3 (20.0%) of hepatotoxicity cases were aged 18–35. For the 36–50 years cohort, 5 cases (33.3%) of hepatotoxicity were documented, while in the 51–60 years group, 7 cases (46.7%) (p=0.93). Gender analysis showed that there were eight males (53.3%) and seven females (46.7%) among hepatotoxicity cases (p=0.39). A notable association was observed between dosing frequency and hepatotoxicity (p=0.01). Patients receiving 25 mg/week had the highest frequency of hepatotoxicity, 10 (66.7%) (Table 3).

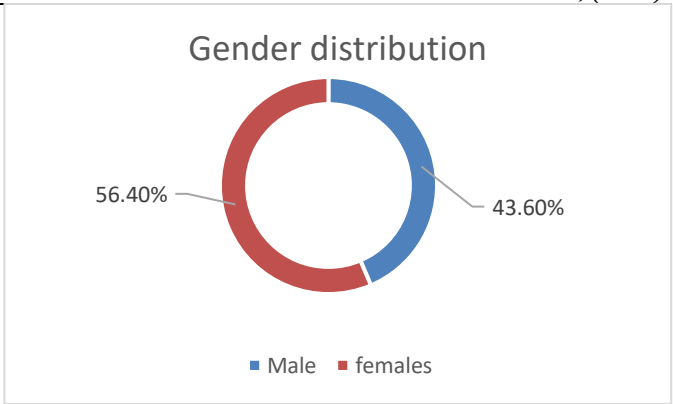

Figure 1: Gender distribution

Table 1: Number of doses of methotrexate

Number of doses	Frequency	Percentage
10 mg/week	22	28.2%
15 mg/week	29	37.2%
25 mg/week	27	34.6%

Table 2: Frequency of Hepatotoxicity

Hepatotoxicity	Frequency	Percentage
Yes	15	19.2%
No	63	80.8%

Table 3: Association of Hepatotoxicity with demographic and clinical parameters

Demographic and clinical parameters		Hepatotoxicity				P value
		Yes		No		
		Frequency	Percentage	Frequency	Percentage	
Age distribution (Years)	18 to 35	3	20.0%	14	22.2%	0.93
	36 to 50	5	33.3%	23	36.5%	
	51 to 60	7	46.7%	26	41.3%	
Gender	Male	8	53.3%	26	41.3%	0.39
	Female	7	46.7%	37	58.7%	
Number of doses	10 mg/week	2	13.3%	20	31.7%	0.01
	15 mg/week	3	20.0%	26	41.3%	
	25 mg/week	10	66.7%	17	27.0%	

DISCUSSION

In the present study involving 78 participants, we found that hepatotoxicity was observed in 19.2% of patients. A notable association was noted between higher weekly doses (25 mg) and hepatotoxicity, while age and gender did not show any association.

In their study, Gilani et al. reported a 27% incidence of MTX toxicity in 140 RA patients, with hepatotoxicity specifically at 8.6%. They demonstrated a serum MTX concentration cutoff of 0.71 µmol/L as a projection of toxicity, reinforcing the dose-dependent relationship observed in our study (15). Similarly, Sotoudehmanesh et al. reported transaminitis in 23.7% of patients, correlating it with longer treatment duration and higher doses, further supporting the role of MTX dosage and exposure time in hepatotoxicity (16). The 19.2% hepatotoxicity in our study falls within this reported range, suggesting consistency in MTX's hepatotoxic potential across diverse populations. In our study, although we didn't observe a notable association of hepatotoxicity with increasing, but we did notice that frequency was higher in patients having age 51 to 60 years which perfectly correlates with the findings of Bilal et al., who noted that hepatotoxicity was higher in patients above 60 years of age (17).

Gender distribution in the current study showed no association with hepatotoxicity, consistent with Gilani et al.. Bilal et al. (15, 17). However, Babar et al. reported a higher female predominance (65.22%) in their study, which is similar to our findings; we found that the frequency of female patients was higher in our study.[18] In our study, the female majority did not translate to higher hepatotoxicity, signifying that gender alone may not be a primary risk factor.

Gilani et al. and Sotoudehmanesh et al. both underscored cumulative dose and treatment duration as potential determinants, reporting a 45.2% hepatotoxicity incidence in patients receiving >1.5 g cumulative MTX (15, 16). We found that higher doses per week were linked with a higher incidence of hepatotoxicity. Our study focused on weekly dosing rather than cumulative intake, which may overlook the long-term risks, suggesting future research should integrate both metrics.

Methodological differences in monitoring and defining hepatotoxicity may also contribute to variability. Our study defined hepatotoxicity as elevated ALT levels, while Parvin et al. used a histopathological criterion; they found no severe fibrosis despite significant ALT increases (19). Bilal et al. also relied on biochemical markers alone to define hepatotoxicity, similar to our study, but emphasized regular monitoring to mitigate risks. At the same time, García et al. advocated for rigorous causality assessment to avoid misattributing liver injury, a practice that could enhance the specificity of hepatotoxicity diagnosis in future studies (17, 20). The findings drawn from our study suggest that although MTX remains a keystone in managing RA, its

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hepatotoxic potential demands strict monitoring, mostly at higher doses.

Our study contributes to the evolving understanding of MTX hepatotoxicity, supporting dose dependency while highlighting gaps in comorbidity screening and causality assessment. By incorporating these considerations, clinicians can improve MTX therapy, balancing efficacy with minimized hepatic risk.

CONCLUSION

In conclusion, we found that 19.2% of patients presenting with rheumatoid arthritis had methotrexate induced hepatotoxicity. Our study confirms that methotrexate-induced hepatotoxicity is dose-dependent; higher weekly doses of 25 mg can pose a greater risk.

DECLARATIONS

Data Availability Statement

All data generated or analysed during the study are included in the manuscript.

Ethics approval and consent to participate

Approved by the department Concerned. (IRB-REF-25/LRH/MTI)

Consent for publication

Approved

Funding

Not applicable

CONFLICT OF INTEREST

The authors declared an absence of conflict of interest.

AUTHOR CONTRIBUTION

IRUM REHMAT (Postgraduate Resident)

Conception of Study, Development of Research Methodology Design, Data Collection, Manuscript revisions, Study Design, manuscript Review, and final approval of manuscript.

MUHAMMAD BILAL AWAN (Associate Professor)

Conception of Study, Critical Input, Development of Research Methodology Design

KALEEM ULLAH (Postgraduate Resident)

Literature Review

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