CP 03: Occurrence of deranged liver enzymes among patients with rheumatoid arthritis treated with methotrexate

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Abstract

Background and objective
Methotrexate is the anchor disease-modifying anti-rheumatic drug for rheumatoid arthritis, but elevations of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) require clinical review and monitoring. This study determined the occurrence of deranged liver enzymes and associated factors among methotrexate-treated patients with rheumatoid arthritis.

Methods
A hospital-based descriptive cross-sectional study was conducted among 221 adults receiving methotrexate for at least six months at the Rheumatology Clinic, Teaching Hospital, Jaffna. Data were collected using an interviewer-administered questionnaire and a clinical-record extraction form. Deranged liver enzymes were defined as ALT or AST exceeding 1.5 times the upper limit of normal in any of the three most recent consecutive reports available at the time of data collection. Categorical and continuous variables were analyzed using the Chi-square/Fisher's exact test and Mann–Whitney U test, respectively, with $p<0.05$ indicating statistical significance.

Results
Deranged liver enzymes were identified in 20 participants (9.0%). Participants were predominantly female (85.5%); median age was 57 years (IQR 48–65), median weekly methotrexate dose was 10 mg (IQR 7.5–12.5), and median treatment duration was 5 years (IQR 2–7). Oral traditional medicine use was associated with deranged liver enzymes (21.7% among users versus 7.6% among non-users; $p=0.042$). Age, sex, alcohol use, concomitant anti-rheumatic therapy, methotrexate dose and treatment duration were not significantly associated.

Conclusions
Approximately one in eleven methotrexate-treated patients had deranged liver enzymes. Concomitant traditional medicine use was the only identified associated factor. Medication reconciliation and evaluation of alternative causes should accompany routine transaminase monitoring; causation cannot be inferred from this cross-sectional study.

Keywords:
rheumatoid arthritis, methotrexate, aminotransferases, traditional medicine, cross-sectional study

Introduction
Rheumatoid arthritis is a chronic inflammatory disease in which early and sustained disease control is required to prevent joint damage, disability and systemic complications. Methotrexate remains the preferred anchor conventional synthetic disease-modifying anti-rheumatic drug because of its effectiveness, long clinical experience and relatively low cost.[1, 2] Despite its favorable benefit–risk profile at low weekly doses, treatment requires regular clinical and laboratory monitoring. Transient elevations of ALT and AST are among the most frequently observed laboratory abnormalities during therapy.[3, 4]

These enzymes are markers of hepatocellular injury rather than direct measures of hepatic function; therefore, an isolated elevation should not automatically be labelled as methotrexate-induced liver toxicity.

The interpretation of abnormal aminotransferases is complicated by obesity, diabetes, metabolic dysfunction-associated steatotic liver disease, alcohol use, viral hepatitis, concomitant medicines and herbal or traditional remedies.[3, 5] Contemporary evidence suggests that serious progressive liver disease attributable solely to appropriately monitored low-dose methotrexate is uncommon, while metabolic risk factors and pre-existing liver abnormalities may be more influential.[5-7]

Folic acid supplementation reduces methotrexate-related adverse effects, including elevations of liver enzymes and treatment discontinuatio.[8]

Evidence from Sri Lankan rheumatology settings is limited. Local prescribing patterns, access to monitoring and use of traditional medicines may influence the occurrence and interpretation of abnormal liver enzymes. This study therefore aimed to determine the occurrence of deranged liver enzymes and identify associated patient- and treatment-related factors among adults with rheumatoid arthritis receiving methotrexate at Teaching Hospital Jaffna.

Methods

This hospital-based descriptive cross-sectional study was conducted at the Rheumatology Clinic, Teaching Hospital Jaffna, Sri Lanka, from October 2023 to November 2024; data collection occurred from July to September 2024. Adults aged 18 years or older with a confirmed diagnosis of rheumatoid arthritis who had received methotrexate for at least six months were eligible. Patients who had missed their previous three clinic follow-up visits were excluded. Because approximately 245 eligible patients attended the clinic, the entire accessible population was approached; 221 participated, giving a response rate of 90.2%.

Data were obtained using an interviewer-administered questionnaire and a clinical-record extraction form. The questionnaire was reviewed by subject experts and refined following a pilot study involving 15 patients at District General Hospital, Vavuniya. Collected variables included age, sex, education, use of oral traditional medicines, alcohol consumption, duration of rheumatoid arthritis, duration and weekly dose of methotrexate, concomitant anti-rheumatic therapy and the three most recent consecutive ALT and AST results.

Deranged liver enzymes were defined as an ALT or AST value greater than 1.5 times the laboratory upper limit of normal. Liver enzyme status was assessed from the three most recent consecutive ALT and AST reports available in each participant's clinical record at the time of data collection, rather than from a single measurement, to reduce misclassification arising from transient fluctuations and laboratory variability. A participant was classified as having deranged liver enzymes if this threshold was exceeded in any of these three reports. As these reports were extracted once, at the single data collection contact, and participants were not followed up prospectively, the study retained a cross-sectional design. Information on the magnitude of elevation was not available; therefore, the severity of enzyme elevation could not be graded. This operational definition identifies biochemical abnormality and does not establish methotrexate-induced hepatotoxicity. Data were analyzed using IBM SPSS Statistics, version 27. Continuous variables were non-normally distributed and are presented as medians and interquartile ranges. Associations were tested using the Chi-square test or Fisher's exact test for categorical variables and the Mann–Whitney U test for continuous variables. Statistical significance was set at $p<0.05$.

Ethical approval was obtained from the Ethics Review Committee, Faculty of Medicine, University of Jaffna. Administrative permission was obtained from Teaching Hospital Jaffna, written informed consent was obtained from all participants, and confidentiality was maintained throughout the study.

Results

The median age of the 221 participants was 57 years (IQR 48–65), and 189 (85.5%) were female. The median duration of rheumatoid arthritis was 6 years (IQR 2–8), the median weekly methotrexate dose was 10 mg (IQR 7.5–12.5), and the median duration of methotrexate use was 5 years (IQR 2–7). Twenty-three participants (10.4%) reported oral traditional medicine use, six (2.7%) reported alcohol use and seven (3.2%) reported smoking (Table 1).

Table 1. Selected characteristics of participants (N=221) **Median (interquartile range).*

Characteristic	**Frequency (n)**	**Percentage / summary**
Age, years	—	57 (48–65)*
Female sex	189	85.5%
Male sex	32	14.5%
Oral traditional medicine use	23	10.4%
Alcohol use	6	2.7%
Smoking	7	3.2%
Duration of rheumatoid arthritis, years	—	6 (2–8)*
Weekly methotrexate dose, mg	—	10 (7.5–12.5)*
Duration of methotrexate use, years	—	5 (2–7)*

Deranged liver enzymes were present in 20 participants (9.0%). Data on the magnitude of ALT or AST elevation were not available; therefore, the severity and pattern of enzyme elevation could not be described. Five of the 23 traditional medicine users (21.7%) had deranged enzymes compared with 15 of 198 non-users (7.6%), showing a statistically significant association (p=0.042). No statistically significant associations were observed for age, sex, alcohol consumption, concomitant anti-rheumatic therapy, duration of rheumatoid arthritis, duration of methotrexate use, methotrexate dose or number of concomitant medications. These findings are shown in Table 2.

Table 2. Factors associated with deranged liver enzymes (N=221) **Median (interquartile range). ‡Mann–Whitney U test. §Chi-square test. Percentages are row percentages within each exposure category. DMARD, disease-modifying anti-rheumatic drug.*

Factor	**Category**	**Deranged enzymes n (%)**	**Normal enzymes n (%)**	**Statistical analysis**
Age, years*		56.5 (51.5–59.0)	58.0 (46.0–65.0)	P=0.453‡ U= 1805.5 Z=-0.750
Sex	Male	1 (3.1)	31 (96.9)	P=0.321§ X^2=1.596 df=1
	Female	19 (10.1)	170 (89.9)	
Oral traditional medicine use	Traditional medicine use	5 (21.7)	18 (78.3)	P=0.042§ X^2=5.022 df=1
	No traditional medicine use	15 (7.6)	183 (92.4)	
Alcohol use	Alcohol use	1 (16.7)	5 (83.3)	P=0.438§ X^2=0.435 df=1
	No alcohol use	19 (8.8)	196 (91.2)	
Concomitant DMARD therapy	Neither prednisolone nor other DMARD	7 (10.8)	58 (89.2)	P=0.872§ X^2=0.705 df=3
	Other DMARD only	2 (7.4)	25 (92.6)	
	Prednisolone only	4 (6.9)	54 (93.1)	
	Prednisolone and other DMARD	7 (9.9)	64 (90.1)	
Duration of rheumatoid arthritis, years*		7.0 (1.3–10.8)	5.0 (2.0–8.0)	P=0.532‡ U=1840.5 Z=-0.625
Duration of methotrexate use, years*		7.0 (1.3–8.0)	5.0 (2.0–7.0)	P=0.454‡ U=1807.5 Z=-0.749
Weekly methotrexate dose, mg*		10 (7.5–12.5)	10 (7.5–12.5)	P=0.148‡ U=1625.5 Z=-1.445
Concomitant medications, number*		2 (1–3)	2 (1–3)	P=0.719‡ U=1914.5 Z=-0.719

Discussion

This study found deranged ALT or AST levels in 9.0% of adults with rheumatoid arthritis receiving methotrexate. The occurrence is within the broad range reported in previous methotrexate cohorts, in which aminotransferase abnormalities are usually mild and intermittent.[3, 4, 9] Differences between studies are expected because thresholds, testing intervals, folate regimens, comorbidity profiles and methotrexate doses vary. The present finding should therefore be interpreted as the occurrence of biochemical abnormalities rather than confirmed drug-induced liver injury.

Traditional medicine use was the only factor significantly associated with deranged liver enzymes. The proportion with enzyme derangement was almost three times higher among users than non-users. Traditional preparations may contain multiple pharmacologically active ingredients, and their composition, dose and potential interactions may be uncertain. Nevertheless, the study did not record the exact products, duration of use or temporal relationship to enzyme elevation. The association cannot establish causation and may also reflect confounding by indication or unmeasured metabolic and hepatic risk factors. Clinically, the finding supports routine, non-judgmental enquiry about herbal and traditional medicines during medication reconciliation.

Age, sex, alcohol consumption, methotrexate dose and treatment duration were not significantly associated with enzyme derangement. The relationship between cumulative methotrexate exposure and liver injury has been examined in several elastography-based cohorts with differing conclusions, whereas baseline ALT abnormality, obesity, diabetes and hepatic steatosis appear more reproducible predictors.[5-7, 9-11] The absence of associations in this study may also reflect the small number of participants in some exposure groups, particularly males and alcohol users. A non-significant result should not be interpreted as evidence that these factors are clinically irrelevant.

Folate supplementation is an important component of safe methotrexate therapy. Systematic-review evidence shows that folic or folinic acid reduces abnormal liver tests and treatment discontinuation without a clinically important loss of methotrexate efficacy (8). Continued counselling about the weekly methotrexate schedule, folic acid use, avoidance of unsupervised medicines and attendance for monitoring is therefore warranted.

The study has several limitations. Baseline liver enzyme values before methotrexate initiation were unavailable; therefore, pre-existing abnormalities could not be separated from new elevations. Only whether ALT or AST exceeded the threshold was available; the magnitude of elevation was not recorded and alkaline phosphatase was not collected, so the severity and pattern (hepatocellular, cholestatic or mixed) of enzyme elevation could not be characterized. Although three consecutive reports were used to reduce misclassification, transient elevations may still have been captured. Folic acid supplementation and adherence to it were not recorded, so their contribution could not be assessed. Body mass index, waist circumference, diabetes control, lipid status and imaging for metabolic dysfunction-associated steatotic liver disease were not comprehensively assessed. Viral hepatitis, biliary disease and other potentially hepatotoxic medicines were not systematically excluded. The cross-sectional design prevents temporal or causal inference, and the single-center setting limits generalizability. The small numbers of traditional medicine users, alcohol users and males reduced statistical power. Finally, the operational threshold of 1.5 times the upper limit of normal does not itself diagnose clinically important liver injury.

Despite these limitations, the study provides useful local evidence. Among methotrexate-treated patients with abnormal transaminases, clinicians should review the complete medicine history, assess metabolic and infectious causes, repeat testing when appropriate and avoid attributing the abnormality automatically to methotrexate. Prospective multicenter studies should document baseline liver enzymes, specific traditional preparations, metabolic risk factors and serial laboratory trends.

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Conflict of interest
The authors declare that they have no conflicts of interest.

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