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Use of Methotrexate for More Than 4 Years Is Not Associated with Liver Fibrosis in Rheumatoid Arthritis Patients

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ABSTRACT

Background. Methotrexate is an anchor drug in the management of rheumatoid arthritis (RA). However, the association between methotrexate and development of liver fibrosis remains a subject of controversy. Non-invasive methods to assess liver fibrosis, such as the FIB-4 score, have been developed. RA patients on methotrexate therapy should be monitored for any signs of liver fibrosis. This study aims to investigate the correlation between methotrexate cumulative dose and the FIB-4 score in rheumatoid arthritis patients who received methotrexate therapy to assess the hepatotoxic effects of methotrexate. **Methods.** This cross-sectional study involved rheumatoid arthritis patients who received methotrexate therapy at Dr. Hasan Sadikin General Hospital Bandung from September 2022 to November 2022. Clinical data, laboratory tests (including platelet values and liver function test), and cumulative methotrexate doses were extracted from medical records. Data were analyzed using the Spearman correlation test. **Results.** This study involved 100 subjects aged between 22-82 years, comprising 93% women and 7% men. The median FIB-4 score was 0.73 (0.24-6.80), while the median methotrexate cumulative dose was 2477.5 mg, with a range of 1005-10400 mg. The results showed that correlation coefficient between the FIB-4 score and methotrexate cumulative dose in rheumatoid arthritis patients was -0.089 (p=0.378). **Conclusion.** There is no significant correlation between FIB-4 score and cumulative dose of methotrexate in rheumatoid arthritis patients. The use of methotrexate in RA patients over 4 years is relatively safe as it does not increase the risk of liver fibrosis.

1. Introduction

Rheumatoid arthritis (RA) is an autoimmune disease characterized by chronic and progressive systemic inflammation.[1] Methotrexate (MTX) is the first choice disease-modifying antirheumatic drug (DMARD) in RA management.[2,3] Increased liver enzymes are the second most common side effect during MTX treatment after gastrointestinal side effects. Given that patients with RA receive MTX for many years, there are concerns on the long-term safety profile of MTX therapy.[4]

Many factors affect liver fibrosis in methotrexate administration including metabolic syndrome, alcohol consumption, chronic viral hepatitis, genetic susceptibility, and cumulative doses of methotrexate.[4] RA patients with metabolic syndrome have a higher

risk of MTX-induced liver fibrosis. RA patients with high cumulative MTX doses, especially patients who also have metabolic syndrome, must be closely monitored to evaluate the incidence of liver fibrosis.[5,6] The gold standard examination to determine the condition of liver fibrosis is liver biopsy, however non-invasive tests such as FIB-4 scorehave been developed to detect MTX hepatotoxicity.[7]

Existing data from previous studies provide conflicting evidence regarding the impact of cumulative dose of methotrexate on liver fibrosis. Data from several studies indicate that the cumulative dose of methotrexate acts as a risk factor for liver fibrosis[8,9,10] but several other studies suggest otherwise.[11,12] This study aimed to determine the correlation between methotrexate cumulative dose and the FIB-4 score in rheumatoid arthritis patients to assess the hepatotoxic effects of methotrexate.

2. Methods

This study has received ethical approval from the Health Research Ethics Committee of Hasan Sadikin General Hospital number LB.02.01/X.6.5/362/2022. It was a retrospective observational study using data from medical records of rheumatoid arthritis patients who visited the outpatient clinic at Hasan Sadikin Hospital Bandung in the period of September 2022 to November 2022. One hundred patients met the inclusion criteria. The inclusion criteria in this study were RA patients aged ≥ 18 years who had been receiving methotrexate therapy for at least 4 years with laboratory results for platelet count, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) within the past one month. We excluded those with a history of alcohol consumption more than 30 grams per day for at least 5 years, chronic viral hepatitis, hepatic cirrhosis, use of drugs that cause thrombocytopenia, use hepatotoxic drugs, or kidney disorders with an eGFR <60 mL/min/1.73m^2.

This research is a correlation analysis with a cross-sectional design. Univariate statistical analyses were performed for subject characteristics such as age, body mass index (BMI), length of illness, length of methotrexate therapy, methotrexate dose, and FIB-4 score, and results were presented in tabular form. All numerical data were tested for normality with the Kolmogorov-Smirnov test. Meanwhile, categorical data such as gender, other RA therapies, and comorbidities were presented in numbers and percentages. The correlation between methotrexate cumulative dose and liver fibrosis based on FIB-4 values was analyzed using numerical correlative bivariate test, namely the Spearman test. Statistical analyses of all collected data was performed using the Statistical Program for Social Science (SPSS) software version 25.0 with statistical significance determined based on a p value of <0.05.

3. Results

Based on our research data, the subjects had a median age of 51 years (min-max 22-82 years), comprising of 93% female and 7% male. Regarding the body mass index, 7% were considered underweight, 54% were normal, 35% were considered overweight, and 4% were classified as obese. The characteristics of the research subjects were shown in Table 1.

Regarding comorbidities among the patients, 5% had diabetes mellitus (DM), 18% had hypertension, and 6% had obesity. The most commonly used additional therapy alongside RA treatment was corticosteroids (60%). In terms of FIB-4 score, 90% of the subjects fell into the category with scores <1.45. The cumulative dose of methotrexate among the study subjects had a median of 2477.5 mg with a range of 1005-10400 mg.

Spearman analysis test was performed to test the correlation between methotrexate cumulative dose and the FIB-4 score, resulting in a correlation coefficient (R-value) of -0.089 (p-value = 0.378). This showed that there was no statistically significant correlation among our rheumatoid arthritis patients. Figure 1 illustrates the correlation between the cumulative dose of methotrexate and FIB-4 score in rheumatoid arthritis patients.

3. Discussion

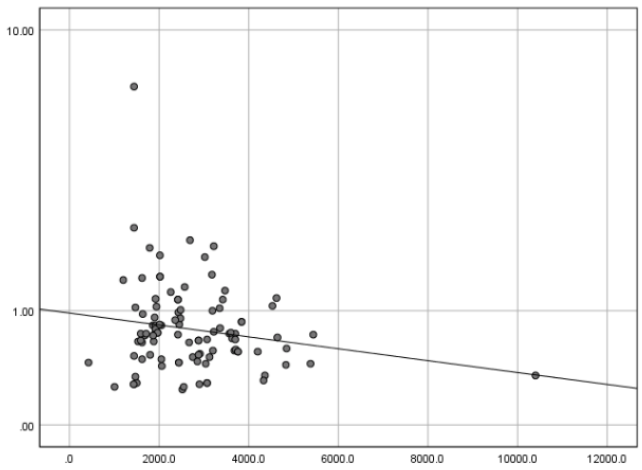
The study showed there was no statistically significant correlation between methotrexate cumulative dose and the FIB-4 score among rheumatoid arthritis patients.

Table 1. Basic Characteristics of the Subjects

Characteristics	Total (n=100)
Age (year), median (IQR)	51(22-82)
Age category (year), n (%)	
<35	11(11)
35-65	84(84)
>65	5(5)
Gender, n (%)	
Male	7(7)
Female	93(93)
Body mass index, n (%)	
Underweight	7(7)
Normal	54(54)
Overweight	35(35)
Comorbidity, n (%)	
Diabetes mellitus	5(5)
Hypertension	18(18)
Obesity	6(6)
Other RA therapy, n (%)	
Corticosteroid	60(60)
NSAIDS	8(8)
Sulfasalazine	7(7)
Azathioprine	0(0)
HCQ	16(16)
Biologic agent	0(0)
Length of MTX therapy (months), median (min-max)	53 (48-140)
FIB-4 score, median (min-max)	0.73 (0.24-6.80)
FIB-4 score category, n (%)	
<1.45	90(90)
1.45-3.25	9(9)
>3.25	1(1)
Cumulative dose of methotrexate (mg), median (min-max)	2477.5 (1005-10400)

Abbreviations: n=frequency, %=percentage, HCQ=hydroxychloroquine, IQR=Inter Quartile Range, MTX=methotrexate, RA=rheumatoid arthritis

FIB-4 score



Methotrexate Cumulative Dose (mg)

Figure 1. Scatterplot of the cumulative dose of methotrexate (mg) and the FIB-4 score in rheumatoid arthritis patients (r= -0.089; p-value = 0.378).

Systemic inflammation plays an important role in the development of liver disease, but the drugs used to treat inflammatory diseases can also cause liver toxicity. Methotrexate is the most commonly used systemic therapy for RA, psoriasis (PsO) and psoriatic arthritis (PsA). Previous publications noticed that patients with psoriasis are more susceptible to methotrexate toxicity than RA but empirical data to support this hypothesis remains limited. The exact mechanism underlying drug distribution differences between psoriasis, PsA, and RA is still unclear, so it appears that the risk of liver disease is lower among RA patients compared to psoriasis and PsA.[12] The relationship between PsO and liver disease is described through the concept of hepato-dermal axis, in which pro-inflammatory cytokines, such as interleukin-6 (IL-6), IL-17, and tumor necrosis factor-α (TNF-α), are produced by lymphocytes and keratinocytes derived from psoriatic skin and circulate to the liver to induce metabolic disturbances such as insulin resistance which spurs the occurrence of non-alcoholic fatty liver disease (NAFLD).[14,15]

This study only included RA patients without involving those with concurrent skin and/or joint inflammatory diseases. In contrast, a study conducted by Ogdie, et al. demonstrated that patients with skin and/or joint inflammatory diseases have an increased risk of developing liver fibrosis. Among these individuals, patients with psoriasis on systemic therapy have the highest risk, while patients with RA have the lowest risk. This study supports a very strong association between psoriasis and the incidence of liver disease. It may support the existence of the hepato-dermal axis.[13] Notably, psoriasis and NAFLD are associated with metabolic conditions such as metabolic syndrome and obesity.[16]

Labadie et al. mentioned that methotrexate-associated liver fibrosis could be caused by other related factors, including alcohol consumption, diabetes mellitus, and obesity, rather than attributed to methotrexate itself.[17] Higher BMI and alcohol consumption were associated with elevated liver stiffness in a study conducted by Laharie et al.18 Choi et al investigated whether MTX cumulative dose in RA patients led to liver fibrosis as determined by ultrasound, but they did not find a significant association between liver fibrosis development and MTX administration. Instead, hypertriglyceridemia and higher BMI were associated with an increased risk of liver fibrosis.19 Another study by Langman et al. involving patients with repeated liver biopsies, found that 13 patients with metabolic syndrome had

histologically proven non-alcoholic steatohepatitis and subsequent liver fibrosis.[20]

Pre-existing moderate to severe fatty deposits in the liver and obesity were the strongest predictive factors for the development of persistent transaminitis during MTX treatment in RA patients. Fat aggregation underlying the conversion of NASH to liver fibrosis may be an important mechanism in the development of liver injury in patients treated with MTX. Given that these fatty deposits were detected in half of MTX-naive RA patients at the start of this study, careful and regular monitoring of transaminases is necessary during MTX treatment. Quantitative evaluation of fatty deposits in the liver before initiation of therapy is useful for identifying patients who are at high risk for liver injury during MTX treatment.[21]

In obese individuals, FIB-4 and ADAPT scoring methods have relatively good performance in assessing liver fibrosis, both of which are not affected by adiposity. FIB-4 calculation is a cost-effective option for use in clinical practice, given its simplicity and ease of calculation. Using FIB-4 score as a screening method for advanced liver fibrosis is recommended in patients with obesity.[22]

The result of this study showed that there was no correlation between the cumulative dose of methotrexate in RA patients over 4 years and the FIB-4 scores. This implies that the use of methotrexate in RA patients over 4 years is not related to liver fibrosis. This aligns with the findings of a study by Avouac et al. which showed that patients receiving long-term MTX maintenance therapy had low FIB-4 values, indicating that MTX is not associated with an increased risk of advanced liver fibrosis, even at high cumulative doses. Additionally, the multivariate logistic regression analysis showed independent associations between increased FIB-4 scores (cut off >1.45) and male gender, low disease activity, and treatment with leflunomide and tocilizumab.[23]

A meta-analysis conducted by Cheema et al. did not show a statistically significant association between the dose of methotrexate and liver fibrosis. Individual studies reported incidences of liver fibrosis related to confounding factors such as diabetes, obesity, and pre-existing chronic liver disease. but not to methotrexate exposure. This study also found a similar result, likewise other comorbidities such as diabetes mellitus in this study were only found in 5% of the research subjects.

The available evidence suggested that advanced liver fibrosis and cirrhosis, which were previously associated with methotrexate, may actually be attributable to metabolic liver disease or other chronic liver conditions, rather than methotrexate itself. Further monitoring should be carried out in patients treated with long-term methotrexate.[21]

The study by Ollson-White, et al. in RA patients treated with MTX showed hepatic fibrosis occurred in a minority of patients. This study found that liver elastography is a better screening tool than Hepascore, FIB-4, or APRI. It is worth noting that this study specifically excluded patients with a BMI exceeding 30, a history of diabetes or high alcohol intake (because of a higher likelihood of alcohol- or non-alcohol-associated steatohepatitis), or on leflunomide, because these variables and the presence of metabolic syndrome have been shown to increase the risk of hepatic fibrosis in individuals treated with MTX. This study also stated that the majority of subjects had ALT and AST values within the normal reference range, even among subjects who were clinically assessed as having significant fibrosis. These findings indicate that current recommendations for liver fibrosis screening by liver function tests alone are inadequate, emphasizing the need for further research using other modalities such as liver elastography to assess liver fibrosis.[24]

There are several limitations of this study. First, its cross-sectional design limits data acquisition only from medical records. To obtain better results, a cohort study would be necessary as it would involve following patients' progress over time in real terms. Another limitation of this study is that it assessed the cumulative dose of methotrexate consumed by the patients but did not assess the cumulative dose present in their bloodstream.

5. Conclusion

In conclusion, our findings indicate that there is no correlation between FIB-4 score and the methotrexate cumulative dose in rheumatoid arthritis patients. The use of methotrexate in RA patients over 4 years is considered safe and does not appear to be related to an increased risk of liver fibrosis.

6. References

1. Tehlirian C V., Bathon JM. Rheumatoid arthritis: clinical and laboratory manifestations. Prim Rheum Dis Thirteen Ed. 2008;114–21.
2. Hidayat R., Suryana BPP, Wijaya LK., Ariane A., Hellmi RY., Adnan E., et al. Diagnosis dan pengelolaan artritis reumatoid (rheumatoid arthritis diagnosis and management). 2021;1-26.
3. Saag K.G., Gim G.T., Patkar N.M., Anuntiyo J., Finney C., Curtis J.R., et al. American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. Arthritis Care Res. 2008;59(6):762–84.
4. Aithal, G. Hepatotoxicity Related to Methotrexate. In book: Drug-induced liver disease. 2013;593–604.
5. Yeo C.M., Chong V.H., Earnest A., Yang W.L. Prevalence and risk factors of methotrexate hepatoxicity in Asian patients with psoriasis. World J Hepatol. 2013;5(5):275–80.
6. McPherson S., Stewart S.F., Henderson E., Burt A.D., Day C.P. Simple non-invasive fibrosis scoring systems can reliably exclude advanced fibrosis in patients with non-alcoholic fatty liver disease. Gut. 2010;59(9):1265–9.
7. West SG. Methotrexate hepatotoxicity. Rheum Dis Clin North Am. 1997;23(4):883–915.
8. Sakthiswary R., Yin G., Chan L., Koh E.T., Leong K.P., Yu B., et al. Methotrexate-associated nonalcoholic fatty liver disease with transaminitis in rheumatoid arthritis. Scientific World Journal. 2014. 234-46.
9. Lertnawapan R., Chonprasertsuk S., Siramolpiwat S. Association between cumulative methotrexate dose, non-invasive scoring system and hepatic fibrosis detected by Fibroscan in rheumatoid arthritis patients receiving methotrexate. Int J Rheum Dis. 2019;22(2):214–21
10. Miyata M., Kuroda M., Unakami M., Tasaki K., Migita K., Ohira H. Validation of the fibrosis-4 (FIB-4) index in the diagnosis of liver disease of rheumatoid arthritis patients treated with methotrexate. Mod Rheumatol. 2019;29(6):936–42.
11. Park S.H., Choe J.Y., Kim S.K. Assessment of liver fibrosis by transient elastography in rheumatoid arthritis patients treated with methotrexate. Jt Bone Spine. 2010;77(6):588–92.
12. Fathi NH, Mitros F, Hoffman J, Straniero N, Labreque D, Koehnke R, et al. Longitudinal measurement of methotrexate liver concentrations does not correlate with liver damage, clinical efficacy, or toxicity during a 3,5 year double blind study in rheumatoid arthritis. The journal of rheumatoly. 2002;2092–8.
13. Ogdie A, Grewal SK, Noe MH, Shin DB, Takeshita J, Chiesa Fuxench ZC, Carr RM, Gelfand JM. Risk of Incident Liver Disease in Patients with Psoriasis, Psoriatic Arthritis, and Rheumatoid Arthritis: A Population-Based Study. J Invest Dermatol. 2018 Apr;138(4):760-767.
14. Nohlgård C., Rubio C.A., Kock Y., Hammar H. Liver fibrosis quantified by image analysis in methotrexate-treated patients with psoriasis. Journal of the American Academy of Dermatology, 1993; 28 (1) 40-45
15. Mantovani, A., Gisondi, P., Lonardo, A., & Targher, G. Relationship between Non-Alcoholic Fatty Liver Disease and Psoriasis: A

Novel Hepato-Dermal Axis? International Journal of Molecular Sciences. 2016; 17(2), 217.

16. Prussick R, Prussick L, Nussbaum D. Nonalcoholic Fatty liver disease and psoriasis: what a dermatologist needs to know. J Clin Aesthet Dermatol. 2015 Mar;8(3):43-5
17. Labadie JG, Jain M. Noninvasive Tests to Monitor Methotrexate-Induced Liver Injury. Clin Liver Dis (Hoboken). 2019 Mar 29;13(3):67-71
18. Laharie D, Seneschal J, Schaeverbeke T, Doutre MS, Longy-Boursier M, Pellegrin JL, et al. Assessment of liver fibrosis with transient elastography and fibroTest in patients treated with methotrexate for chronic inflammatory diseases: A case-control study. J Hepatol 2010;53: 1035-40
19. Choi Y, Lee CH, Kim IH, Park EH, Park S, Yoo WH. Methotrexate use does not increase the prevalence of hepatic steatosis: a real-world retrospective nested case-control study. Clin Rheumatol 2021; 40: 2037-2045
20. Langman G, Hall P, Todd G. Role of non-alcoholic steatohepatitis in methotrexate-induced liver injury. J Gastroenterol Hepatol. 2001;16(12):1395–401.
21. Mori S, Arima N, Ito M, Ueki Y, Abe Y, Aoyagi K, Fujiyama S. Incidence, predictive factors and severity of methotrexate-related liver injury in rheumatoid arthritis: a longitudinal cohort study. Rheumatol Adv Pract. 2020 Jun 5;4(2)
22. Qadri S, Ahlholm N, Lønsmann I, Pellegrini P, Poikola A, Luukkonen P, et.al. Obesity Modifies the Performance of Fibrosis Biomarkers in Nonalcoholic Fatty Liver Disease. The Journal of Clinical Endocrinology & Metabolism. 2022; 107; e2008–e2020
23. Avouac J, Degrave R, Vergneault H, Combier A, Wanono S, Boisson M, Frantz C, Allanore Y. Risk of liver fibrosis induced by methotrexate and other rheumatoid arthritis medications according to the Fibrosis-4 Index. Clin Exp Rheumatol. 2022 Jan;40(1):150-157
24. Olsson-White, D.A., Olynyk, J.K., Ayonrinde, O.T., Paramalingam, S. and Keen, H.I, Assessment of liver fibrosis markers in people with rheumatoid arthritis on methotrexate. Intern Med J, 2022; 52: 566-573