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The relationship between dose of methotrexate and incidence of liver fibrosis in patients with rheumatoid arthritis

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Abstract

Introduction: Methotrexate (MTX) is a chemotherapy agent and immune system suppressant that can cause liver fibrosis in long-term usage. This study aimed to investigate the relationship between the dose of MTX and the incidence of liver fibrosis in patients with rheumatoid arthritis (RA).

Material and methods: This cohort study was conducted on RA patients with normal liver function who took MTX. Liver FibroScan and laboratory tests, including α_2-macroglobulin, total bilirubin, γ-glutamyltransferase, apolipoprotein A1, haptoglobin, and alanine transaminase was performed. The patients were divided into 2 groups regarding their cumulative dose of MTX and the rate of liver fibrosis incidence was compared between the 2 groups.

Results: In total, 60 RA patients with the mean age of 55.2 ±11.8 years were enrolled. The mean duration of MTX use in patients was 6.9 ±3.8 years, and it was higher in the higher cumulative dose MTX group (> 2 g) than in the lower cumulative dose group (< 2 g; $p < 0.0001$). The overall prevalence of grade 3 fibrosis was 3.33%. The prevalence of second- and third-degree liver fibrosis in patients receiving a lower cumulative dose was respectively 9 (28.1%) and 1 (3.1%), and in patients receiving a higher cumulative dose it was 7 (25%) and 1 (3.6%), respectively. There was no statistically significant difference between the 2 groups regarding the prevalence of liver fibrosis ($p = 0.88$). Both aspartate aminotransferase to platelet ratio index and Fibrosis Index Based on 4 Factors indices showed no significant difference between the 2 groups ($p = 0.594$, $p = 0.232$).

Conclusions: These results suggest that long-term treatment with a higher cumulative dose of MTX is not associated with a higher incidence of liver fibrosis in RA patients.

Key words: methotrexate, liver fibrosis, cumulative dose, rheumatoid arthritis.

Introduction

Rheumatoid arthritis (RA) is one of the most common chronic diseases that occur as an inflammatory and systemic disease with joint involvement. Due to the destruction of articular cartilage, RA usually results in disability and may have a slow or very destructive course [1]. Drugs used to treat the disease restrict it by non-specific suppression of the inflammatory or immunological phenomenon. These drugs work together to maintain motor function, control pain, and prevent the progressive destruction of joint structures [2].

Methotrexate (MTX) is an immunosuppressive drug and is one of the disease-modifying anti-rheumatic drugs (DMARD), that change the course of the disease, which in addition to improving the symptoms, also slows down the course of the disease [3]. Methotrexate should be part of the first treatment strategy. In patients with a contraindication to MTX (or early intolerance),

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leflunomide or sulfasalazine should be considered as part of the (first) treatment strategy [3]. Inadequate response to MTX necessitates a transition to combination DMARD therapy, such as MTX with sulfasalazine and hydroxychloroquine (oral triple therapy), leflunomide, or a biologic [4].

Methotrexate is commonly prescribed to treat RA as well as lupus, psoriatic arthritis, myositis, vasculitis, and some other rheumatic diseases [5]. Liver toxicity and fibrosis are known as the major side effects of the long-term use of this drug [6]. Hepatotoxicity, although infrequent, may be intensified by specific risk factors such as a familial predisposition to hereditary liver failure, a history of alcohol consumption, diabetes, insufficient folate supplementation, exposure to high levels of hepatotoxic chemicals, and dyslipidemia [7]. The duration of medication, the interval between doses, higher cumulative dose, and the total amount of medication taken so far affect the risk of liver fibrosis. The cumulative dose of more than 3 g of this drug causes liver tissue changes in 20% of cases. However, advanced fibrosis is seen in only 3% of these cases [8]. Nonetheless, the characterization of MTX toxicity has been moderated over the years. According to American College of Rheumatology (ACR) 2021 guideline [9], MTX is conditionally recommended for DMARD-naive patients with nonalcoholic fatty liver disease (NAFLD), normal liver tests, and no advanced liver fibrosis, who exhibit moderate-to-high disease activity. In addition, MTX treatment is conditionally allowed at a therapeutic dose (i.e. > 15 mg/week) in patients with fatty liver disease. Despite the dose reduction and weekly use (5–15 mg per week) instead of daily use, liver toxicity is only partially controlled. The widespread and long-term use of this drug, especially in RA, has led to the spread of liver toxicity, which, if neglected, can lead to cirrhosis and liver failure [10]. Consequently, it is essential to monitor and diagnose the liver damage caused by MTX during treatment [11]. Due to hepatotoxicity risks, its use should be limited to patients without significant liver disease or fibrosis (stage 3 or 4). Noninvasive fibrosis assessment and gastroenterology consultation are advised before initiation, with monitoring every 4–8 weeks. The conditional recommendation reflects variability in risk tolerance among patients and clinicians [9].

The Ishak [12], Scheuer [13], Metavir [12], Batts-Ludwig [12], and non-alcoholic steatohepatitis (NASH) Clinical Research Network [14] systems were utilized to categorize fibrosis stages across various studies. These stages were summarized as nil-to-mild fibrosis (F0–1), significant fibrosis (F2), advanced fibrosis (F3), and cirrhosis (F4), with the Ishak system defining stages as F0–2, F3, F4, and F5, respectively. Liver biopsy is used as the gold standard for fibrosis assessment. This procedure is invasive, with complications such as the risk of bleeding. Another way to assess fibrosis is to use biochemical markers of the liver (liver enzymes) that are not accurate and reliable enough to diagnose liver fibrosis [15]. The laboratory criteria used to assess liver stiffness include the BARD score, which includes body mass index (BMI), aspartate aminotransferase/alanine aminotransferase (AST/ALT) ratio, and type 2 diabetes mellitus [16], and the BAAT score, which includes BMI, age, ALT, and triglyceride (TG) [17]. Another laboratory criterion is the AST to platelet ratio index (APRI), which is associated with increased liver fibrosis [18]. A meta-analysis encompassing 40 studies indicated that an APRI cutoff of 0.7 for predicting significant fibrosis (F2 to F4) demonstrated a sensitivity of 77% and a specificity of 72% [19]. An APRI cutoff of 1.0 for predicting cirrhosis (F4) demonstrated a sensitivity of 76% and a specificity of 72%. Accuracy was diminished in patients coinfected with human immunodeficiency virus (HIV) and hepatitis C virus (HCV) [19]. Consequently, the APRI is particularly effective for ruling out significant fibrosis in individuals with chronic HCV [20].

The Fibrosis Index Based on 4 Factors (FIB-4) (age (years) × AST (U/l)/[PLT (10^9/l) × $\sqrt{\text{ALT (U/l)}}$]) is suggested as a measure of liver fibrosis in patients with concomitant infection HIV/HCV.

The FIB-4 could be interpreted as follows:

- FIB-4 < 1.3: excludes advanced fibrosis (≤ F1),
- FIB-4 1.3–2.67: intermediate risk; further evaluation needed (F2),
- FIB-4 > 2.67: indicates advanced fibrosis (≥ F3) [21].

Due to the ease of measurement and availability of this index, efforts have recently been made to validate it in patients with RA [22]. Transient elastography (TE) is a new imaging technique that uses ultrasound to determine the firmness of the liver and estimate liver fibrosis [23]. This method has recently been recognized as an accurate method for diagnosis and evaluation of the progression of liver fibrosis in chronic liver disease, and it easily and non-invasively measures the firmness of the liver [24].

Given the difficulties and complications such as bleeding as well as the invasiveness of biopsy, the use of TE in the detection of liver fibrosis is a practical solution for future research and development [25]. However, since this method is only available in a limited number of centers and is expensive, the use of inexpensive and available tests to identify liver fibrosis is considered important. However, laboratory tests are not accurate enough. Therefore, considering different results of liver firmness with regard to the cumulative dose of MTX, this study aimed to evaluate the rate of liver fibrosis in patients with RA treated with MTX and its association

Table I. Baseline characteristics of subjects in 2 groups of methotrexate at lower and higher cumulative doses, at the beginning of the study

Variables	Total number (n = 60)	Lower cumulative dose (< 2 g) group (n = 32)	Higher cumulative dose (> 2 g) group (n = 28)	p
Age [years] Mean ±SD	55.2 ±11.8	53.9 ±12.3	56.6 ±11.1	0.308
Sex (female)	90%	93.8%	85.7%	0.404*
Usage duration Mean ±SD	6.9 ±3.8	4.5 ±2.4	8.9 ±3.7	< 0.0001

** Fisher's exact test was used to compare the 2 groups. The independent t-test was used to compare the 2 groups.*

with the cumulative dose of MTX and the duration of the treatment, using FIB-4 and APRI criteria and the FibroTest Panel.

Material and methods

This cohort study was conducted on 60 patients with a definitive diagnosis of RA according to the ACR/European Alliance of Associations for Rheumatology (EULAR) Criteria 2010 [26]. The patients received MTX as monotherapy, except during flares or severe disease, for which glucocorticosteroids (GCs) or acetaminophen were prescribed, at the Rheumatology Research Center of Ghaem Educational, Research, and Medical Center, affiliated to Mashhad University of Medical Sciences, from 2017 to 2019. The entry criteria included a normal liver status in a laboratory evaluation before the treatment. Subjects who had diabetes or viral hepatitis, and who took any hepatotoxic medication during the treatment with MTX, consumed alcohol, or had chronic kidney disease, chronic heart failure, or NAFLD, were excluded from this study. After obtaining informed consent, patients were evaluated for liver fibro scanning, and 10 ml of morning venous blood sample was drawn and kept at –20°C until the laboratory tests. These tests included fibro panel tests (α_2-macroglobulin, haptoglobulin, apolipoprotein A1, γ-glutamyltransferase), total bilirubin, alanine transaminase, partial thromboplastin time (PTT), international normalized ratio (INR), albumin, bilirubin direct, AST, ALT, ALP, and platelet (PLT) count.

At first, the APRI and FIB-4 were calculated. In the next step, patients were categorized into 2 groups based on the cumulative dose[1] of MTX (more than 2 g and less than 2 g), and the incidence of liver fibrosis was compared between the 2 groups. We divided patients into low risk (APRI < 0.7) and high risk (APRI > 0.7) groups based on the APRI score, mentioned in the article by Lin et al. [19]. We also divided patients into low risk (FIB-4 < 1.3) and high risk (FIB-4 > 2.67) based on the FIB-4, which was mentioned in the article by McPherson et al. [21].

FibroScan was performed by an experienced gastroenterologist. The measurement was taken from the right lobe of the liver through the rib cage while the patient was lying on her/his back with her/his arms at maximum abduction. The result of FibroScan is usually in the range of 2–6 kPa, and it is divided into 5 stages (F0 to F4).

Statistical analysis

The data were statistically analyzed using IBM SPSS software (V 27.0). Fisher's exact test and the independent t-test were used for quantitative variables. In all reports, a p-value less than 0.05 is considered statistically significant.

Bioethical standards

This study was approved by the Ethics Committee of Mashhad University of Medical Sciences with the reference code of IR.MUMS.MEDICAL.REC.1397.759.

Results

Demographic characteristics

In this study, as can be seen in Table I, 60 patients with RA were examined. Most of the patients were female (54, 90%). The mean age of the patients was 55.2 ±11.8 years. The mean duration of taking MTX in all patients was 6.9 ±3.8 years. Based on the cumulative dose of MTX, the patients were divided into 2 groups of a higher cumulative dose (more than 2 g) and a lower cumulative dose (less than 2 g). A higher cumulative dose in a patient is attributable to the duration of MTX administration rather than the weekly dosing regimen. The results showed that the average age of patients in the higher cumulative dose group was higher than in the lower cumulative dose patients; however, the observed difference was not significant (56.6 ±11.1 years vs. 53.9 ±12.3 years with p = 0.308).

The 2 groups did not differ in terms of sex frequency distribution (the percentages of female patients in

[1] In this study, we defined cumulative dose as the amount of medication that the subject had taken from the beginning of the treatment until the day he participated in the study.

Table II. FibroScan fibrosis result

FibroScan	Number of patients (%)		
	Lower cumulative dose group (< 2 g)	Higher cumulative dose group (> 2 g)	Total
F0	22 (68.8)	19 (67.9)	41 (68.3)
F1	0 (0.0)	1 (3.6)	1 (1.7)
F2	9 (28.1)	7 (25.0)	16 (26.7)
F3	1 (3.1)	1 (3.6)	2 (3.3)
F4	0 (0.0)	0 (0.0)	0 (0.0)
Total	32 (100.0)	28 (100.0)	60 (100)

Table III. FibroScan steatosis result

FibroScan	Number of patients (%)		
	Lower cumulative dose group (< 2 g)	Higher cumulative dose group (> 2 g)	Total
S0	8 (25.0)	9 (32.1)	17 (28.3)
S1	10 (31.3)	6 (21.4)	16 (26.7)
S2	4 (12.5)	4 (14.3)	8 (13.3)
S3	10 (31.3)	9 (32.1)	19 (31.7)
S4	0 (0.0)	0 (0.0)	0 (0.0)
Total	32 (100.0)	28 (100.0)	60 (100.0)

Table IV. Frequency of patients according to the APRI and FIB-4 classification

Variable	Total (n = 60) n (%)	Lower cumulative dose group (n = 32) n (%)	Higher cumulative dose group (n = 28) n (%)	p
APRI				
Low risk	57 (95)	31 (96.9)	26 (92.9)	0.594*
High risk	3 (5)	1 (3.1)	2 (7.1)	
FIB-4				
Low risk	45 (75)	26 (81.3)	19 (67.9)	0.232**
High risk	15 (25)	6 (18.8)	9 (32.1)	

** Fisher's exact test was used to compare the 2 groups.*
*** χ^2 test was used to compare the 2 groups.*
APRI – aspartate aminotransferase to platelet ratio index, FIB-4 – Fibrosis Index Based on 4 Factors.

the higher cumulative and lower cumulative dose groups were 85.7% and 93.8%, respectively, with p = 0.404). The duration of MTX consumption was significantly higher in high-dose patients than in lower cumulative dose patients (8.9 ±3.7 years and 4.5 ±2.4 years, respectively, with p < 0.0001).

Liver fibrosis and steatosis

The overall prevalence of grade 3 fibrosis and steatosis based on the results of FibroScan in all patients was 3.33% and 31.7%, respectively. The prevalence of second- and third-degree liver fibrosis in lower cumulative dose patients was 9 (28.1%) and 1 (3.1%), respectively, and in patients receiving higher cumulative dose MTX 7 (25%) and 1 (3.6%), respectively. The difference was not statistically significant (p = 0.751). The results are also shown in Tables II and III.

Aspartate aminotransferase to platelet ratio index and Fibrosis Index Based on 4 Factors results

In this study, 2 low-risk and high-risk groups of patients are considered based on the APRI (the ratio of AST to PLTs), a touchstone to estimate the liver's cirrhosis. A comparison between the 2 groups demonstrated that among higher cumulative dose and lower cumulative dose patients, 3.1% and 7.1% respectively were high-risk regarding the APRI score. However,

the observed difference was not statistically significant (p = 0.594), as reported in Table IV.

The mean APRI score in patients taking lower cumulative dose MTX was 0.24 ±0.11 and in patients taking higher cumulative dose MTX was 0.28 ±0.22, with no significant difference (p = 0.481; Fig. 1).

After dividing the FIB-4, the results showed that, considering this index, 18.8% of lower cumulative dose patients and 32.1% of higher cumulative dose patients were at high risk of chronic liver diseases, although the observed difference was not statistically significant (p = 0.232).

The mean FIB-4 score in patients taking lower cumulative dose MTX was 1.05 ±0.59 and in patients taking higher cumulative dose MTX was 1.29 ±1.10, and the difference was not statistically significant (p = 0.295; Fig. 1).

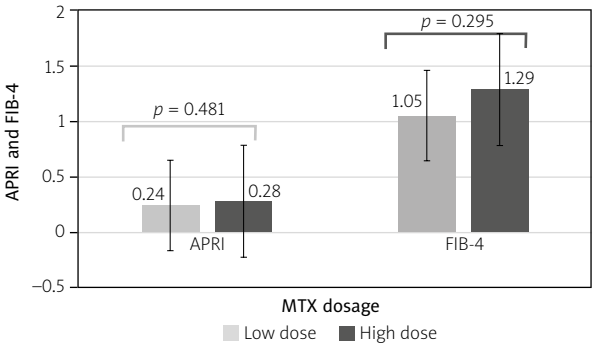

Fig. 1. Aspartate aminotransferase to platelet ratio index and FIB-4 score in 2 groups of methotrexate (MTX) at lower and higher cumulative doses.

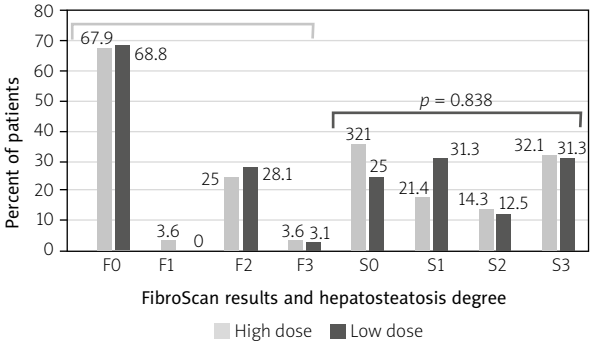

Fig. 2. Baseline characteristics of subjects in 2 groups of methotrexate at lower and higher cumulative doses based on FibroScan and hepatic steatosis degrees.

Discussion

The patients were mostly taking MTX as monotherapy. Patients were administered GCs as adjunctive therapy in case of flares or severe diseases; however, due to the absence of significant hepatotoxicity associated with these medications, this criterion was excluded from the inclusion criteria. As non-steroidal anti-inflammatory drugs could increase or prolong MTX levels [27], we tend to prescribe other analgesics such as low dose acetaminophen more, in order to avoid any drug interactions that may adversely affect our results.

The findings of the present study are similar to most studies on this subject, as the frequency of specific liver fibrosis according to FibroScan in patients treated with MTX has been reported to be about 5% (–0.33%), and the incidence of cirrhosis has been estimated to be 1–2% (–0.26%) [28, 29].

In their study, Barbeo-Villaris et al. [24] used FibroScan to detect liver stiffness in 46 patients with various diseases who were on long-term treatment with MTX (including 17 patients with RA). The cumulative dose of MTX used was 1,242 mg. Similar to ours, the results of the study by Barbeo-Villaris et al. [30] did not reveal a relationship between MTX dose and liver stiffness. Another comparable point in that study was the frequency of hepatic fibrosis. Considering the stiffness cut-off point of > 7 kPa, for the detection of second- and third-degree fibrosis, the frequency of stiffness diagnosis was 23.9%, which is relatively similar to the value observed in the present study.

In another study by Laharie et al. [31], using FibroScan, they examined liver stiffness in 518 patients treated with long-acting MTX at a cumulative dose of 1,950 mg (149 patients had RA). The results of their study were similar to ours; i.e., there was no relationship between MTX cumulative dose and liver stiffness and liver fibrosis. Severe fibrosis (grade 3) was reported in the study of Laharie et al. [31] in 8.5% of patients, which is higher than the results of our study.

Considering the findings of the present study and the results of the previous ones (based on different methods of liver damage assessment regarding MTX use), there seem to be no major concerns about the occurrence of severe hepatic fibrosis or liver cirrhosis in long-term use of MTX on a weekly basis with a cumulative dose of less or more than 2 g.

Regarding the duration of MTX use, the prevalence of second- and third-degree liver fibrosis in patients who used MTX for less than 5 years was 5 (15.6%) and 1 (3.1%), and in patients who had been taking MTX for more than 5 years it was 9 (36%) and 1 (4%), respectively. The observed difference was not statistically significant (p = 0.079).

Moreover, as illustrated in Figure 2, the prevalence of second- and third-degree hepatic steatosis in lower cumulative dose patients was 4 (12.5%) and 10 (31.3%), respectively, and in patients receiving higher cumulative dose MTX, 4 (14.3%) and 9 (32.1), respectively. The ob-

Table V. Comparison of laboratory tests for liver function according to methotrexate dose

Variable	Lower cumulative dose group (n = 32)	Higher cumulative dose group (n = 28)	$p^{\dagger}$
AST [IU/l] Mean ±SD	20.68 ±6.79	19.75 ±7.18	0.606
ALT [IU/l] Mean ±SD	17.96 ±10.61	16.42 ±7.61	0.526
ALP [IU/ml] Mean ±SD	207.96 ±78.30	173.89 ±41.71	0.044
α_2M [mg/dl] Mean ±SD	198.42 ±91.91	183.81 ±73.89	0.504
Haptoglobin [g/l] Mean ±SD	135.62 ±51.17	121.53 ±43.02	0.527
Apo-A1 [U/l] Mean ±SD	163.78 ±42.16	166.69 ±31.07	0.764
GGT [IU/l] Mean ±SD	21.19 ±7.72	21.19 ±9.62	0.912
Bilirubin total [U/l] Mean ±SD	0.57 ±0.21	0.66 ±0.39	0.256
Bilirubin direct [U/l] Mean ±SD	0.1 ±0.05	0.13 ±0.07	0.159
Albumin [g/dl] Mean ±SD	3.97 ±0.23	4.04 ±0.20	0.251
PLT [× 10^9/l] Mean ±SD	287.59 ±65	271.78 ±70.8	0.371
PT [min] Mean ±SD	12.53 ±0.12	12.73 ±0.51	0.037
PTT [s] Mean ±SD	34.09 ±6.01	34.25 ±5.28	0.916
INR Mean ±SD	1 ±0.01	1 ±0.07	0.043

† *Independent t-test was used to compare the two groups.*
α_2M – α_2-macroglobulin, ALP – alkaline phosphatase, ALT – alanine aminotransferase, Apo-A1 – apolipoprotein A, AST – aspartate aminotransferase, GGT – gamma-glutamyl transferase, INR – international normalized ratio, PLT – platelet count, PT – prothrombin time, PTT – partial thromboplastin time.

served difference was not statistically significant either (p = 0.838).

In the study of Miyata et al. [15], they examined 395 patients with RA treated with MTX, considering FIB-4 and its relationship with liver toxicity. The results of their study showed that the mean MTX cumulative dose in patients with an elevated FIB-4 was significantly higher than in patients with low FIB-4 levels. The present study and the study of Miyata et al. [15] are among the few studies that have used these indices in patients with RA; thus, further studies are required to investigate these indices.

In the study by Gian Luca et al. [32], the extent of hepatic stiffness and liver fibrosis in patients with RA treated with MTX was specifically discussed. In contrast to our study, where the mean age of patients in the higher cumulative dose group was higher than that of lower cumulative dose patients, they studied 2 groups with the same mean age. The results of that study similarly showed that the degree of liver stiffness was not related to the cumulative dose and duration of MTX use [30]. Similar results were obtained in the review study of Rohi et al. [33]. The role of MTX as a factor in hepatic fibrosis in patients with RA was investigated in 4 articles [31, 34–36], and MTX was not recognized as a risk factor for hepatic fibrosis. Moreover, in these studies, other factors such as alcohol consumption [31] and high BMI [31, 37] seemed to play a greater role in liver stiffness and fibrosis in RA patients.

The study of Khandpur et al. [38] was conducted on 54 patients with psoriasis and reactive arthritis with a mean age of 40.3 years and a male to female ratio of 5 : 1. Similar to the present study and based on the results of FibroScan, the APRI score, and the FIB-4, there was no relationship between the incidence of liver damage and the dose and duration of MTX use in these patients [38].

Table VI. Evaluation of the relationship between cumulative dose of methotrexate and other variables

Variable	Mean ±SD	*p*	Correlation *R*
MTX dose	2.5 ±1.7		
FIB-4	1.1 ±0.8	0.8	–0.03
APRI	0.2 ±0.1	0.09	+0.2
α_2M	191.6 ±83.6	0.2	–0.1
Haptoglobin	129.0 ±47.6	0.2	–0.1
Apo-A1	165.1 ±37.1	0.9	–0.01
GGT	21.0 ±8.5	0.6	+0.05
PT	12.6 ±0.37	0.01	+0.3
PTT	34.1 ±5.6	0.1	+0.1
Albumin	4.0 ±0.22	0.7	+0.03
AST	20.2 ±6.9	0.3	–0.1
ALT	17.2 ±9.2	0.06	+0.05
ALP	192.0 ±65.6	0.1	–0.1

** Pearson's correlation test was used to examine the relationship between the MTX dose and other variables.*
α_2M – α_2-macroglobulin, ALP – alkaline phosphatase, ALT – alanine aminotransferase, Apo-A1 – apolipoprotein A, AST – aspartate aminotransferase, GGT – gamma-glutamyl transferase, INR – international normalized ratio, PLT – platelet count, PT – prothrombin time, PTT – partial thromboplastin time.

According to Table V, in the comparison of aminotransferase levels, ALT, α_2-macroglobulin, haptoglobin, apolipoprotein A1, γ-glutamyltransferase, total bilirubin, albumin, PLT, and PTT, no significant difference was observed in terms of MTX consumption. Platelet and INR levels were significantly higher in patients taking higher cumulative dose MTX than in those taking lower cumulative dose MTX (p = 0.037 and 0.043, respectively). The mean serum level of ALP in patients taking lower cumulative dose MTX was 207.96 ±78.30 mg/ml and in patients taking higher cumulative dose MTX was 173.89 ±41.81 mg/ml, and the difference was significant.

In Table VI, Pearson's correlation test was used to evaluate the relationship between the cumulative doses of MTX with other variables. The results showed that there is only a significant positive relationship between the cumulative dose of MTX and PT.

A liver biopsy represents the established standard for evaluating liver histology, particularly in the assessment of portal fibrosis. While the test is highly effective, it is not without limitations; a needle biopsy captures only 1/50,000 of the liver, resulting in a potential sampling error of 20–30% [39]. Several studies have utilized non-invasive methods for the evaluation of liver fibrosis, such as FibroScan [40–44]. The use of non-invasive methods such as FibroScan could be advantageous compared to invasive methods such as liver biopsy, to assess the extent of liver fibrosis. Nevertheless, they are expensive, and the report depends on the patient. The implementation of FibroScan is often associated with dermatology cases treated with MTX; however, the aforementioned indices can serve to evaluate the patient, particularly in situations where FibroScan is either unaffordable or unavailable. Additionally, a prospective evaluation would be preferable, such as monitoring the progression of fibrosis over a 2-year period. This would facilitate the identification of patients who discontinued the medication, for instance, due to elevated liver enzymes, and determining whether this was associated with the changes observed during the study.

Finally, considering that the other factors involved in the development of liver fibrosis such as metabolic syndrome, NASH, and NAFLD were not investigated in this study, these cofounders may have impacted the findings and observations. It is recommended to consider these factors in future studies.

Conclusions

Based on the results of FibroScan, APRI, and the FIB-4, no significant relationship was found between the incidence of hepatic impairment and the duration of MTX usage in RA patients. Overall, the results of this study showed that patients with RA who take MTX long term with a cumulative dose of more than 2 g are not subject to a higher risk of liver complications when compared with the group who take lower cumulative doses. Since FibroScan and FibroTest Panel methods are uncomplicated and easily renewable, they are recommended to be used for monitoring patients treated with MTX, as a follow-up plan, to detect any possible liver complications.

Disclosure

Mina AkbariRad, Zahra Rezaieyazdi and Ali Tajik participated equally in preparing this study.

Conflicts of interest: The authors declare no conflicts of interest.

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Ethics: This study was approved by the Ethics Committee of Mashhad University of Medical Sciences with the reference code IR.MUMS.MEDICAL.REC.1397.759.

Data availability: The data that support the findings of this study are available on request from the corresponding author (A.F.).

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