ORIGINAL ARTICLE

Monitoring Methotrexate-induced Increased Liver Stiffness and Significant Liver Fibrosis in Rheumatoid Arthritis Patients: A Cross-sectional Controlled Study with Real-time Two-dimensional Shear Wave Elastography

Debraj Chattopadhyay[1], Surajit Das[2], Kripasindhu Gantait[3]

Received on: 25 June 2023; *Accepted on:* 25 July 2023; *Published on:* 04 August 2023

Abstract

Objective: To explore the significance of the association between treatment with methotrexate (MTX) and liver stiffness in rheumatoid arthritis (RA) patients by transient elastography (TM).

Methodology: In this cross-sectional study, a total of 100 adult patients of RA were selected randomly as the study population, and 50 were the control population. Out of the total study population, half of them were taking MTX for >2 years to 5 years, and the rest for >5 years. Hepatic fibrosis was determined by measuring the hepatic stiffness by TE method (by FibroScan) in kilopascal unit (kPa), where >9 kPa value was considered to be significant for developing hepatic fibrosis. The hepatic stiffness of the patient group was compared with that of healthy controls.

Result: The mean BMI value between the two groups taking methotrexate therapy for < 5 years and >5 years was 22.37 ± 2.67 kg/m^2 and 25.13 ± 3.09 kg/m^2, and the control population was 20.71 ± 2.06 kg/m^2. *P*-value came to be < 0.0001, which was statistically significant, and the effect of mean BMI on liver stiffness was also found significant ($p = 0.04$). The mean (mean ± SD) kPa value among the study population and control group is 6.04 ± 0.95, 6.67 ± 1.68, and 3.83 ± 0.52. Having compared among three groups, *p*-value was < 0.0001. A significant association was also found regarding the duration of MTX therapy with increased liver stiffness ($p = 0.018$). SDAI has been found to be positively correlated with increased hepatic stiffness ($r = 0.077$).

Conclusion: The long-term use of methotrexate therapy in RA patients has been found to be significantly associated with progressive liver fibrosis and increased hepatic stiffness.

Keywords: Elastography, Hepatic fibrosis, Methotrexate, Rheumatoid arthritis.

Bengal Physician Journal (2023): 10.5005/jp-journals-10070-8017

Introduction

Rheumatoid arthritis is the most common form of chronic inflammatory disorder that typically affects small- and medium-sized joints symmetrically, the primary lesion being synovitis. Methotrexate is the anchor drug in the treatment of rheumatoid arthritis (RA).[1] Because of low expenses, less toxicity, and easy availability, methotrexate (MTX) remains the first-line therapy of RA, inspite of several studies and advancements being conducted since the last two decades.[2] Immune modulation, regulation of inflammatory response, and anti-atherosclerotic effect are the principal beneficial actions of MTX.[3] However, MTX-induced liver toxicity includes elevation of liver enzymes, liver fibrosis, and even cirrhosis.[4]

Since associated risk factors like obesity, alcohol consumption, and diabetes govern the chances of liver toxicity in RA patients under MTX, so MTX as an independent risk factor for liver fibrosis is still arguable.[5]

Methotrexate might have some hidden side effects that need to be evaluated with new techniques like ultrasonic elastography. Recent European guidelines now advocate the use of ultrasonic elastography[6] as the first-line test for the assessment of fibrosis in alcohol- or hepatitis-related liver disease, including nonalcoholic fatty liver disease. Ultrasonic elastography stands out nowadays as a useful noninvasive significant tool to assess and quantify hepatic fibrosis.[7]

[1,2]Midnapore Medical College, West Bengal, India

[3]Jhargram Government Medical College, Jhargram, West Bengal, India

Corresponding Author: Kripasindhu Gantait, Jhargram Government Medical College, Jhargram, West Bengal, India, Phone: +91 94342243054, e-mail: drkripa2000@gmail.com

How to cite this article: Chattopadhyay D, Das S, Gantait K. Monitoring Methotrexate Induced Increased Liver Stiffness and Significant Liver Fibrosis in Rheumatoid Arthritis Patients: A Cross-sectional Controlled Study with Real-time Two-dimensional Shear Wave Elastography. Bengal Physician Journal 2023;10(2):43–46.

Source of support: Nil

Conflict of interest: None

Aim

To investigate the association between treatment with methotrexate and liver stiffness in rheumatoid arthritis patients by transient elastography.

Objectives

General

- To assess the hepatic fibrosis in rheumatoid arthritis patients who have been on methotrexate therapy.

- To study the correlation, if any, between significant hepatic fibrosis and disease activity and duration of rheumatoid arthritis who have been receiving methotrexate therapy for a long time.

Specific

- To compare hepatic fibrosis in case of patient with rheumatoid arthritis taking methotrexate therapy as compared with healthy controls.
- To find out the correlation between hepatic fibrosis and CDAI score in RA patients having methotrexate therapy.
- To find out the correlation between hepatic fibrosis and SDAI score in RA patients having methotrexate therapy.
- To find out the correlation between hepatic fibrosis and DAS28ESR score in RA patients having methotrexate therapy.
- To find out the correlation between hepatic fibrosis and DAS28CRP score in RA patients having methotrexate therapy.

Materials and Methods

Study Type

A hospital-based cross-sectional observational study.

Study Site

Patients attending the Rheumatology Clinic of Midnapore Medical College, Paschim Medinipur, West Bengal.

Study Duration

From January 2021 to December 2021.

Study Participants

A total of 150 in number and comprises of three groups:

Group A : Methotrexate-treated RA (for > 2 years but <5 years) = 50

Group B : Methotrexate-treated RA (for > 5 years) = 50

Group C : Control = 50

After the approval of the Institutional Ethics Committee, this study was conducted.

Inclusion Criteria

Patients diagnosed with RA according to ACR-EULAR revised criteria 2010.

Exclusion Criteria

- Patients who are unwilling to take part in the study.
- Patients with RA taking methotrexate for less than 2 years.
- History of chronic liver infection.
- Diabetes mellitus.
- Pregnancy.
- Treatment with hepatotoxic drugs other than RA-specific drugs.
- Dyslipidemia.
- Known alcoholic patients.
- Patients with nonalcoholic fatty liver disease (NAFLD).
- Cancer.
- Wilson's disease.
- Autoimmune liver disease.

Statistical Analysis

Data were collected and recorded with a predesigned proforma that was then tabulated to prepare a master chart. Test of proportion was used to find the standard normal deviate (Z) to compare the difference in proportions, and Chi-square (χ^2) test was performed to find the associations. The statistical analysis of data was performed using Epi Info (TM) 7.2.2.2. The results on continuous measurements were presented as mean ± SD. *t*-test was used to compare the means of the two groups. $p < 0.05$ was taken to be statistically significant.

Table 1: Distribution of the patients according to duration of methotrexate (MTX) treated for rheumatoid arthritis

Group	*Number*	*%*
2 years <MTX<5 years	50	33.3
MTX ≥ 5 years	50	33.3
Control	50	33.4
Total	150	100.0

Table 2: Comparison of the association between duration and EMedian of the patients

Duration	*<5*	*5–9*	*9–13*	*>13*	*Total*
>2 to <5 years	2	48	0	0	50
ROW%	4.0	96.0	0.0	0.0	100.0
COL%	40.0	54.5	0.0	0.0	50.0
>5 years	3	40	7	0	50
ROW%	6.0	80.0	14.0	0.0	100.0
COL%	60.0	45.5	100.0	0.0	50.0
Total	5	88	7	0	100
ROW%	5.0	88.0	7.0	0.0	100.0
COL%	100.0	100.0	100.0	0.0	100.0

$\chi^2 = 7.92$; $p = 0.018$; *S*, significant. Chi-square (χ^2) test showed that there was significant association between duration with EMedian ($p = 0.018$). 5 = normal, 5–9 = cACLD to be ruled out, 9–13 = suggestive of cACLD, >13 = significant fibrosis

Results

In this study, 150 subjects were included randomly, out of which 100 patients were under treatments for RA and 50 subjects were control. Out of 100 patients of RA, 50 patients were treated with MTX for a duration of more than 2 years but less than 5 years (2 years <MTX<5 years), and the rest of 50 patients were treated with MTX for a duration of more than 5 years. Thus, the patients in the three groups were in the ratio 1:1:1 (Table 1).

The duration of methotrexate therapy has been found to be significantly associated with the impact on liver stiffness measured by ultrasound elastography. The mean (mean ± SD) kPa values among the study population and control population were found to be 6.04 ± 0.95, 6.67 ± 1.68, and 3.83 ± 0.52.

Therefore, having compared between these three groups, *p*-value came to be statistically significant (p=0.018) (Table 2).

The effect of the total dose of methotrexate therapy between the two groups has not been significantly associated with the liver stiffness, as evidenced by elastography. The kPa value of mean dose 13.50 ± 4.87 consumed by 5% population was 9–13. As the *p* value came to be 0.379, therefore, no statistical significance could be established (Table 3).

It has been also found that neither the disease activity index of rheumatoid arthritis, like CDAI, nor the disease activity score, like DAS28 ESR, DAS28 CRP has got nothing to do with the effect on liver stiffness between the two groups of the study population

Table 3: Association of EMedian with dose of MTX

EMedian	*N*	*Mean*	*SD*	*F value*	*p-value*
<5	5	13.50	4.87	0.979	0.379 NS
5–9	88	12.59	4.56		
9–13	7	15.00	4.08		

Table 4: Correlation with EMedian between CDAI and SDAI

Correlation with EMedian	*Pearson's correlation coefficient (r)*	*Inference*
CDAI	0.111	Negatively correlated
SDAI	0.077	Positively correlated

Table 5: Comparison of parameters of the patients of the three groups

Parameters	*Group*	*Mean*	*SD*	*F2, 147 value*	*p-value*
Age (years)	2<MTX<5	42.50	10.80	0.86	0.43 NS
	MTX≥5	45.14	10.32		
	Control	44.08	9.21		
BMI (kg/m^2)	2<MTX<5	22.37	2.67	35.85	<0.0001 S
	MTX≥5	25.13	3.09		
	Control	20.71	2.06		
LDL (mg/dL)	2<MTX<5	62.40	12.42	16.58	<0.0001 S
	MTX≥5	69.98	14.45		
	Control	77.02	10.99		
HDL (mg/dL)	2<MTX<5	54.06	10.98	0.01	0.99 NS
	MTX≥5	53.98	10.18		
	Control	53.90	8.64		
TSH (IU/L)	2<MTX<5	2.98	0.98	0.24	0.79 NS
	MTX≥5	2.86	0.90		
	Control	2.96	0.80		
Creatinine (mg/dL)	2<MTX<5	0.66	0.22	1.12	0.33 NS
	MTX≥5	0.68	0.22		
	Control	0.62	0.20		

Table 6: Comparison of erosion of X-ray of the patients of the two groups

Erosion of X-ray	*2<MTX<5*	*MTX≥5*	*Total*
Yes	23	15	38
Row %	60.5	39.5	100.0
Col %	46.0	30.0	38.0
No	27	35	62
Row %	43.5	56.5	100.0
Col %	54.0	70.0	62.0
Total	50	50	100
Row %	50.0	50.0	100.0
Col %	100.0	100.0	100.0

$\chi^2 = 5.51$; $p = 0.018$; S, significant. Chi-square (χ^2) test showed that there was significant association between erosion of X-ray and the patients of the three groups (p=0.018). Erosion of X-ray (46.0%) was among 2<MTX<5 groups (46.0%) as compared with MTX≥5 (30.0%) ($Z = 2.33$; $p = 0.019$).

who had been on methotrexate therapy for RA. But SDAI value has been found to be positively correlated with increased hepatic stiffness (Tables 4 to 6).

Discussion

With long-term low-dose MTX therapy in RA, liver fibrosis development is quite significant; while earlier studies showed the prevalence of lung fibrosis and cirrhosis up to 30%,[8] more recent studies showed it between 0 and 1.3%.[9,10] In this study, the duration of methotrexate therapy has been found to be significantly associated with the impact on liver stiffness measured by ultrasound elastography. The mean (mean ± SD) kPa value among the study population who were taking methotrexate therapy for RA for more than 2 years but less than 5 years was 6.04 ± 0.95, while the mean (mean ± SD) kPa value of the other group taking methotrexate therapy for more than 5 years was 6.67 ± 1.68. The mean kPa value of the control population was 3.83 ± 0.52. Therefore, comparison among these three groups was found to be statistically significant as p-value is < 0.0001. There has been also a significant association found between duration of MTX therapy with increased liver stiffness ($p = 0.018$).

This study comprised 20% study population in the age group of 21–35 years, 70% of 36–55 years, 10% within 56–65 years, and mean (mean ± SD) age was 42.50 ± 10.80 years among the patients taking methotrexate of both groups, which was lower than the study conducted by Kumar A et al.,[11] where it was 51 ± 10.9 years. In this study, 22% study population was male and 78% was female among the patients taking methotrexate for more than 2 years but less than 5 years and this is similar for those taking methotrexate >5 years.

Body mass index (BMI) was significantly associated with the effect on increasing liver stiffness. The mean BMI value between the two groups taking methotrexate therapy for less than 5 years and more than five years was 22.37 ± 2.67 kg/m^2 and 25.13 ± 3.09 kg/m^2. The mean BMI of control population was 20.71 ± 2.06 kg/m^2. *P*-value came to be <0.0001, which was statistically found to be significant and the effect of mean BMI on liver stiffness has been also found to be significant ($p = 0.04$).

In this study, mean LDL value has not been positively correlated with the effect on hepatic stiffness between the two groups. The mean LDL value between the two groups was 62.40 ± 12.42 and 69.98 ± 14.45. The control group had mean LDL 77.02 ± 10.99. Comparing the mean LDL with the EMEDIAN, p-value came to be 0.327, so it is statistically not significant. No significant correlation has been found on the effect of hepatic stiffness between the two groups of the study population regarding their age, sex, liver enzymes, fasting blood sugar, as well as serum TSH level and creatinine level. It has been also found that neither the disease activity index of rheumatoid arthritis like CDAI, nor the disease activity score like DAS28 ESR, DAS28CRP has got nothing to do with the effect on liver stiffness between the two groups of the study population who had been on methotrexate therapy for RA but SDAI value has been found to be positively correlated with increased hepatic stiffness.

The main limitation of our study is lack of histological confirmation of hepatic fibrosis.

Conclusion

The long-term use of methotrexate therapy in RA patients has been found to be significantly associated with progressive liver injury and increased hepatic stiffness, but the total dose of methotrexate therapy has been observed to be insignificant in relation to liver fibrosis as assessed by elastography among the patients of rheumatoid arthritis group. Concurrent metabolic syndrome (like

increased BMI) among the RA patients on MTX can be considered to be a secondary risk factor for increased liver stiffness/fibrosis. Although liver biopsy remains the "gold standard" technique for the detection of hepatic fibrosis, but because of its potential adverse procedure-related complications, off late, transient elastography (TE) is being preferred over any invasive procedures. Transient elastography (FibroScan) is a new, noninvasive, cost-effective, accurate, rapid, and reproducible method and can be used as a valuable tool for assessment of hepatic fibrosis in RA patients on long-term MTX therapy.

References

1. Smolen JS, Landewe R, Bijlsma J, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. Ann Rheum Dis 2017;76(6):960–977. DOI: 10.1136/annrheumdis-2016-210715.
2. Lertnawapan R, Chonprasertsuk S, Siramolpiwat S. Association between cumulative methotrexate dose, noninvasive scoring system and hepatic fibrosis detected by Fibroscan in rheumatoid arthritis patients receiving methotrexate. Int J Rheum Dis 2019;22(2):214–221. DOI: 10.1111/1756-185X.13442.
3. Mangoni AA, Zinellu A, Sotgia S, et al. Protective effects of methotrexate against proatherosclerotic cytokines: A review of the evidence. Mediators Inflamm 2017;2017:9632846. DOI: 10.1155/2017/9632846.
4. Kremer JM, Alarcòn GS, Lightfoot RW, et al. Methotrexate for rheumatoid arthritis. Suggested guidelines for monitoring liver toxicity. American College of Rheumatology. Arthritis Rheum 1994;37(3):316–328. DOI: 10.1002/art.1780370304.
5. Whiting-O'Keefe QE, Fye KH, Sack KD, et al. Methotrexate and histologic hepatic abnormalities: A meta-analysis. Am J Med 1991;90(6):711–716. PMID: 1828327.
6. Herrmann E, de Lédinghen V, Cassinotto C, et al. Assessment of biopsy proven liver fibrosis by two-dimensional shear wave elastography: An individual patient data based metaanalysis. Hepatology 2018;67(1):260–272. DOI: 10.1002/hep.29179.
7. Kim TY, Kim JY, Sohn JH, et al. Assessment of substantial liver fibrosis by real time shear wave elastography in methotrexate treated patients with rheumatoid arthritis. J Ultrasound Med 2015;34(9): 1621–1630. DOI: 10.7863/ultra.15.14.10035.
8. Kremer JM, Kaye GI, Kaye NW, et al. MTX for RA. Light and electron microscopic analysis of sequential liver biopsy samples from RA patients receiving long-term MTX therapy. FU over long-term interval and correlation of clinical and laboratory variables. Arthritis Rheum 1995;38(9):1194–1203. DOI: 10.1002/art.1780380904.
9. Conway R, Low C, Coughlan RJ, et al. Risk of liver injury among MTX users: A meta-analysis of RCT. Semin Arthritis Rheum 2015;45(2): 156–162. DOI: 10.1016/j.semarthrit.2015.05.003.
10. Visser K. Risk and management of liver toxicity in Ra & PsA : Systemic review of the literature. Clin Exp Rheumatol 2009;27(6):1017–1025. PMID: 20149325.
11. Kumar A, Vasdev V, Manrai M, et al. Assessment of hepatic fibrosis in patients with rheumatoid arthritis on long-term methotrexate therapy using transient elastography. J Indian J Rheumatol Assoc 2018;13(4):246–251. DOI: 10.4103/injr.injr_92_18.