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STUDY ON THE PREVALANCE OF HEPATIC FIBROSIS IN PATIENTS ON METHOTREXATE THERAPY IN A TERTIARY CARE CENTER

Gastroenterology

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ABSTRACT

INTRODUCTION: Methotrexate(MTX) as a DMARD, is mainstay in the treatment of variety of autoimmune diseases including psoriasis and rheumatoid arthritis (RA). Although MTX has good efficacy and safety profile, hepatotoxicity has been well described. Fibroscan has found to be reliable, noninvasive method for the detection of hepatic fibrosis without any side effects. This study was conducted to assess the degree and prevalence of hepatic fibrosis in patients on MTX therapy by Fibroscan. **MATERIALS AND METHODS:** A observational study was carried out in Department of medical gastroenterology for a period of 6 months from April 2021. This study included patients aged ≥ 18 years, who had been on MTX. Patients with cumulative dose > 1.5g were subjected to Fibroscan to assess the degree of hepatic fibrosis and the cut off value of 7.1 kPa (kilopascal) was considered abnormal (liver fibrosis) . Statistical methods: Data was analysed using SPSS version 21. Pearson Correlation test was used to assess the correlation between the cumulative dose of MTX and Fibroscan score and independent 't' test was used for continuous variables. **RESULTS:** Total of 64 patients on methotrexate were included in the study, out of which 29 were males, 35 were females. Mean age of patients was 40.9 ± 10.3yrs. Mean BMI was 21.8 ± 1.8kg/m2 The mean CD- 24.2 ± 5.1g. The mean duration was 246 weeks. mean fibroscan value of 5.7 ± 1.1kpa. mean dose 9.5mg/week. Taking 7.1kpa as the upper limit of normal, we found that 6 patients had hepatic fibrosis, 6 of them had F-1 stage fibrosis. Fibroscan scores were significantly correlated with cumulative dose of MTX (r= 0.41, p = 0.01) We found prevalence of hepatic fibrosis in 9.5% of patients on methotrexate therapy. **CONCLUSION:** The study revealed that Long-term MTX therapy is associated with increased risk of liver fibrosis. Fibroscan is a useful non invasive tool for monitoring MTX-induced liver fibrosis.

KEYWORDS

Hepatic fibrosis, Methotrexate, Fibroscan

INTRODUCTION:

- Methotrexate(MTX) was initially developed as a chemotherapeutic agent in the 1950s, but low-dose weekly MTX, given either orally or subcutaneously, as a DMARD, has become a mainstay in the treatment of a variety of autoimmune diseases including psoriasis (PsO),psoriatic arthritis (PsA), and rheumatoid arthritis (RA). Although MTX overall has good efficacy and safety profile, hepatotoxicity has been well described.

- The precise mechanisms of MTX-induced hepatotoxicity are unknown, a variety of both folate-dependent and -independent pathways have been postulated1.

- Patients at high risk for MTX hepatotoxicity are2-

1. History of moderate-to-severe alcohol consumption
2. Personal and family history of liver disease (including hepatitis)
3. Diabetes
4. Obesity
5. NAFLD
6. Hepatotoxic drugs (other than MTX)
7. Hyperlipidemia
8. Absence of folate supplementation during MTX administration

- Recent recommendations3,4 suggest regular monitoring (every 1-3 months) of serum aminotransferases (AST and ALT), while drug discontinuation is recommended in the presence of an increase in transaminases greater than 3 times the upper limit of normal (ULN) values, and liver biopsy is suggested in the case of persistently elevated aminotransferases after drug discontinuation.

- Liver biopsy is the gold standard method for assessing the stage of the liver diseases. It is an invasive procedure and is complicated by both sampling error and procedural risk. the procedure is poorly accepted and difficult to repeat in asymptomatic subjects.

- Fibrosis index (FIB-4)5 is based on the four factors: evaluation of age, AST, platelets and ALT. The FIB-4 index helps to evaluate significant fibrosis of liver. A FIB-4 >3.25 would have a 97% specificity and a positive predictive value of 65% for advanced fibrosis.

- Aspartate transaminase-to-platelet ratio index (APRI)6, it was first developed in the study of patients with chronic HCV infection , but it has been concluded that has moderate sensitivity and accuracy when it comes to detect hepatic fibrosis.

- Off late, transient elastography (TE)7 has been found to be a reliable, noninvasive method for the detection of hepatic fibrosis without any side effects and has been used to assess hepatic fibrosis in many conditions like chronic hepatitis B and C, non-alcoholic fatty liver disease (NAFLD) and alcoholic liver disease.

- TE measures the liver stiffness (LS) which by itself is associated with the degree of fibrosis. Over a period of time, it has now become a validated method for the assessment of liver fibrosis. This study was conducted to assess the degree and prevalence of hepatic fibrosis in patients on MTX therapy by Fibroscan.

AIM OF THE STUDY

- To study the prevalence of hepatic fibrosis in patients on Methotrexate therapy in a tertiary care center

MATERIALS AND METHODS

Study place: Department of Medical gastroenterology, Govt. Stanley Medical College

Study design: A observational study
Sample size: 64 patients
Study duration: From April 2021 to September2021(6 months)

Study population: All patients with more than 18 years of age, attending the Medical Gastroenterology OPD or hospitalized in ward, and receiving weekly oral or injectable MTX are included in this study

Exclusion criteria:
All patients with history of Alcohol intake, Hepatitis B, Hepatitis C, HIV, Autoimmune hepatitis, Diabetes, Wilsons disease, HCC and any other etiology of Chronic liver disease are excluded

METHODS:
- Written consent of all the patients participating in the study was taken.
- All patients with >18 years of age, attending Medical Gastroenterology OPD , and receiving MTX were included in this study
- Each patient was enquired with detailed history and subjected to thorough clinical examination, and cumulative dose of methotrexate was calculated.
- Each patient was subjected to investigations including LFT, CBC, RFT, PT/INR, RBS, Lipid profile, USG abdomen
- Patients with cumulative dose of methotrexate more than 1.5g was subjected to Fibroscan
- Fibroscan, was used to asses the degree and prevalence of methotrexate induced liver fibrosis.

STASTICALANALYSIS:
Numerical data were expressed as mean and standard deviation whereas categorical data as frequency and percentage. The difference between the groups was tested by unpaired ttest. Pearson Correlations test was used to assess the correlation between the cumulative dose of MTX and Fibroscan score and independent 't' test was used for continuous variables. A p-value < 0.05 was considered significant.
All relevant data was analyzed using SPSS software 20.0

RESULTS
The study included 35 females and 29 males with a mean age of 40.9 ± 10.3yrs. The majority of patients had a disease duration of 3-4 years, with a duration of exposure to MTX (median, 246 weeks). All patients were on at least 10 mg per week . The baseline characteristics of the study participants are shown in Table 1

Table: 1 Baseline characters of patients

Parameters (mean ± SD)	Value
Age	40.9 ± 10.3yrs
Sex(female)	35(54%)
BMI	21.8 ± 1.8kg/m^2
Duration of MTX use	245(150-355)
Cumulative dose	2406(1500-3600)
Platelet count	2.01 ± 0.59
SGOT	28.13 ± 13.9
SGPT	30.67 ± 16.6
ALP	165.4 ± 49.
Albumin	3.7 ± 0.3

We found prevalence of hepatic fibrosis in 9.5% of patients on methotrexate therapy. The mean liver stiffness was 5.7 ± 1.1 kPa. All the 6 patients (9.5%) had mild fibrosis (7.1–9.5 kPa). The study included patients who are on methotrexate without risk factors for hepatic fibrosis. The clinical characteristics of patients with (≥ 7.1 kPa) and without (< 7.1 kPa) fibrosis are compared in Table 2. Patients with fibrosis on Fibroscan had significantly higher cumulative dose of MTX. Serum albumin was significantly lower in patients with fibrosis (p = 0.04).

Table:2 The clinical characteristics of patients with (≥ 7.1 kPa) and without (< 7.1 kPa) fibrosis

Values (mean±SD	Fibrosis >7.1	Fibrosis<7.1	P value
BMI kg/m^2	22.2	21.1	0.21
Cumulative MTX dose, mg	3265	2350	0.03
Duration of MTX use, wks	324	238	0.04
SGOT(5-40IU/L)	24.2	28.4	0.43
SGPT(5-40IU/L)	33.2	30.2	0.58
S. Albumin(3.4-5.4g/dl)	3.4	3.7	0.04

The majority of patients (59%) received a cumulative MTX dose between 1.5 and 3.6 g. The cumulative dose of methotrexate showed a significant positive correlation with Fibroscan score(r= 0.41, p = 0.01). On multivariate analysis using a linear model, there was positive correlation between Fibroscan scores and duration, and cumulative dose of MTX and serum albumin (p < 0.05). No correlation was found between Fibroscan scores and age, gender, BMI, SGOT, SGPT.

Correlations			
		CD	FIBROSCAN
CD	Pearson Correlation	1	.415**
	Sig. (2-tailed)		.001
	N	64	64
FIBROSCAN	Pearson Correlation	.415**	1
	Sig. (2-tailed)	.001	
	N	64	64
**. Correlation is significant at the 0.01 level (2-tailed).			

Discussion
This study found an increased prevalence of liver fibrosis by transient elastography in patients of psoriasis on long-term MTX and a significant correlation with cumulative dose of MTX. The proposed mechanisms of MTX-induced hepatotoxicity are oxidative stress or excessive activation of hepatic "Ito" cells leading to collagen deposition in perisinusoidal extracellular matrix, particularly at higher cumulative MTX doses[8].

The prevalence of liver fibrosis and cirrhosis in psoriasis/psoriatic arthritis patients taking MTX treatment ranges from 2–23% and 0–4%, respectively[9]. The retrospective studies by Arena et al. and Lertnawapan et al, included 100 and 108 RA patients, respectively, and they reported significant correlation between the cumulative dose of MTX and liver fibrosis by Fibroscan; In contrast, Kumar et al. found no such correlation[10-12]

The mean Fibroscan score was 5.7 ± 1.1 kPa and it was similarly reported in previous studies[10]. The prevalence of liver fibrosis (Fibroscan score ≥ 7.1 kPa) was 9.5%, compared to the studies by Kumar et al. reported 7.5% and Arena et al. reported 11%, in their cohort. The median duration of MTX use and median cumulative dose was lesser in our study population compared to the studies by Kumar et al. and Arena et al.

Patients having liver fibrosis (≥ 7.1 kPa) had longer duration of disease and high cumulative dose of MTX, which was similarly reported by Lertnawapan et al. Similarly, in our study, liver fibrosis was more common in patients with MTX use for 6 years. The mean hemoglobin, platelet count, SGOT, SGPT, and FBS were comparable between patients with and without fibrosis; Lertnawapan et al. had reported higher SGPT in patients with fibrosis (37.6 ± 26.5; p = 0.003) in their study but was not clinically significant. This shows that patients with liver fibrosis may have normal liver enzymes.

There was no difference in ultra-sonographic abnormalities in patients with or without liver fibrosis . Ultrasonography revealed fatty liver in 10 out of 64 patients (15%). The patients having fibrosis as evidenced by TE did not have altered liver parenchymal echotexture on ultrasonography, indicating it is a less sensitive test to detect early liver fibrosis and has also been found in previous studies[13,14]

Traditionally a Fibroscan score cutoff of >7.1kPa is considered mild liver fibrosis, cutoff of > 9.5 kPa is considered as severe liver fibrosis, and a cutoff of > 12.5 kPa is considered as cirrhosis. However in our study all 6 patients with significant fibrosis had mild fibrosis (7.1 to 9.5kPa). Maybe because in our study participants were included after excluding risk factors for fibrosis and lower duration of Methotrexate therapy compared to other studies.

The limitations of current study were: (i) it was an observational, cross-sectional study. A prospective study to follow up these patients and to asses the reversibility of MTX-induced liver fibrosis would be ideal (ii) Patients diagnosed with liver fibrosis by transient elastography were not confirmed by liver biopsy.

Conclusion
Long-term use of MTX in patients was associated with increased liver

stiffness on Fibroscan.. There was a significant correlation between higher cumulative MTX dose and Fibroscan scores. Fibroscan is a useful non tool for monitoring MTX-induced liver fibrosis.

A larger, longer study is warranted with follow-up Fibroscan, to better identify the values defining irreversibility in rheumatological disorders which would possibly better correlate with histopathology.

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