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Original Research Paper

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TRANSIENT ELASTOGRAPHY AS A SCREENING TOOL FOR LIVER FIBROSIS FOR RHEUMATOID ARTHRITIS PATIENT ON LONG TERM METHOTREXATE.

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ABSTRACT

Background: Methotrexate is used as a first line disease modifying antirheumatic drug (DMARD) in Rheumatoid Arthritis patients. There has been a concern of liver fibrosis with long term use of Methotrexate. There are different ways to screen for liver fibrosis, liver biopsy being the gold-standard, but its invasive nature and associated adverse effects limits its use as a screening tool. Transient elastography (Fibroscan) is an established method for assessing liver fibrosis by calculating liver stiffness. **Methods:** This cross-sectional observational study was conducted in patients on long term methotrexate to study the incidence of liver fibrosis using transient elastography (Fibroscan) **Results:** There is a correlation between the cumulative dose of methotrexate and Fibroscan score which was statistically significant in patients with cumulative dose of more than 1000 mg, but none of the study participants developed significant fibrosis suggesting that if monitored periodically Methotrexate is a safe drug for long term use in patients with Rheumatoid Arthritis. **Conclusion:** Fibroscan can be used as a non-invasive tool to monitor patients on long term Methotrexate for risk of liver fibrosis.

KEYWORDS :

INTRODUCTION

Methotrexate, an antifolate agent has been used as the cornerstone drug in management of Rheumatoid Arthritis since the 1980s. While Methotrexate is a well-tolerated drug it has potential safety concerns like Liver fibrosis.

Various mechanisms by which Methotrexate can cause liver fibrosis are Methotrexate induced hepatotoxicity is due to oxidative stress mediated abnormal activation of hepatic "Ito" cells, which leads to collagen deposition in the perisinusoidal extracellular matrix. Another mechanism is inhibiting purine and pyrimidine synthesis by blocking assorted enzymes, and responses from this blockage are accountable for many toxicities such as bone marrow suppression, stomatitis, and hepatotoxicity(Kim et al., 2015). While liver biopsy remains the gold standard for detection of fibrosis due to its invasive nature it limits its use as screening tool.

Transient elastography is an established method to detect liver fibrosis. (Bafna et al., 2021). With this background we aim to study the relation between cumulative dose of methotrexate and liver fibrosis with the help of Fibroscan.

METHODS

This cross-sectional observational study was carried out in a tertiary care centre hospital in Pune, Maharashtra over a period of 1 month. Data of Rheumatoid Arthritis patients visiting OPD meeting the inclusion and exclusion criteria who underwent Fibroscan was taken. Demographic parameter, BMI, history of alcohol use and liver function test was collected.

Sample size- 19 patients

Inclusion criteria-1. Duration of methotrexate use more than 1 year.

Exclusion criteria-

1. Alcohol use.
2. Known case of Liver disease.
3. Pregnant female.
4. Concurrent use of other hepatotoxic drugs such as Leflunomide, Sulphasalazine, Azathioprine.

Liver stiffness scores were reported in kilopascal (kPa). Liver stiffness outcome was represented both as a continuous variable, and as an ordinal classification from F0 to F4, as the following:

- F0 = No fibrosis
- F1 (0.0 kPa ≤ FibroScan score < 7.1 kPa) = Portal fibrosis without septa
- F2 (7.1 kPa ≤ FibroScan score < 8.7 kPa) = Portal fibrosis with few septa
- F3 (8.7 kPa ≤ FibroScan score < 10.4 kPa) = Numerous septa without cirrhosis
- F4 (FibroScan score ≥ 10.4 kPa) = Cirrhosis

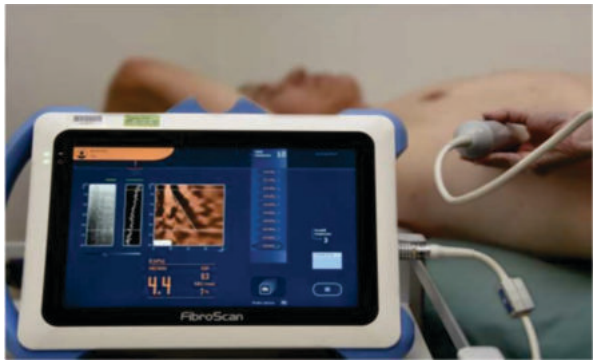

Figure no. 1: Patient undergoing Transient Elastography (Fibroscan)

RESULTS:

A total of 19 patients of rheumatoid arthritis on long term methotrexate were recruited in the study carried out in the tertiary care teaching hospital in suburban Pune. 18 of the 19 participants were female. The average age of the participant was 42.84 ± 8.48 years.

Mean Fibroscan score was 5.50 ± 0.8 kPa, with the highest being 7.0 kPa and lowest being 3.9 kPa.

The mean BMI of the participants was 24.75 ± 2.331 kg/m2 Out of the 19 patients included in the study none of them had Fibroscan score more than 7.1 which is suggestive of stage 1 fibrosis (f1).

Table no.1: Demographic, Biochemical parameter and Fibroscan score in patients on long term Methotrexate.

	Age	Methotrexate use (in months)	Fibroscan score	AST	ALT	BMI
Mean	42.842	39.421	5.505	34.263	34.895	24.753
Std. Deviation	8.487	20.643	0.801	7.943	8.844	2.331
Minimum	21	14	3.9	21	20	20.7
Maximum	58	84	7	48	55	28.2

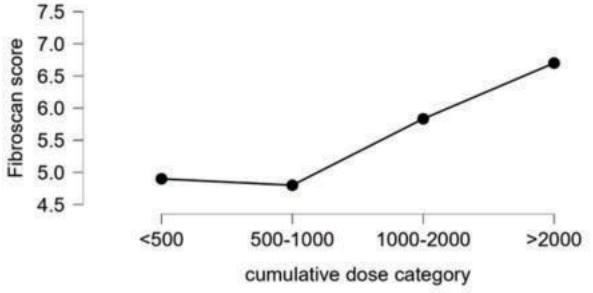

Figure no. 2: Fibroscan score according to cumulative dose category.

The patients were divided into four groups depending upon the cumulative dose of methotrexate. First one being patients having total cumulative dose less than 500, second being total cumulative dose between 500-1000, third group having total cumulative dose between 1000-2000 and fourth group having total cumulative dose more than 2000.

Table no. 2: mean Fibroscan score, mean ALT and mean AST on basis of different categories of cumulative dose.

	number of patients	mean ALT	mean AST	fibroscan score	p value
cumulative dose (<500mg)	(n=3)	26.66	26.33	4.9	
cumulative dose (500 mg-1000mg)	(n=5)	30.4	29.6	4.8	0.798
cumulative dose (1000 mg-2000 mg)	(n=9)	38.33	37.66	5.83	0.018
cumulative dose (>2000 mg)	(n=2)	43	42.5	6.7	0.002
<0.05 is statistically significant.					

It was observed that the Fibroscan score increased with increase in cumulative dose in the third and fourth group. The mean ALT and AST also increased with increase in the cumulative dose of Methotrexate.

In group three and four i.e., Patients who had cumulative dose more than 1000 had increase in Fibroscan score as compared to first group i.e. cumulative dose less than 500 and it was statistically significant.

DISCUSSION

Hepatic fibrosis has been a major safety concern with long term usage of Methotrexate therapy. Several risk factors such as diabetes, obesity, alcohol, and non-alcoholic fatty liver disease (NAFLD) have been ascribed for Methotrexate induced hepatotoxicity. Thus, in patients who have been on long term Methotrexate therapy, periodic assessment of liver function is advised.(Roy et al., 2022)

Till date, biopsy is considered standard for liver fibrosis. However, the procedure is associated with sampling errors, observer variability and poor repeatability. As methotrexate-induced liver injury is uncommon, the risk/benefit ratio of liver biopsy has been questioned.

Over a 24- year period, only 0.07% of adult liver transplantation listings for liver failure in the USA were attributed, wholly or partly, to Methotrexate therapy.(Dawwas & Aithal, 2014) Fortunately, new technologies have been developed for the diagnosis of chronic liver disease, including transient elastography (TE). TE is a type of shear wave ultrasound elastography, which measures the speed of shear waves used to estimate hepatic tissue stiffness. Recent European guidelines now advocate the use of TE as the first-line test for the assessment of fibrosis in alcohol- or hepatitis related liver disease, including non-alcoholic fatty liver disease (NAFLD). As the prevalence of obesity and metabolic syndrome, including NAFLD, is significantly elevated TE may be worth considering as a routine investigation for any patient with Rheumatoid Arthritis on Methotrexate. (Darabian et al., 2022)

CONCLUSION:

In conclusion, we found no association between Methotrexate cumulative dose or duration and liver stiffness in patients with RA. This indicates that the risk of liver fibrosis due to Methotrexate itself is overestimated in population who are at higher risk of metabolic syndrome and NAFLD. Hence, this supports the current evidence on the need to improve patients metabolic risk factors that are associated with liver fibrosis.(Atallah et al., 2023)

Ideally, a non-invasive test of liver fibrosis should be specific to the liver, be easy-to-perform in any laboratory, reflects the stage of fibrosis, be cost-effective, and be reproducible between laboratories, and the results should be independent of any associated inflammation. None of the available tests fulfil all these criteria; therefore, monitoring should be tailored to the individual patient and their comorbidities. At present, a combination of testing methods is the optimal approach, using biochemistry, TE, and when appropriate liver biopsy.(Cheng & Rademaker, 2018)

While TE has largely replaced liver biopsy as the diagnostic test for liver fibrosis in many clinical settings, available studies on methotrexate-treated Rheumatoid Arthritis patients remain limited. However, it is unlikely that large high-quality studies will be conducted, as methotrexate-induced liver injury is uncommon. Evidence must therefore be generalized from studies with less targeted populations, which indicates that TE will be a valuable test in the monitoring of patients with Rheumatoid Arthritis.

Study Limitations:

1. Lack of liver biopsy to study correlation with Fibroscan results.
2. Single centre study observational study.

Declarations

Funding: none
Conflict of interest: No conflict of interest.
Ethical Approval: Not required.

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