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ORIGINAL ARTICLE

Hepatic safety of low dose methotrexate therapy in patients with Rheumatoid Arthritis.

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ABSTRACT… Objective: To determine the Hepatic safety of low dose methotrexate therapy in patients with Rheumatoid Arthritis. **Study Design:** Prospective and Descriptive study. **Settings:** Department of Medicine, Peshawar Institute of Medical Sciences. **Period:** May 2020 to May 2021. **Material & Methods:** A total of 151 patients with rheumatoid Arthritis were included in this study. All diagnosed patients were advised baseline liver function tests and routine blood investigations. Patients were started on methotrexate 7.5 mg weekly. On each monthly follow-up visit, liver function tests were done to detect hepatotoxicity. **Results:** A total of 151 patients of rheumatoid arthritis were included in this study with a female to male ratio of 1.4:1. Average age of the patients was 43.76 years -+ 12.7 SD with range 17-72 years. Only in 17 (11.26%) of patients on 7.5 mg /weekly dose of methotrexate, mild hepato-toxicity was observed based on the elevation of aminotransferases more than two times upper limit of Reference(ULR). **Conclusion:** Although Hepato-toxicity can occur in a minority of patients on low dose methotrexate therefore in low dose it is a safe drug for the treatment of Rheumatoid Arthritis.

Key words: Rheumatoid Arthritis, Methotrexate, Hepato-toxicity.

INTRODUCTION

Rheumatoid Arthritis (RA) is a chronic autoimmune inflammatory, multi-systemic disease with a prevalence of 0.5-1% in general population.[1,2] The incidence of RA is 3 times more common in females compare to males with peak age of onset in the 4th and 5th decades in females and the 6th to 8th decades in men.[3] It is characterised by a chronic polyarticular synovial inflammation due to increased release of cytokine leading to irreversible joint damage.[1] Due to this, RA is associated with substantial morbidity in most patients and can lead to early death.[4,5] However, the developments of disease modifying therapies and understanding of the underlying molecular mechanisms have dramatically changed the management of RA. Methotrexate is one of disease modifying drug, being actively used in the treatment of RA ever since its first reported use in 1951.[5,6]

Because of its low cost, proven efficacy and years of clinical experience with its use, methotrexate is the drug of choice of most clinicians for the treatment of RA.[7] It is effective both as a monotherapy as well in combination therapy with each of the newer biological agents.[1,7]

However, methotrexate usage is associated with certain adverse effects. Some of the common side effects include liver injury, nephrotoxicity, myelosuppression, gastro-intestinal and lung fibrosis.[8,9] Hepatotoxicity of methotrexate is believed to be dose and duration dependent. Elevation of liver transaminases occur in 1% of the patients in some studies but in no case this was more than 2 times the upper limit of reference (ULR).[10] In another study elevation in liver transaminases occurred in 23.7% of patients but in those the dose of methotrexate was 15mg/week.[11] In other studies, elevation of liver transaminases, twice the upper limit of normal had

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occurred in up to 13% but mostly return to normal with continued therapy, requiring discontinuation only in few cases.[12]

Methotrexate causes a range of liver problems which include mild fatty liver, hepatic fibrosis and cirrhosis. Hepatotoxicity is increased by several factors including age, use of alcohol and other co-morbid states.[9,11] In previous studies methotrexate induced hepatotoxicity has been evaluated either with a dose of 15mg/week or the cut-off value for liver enzymes was less than twice the upper limit of normal.

The aim of this study is to evaluate the hepatic safety profile of low dose methotrexate of 7.5mg/ week. Since methotrexate is the bread and butter drug of RA, and no local data regarding the hepatotoxicity was available, therefore the purpose of this study was to determine its frequency, so that a local data can be provided to the regional physicians dealing with RA patients. Moreover, health care professionals will be more confident in prescribing Methotrexate to the RA patients.

MATERIAL & METHODS

This descriptive study was conducted in the Department of Medicine Peshawar Institute of Medical Sciences Peshawar from May 2020 May 2021. A total of 151 RA patients aged 17-72 years of either gender were included in the study through consecutive sampling after fulfilling the inclusion and exclusion criteria after approval from hospital ethical committee (06/DMR/PMC). Inclusion criteria were.

- All adult patients > 12 years of age
- Either gender diagnosed as Rheumatoid arthritis
- Normal baseline liver function tests.
  Exclusion criteria included
- Patients with viral hepatitis
- Patients with autoimmune hepatitis
- Patients taking other hepato-toxic drugs
- Obese patients
- Patients with hemochromatosis
- Wilsons disease
- Any another co-morbid conditions that affect the liver
- Pregnant ladies

Rheumatoid arthritis was defined on the basis on ACR 2010 criteria for Rheumatoid Arthritis. Similarly hepatotoxicity was defined as patients having Alanine transaminase levels two times the upper limit of normal i.e more than 62mg/dl.

Detailed history was taken from each patient and a thorough examination was conducted by a medical specialist from all patients with Rheumatoid Arthritis. All the routine investigations including liver function were done on all enrolled patients and were started on methotrexate 7.5mg/ week. On each Monthly follow-up visit routine blood tests including liver function tests were done to detect hepatotoxicity of methotrexate. Investigations were done in the same laboratory and by the same biochemist with more than 5 years of experience.

The data so collected was used to fill up a specially designed pro forma. The collected data was analyzed by SPSS- version 16. Mean and standard deviation were calculated for age. Frequencies and percentages were calculated for categorical variables like gender and hepatotoxicity. All collected data were shown in charts, tables and graphs. To know the significant difference between gender, chi square test was applied.

RESULTS

A total of 151 patients of rheumatoid arthritis were included in the study. There were 87 (57.62%) females and 64 (42.38%) males. Female to male ratio was 1.4:1. (Table-I).

Average age of patients was 43.76 years+12.7 SD with range 17-72 years. Age wise distribution is shown in Table-II.

The low dose methotrexate induced hepato-toxicity in patients with rheumatoid arthritis was observed in 17 (11.26%) while in 134(88.74%) patients no low dose methotrexate induced hepato-toxicity was shown (Figure-1).

Age wise distribution of low dose methotrexate hepato-toxicity in patients with rheumatoid arthritis was high in old age as compared to younger age group. Patients with age less than 30 years had hepato-toxicity of 3.2%, age group 31-45 years had 8.3%, in age group 46-60 years 14.7% and in age group more than 60 years the hepato-toxicity was 22.2% among newly diagnosed patients of rheumatoid arthritis (Table-III).

Gender wise low dose methotrexate induced hepato-toxicity among newly diagnosed patients of rheumatoid arthritis shows that gender has minor role in low dose methotrexate hepato-toxicity. Hepato-toxicity was observed in 12.6% in males and 9.4 % female patients. (Table-IV)

Variables	N
Total Patients	151
Age	43.76 years+12.7
Males	64 (42.38%)
Females	87 (57.62%)

Table-I. Baseline characteristics of patients.

Age in Years	Frequency (%)
< 30	31 (20.5%)
31– 45	36 (23.8%)
46 – 60	75 (49.7%)
61.00+	9 (6.0%)
Total	151 (100.0%)

Table-II. Age wise distribution of the patients.

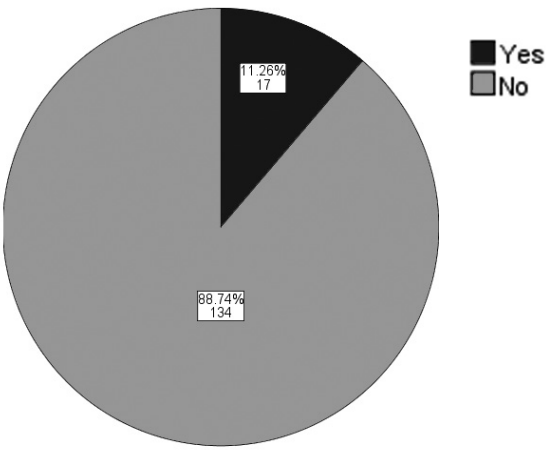

Figure-1. Low dose methotrexate induced hepatotoxicity in patients with rheumatoid arthritis.

Age In Years	Hepatotoxicity		Total
	Yes	No	
< 30	1 (3.2%)	30 (96.8%)	31 (100%)
31– 45	3 (8.3%)	33 (91.7%)	36 (100%)
46 – 60	11 (14.7%)	64 (85.3%)	75 (100%)
61.00+	2 (22.2%)	7 (77.8%)	9 (100%)
Total	17 (11.3%)	134 (88.7%)	151 (100%)

Table-III. Age wise distribution of low dose methotrexate induced hepatotoxicity.

Gender	Hepatotoxicity		Total	P-Value
	Yes	No		
Female	11 (12.6%)	76 (87.4%)	87 (100%)	0.4
Male	6 (9.4%)	58 (90.6%)	64 (100%)	
Total	17 (11.3%)	134 (88.7%)	151 (100)	

Table-IV. Gender wise distribution of low dose methotrexate induced hepatotoxicity.

DISCUSSION

In this study, we observed that only 11.26% of patients developed deranged LFTs after taking low dose methotrexate. Moreover, we observed that hepatotoxicity of methotrexate is irrespective of patients' gender, though frequency of deranged ALTs increases with increasing age.

In one study, the frequency of raised ALT two times upper limit of normal was found in 16.8% of the study group[8], which was in accordance to our study. Similar findings were also reported by Salliot C et al[13] who observed that hepatotoxicity occurred in 13% of the patients on methotrexate who took treatment for one year. They in their review article observed that out of the total 3808 patients, 20% of the patients developed some elevation of their ALT, while in 13% patients the ALT levels went beyond 2 times upper limit of normal with 3.7% discontinuing their treatment.[13] In our study, no patient stopped their treatment due to hepatotoxicity. In another studies low dose methotrexate toxicity was reported varying from 7.5-26%.[14] Similarly, Tanveer et al reported that methotrexate toxicity developed in 27% of the patients.[15] In yet another study, approximately 9% of the patients the methotrexate dose was reduced to prevent or manage those adverse

events.[16]

We observed that the frequency of hepatotoxicity of methotrexate was similar in both genders (12.6 vs 9.4) with a P-value of 0.4. This is in contrast to Hoeskstra et al[17] who reported that the side effects of methotrexate were affected by gender. As regards age, Dorosos et al[18] in their review article studied methotrexate intolerance in elderly patients and observed that ageing does not increases the probability of having adverse effect irrespective of methotrexate dose. Though Kremer et al[19], have reported that increasing methotrexate dose is associated with increased frequency of adverse effects, however in their work they studied methotrexate treatment in combination with etanercept while in our study patients were only on methotrexate. Similarly, Ruperto et al[20], also reported that there exists no relationship between the frequency of adverse effects of methotrexate and age, which is in accordance with our study.

The exact pathogenesis of methotrexate induced liver injury is not known, however, it is believed that methotrexate depletes the folic acid stores within the liver.[21,9] This is believed to be the cause of liver injury though exact relationship between folate deficiency and liver damage has not yet been established. Some of these stores are replenished with oral folic acid which is usually prescribed with methotrexate in RA patients.[9,21,22] Indeed, oral folic acid supplements are found to reduce the frequency of hepatotoxicity. It is due to these reason, and the fact that recommended monitoring strategies are being regularly followed, has recently led to marked reduction in the frequency of methotrexate induced liver injury.[23]

The strength of our study include; this was the first study conducted in the Khyber Pakhtunkhwa. Secondly, our results provide guidance to the local physicians regarding the hepatic safety profile of methotrexate, and that low dose can be used safely in RA patients. Thirdly, we observed that gender and age does not affect the hepatotoxicity of methotrexate, and hence can be safely prescribed.

Since we studied the low dose of methotrexate only, while did not take into account doses greater than 7.5mg/week, therefore one the limitation is that our results cannot be generalised to all recommended doses of methotrexate in RA. Moreover, we followed the patients for 4 months only, while many patients are known to develop side effects after a more prolonged use. Therefore, we recommend larger studies that include methotrexate doses up to 25mg/week and longer follow up to have a better over view of safety profile of Methotrexate in RA patients.

CONCLUSION

In conclusion low dose methotrexate is a safe treatment option for patient with rheumatoid arthritis and are generally safe drugs with regard to liver toxicity.

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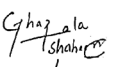
AUTHORSHIP AND CONTRIBUTION DECLARATION

No.	Author(s) Full Name	Contribution to the paper	Author(s) Signature
1	Muhammad Bilal	Concept and Design of the study.	
2	Ghazala Shaheen	Data Analysis and Data Collection.	
3	Syed Hassan Mustafa	Manuscript Writing, Data Analysis and Interpretation.	
4	Muhammad Nazir	Manuscript Writing.	
5	Zulfiqar Ahmad	Data Analysis and Data collection.	
6	Taj Muhammad Khan	Data collection.	
7	Rabnawaz Khan	Proof reading, Study design and data interpretation.