Original Article

# Hepatotoxicity with Low Dose Methotrexate in Rheumatoid Arthritis Patients



**Muhammad Abbas, Sajjad Ali and Amir Khan**


## ABSTRACT

**Objective:** To find out the frequency of Methotrexate induced hepatotoxicity in rheumatoid arthritis patients treated for six months with low dose, 7.5 mg of Methotrexate once weekly.

**Study Design:** Descriptive / cross sectional study.

**Place and Duration of Study:** This study was conducted at the Medical Units of Mardan Medical Complex, Mardan from January 2015 to December 2016.

**Materials and Methods:** Study included 186 diagnosed adult patients of rheumatoid arthritis. They were treated with 7.5 mg Methotrexate per week and were followed up for 6 months with regularly monthly Liver function test (L.F.T's).

**Results:** Out of 186 diagnosed cases of RA, 39 (24.3%) were males and 147 (75.7%) were females. Age range was from 21years to 68 years with mean age of 38.06 years. Mean Alt was 45.34, mean billirubin was 0.93, mean Alkaline phosphatase was 23.90, mean hemoglobin was 12.63 while mean weight was 67.79 kg. Serum A.L.T was raised in 17 (9.1%) patients while it was normal in 169 (90.9%) patients. Hepatotoxicity was defined as serum A.L.T of more than two times of upper limit of reference range.

**Conclusion:** Hepatotoxicity is a common side effect of methotrexate therapy and regular monitoring with serum alanine transaminase of these patients is required for early recognition and treatment.


**Key Words:** Methoraxate. Hepatotoxicity. rheumatoid Arthritis (RA)

**Citation of article: Abbas M, Ali S, Khan A. Hepatotoxicity with Low Dose Methotrexate in Rheumatoid Arthritis Patients. Med Forum 2017;28(11):85-88.**

## INTRODUCTION

Rheumatoid arthritis is a chronic systemic autoimmune disorder characterized by a chronic polyarticular synovitis due to increase release of cytokines that may cause irreversible joint damage and may lead to deformities. Methotrexate is commonly used in weekly doses for rheumatoid arthritis, because of its effectiveness, low toxicity and cost[1]. It acts by increasing the adenosine concentration and reducing the cytokines thus decreasing the inflammation. 7-10 hrs is the plasma half life of Methotrexate, it is metabolized mainly by the liver and excreted by kidneys[2].

Hepatic folate stores are depleted by Methotrexate in doses used for rheumatoid arthritis and they can be replenished by short term administration of oral folinic acid[3]. Supplementation of oral folic acid in doses of 1 mg/day or 2.5 mg of folinic acid/week is associated with reduced incidence of hepatotoxicity[4,5]. The abnormal liver enzymes resolves within a month of decreasing the dose or stopping the drug[1].

Department of Medicine, BKMC, Mardan Medical Complex, Mardan.

Correspondence: Dr. Muhammad Abbas, Assistant Professor, Department of Medicine, BKMC / Mardan Medical Complex, Mardan.
Contact No: 0300-9053406
Email: docabbas1@hotmail.com

Received: July 10, 2017; Accepted: September 18, 2017

The raised liver enzymes above two times upper limit reference range (ULR) has been found in 13%, 3.7% of patients were forced to stop it permanently, while incidence of fibrosis after four years administration of MTX was 2.7%[6,7,8]. Hepatotoxic effects of MTX can be increased by certain risk factors such as age, duration of exposure to Methotrexate, history of NASH, diabetes mellitus, obesity, HBV or HCV infection, alcohol consumption, and hepatotoxic drugs[9,10].

In Pakistan Methotrexate is still the corner stone of therapy in patients with rheumatoid arthritis. It is very effective in arresting the disease process and preventing the joint damage but may be associated with certain undesirable side effects including hepatotoxicity, Which may disturb the quality of life by putting an extra physical and financial burden on these patients. Therefore this study is aimed at to know the exact prevalence of hepatoxicity and some important risk factors in these patients which may help in early recognition and treatment of this problem and thus further improving the management of the rheumatoid arthritis patients.

## MATERIALS AND METHODS

This was a descriptive study carried out on 186 diagnosed cases of RA at the medical unit of Mardan medical complex (MMC) from January 2015 to December 2016. ACR/EULAR 2010 criteria was used for diagnosing rheumatoid arthritis[11]. The Objective of study was to find out the frequency of Methotrexate

induced hepatotoxicity in rheumatoid arthritis patients treated for six months with low dose, 7.5 mg of Methotrexate once weekly. Approval for the study was obtained from the ethical and research committee of the hospital. These patients were selected by non-probability convenient sampling method after an informed verbal consent. Adult Patients irrespective of gender were enrolled in the study. Detailed history of illness, physical examination and routine base line investigations were carried out at start of study. These patients were treated with 7.5 mg of MTX once weekly and were followed up for six months with monthly liver function test (L.F.T's). Patients with known liver disease, renal insufficiency, leucopenia, and thrombocytopenia, were excluded. As majority of rheumatoid arthritis patients were female of child bearing age and most of them were anaemic but despite of this limitation only females with mild anaemia were included and patients with moderate to severe anaemia were excluded (Hb less than 10.50 gm/l) Similarly patients with concomitant illness like DM,HTN,IHD were also excluded. However patients already taking other disease modifying anti-rheumatic drugs with normal ALT were included. Hepatotoxicity was defined as serum ALT of more than two times upper limit of reference range (ULR)[7,12,13].

# RESULTS

A total of 186 rheumatoid patients comprising of 39 males(24.3%) and 147 females(75.7%), ranging from 21years to 68 years with mean age of 38.06 years participated in the study. Age of male rheumatoid patient ranges between 22 years to 68 years with a mean age of 44.07 while of female rheumatoid patient age ranges between 21 years to 65 years with a mean age of 36.47 years (Table 1).

Variables included were serum billirubin, serum Alt, serum Alkaline phosphatase, hemoglobin and weight of patient. Mean values along with standard deviations of Alt, serum billirubin, Alkaline phosphatase, hemoglobin and body weight are given in Table 2.

**Table No. 1 : Age and gender of patients**

| Gender | No of patients | % of Total Sum | Minimum age | Maximum age | Mean age | Std. Deviation |
|---|---|---|---|---|---|---|
| Male | 39 | 24.3% | 22.00 | 68.00 | 44.0769 | 12.22247 |
| Female | 147 | 75.7% | 21.00 | 65.00 | 36.4762 | 8.71727 |
| Total | 186 | 100.0% | 21.00 | 68.00 | 38.0699 | 10.01407 |

**Table No. 2: Different Variables**

| Variables | Alanine Tranaminase | Hemoglobin | Weight Of Patient | Serum Billirubin | Alk Phosp |
|---|---|---|---|---|---|
| Mean | 45.3441 | 12.6339 | 67.7903 | .9310 | 233.9086 |
| Std. Deviation | 25.29779 | .85398 | 20.82317 | .17027 | 18.80504 |
| Minimum | 12.00 | 10.50 | 42.00 | .20 | 200.00 |
| Maximum | 156.00 | 14.80 | 145.00 | 1.20 | 270.00 |

**Table No. 3: Different parameters in hepatitis / non hepatitis groups**

| Different parameters in hepatitis / non hepatitis groups | | No. of patients | Mean | Std. Deviation | P value |
|---|---|---|---|---|---|
| Age of patient | Hepatotoxicity | 17 | 37.3529 | 9.61081 | 0.758 |
| | Non Hepatitis | 169 | 38.1420 | 10.07844 | |
| Hemoglobin | Hepatotoxicity | 17 | 11.3000 | .47958 | 0.00 |
| | Non Hepatitis | 169 | 12.7680 | .76356 | |
| Weight of patient | Hepatotoxicity | 17 | 70.8235 | 20.99772 | 0.530 |
| | Non Hepatitis | 169 | 67.4852 | 20.84384 | |
| Serum billirubin | Hepatotoxicity | 17 | .9753 | .12228 | 0.262 |
| | Non Hepatitis | 169 | .9266 | .17402 | |
| Alkaline phosphatase | Hepatotoxicity | 17 | 239.7059 | 15.65952 | 0.183 |
| | Non Hepatitis | 169 | 233.3254 | 19.03460 | |

Serum Alt was raised (2 times upper limit of normal) in 17 patients (9.1%) while it was within normal range in 169 patients (90.9%)

Min range of serum Alt in hepatotoxic group was 90 and max was 156 with median value of 110 having std Deviation of 23.99280.In non hepatotoxic group min range of Alt was 12 and max was 61 with median value of 40.00 having std Deviation of 10.33508.

20 patients in study were smokers in which only 2 patients showed hepatotoxicity while in remaining 18 smoker patient serum Alt was found to be within normal range. The association of smoking with hepatotoxicity was not statistically significant (p value

> 0.05).Total 39 male rheumatoid patients were included in study only 4 showed hepatotoxicity while remaining 35 comes to be under non hepatitis group. Female patients in study were 147 and 13 patients were found to be hepatotoxic and 134 rheumatoid patients were within non hepatitis group. The association of gender with hepatotoxicity was not statistically significant (p value > 0.05).

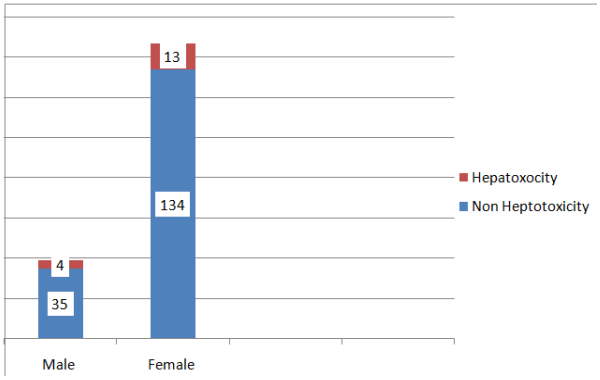


**Figure No.1: Association of hepatotoxicity with gender of patient (P value : 0.785)**

# DISCUSSION

Among the disease modifying anti rheumatic drugs (DMARD's) Methotrexate is most commonly used and usually considered to be the first line of drug for treating rheumatoid arthtritis. Methotrexate is a well recognized cause of hepatic enzyme elevation. In our study hepatotoxicity was found in 17 patients (9.1%). A study from Rawalpindi by gilani et al has reported similar frequency of hepatotoxicity in these patients[14]. Another study conducted by R Sotoudehmanesh, B Anvari, showed hepatic enzyme elevation with methotrexate at the rate of 23.7% and this was directly related to duration of treatment.[15] In comparison with our study proportion of hepatotoxicity was lower and this difference may be explained by the greater duration of treatment with methotrexate in the study conducted by R Sotoudehmanesh, B anvari, etal. Other studies has reported that chronic low to moderate dose of MTX can cause hepatic enzyme elevation in 15 % to 50 % of cases[16,17] which is usually reversible on stopping the drug or reducing its dose[4,18]. Moreover, folate supplementation markedly diminishes liver toxicity.[4,5] Therefore, it is advisable to regularly monitor liver enzymes during MTX therapy in RA patients.

We also analyzed and compared different parameter in these patients, among these we found that serum ALT elevation was found in young as well as old patients and age was not a significant risk factor for developing hepatoxicity. In support of our results, Similar finding was noted by another local study from Pakistan.[14] Similarly no significant association was found between gender, smoking and weight with hepatotoxicity in these patients. However our study showed that hepatotoxicity was more common in anaemic patients and this association of hepatotoxicity with hemoglobin level was statiscally significant with p-value < 0.05. This means that patients who developed hepatotoxicity were also anemic. To our knowledge most female patients of child bearing age in our society are usually anemic. Moreover our study population consisted mostly of female patients. Therefore this could be either an incidental finding or may be the effect of MTX on hemoglobin level. We do not know that exact mechanism of this finding and need further work up.

The main limitation in our study was the simultaneous use of other DMARD's besides MTX to our patients which could not be controlled. Although we included only those patients who were having normal baseline liver function tests to reduce this bias. Induction of liver enzymes due to hydroxychloroquine or prednisolone are extremely rare and have been reported only in isolated cases[19,20,]. Also Sulphasalazine induced liver toxicity is relatively low (1 per 1000 cases)[21]. So contributing role of other DMARD's induced hepatotoxicity is minimum in our patients but can't be over ruled. In our study only those patients were included whose disease was limited to joints and there was no involvement of other systems. So we can assume that hepatic enzyme elevation in our patients was mainly due to methotrexate and not because of Rheumatoid disease itself. Furthermore most of our patients were female of child bearing age and they are usually anaemic and hepatic enzyme elevation in such patients was more evident as compared to patients with normal Hb level.

# CONCLUSION

In conclusion treatment of rheumatoid arthritis patients with methotrexate is commonly associated with mild to moderate hepatic enzyme elevation and therefore we recommend regular monitoring of these patients with serum ALT.

**Author's Contribution:**

| | |
|---|---|
| Concept & Design of Study: | Dr. Muhammad Abbas |
| Drafting: | Dr. Muhammad Abbas |
| Data Analysis: | Dr. Sajjad Ali |
| Revisiting Critically: | Prof. Amir Khan |
| Final Approval of version: | Prof . Amir Khan |

**Conflict of Interest:** The study has no conflict of interest to declare by any author.

# REFERENCES

1. Visser K,Van der Heijde D. Optimal dosage and route of administration of MTX in RA. Ann Rheum Dis 2009;68:1094-9.
2. Cronstein BN. low dose MTX: a mainstay in treatment of RA. Pharmacol Rev 2005;57:163-72.
3. Rodenhuis S, Kremer JM, Bertino JR. Increase of dihydrofolate reductase in peripheral blood

lymphocytes of RA patients treated with low dose of MTX. Arthritis Rheum 1987;30:369.
4. Prey S, Paul C. Effects of folic acid or folinic acid supplementation on MTX associated safety and efficacy in inflammatory bowel disease: a systemic review. Br J Dermatol 2009;160:622.
5. Van Ede AE, Laan RF, Rood MJ, et al. Effects of folic or folinic acid supplementation on toxicity and efficacy of MTX in RA: a forty eight week, multicentric randomized, double blind, placebo controlled study. Arthritis Rheum 2001;44:1515.
6. Salliot C, Van der Heijde D. Long term safety of MTX monotherapy in patients with RA: a systemic literature research. An Rheum Dis 2009;68:1100-4.
7. Visser K, katchamart W, loza E, Martinez-lopez JA, Salliot C, Trudeau J, et al. Multinational evidenced-based recommendations for use of MTX in rheumatoid disorders: integrating systematic literature research and expert opinion of broad international panel of rheumatologist in the 3E initiative. Ann Rheum Dis 2009;68:1086-93.
8. Buhroo AM, Baba AN. Adverse effects of low dose MTX in patients with RA. Ind J Physical Med Rebabil 2006;17:21-5.
9. Diouf ML, Diallo S, Mbengue M, et al. MTX, liver and RA in tropical areas. Santé 2001;11:195-200.
10. Kremer JM, Petrillo GF, Hamilton RA. Pharmacokinetics and renal function in patients with RA receiving a standard dose of oral weekly MTX: association with significant decrease in creatinine clearance and renal clearance of the drug after six months of therapy. J Rheumatol 1995;22:38-40.
11. Scott DL, Wolfe F, Huizinga TW, .Rheumatoid arthritis. Lancet 2010;376:1094-1108.
12. Uraz S, Tahan V, Aygun C, Eren F, Unluguzel G, Yuksel M, et al. Role of ursodeoxycholic acid in prevention of MTX induced liver toxicity. Dig Dis Sci 2008;53:1071-7.
13. Faltaos DW, Hulot JS, Urien S, Morel V, Kaloshi G, Fernandez C, et al. Population pharmacokinetic study of MTX in patient with lymphoid malignancy. Cancer Chemother Pharmacol 2006; 58:626-33.
14. Gilani STA, Khan DA, Khan FA, Ahmad M. Adverse effects of low dose methotrexate in rheumatoid arthritis patients. JCPSP 2012; 2(22):101-104.
15. Sotoudehmanesh R, Anvari B, Akhlaghi M, Shahraeeni S. Methotrexate hepatotoxicity in rheumatoid arthritis patients. Middle East J Dig Dis 2010;2(2):104-9.
16. Bath RK, Brar NK, Forouhar FA. A revive of MTX associated hepatotoxicity. J Dig Dis 2014; 15:517-21.
17. Curtis JR, Benkalman T, Onofrei A, et al. Elevated liver enzymes tests among patients with RA or psoriatic arthritis treated with MTX or Leflunamide. Ann Rheum Dis 2010;69:43-7.
18. Hoekstra M, Van Ede AE, Haagsma CJ, et al. factors associated with toxicity, final dose and efficacy of MTX in patients with RA. Ann Rheum Dis 2003;62:423-6.
19. Smolen JS, Landewe R, Breedveld FC, Buch M, Burmester G, Dougados M, et al. EULAR recommendation for the management of rheumatoid arthritis with synthetic and biological disease- modifying anti rheumatic drugs:2013 update. Ann Rheum Dis 2014;73:492-509.
20. Rodriguez-Caruncho C, Bielsa Marsol I. Anti malarials in dermatology:mechanism of action, indications and side effects. Actas Dermosifiliogr 2014;105:243-52.
21. De Abajo FJ, Montero D, Madurga M, Garcia Rodriguez LA. Acute and clinically relevant drug-induced liver injury: a population based case-control study. Br |J Clin Pharmacol 2004;58:71-80.