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LiverToxicity in Patients with Rheumatoid arthritis on methotrexate therapy

N Archana[1], S B Rai[2], S Sailo[3], N Reema[4], N Santa[5], S Kenny[6], Th Shanti Devi[7]
[1](Department of Medicine, Regional Institute of Medical Sciences, Imphal, Manipur, India)
[2](Department of Medicine, Regional Institute of Medical Sciences, Imphal, Manipur, India)
[3](Department of Medicine, Regional Institute of Medical Sciences, Imphal, Manipur, India)
[4](Department of Medicine, Regional Institute of Medical Sciences, Imphal, Manipur, India)
[5](Department of Medicine, Regional Institute of Medical Sciences, Imphal, Manipur, India)
[6](Department of Medicine, Regional Institute of Medical Sciences, Imphal, Manipur, India)
[7](Department of Medicine, Regional Institute of Medical Sciences, Imphal, Manipur, India)*
**corresponding author*: *Th Shanti Devi*

Abstract:
Background*: Rheumatoid arthritis (RA) is a chronic multisystem disease affecting joints, connective tissues and fibrous tissues. Methotrexate (MTX) is a folate antagonist used as a first line treatment in RA. Hepatotoxicity is a common side effect of MTX. This study was done to evaluate abnormalities of liver function with respect to cumulative dose and duration of MTX.*
Materials and methods: *In this cross sectional analytical study 109 patients of RA aged ≥18years on methotrexate therapy were analyzed for abnormal liver profile by using Liver Function Test (LFT), Ultrasonography (USG) abdomen. The weekly dose, cumulative dose and duration of treatment were compared between patients with and without elevated liver enzymes.*
Results: *Of 109 patients, transaminitis was observed in 22 patients (20.1%,95% CI: 13.3%-29.2%). The mean SGOT and SGPT were 44.04 ± 29.15 IU/L and 35.85 ± 23.26 IU/L respectively. The mean weekly dose, cumulative dose and duration of MTX therapy were 8.74 ±2.51 mg/wk, 2131.82 ± 1283.26 mg and 4.9 ± 2.47 years respectively. The mean weekly dose and cumulative dose of MTX was higher among the patients with transaminitis (11.19 ±2.18 mg/wk vs 8.15 ± 2.23 mg/wk and 3188.57 ± 1100.19 mg vs 1879.64 ±1196.71mg) which was statistically significant (p<0.001). Fatty liver was present in 15.6% of the study participants. Majority (87.1%) of the participants were females.*
Conclusion: *transaminitis was the major abnormality observed, the prevalence of which was higher among patients with longer duration of treatment with MTX and with higher cumulative dose. However, there was no significant association for gender and age with transaminits. The prevalence of fatty liver was also higher among the patients receving higher dose of MTX.*

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I. Introduction

Rheumatoid arthritis (RA) is a chronic multisystem autoimmune disease that affects joints, connective tissues, muscle, tendons, and fibrous tissue.[1]The worldwide prevalence of RA has been estimated as 0.24 percent based upon the Global Burden of Disease 2010 Study.[1]Women are affected approximately three times more often than men.[2] Persistent symmetrical inflammatory synovitis of the peripheral joints is one of the characteristic features. Methotrexate (MTX) is a folate antagonist with anti-proliferative, immunosuppressive and anti-inflammatory action used in the treatment of arthritis .[3]It is the initial preferred antirheumatic drug and is considered the gold standard for treatment of RA.[5] Anti-inflammatory action of MTX is due to increased adenosine release at inflamed sites.[6]

Hepatotoxicity is a common complication of long term treatment with MTX with liver enzyme elevation which is related to the duration of therapy.[7] Guidelines, including the widely used American College of Rheumatology guidelines, recommend testing of liver enzymes at intervals of 2-4 weeks, 8-12 weeks and 12 weeks for the duration of therapy of <3months,3-6months and >6 months respectively.[8] Predictors of liver toxicity have not been consistent between studies which may be due to differences in the studied populations.[8,9,10,11] A good knowledge on cumulative dose and duration of MTX at which liver function derangements occur will help modify and revise treatment thereby reducing hepatotoxic effects. In most studies, risk factors for pre-existing liver disease such as alcohol use, obesity and diabetes and other associated causes that may provoke hepatotoxicity were insufficiently reported. Our aims is to study liver function abnormalities

in patients with RA on MTX therapy and determine their correlation with duration and cumulative dose of methotrexate.

II. Materials And Methods

The current study is a hospital based cross sectional analytical study conducted at Regional Institute of Medical Sciences, Imphal, Manipur for a period of two years from September 2018 to August 2020.

Inclusion criteria:

1. Patients diagnosed with Rheumatoid arthritis according to 2010 American college of Rheumatology/European League Against Rheumatism Classification criteria who were on Methotrexate therapy for >3months
2. Age ≥18 yrs.

Exclusion criteria

1. Preexisting liver diseases
2. Diabetes mellitus
3. Alcohol intake (>20g/day)
4. Dyslipidemia
5. Obesity (BMI ≥ 25 kg/m^2)
6. Patients on hepatotoxic drugs
7. Patients unwilling to participate in the study

Study procedure

After obtaining permission from the institution ethics committee and informed consent from the participants, the patients were subjected to detailed history and clinical examination as described in the pre-defined proforma. Laboratory investigations including LFT, RBS, lipid profile, ESR, HBsAg, anti HCV Ab, CRP and RF were done. Ultrasonography of abdomen was performed. All the data collected was checked for the completeness and they were later used for the analysis. The patients were divided into two groups (group 1 comprising patients with raised transaminase levels and group 2 comprising patients with normal transaminase level) and the difference between the weekly dose, cumulative dose, duration of treatment and USG findings were compared for statistical significance.

Study tools and instruments

1. Pre-defined proforma consisting of the following sections
a. Sociodemographic characteristics
b. Clinical history
c. Clinical examination findings
d. Laboratory investigations
2. LFT, RBS and Lipid Profile using RandoxRximola fully automatic analyser
3. Erythrocyte sedimentation rate (ESR) using Marienfeld ESR tubes
4. Hemoglobin (Hb) values and RBC indices (MCV, MCH, and MCHC) were calculated using the ABX Micros 60 Hematology Analyzer (Horiba-ABX, Montpellier, France)
5. HBsAg, Anti HCV Ab using Virucheck Kit
6. CRP, RF test using Rhelax-CRP
7. RF test using Rhelax-RF
8. USG abdomen using Phillips Diagnostic Ultrasound System
9. PT-INR(Prothrombin time- International Normalized ratio)

Working definitions

1.Transaminitis: Elevation of SGOT or SGPT >1.5 times the upper limit of normal (SGOT-5-40 IU/L, SGPT:-5-30 IU/L)

2..Rheumatoid Arthritis (2010 American college of Rheumatology/European League against Rheumatism Classification Criteria)[7]

3. Diabetes was diagnosed according to American Diabetic Association (ADA) criteria[34]

4. Dyslipidemia was defined as total serum cholesterol levels of 200 mg/dl or higher, low density lipoprotein cholesterol (LDL-C) levels of 150 mg/dl or higher, serum triglycerides 250mg/dl or higher and high density lipoprotein (HDL-C) levels of 40 mg/dl or lower. [35]

5. PT & INR

a. PT: 12-14sec

b. INR: 0.9-1.2

Statistical analysis: Data was entered and analyzed using SPSS V21 (IBM Corp., Armonk, NY, United States) for windows. Categorical variables like gender, duration of treatment were expressed as frequency and percentages. Continuous variables like age, SGOT, SGPT levels and cumulative dose were expressed as mean (SD) or median (IQR), depending on the type of distribution. Chi square test was used to determine the association between two proportions. Independent samples t test was used to determine the association between duration of treatment and liver function abnormality. A p value of <0.05 was considered significant.

III. Results

A total of 109 patients with Rheumatoid Arthritis on Methotrexate therapy were included in the study. Majority of the participants 58(53.2%) were in the age group of 46-60 years and 95(87.1%) patients were female. Out of 109 patients, 22(20.18%) were found to have transaminitis while 87 patients had normal transaminase levels. The mean age was 50.04 ± 9.43 years in patients with transaminitis and 49.92 ± 10.30 years in patients without transaminitis. The mean BMI was 22.50 ± 1.68 kg/m^2 and 22.96 ± 1.41 kg/m^2 respectively. Mean cumulative dose of methotrexate were3188.57 ± 1100.19mg and 1879.64 ±1196.71 mg in the two groups whereas mean weekly dose were 11.19 ±2.18 mg/wk and 8.15 ± 2.23mg/wk respectively. Fatty liver was present in 17(15.6%) study participants (14 in patients with transaminitis and 3 in patients without transaminitis, p value <0.001).

Table 1: Baseline demographic, biochemical and ultrasonography findings of patients with RA on MTX therapy

Variables	Total population (n=109)	Group 1 (n=22)	Group 2 (n=87)
Age (years)	49.95 ± 10.10	50.04 ± 9.43	49.92 10.30
BMI (kg/m^2)	22.87 ± 1.27	22.50 ± 1.68	22.96 1.41
Male	14(12.8%)	2(1.8%)	12(11%)
Female	95(87.1%)	20(18.3%)	75(68.8%)
Total bilirubin(mg/dL)*	0.6 ± 0.2	0.8 ± 0.3	0.5 ± 0.1
Direct bilirubin(mg/dL)*	0.2 ± 0.1	0.4 ± 0.2	0.1 ± 0.04
SGOT (IU/L)*	44.04 ± 29.15	95.86 ± 19.43	31.67 12.84
SGPT (IU/L)*	35.85 ± 23.26	78.62 ± 12.86	25.64 9.32
GGT(IU/L)*	24 ± 12	23 ± 17	25 10
ALP(IU/L)*	204 ± 79	197 ± 69	206 81
Total protein(gm/dL)*	7.2 ± 0.4	7.4 ± 0.3	7.1 ± 0.5
Albumin(gm/dL)*	4.0 ± 0.3	4 ± 0.2	4.0 ± 0.3
Globulin(gm/dL)*	3.3 ± 0.4	3.4 ± 0.3	3.2 ± 0.4
PT(secs)*	13 ± 2	14 ± 1	13 2
INR	1.09 ± 0.1	1.2 ± 0.1	1.06 0.1
Duration (years)*	4.9 ± 2.47	5.93 ± 1.71	4.67 2.56
Cumulative dose (mg)*	2131.82 ± 1283.26	3188.57 ± 1100.19	1879.64 1196.71
Weekly dose (mg)*	8.74 ±2.51	11.19 ±2.18	8.15 2.23
Fatty liver	17(15.6%)	14(12.8%)	3(2.75%)

*mean and standard deviation

Table 2: Difference in SGOT, SGPT, weekly dose, cumulative dose and duration of MTX treatment and presence of fatty liver between in two groups

Variables	Group 1 (n=22)	Group 2 (n=87)	p value
SGOT (IU/L)	95.86	31.67	<0.001
SGPT(IU/L)	78.62	25.64	<0.001
Cumulative dose(mg)	3188.57	1879.64	<0.001
Duration(years)	5.93	4.67	0.01
Weekly dose (mg/wk)	11.19	8.15	<0.001
Fatty liver	14	3	<0.001

IV. Discussion

Majority 95(87.2%) of the participants in our study were females. The sex ratio in our study was approximately 9:1. Garcia et al[15] and Sundbaum et al[20] also reported that females were the majority (88.3% and 66.7% respectively). Most of the studies on rheumatoid arthritis across the countries had similar results, where females are more than the males.[17,18,19] The reasons for this over representation of women is not clear, but genetic (X-linked) factors and hormonal aspects are likely involved.[23,32].

Autoimmune diseases like rheumatoid arthritis commonly affects middle aged females. The mean age of the patients in this study was 49.95 ± 10.10 years for the entire study population, 50.04 ± 9.43 years for patients with transaminitis and 49.92 ± 10.30 years for patients without transaminitis. This is in concordance with several other studies globally.[12,15,21,22]

In our study 22(20.18%) out of 109 patients were found to have increased liver enzymes. A study by Mori et al had reported a similar findings among the patients on methotrexate therapy.[12] The prevalence in large population-based studies ranges from 11% to 24%.[25,26] Methodological, ethnic, and genetic variations may account for the discrepancy between our finding and the aforementioned studies. Fatty liver was detected in 17(15.6%) patients on ultrasonography of the abdomen of whom 14(12.8%) were in those patients with transaminitis and 3(2.75%) in those without transaminitis. The difference in the prevalence of fatty liver in the two groups was statistically significant ($p<0.001$). This finding supports a study conducted by Mori et al who concluded that there is a strong association between MTX treatment and non alcoholic fatty liver/ non alcoholic steatohepatitis like histological finding on liver biopsy.[15]

When mean SGOT, SGPT, cumulative dose and weekly dose of methotrexate in the two groups were compared, a significant difference was observed ($p<0.001$). This finding was similar to various other studies which supports the phenomenon of mean dose of methotrexate being higher among the patients with transaminitis ($p<0.001$).[12,14,15,16] Leonard PA et al conducted a study on 163 RA patients over a period of 8 years and concluded that liver function abnormalities were seen more frequently in patients with longer duration of methotrexate therapy and in those with higher total dose.[12] Van der Heijde and Walker et al reported that liver toxicity, cirrhosis and liver failure were MTX-dose related in RA, which was similar to our finding. [27, 28] The other parameters of liver function like total bilirubin, total protein, alkaline phosphatase, gamma glutaryl transferase, prothrombin time and INR were unaffected and there was no significant difference between those with and without raised transaminase levels.

The exact mechanism linking cumulative MTX dose to transaminitis remains unclear. Several processes and pathways have been implicated in MTX related hepatotoxicity but folate antagonism probably takes the lead role.[29] Cáliz et al demonstrated that the C677T polymorphism in the MTHFR gene is associated with MTX toxicity in a Spanish RA population.[30] In a recently published meta-analysis, however, the authors concluded that neither C677T nor A1298C gene polymorphism showed association with MTX toxicity.[31]

The major strength of our study is that it was carried out on a representative sample of population and other causes of deranged liver enzymes like diabetes mellitus, dyslipidemia, obesity, hepatitis B and C infection, patients with significant alcohol consumption and those taking other hepatotoxic drugs were excluded. One of the major limitations of the study is that fatty liver was diagnosed by USG and not by liver biopsy. Therefore USG could have underestimated the actual prevalence of fatty liver in our patients. Also baseline ultrasonography prior to commencement of MTX was not available. Therefore the cause effect relationship could not be ascertained and it warrants a longitudinal study with a longer follow up.

V. Conclusion:

Hepatotoxicity is a common complication of long term treatment with MTX. However, it is mostly self limiting by dose reduction or discontinuation. Nevertheless, liver function should be monitored regularly and folate supplement given to all patients on this medication. Better understanding of the mechanism of hepatoxicity will help in prevention and management more effectively.

References:

[1]. Cutolo M, Sulli A, Pizzorni C, Seriolo, Straub RH. Anti-inflammatory mechanisms of methotrexate in rheumatoid Arthritis. Ann Rheum Dis 2001;60:729–35.

[2]. Singh JA, Saag KG, Bridges Jr SL, Akl EA, Bannuru RR, Sullivan MC, et al. American College of Rheumatology guideline for the treatment of rheumatoidarthritis. Arthritis Rheum 2016;68:1–26.

[3]. Shinde CG, Venkatesh MP, Pramod Kumar TM, Shivakumar HG. Methotrexate: a gold standard for treatment of rheumatoid arthritis. J Pain Palliat Care Pharmacother2014;28:351–8.

[4]. Lopez-Olivo MA, Siddhanamatha HR, Shea B, Tuqwell P, Wells GA, Suarez-Almazor ME. Methotrexate for treating rheumatoid arthritis. CochraneDatabaseSyst Rev 2014;(6):CD000957.

[5]. Gossec L, Smolen JS, Ramiro S, de Wit M, Cutolo M, Dougados M, et al. European League against Rheumatism (EULAR) recommendations for the managementof psoriatic arthritis with pharmacological therapies: 2015 update. Ann RheumDis 2016;75:499–510.

[6]. Chan ES, Cronstein BN. Molecular action of methotrexate in inflammatory diseases. Arthritis Res 2002, 4:266-73.

[7]. Cronstein BN, Naime D, Ostad E. The anti-inflammatory mechanism of methotrexate. Increased adenosine release at inflamed sites diminishes leukocyte accumulation in an in vivo model of inflammation. J Clin Invest 1993, 92:2675-82.

[8]. Dahl MG, Gregory MM, Scheuer PJ. Methotrexate hepatotoxicity psoriasis –comparison of different dose regimens. Br Med J 1972;1:654–6.

[9]. van Ede AE, Laan RF, Rood MJ, Huizinga TW, van de Laar MA, van DenderenCJ, et al. Effect of folic or folinic acid supplementation on the toxicity and efficacy of methotrexate in rheumatoid arthritis: a forty-eight week, multi-center, randomized, double-blind, placebo-controlled study. Arthritis Rheum2001;44:1515–24.

[10]. Whittle SL, Hughes RA. Folate supplementation and methotrexate treatment in rheumatoid arthritis: a review. Rheumatology 2004;43:267–71.

[11]. Kent PD, Luthra HS, Michet C. Risk factors for methotrexate-induced abnormal laboratory monitoring results in patients with rheumatoid arthritis. J Rheumatol 2004;31(9):1727-31.

[12]. Leonard PA, Clegg DO, Carson CC, Cannon GW, Egger MJ, Ward JR. Low dose pulse methotrexate in rheumatoid arthritis: A 8-year experience with hepatotoxicity. ClinRheumatol 1987;6(4):575-82.
[13]. McKendry RJ, Dale P. Adverse effects of low dose methotrexate therapy in rheumatoid arthritis. J Rheumatol 1993;20(11):1850-6.
[14]. Hoekstra M, van Ede AE, Haagsma CJ. Factors associated with toxicity, final dose, and efficacy of methotrexate in patients with rheumatoid arthritis. Ann Rheum Dis 2003;62(5):423-6.
[15]. Mori S, Arima N, Ito M, Fujiyama S, Kamo Y, Ueki Y. Non-alcoholic steatohepatitis-like pattern in liver biopsy of rheumatoid arthritis patients with persistent transaminitis during low-dose methotrexate treatment. PLoS ONE 2018;13(8):e0203084. Available at: https://journals.plos.org/plosone/article
[16]. ?id=10.1371/journal.pone.0203084. Accessed on September 30,2020.
[17]. Schmajuk G, Miao Y, Yazdany J, Boscardin WJ, Daikh DI, Steinman MA. Identification of risk factors for elevated transaminases in methotrexate users through an electronic health record. Arthritis Care Res (Hoboken) 2014 Aug 66(8):1159-66.
[18]. Phillips CA, Cera PJ, Mangan TF, Newman ED. Clinical liver disease in patients with rheumatoid arthritis taking methotrexate. J Rheumatol 1992 Feb;19(2):229–33.
[19]. García DS, Saturansky EI, Poncino D, Martínez-Artola Y, Rosenberg S, Abritta G, et al. "Hepatic toxicity by methotrexate with weekly single doses associated with folic acid in rheumatoid and psoriatic arthritis. What is its real frequency?". Ann Hepatol 2019 Sep-Oct;18(5):765-9.
[20]. Selmi C, De Santis M, Gershwin ME. Liver involvement in subjects with rheumatic disease. Arthritis Res Ther 2011 Jun 30;13(3):226.
[21]. Whiting-O'Keefe QE, Fye KH, Sack KD. Methotrexate and histologic hepatic abnormalities: a meta-analysis. Am J Med. 1991 Jun;90(6):711–6.
[22]. Boulton JG, Bax DE. An unusual cause of abnormal liver function in a patient with rheumatoid arthritis. Rheumatology 2008 Feb 1;47(2):226–7.
[23]. Sundbaum JK, Eriksson N, Hallberg P, Lehto N, Wadelius M, Baecklund E. Methotrexate treatment in rheumatoid arthritis and elevated liver enzymes: A long-term follow-up of predictors, surveillance, and outcome in clinical practice. Int J Rheum Dis 2019;22(7):1226–32.
[24]. Gilani STA, Khan DA, Khan FA, Ahmed M. Adverse effects of low dose Methotrexate in rheumatoid arthritis patients. J Coll Physicians Surg Pak 2012;22(2):101-4.
[25]. Willkens RF, Leonard PA, Clegg DO, TolmanKG,Ward JR, Marks CR et al. Ann Rheum Dis 1990;49(1):591-593
[26]. Van Vollenhoven RF, McGuire JL. Estrogen, Progesterone, and Testosterone: Can they be used to treat Autoimmune Diseases? Cleveland Clinic J Med1994;61:276-84.
[27]. Cutolo M, Villaggio B, Seriolo B, MontagnaP,Capellino S, Straub RH, et al. Synovial fluid estrogens in rheumatoid arthritis. Autoimmun Rev2004;3:193–8.
[28]. Foster F, Anania FA, Li D, Katz R, Budoff R. The prevalence and clinical correlates of non-alcoholic fatty liver disease (NAFLD) in African Americans: the multi-ethnic study of atherosclerosis (MESA). Digest Dis Sci2013;58(8):2392-8.
[29]. Niaz A, Ali Z, Nayyar S, Fatima N.Prevalence of NAFLD in healthy and young male individuals. ISRN Gastroenterol2011;2011(1):1-4.
[30]. Visser K, van der Heijde DMFM. Risk and management of liver toxicity during methotrexate treatment in rheumatoid and psoriatic arthritis: a systematic review of the literature. ClinExp Rheumatol2009;27(6):1017-25.
[31]. Walker AM, Funch D, Dreyer NA. Determinants of serious liver disease among patients receiving low-dose methotrexate for rheumatoid arthritis.Arthritis Rheumat 1993;36(3):10-4.
[32]. van Ede AE, Laan RFJM, Blom HJ, de Abreu RA, van de Putte LBA. Methotrexate in rheumatoid arthritis: an update with focus on mechanisms involved in toxicity. Semin Arthritis Rheum 1998;27(5):277-92.
[33]. Cáliz R, delAmo J, Balsa A. The C677T polymorphism in the MTHFR gene is associated with the toxicity of methotrexate in a Spanish rheumatoid arthritis population. Scand J Rheum2012;41(1):10-4.
[34]. Owen SA, Lunt M, Bowes J. MTHFR gene polymorphisms and outcome of methotrexate treatment in patients with rheumatoid arthritis: analysis of key polymorphisms and meta-analysis of C677T and A1298C polymorphisms. Pharmacogenomics 2013;13(2):137-47.
[35]. American diabetes association. Diagnosis and classification of Diabetes Mellitus. Diabetes Care. 2010 Jan; 33(Suppl 1): S62–S69. doi: 10.2337/dc10-S062
[36]. P G Talwalkar, C G Sreenivas, A Gulati,Hemang Baxi. Journey in guidelines for lipid management: From adult treatment panel (ATP)-I to ATP-III and what to expect in ATP-IV.Indian J Endocrinol Metab. 2013 Jul-Aug; 17(4): 628–35. doi: 10.4103/2230-8210.113753

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