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**Title**

Methotrexate hepatotoxicity in patients with rheumatoid arthritis.

**Permalink**

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**Journal**

Middle East Journal of Digestive Diseases, 2(2)

**ISSN**

2008-5230

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**Publication Date**

2010-09-01

Peer reviewed

# Methotrexate Hepatotoxicity in Patients with Rheumatoid Arthritis

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## ABSTRACT

### BACKGROUND

Increases in aminotransferases (transaminitis) are potential major adverse reactions seen with long-term use of methotrexate (MTX). The aim of this study, therefore was to evaluate the incidence of MTX induced hepatotoxicity and its risk factors among rheumatoid arthritis (RA) patients.

### METHODS

This retrospective study described 286 patients with RA who received  $\geq 7.5$  mg MTX weekly in an academic rheumatology clinic over a 15 year period. The results of serial liver function tests, concurrent MTX dose, cumulative dose and use of hepatotoxic drugs were collected and statistically analyzed according to a consecutive elevation in aminotransferases which occurred over at least a two week interval.

### RESULTS

During the study period, 286 patients (84.4% female) with mean age of  $46.6 \pm 12.7$  years (18-84 years) were enrolled. Transaminitis occurred among 23.7% of patients (incidence: 6.9 per 100 person-years) during  $40.5 \pm 34.6$  month's exposure to MTX (989.6 person-years). The time difference between onset of therapy and occurrence of transaminitis was  $22.1 \pm 22.0$  months.

The only significant factor related to the occurrence of transaminitis was the duration of MTX therapy. The average duration of treatment among patients with transaminitis ( $59.6 \pm 42.3$  months) was greater than those with no transaminitis ( $p < 0.001$ ). The cumulative dose of MTX was significantly related to the occurrence of transaminitis ( $p < 0.001$ ).

### CONCLUSION

MTX hepatotoxicity is a common complication of long-term treatment with MTX. It is associated with mild liver enzyme elevation and related to the duration of therapy.

### KEYWORDS

Methotrexate; Arthritis; Rheumatoid; Drug toxicity

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Received: 6 May 2010  
Accepted: 10 August 2010

## INTRODUCTION

Methotrexate (MTX), as the most disease modifying anti-rheumatic drug used for rheumatoid arthritis (RA), has been available for clinical use since 1951.<sup>1</sup> Its widespread availability along with the high prevalence of RA which requires long-term therapy has attracted physicians' attention to the adverse reactions of MTX. The increases in aminotransferases (transaminitis) are a potential major adverse reaction seen with long-term use of MTX.

Many risk factors such as age, duration of exposure to MTX and its cumulative dose, history of non alcoholic steatohepatitis (NASH), diabetes and obesity, hepatitis B or C virus infection, alcohol consumption and hepatotoxic drugs can increase the hepatotoxic effect of MTX.<sup>2-11</sup>

The incidence of MTX-induced transaminitis varies according to different definitions. Some papers<sup>10,12</sup> have defined it as elevated liver enzymes 2-3 times greater than the normal range. These studies have estimated the frequency of transaminitis to be 7.5 to 26% of all patients treated with MTX. Others have histologically defined it as grades III B and IV based on the Roenigk classification. In this group, the frequency varied from 1% by Kremer et al.<sup>13</sup> who analyzed pooled data from 17 studies, 7.5% by Erickson et al.<sup>14</sup> and as high as 27 or 29% in other studies.<sup>5,15</sup>

In this retrospective study, the incidence of MTX induced transaminitis among RA patients and its risk factors are evaluated in a large referral university clinic.

## MATERIALS AND METHODS

Data were obtained in three different questionnaires, which were completed by RA patients in an academic rheumatology clinic. Patients had received  $\geq 7.5$  mg MTX weekly for at least one month during their follow up from 1991-2006.

Abnormal LFT was defined as above normal laboratory range.

Patients who used less than 7.5mg or with a duration of less than one month were excluded. In addition, patients were excluded from the study if their liver function tests (LFT) were checked once during the treatment period or positive hepatitis viral markers (HBs-Ag, HCV Antibody) were noted.

The first questionnaire was completed by patient interviews and chart reviews. This questionnaire consisted of primary data regarding age, gender, BMI, disease activity, alcohol consumption, cigarette smoking, presence of liver disease including fatty liver or non-alcoholic steatohepatitis (NASH) and autoimmune hepatitis, presence of diabetes, dyslipidemia, renal failure and congestive heart failure and use of concurrent hepatotoxic drugs.

In the second questionnaire, documents of the patients' charts of every visit date from 1991 in addition to the concurrent weekly dose of MTX, its cumulative dose and results of serial laboratory tests (longitudinal course) which included complete blood cell counts (CBC), fasting blood sugar (FBS), lipid profiles, blood urea nitrogen (BUN), creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, serum albumin, prothrombin time and bilirubin were obtained. Moreover, if MTX was discontinued during the patient's follow up, the cause for discontinuation was identified based on chart review.

Among patients with incidental abnormal liver function tests (LFT), further evaluations of HBs antigen, HCV antibody, liver sonography and liver biopsies (if noted in the charts or as reported by the patients) were collected in the third questionnaire.

Finally the database that included 295 patients who received  $\geq 7.5$  mg MTX weekly for at least one month were prepared for analysis by SPSS. Reliable *p*-values by chi-square or T -test and Multi-variant analysis were gathered. Other findings which included the time

of the first enzyme assay after onset of therapy, the time and intervals of LFT measurement throughout the treatment, creatinine clearance (Crcl), BMI and total cumulative dose of MTX were calculated.

In the presence of an abnormal LFT, the time of the enzyme assay, concurrent dose of MTX and concurrent cumulative dose, times of LFT abnormalities, presence of the abnormal liver enzyme level 2-3 times above the normal range and any change in the treatment strategy such as changes in MTX dose or intervals of LFTs and the level of the next consecutive enzyme (normal or high) were all evaluated.

For better evaluation of MTX-induced transaminitis and exclusion of incidental findings for abnormal enzymes (e.g., laboratory errors) and other causes of liver enzyme elevation, four categories were defined:

1. Patients who had two consecutive enzyme elevations with at least a two week interval or those with synchronous changes in enzyme levels by MTX doses (decreased enzyme levels after reduced dose or discontinuation) were defined as “definite cases of MTX-induced transaminitis” in the absence of any other absolute cause for LFT abnormalities.
2. Patients with at least two non-consecutive enzyme elevations without another explanation for the elevation were assumed to be “probable cases of MTX-induced transaminitis”.
3. Patients with only one abnormal LFT detected during the treatment period and subsequent normal levels of enzymes, without any synchronous change in MTX dose, were categorized as “less probable cases of MTX-induced transaminitis”.
4. Patients who had other documented causes of LFT abnormalities such as autoimmune hepatitis, CHF and hepatic congestion, NASH and the use of other hepatotoxic drugs were assumed as “others”.

In this classification, groups 1 and 2 were defined as MTX-induced transaminitis and used for risk factor evaluation.

In order to eliminate the significant treatment duration effects on the total cumulative dose and for better evaluation of pure MTX dose effects on transaminitis, the proportion of cumulative dose (mg) to duration of therapy (months) was calculated in each group and determined to be the total density of MTX dose per month.

## RESULTS

Totally, 286 patients were treated with MTX for  $40.5 \pm 34.6$  months (range: 1-168 months; 989.6 person-years exposure to MTX) with 2567 LFT recorded and 177 (35.7%) abnormal tests. The mean LFT interval measurement was  $4.7 \pm 3.0$  (0.7-30) months. Transaminitis occurred among 23.7% of patients (95% CI: 18.4-29.5). The incidence of transaminitis was 6.9 per 100 person-years exposure to MTX (95% CI: 5.3-8.7).

High level enzyme elevation (at least  $> 2 - 3$  times of normal range) was found only by 3.5% of patients and only one of them discontinued treatment permanently. The mean age during the treatment period was  $46.6 \pm 12.7$  (18-84) years. Most (84.4%) were female, of which 68.1% had active disease at the last visit during the study period. Mean BMI was  $27.3 \pm 4.7$  ( $16.4 - 42$ )  $\text{kg}/\text{m}^2$  and it was higher in females than males ( $p < 0.001$ ).

Table 1 shows the liver enzyme elevation according to gender, coexisting medical problems and hepatotoxic drug consumption.

Crcl levels in 8.1% of patients (by Cockcroft-Gault equation) ranged from 30-60 ml/min/ $1.73\text{m}^2$  and four patients had Crcl values  $< 50$  ml/min/ $1.73\text{m}^2$ .

**Table 1:** Enzyme elevation according to gender, coexisting medical problems and hepatotoxic drug consumption.

|                                | Group with hepatotoxicity (%) | Group with no-hepatotoxicity (%) | p-value |
|--------------------------------|-------------------------------|----------------------------------|---------|
| Gender (female)                | 25                            | 16.2                             | 0.89    |
| Liver disease*                 | 50                            | 22.7                             | 0.09    |
| Congestive heart failure       | 41.7                          | 22.7                             | 0.16    |
| Alcohol consumption            | 1.8                           | 0.5                              | 0.42    |
| Cigarette smoking              | 12.5                          | 24.4                             | 0.38    |
| Diabetes mellitus              | 30.4                          | 23                               | 0.44    |
| Hypertriglyceridemia           | 26.8                          | 23                               | 0.69    |
| Hypercholesterolemia           | 32.3                          | 22.4                             | 0.44    |
| Hepatotoxic drug consumption** | 31.3                          | 14                               | 0.001   |
| Use of chloroquine             | 22.8                          | 26.9                             | 0.69    |

\* Autoimmune hepatitis, non-alcoholic steatohepatitis, liver congestion due to congestive heart failure and mitral stenosis, Gilberts' disease, autoimmune hepatitis and liver hemangioma.

\*\* NSAID, Sulfasalazine, Angiotensin Converting Enzyme inhibitors and Angiotensin Receptor Blockers, Statins and Omeprazole. (Prednisolone has been used in all of the patients).

The time difference between the onset of therapy and occurrence of transaminitis was  $22.1 \pm 22.0$  (0.3-115) months where 75% of the abnormal LFT levels occurred prior to 32 months.

The duration of treatment and total cumulative dose of MTX was significantly related to transaminitis, in that 45.2% of the patients who received  $>1.5$  g MTX had evidence of elevated enzymes.

According to the duration of treatment, 217/286 (75.9%) of the patients were treated for less than five years, 56/286 (19.6%) between five to ten years and 13/286 (4.6%) above ten years.

After the classification of patients according to the duration of treatment, again the cumulative dose was significantly different in those with transaminitis in comparison to the others ( $p < 0.001$ ).

The mean monthly MTX dose was  $34.5 \pm 10.4$ , and  $36 \pm 11.5$  mg/month in groups with and without transaminitis, respectively which was not significantly different (Table 2), although this proportion was significantly higher in pa-

tients who were treated less than five years in comparison with other patients ( $p < 0.001$ ).

**Table 2:** Risk factor comparison between patients with or without liver enzyme elevation.

|   | Patients with abnormal LFTs (SD) | Patients with normal LFTs (SD) | p-value |
|---|----------------------------------|--------------------------------|---------|
| Age (years)                             | 46.1 (13.1)                      | 46.4 (12.4)                    | 0.89    |
| BMI (kg/m <sup>2</sup> )                | 27.4 (5.1)                       | 46.9 (4.6)                     | 0.55    |
| Crcl (cc/min/1.73 m <sup>2</sup> )      | 107 (42.3)                       | 103.3 (32.4)                   | 0.45    |
| Duration of treatment with MTX (months) | 59.6 (42.3)                      | 35.6 (31.0)                    | <0.001  |
| Interval of LFTs (months)               | 4.5 (2.4)                        | 4.8 (3.3)                      | 0.34    |
| Total cumulative dose of MTX (mg)       | 1707.3 (1231.1)                  | 1205.7 (1086.9)                | <0.001  |
| Mean MTX dose per month (mg/month)      | 34.5 (10.4)                      | 36 (11.5)                      | 0.78    |

Concurrent dose and concurrent cumulative dose of MTX at the time of enzyme elevation were measured as  $8.3 \pm 4.1$  mg weekly and  $753.7 \pm 743.4$  mg, respectively. This concurrent cumulative dose was lower than the total cumulative dose in both groups but again after dividing the duration of treatment ( $35.5 \pm 9.1$  mg/mo), there was no difference between this proportion and the mean monthly MTX dose, as noted earlier.

After the first enzyme elevation, the MTX dose was either reduced or discontinued in 31.4% of these patients. As a result, normalization of liver enzymes were seen among 73.5% of the patients after  $3.5 \pm 2.3$  months. MTX dose was reduced or discontinued in 33.3% of the remainder of high risk patients who had two consecutive enzyme elevations with normalization seen with the third enzyme among 73.3% of these high risk patients. One patient, herself, with NASH discontinued MTX treatment after 15 months with normalization in her enzymes.

No evidence of clinical cirrhosis was seen until the last visit in the study period.

**DISCUSSION**

This study showed that transaminitis occurred among 23.7% of patients who received  $\geq 7.5$ mg MTX per week.

The average duration of treatment among patients with transaminitis was significantly higher than the other patients and it was noted that the cumulative dose of MTX was also significantly related to the occurrence of transaminitis.

Yazici et al. estimated the frequency of AST elevation above 40 or ALT above 50 by 16.5% in their first article.<sup>16</sup> In their second paper, the incidence of MTX-induced transaminitis was reported in a cohort study to be 7.1 per 100 person-years exposure to MTX.<sup>17</sup> In comparison with our study, the incidence of transaminitis was significantly lower. This difference may be partially attributed to different intervals of enzyme measurements, which were longer in our study.<sup>16, 17</sup> Additionally, in the second article by Yazici et al., the likelihood of a clinically severe abnormality (including AST value above 80) was similar during each year of the five years of observation, which contradicted the findings of our study where the maximum incidence of enzyme elevation occurred during the initial years of treatment with MTX.<sup>17</sup>

The age of our study population was lower than other studies<sup>14,15,17</sup>; thus the younger age of patients in this study may be a reason for masking the effect of age on transaminitis, probably due to better MTX hepatic clearance.

As with other studies,<sup>3,18</sup> in our study the BMI was higher among women. In addition, transaminitis may be influenced by numerous other factors such as younger age and lower dose of MTX administration.

Hydroxychloroquine, as previously noted to be a protective factor of MTX-induced transaminitis<sup>19</sup>, was used by the majority of patients and might be one of the above factors, however multivariate analysis did not support this hypothesis.

BMI was higher when compared to the other reports<sup>3,18</sup> but despite of high BMI among the patients in our study, no significant relation was found between the risk factors of NASH and presence of transaminitis (such as hypertriglyceridemia, diabetes and obesity), against to Langman et al.<sup>7</sup> study about NASH.

The limitation of this study was that no liver biopsies were performed for determining the real importance of transaminitis.<sup>20</sup> However, histology-based studies favor the effect of MTX on the progression of fibrosis<sup>21</sup> and show a positive predictive value of 30% for fibrosis by serial abnormal liver function tests.<sup>15</sup> In addition, many trials show the incoherency of liver enzymes and histological findings.<sup>15, 22</sup>

In conclusion, MTX transaminitis is a common complication of long-term treatment with MTX as based on liver enzyme elevation. Transaminitis is associated with mild liver enzyme elevation and is related to the duration of therapy.

**CONFLICT OF INTEREST**

The author declare no conflict of interest related to this work.

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