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Original Article

Safety of liver function monitoring every 3 months in patients treated with low dose methotrexate

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Abstract

Introduction: The objective of this study was to evaluate the safety of liver transaminases monitoring every 12 weeks in patients with inflammatory connective tissue disorders who are treated with methotrexate (MTX).

Methods: In a retrospective study, the data from the rheumatic patients receiving MTX were analyzed. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were measured at baseline and every 12 weeks. The patients were classified according to their ALT and AST levels as no change, 1-2 times increase, 2-3 times increase, and more than 3 times increase in their ALT or AST levels. Based on the physician's decision on the dose of MTX, the patients were classified into no change in MTX dose, decrease in MTX dose, and discontinuation of MTX. Based on the physician's final decision about the continuation of MTX, the patients were classified into one of the following groups: continuation of MTX without MTX dose reduction; MTX dose reduction; MTX discontinuation due to liver complication; and MTX discontinuation due to other reasons.

Results: A total of 809 patients who were on MTX were included in the study. The mean follow-up duration and the mean duration of treatment with MTX were 31.22 and 19.76 months, respectively. The mean accumulation dose of MTX was 865.85 mg. Due to the increase in the level of transaminases in 26 (3.2%) of the patients the dose of MTX was reduced, and in 9 (1.1%) cases it was temporarily discontinued. During the follow-up of the patients with elevated transaminases levels, they returned to normal limits in 90 (99.5%) of the patients; however, in 4 of the cases (0.5%) they remained elevated and MTX was discontinued. The probability of the patients remaining on MTX for 5 years without discontinuation for liver complications was 98.5%.

Conclusion: Liver transaminases monitoring every 12 weeks for MTX treated patients is safe.

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Introduction

Methotrexate (MTX) is a folate antagonist, and the most frequently used disease-modifying antirheumatic drug (DMARD) in the treatment of rheumatoid arthritis (RA) and other inflammatory connective tissue disorders.[1,2] MTX is applied at a low dose (5-25 mg weekly) in the treatment of rheumatic disorders. It can be used via oral, intramuscular, and subcutaneous routes as either monotherapy or in combination with other DMARDs or biologic drugs. Its adverse

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effects have been a concern, but long-term experience found that this drug is one of the safest DMARDs. The increase of liver transaminases [alanine aminotransferase (ALT), aspartate aminotransferase (AST)] is a common complication of MTX reported in 10-43% of the cases.[3-11] However, this increase is often mild (2 times) and disappears spontaneously with decreasing the dose or discontinuing MTX temporarily.[3,12] The main concern is the persistent elevation of transaminases which can be accompanied with histologic changes in liver and most importantly fibrosis.[13] However, studies in RA patients who were on MTX showed that the rate of liver cirrhosis was less than 2% and that there was a low risk of mild liver fibrosis.[14-18] Serial liver transaminases measurement is a relatively sensitive and specific method of predicting severe liver damage like fibrosis and cirrhosis in patients that are on MTX.[14,19] In 1994, the American College of Rheumatology (ACR) published guidelines for monitoring the development of MTX induced liver toxicity.[16] These recommendations included measuring ALT and AST every 4–8 weeks. The evidence for the ACR guideline was only based on two studies. These studies consisted of 18 patients who received MTX for a mean period of 102 months, and 45 patients who were treated for a mean period of 30 months.[10] The optimal frequency of ALT and AST monitoring was 4-8 weeks. Based on these data, the experts recommended a monitoring schedule that is widely used in their clinical practice. In their survey, Yazici et al. reported that 22% of American rheumatologists who participated in this survey monitored liver transaminases less frequently. Less than 5% of their patients had persistent transaminase elevation requiring an alteration in the treatment, and 41% of the participants believed that the ACR guideline for monitoring MTX induced liver toxicity should change.[20] The guideline of Pavy et al. published in 2006 recommended the monitoring of ALT and AST every 4-12 weeks, but the recommended level and power were 3 and D, respectively.[21,22]

In spite of more than 5 decades of the use of MTX in the treatment of inflammatory connective tissue disorders, there is not enough evidence for the appropriate frequency of liver transaminases monitoring. The aim of our study was considering the safety of liver transaminases monitoring every 12 weeks in patients with inflammatory connective tissue disorders who are on MTX.

Methods

In the current retrospective study, the data from the rheumatic patients receiving MTX in the subspecialty clinics of Tabriz University of Medical Sciences, Iran, were analyzed. The design of the study was approved by the Ethics Committee of Tabriz University of Medical Sciences (TUMS). All the patients with inflammatory connective tissue disorders who had at least one follow-up visit were entered into this study. Patients with abnormal baseline liver function tests, carriers of hepatitis B surface antigen and hepatitis C virus, patients with renal failure defined by a serum creatinine more than 1.4, and active bone marrow disease defined by leukopenia (white blood cell count of less than 4000) or thrombocytopenia (platelet count of less than 100000) were excluded from the study.

According to the discipline of the rheumatology clinics, in patients who receive MTX, blood cells count, ALT, AST, alkaline phosphatase, albumin, urea, and creatinine should be measured at baseline. In our study patients, the dose of MTX was 5-25 mg per week orally or intramuscular, accompanied by folic acid 1 mg per day. A physical examination was carried out looking for the clinical signs of liver disease in each follow-up visit. Blood cells were counted, and ALT and AST were measured every 12 weeks. ALT and AST were measured after overnight fasting using the International Federation of Clinical Chemistry (IFCC) method. The upper limit of normal (ULN) reference values for ALT and AST ranged from 31-45 IU/l for women and from 40-45

IU/l for men. The measurement was repeated in patients with ALT or AST of higher than twice the ULN. ALT or AST of > 2 × ULN was considered a significant abnormality. Persistence was defined as ALT or AST of > 2 × ULN continued for more than 6 months after the first incidence. The patients were classified according to their ALT and AST levels as no change, 1-2 times increase, 2-3 times increase, and more than 3 times increase in ALT or AST levels. Based on the physician's decision on the dose of MTX, the patients were classified into groups of no change in MTX dose, decrease in MTX dose, and discontinuation of MTX. According to our center discipline, if ALT or AST was 1-2 × ULN, no change in the MTX dose was made; if it was 2-3 × ULN, the MTX dose was reduced; and if it was > 3 × ULN, MTX was temporarily discontinued. After 2-4 weeks, ALT and AST were measured again. If ALT and AST reached the normal level, MTX was started again with a lower dose; however, if they were higher than ULN, the following tests were performed: albumin, alkaline phosphatase, prothrombin time, bilirubin, viral hepatitis markers, autoimmune hepatitis markers, and liver ultrasonography. A clinically serious liver disease was defined as clinical evidence of liver disease including ascites, esophageal varices, hepatic encephalopathy, or hyperbilirubinemia (> 5 mg/dl), shrunken liver on imaging, and splenomegaly. Disease duration, MTX dose, duration of treatment with MTX, and MTX cumulative dose were entered in a checklist. Based on the physician's final decision about the continuation of MTX, the patients were classified into one of the following groups: continuation of MTX without MTX dose reduction; MTX dose reduction; MTX discontinuation due to liver complication; and MTX discontinuation due to other reasons.

Descriptive statistics and Kaplan Mayer were used for the analysis. All the analyses were performed using SPSS for Windows (version 16; SPSS Inc., Chicago, IL, USA).

Results

A total of 809 patients (605 women, 204 men) with inflammatory connective tissue disorders (Table 1) who were on MTX from December 2007 to July 2013 were included in the study. They had a mean age of 44.88 ± 1.6 (min 3, max 93) years and a disease duration of 61.75 (min 4, max 531, mode 36) months. The mean follow-up duration after the diagnosis of rheumatic disease and the mean duration of treatment with MTX were 31.22 (min 1, max 144, mode 6) and 19.76 (min 1, max 144, mode 12) months, respectively. The mean accumulation dose of MTX was 865.85 (min 30, max 11200, mode 90) mg. Table 1 shows the other medications used for the treatment of the patients under study.

Table 1. Disease type and other medications of study patients

Disease type	Number	Percent
RA	608	75.2
Seronegative spondyloarthritis	60	7.4
Undifferentiated inflammatory arthritis	29	3.6
Systemic lupus erythematous	21	2.6
Systemic sclerosis	19	2.3
Behcet's disease	15	1.9
Idiopathic inflammatory myopathies	12	1.5
Vasculitis	11	1.4
Juvenile RA	7	0.9
Others	27	3.2
Medications		
Prednisolone	781	96.5
Hydroxychloroquine	656	81.2
Sulfasalazine	86	10.6
Non-steroidal anti-inflammatory drugs	52	6.4
Cyclosporine A	21	2.6
Azathioprine	10	1.2
Cyclophosphamide	2	0.2
Mycophenolate	1	0.1

RA: Rheumatoid arthritis

In the follow-up period, ALT and AST were measured 5236 times. In 108 (13.3%) of the patients the level of ALT and/or AST increased. In 75 (9.3%) of the cases they increased 1-2-fold; in 27 (3.3%) of them the increase was up to 2-3-fold, and in 6 (0.7%) of the patients it was > 3-fold. The mean number of episodes of transaminases elevation was 1.44 ± 0.9 (min 1, max 5). In 32 (29.6%) of the

patients transaminases increased more than 1-fold. In 69 (63.9%) of the 108 patients with elevated transaminases, the first episode was in the first 12 months after starting MTX (10.86 ± 7.4). Due to the increase in the level of transaminases, in 26 (3.2%) of the patients, the dose of MTX was reduced, and in 9 (1.1%) of the patients, it was temporarily discontinued. During the follow-up of the patients with elevated transaminases, transaminases returned to normal limits in 90 (99.5%) of the patients and in only 4 of the cases (0.5%) they remained elevated and MTX was discontinued. Altogether MTX was discontinued in 131 (16.2%) of the patients during the follow-up period (Table 2). Table 2 shows that MTX was discontinued for liver complications only in 0.5% of the patients. In all the patients, transaminases reached the normal level after discontinuation of MTX, and liver biopsy was not performed in any of our participants. No cases of hepatic insufficiency, cirrhosis, or death due to liver complications were observed. The study showed a statistically meaningful relationship between cumulative MTX dose and duration of the treatment, and an increase in transaminase level ($P > 0.001$). The probability of transaminase elevation rose with the increase in MTX dose and treatment duration. The study showed no relationship between the underlying disease and other medications of the patients, and the increase in transaminase level.

Table 2. Reason of MTX (Methotrexate) discontinuation in the study patients

Reason of MTX discontinuation	Number	Percent
Remission	89	11.0
Pregnancy planning, pregnancy	17	2.1
Incompliance	9	1.1
In effectiveness	5	0.6
Transaminases elevation	4	0.5
Nausea, vomiting	2	0.2
Other complications	4	0.5

MTX: Methotrexate

According to the Kaplan-Meier analysis, the probability of the patients remaining on treatment 5 years after starting MTX was 48.2% (Figure 1). After excluding MTX discontinuation for remission, the probability went up to 84.2% (Figure 2). Finally, the Kaplan-Meier analysis showed that the probability of the patients remaining on MTX 5 years without discontinuation for liver complications was 98.5% (Figure 3).

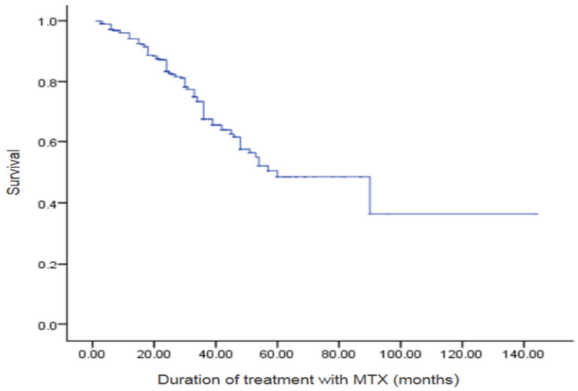

Figure 1. Cumulative probability of continuation of MTX (Methotrexate)

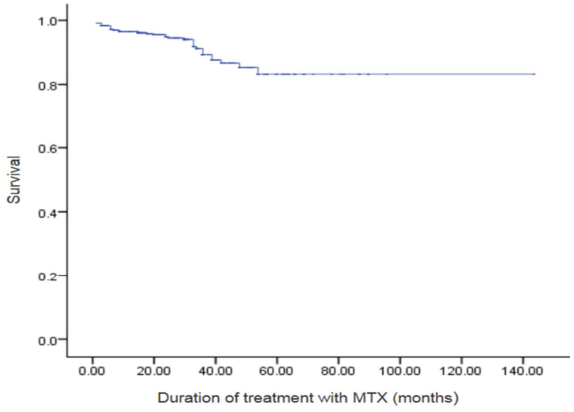

Figure 2. Cumulative probability of continuation of MTX (Methotrexate) after excluding remission

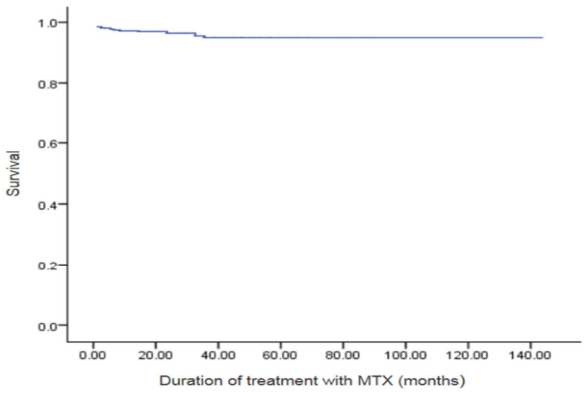

Figure 3. Cumulative probability of continuation of MTX (Methotrexate) without liver complication

Discussion

The 809 patients with inflammatory connective tissue disease accumulated 1332 person-years of treatment with MTX. Transaminase monitoring was performed every 12 weeks. A significant increase in transaminase was observed in only 4% of the patients, and MTX was discontinued permanently due to transaminase elevation in 0.5% of the cases. In all the patients with transaminase elevation, enzymes returned to the normal level with dose reduction or discontinuation of MTX. No cases of persistent liver transaminase elevation or clinically serious liver disease were observed. This means that monitoring liver transaminase every 12 weeks is safe.

In agreement with our study, Beyeler et al. showed that only in 2 cases out of the 117 RA patients who were on MTX for 7 years, MTX was discontinued due to liver complications.[23] Liver biopsy was performed in 16 patients, 14 of whom had Roenigk grades I and II, and only 2 of the patients had Roenigk grades III. In another study on 248 RA patients who accumulated 1000 patient-years of treatment with MTX, an AST over 80 U/l was reported in 0.9/100 patient-years.[24] No cases of progression to clinical disease or further worsening were seen, and no liver biopsies were performed. In the study by Alarcon et al. on 152 RA patients treated with MTX, the overall probability of continuing MTX was 50% in 5 years.[25]

In another study, Kaplan-Meier's analysis of the 224 RA patients on MTX showed that the probability of patients remaining on treatment 5 years after starting MTX was 58.5%.[26] No case of severe liver complications was reported. In a systematic literature research which included 88 published studies, Salliot and van der Heijde showed that in 3808 patients who were on low dose MTX during a period of 55.8 months of follow-up, 20.2% of the cases had an increase in their ALT or AST, in 12.9% of the patients the increase was up to two times the ULN, and 3.7% of the patients stopped MTX due to liver toxicity.[9] In a recent study by Dirven et al. on RA patients treated with MTX mono- or combination therapy, the increased levels of ALT of > 2× ULN was reported in 6.3/100 patient-years, which is lower than that previously reported.[27] Persistence of ALT of > 2× ULN was rare.

Studies about the hepatic complications of MTX and monitoring of liver function tests were not arranged according the appropriate intervals of liver transaminases monitoring. The only evidence of the frequency of liver transaminases monitoring is gained from a meta-analysis of two uncontrolled studies.[16] These two studies reported the results of liver transaminases monitoring every 2–6 weeks in 45 and 18 RA patients who were on MTX for 30 and 102 months, respectively.[10]

Based on these data, the experts recommended the monitoring of liver transaminases every 4-12 weeks. However, our study was performed on 809 patients (1332 person-years of treatment with MTX) and showed that monitoring of liver transaminases every 12 months is safe. Our study has a number of limitations. First, we did not have the patients' history of alcohol consumption. Second, liver biopsy was not performed in our patients and we do not have information about subclinical hepatic damage.

Conclusion

MTX is a safe drug for long-term application in the doses used to treat chronic inflammatory diseases. Severe hepatotoxicity may develop in a very low percentage of patients who are treated with MTX and liver transaminases monitoring every 12 weeks for MTX treated patients is desirable.

Conflict of Interests

Authors have no conflict of interest.

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