ORIGINAL ARTICLE

Liver Toxicity in Rheumatoid Arthritis Patients Treated with Methotrexate

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Abstract

Background: Methotrexate (MTX) is one of the most commonly used disease-modifying antirheumatic drugs in the treatment of rheumatoid arthritis (RA) which can be associated with toxic effects on different organs. This study was designed to investigate the hepatotoxic effects in RA patients treated with MTX.
Methods: In this cross-sectional observational study, RA patients who received standard dose regimen of methotrexate (7.5-15 mg/week) for a minimum of 3 months were included. Liver function parameters including serum alanine aminotransferase (ALT), aspartate aminotransferase (AST) and albumin as well as prothrombin time (PT) were assessed for all patients. The patients were divided into two groups according to the MTX dose received: (1) low-dose group (≤ 7.5 mg/week) and (2) high-dose group (> 7.5 mg/week).
Results: One-hundred patients (64% women) with mean age of 45.8 ± 7.5 years were studied. Eighty patients (80%) received low-dose MTX and the rest received high-dose MTX. Mean values of AST (P = 0.004), ALT (P = 0.001) and PT (P = 0.014) were significantly higher in patients receiving high-dose MTX compared with those who received low-dose MTX. Mean serum albumin was significantly lower in high-dose MTX receiving patients (P = 0.014). Moreover, elevated AST (RR (95% CI): 4.3 (2.1-8.7), P < 0.001), increased ALT (RR (95% CI): 4.9 (2.4-9.9), P < 0.001), and hypoalbuminemia (RR (95% CI): 2.3 (1.1-4.7), P = 0.030) were significantly more common in patients treated with high-dose MTX. The liver parameters restored to normal values after discontinuation of the treatment.
Conclusion: MTX therapy especially in doses higher than 7.5 mg/week can be associated with increased risk for hepatotoxic effects. Regular monitoring for patients under MTX treatment is necessary.

Keywords: Drug-Induced Liver Injury; Liver Function Tests; Methotrexate; Rheumatoid Arthritis; Toxicity

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INTRODUCTION

Rheumatoid arthritis (RA) is a chronic multisystem autoimmune disease with yet unfolded pathogenesis (1,2). The prevalence of RA is globally estimated to be around 1% of the general population; however, in Asian Pacific countries, it is lower than this rate (3). In Iran, 0.37% of urban population is involved with RA (3). Women are affected approximately three times more often than men. The prevalence increases with age, and sex differences diminish in the older ages.

MTX is one of the most commonly used disease-modifying antirheumatic drugs in the initial treatment and as the main drug in combination therapies for RA (4,5). Despite being well tolerated, long-term use of MTX in recommend dose regimens might be associated with toxic effects especially on bone marrow, liver and gastrointestinal system (5-10). This study was designed to investigate the hepatotoxic effects in RA patients treated with MTX.

METHODS

In this cross-sectional observational study carried out in March 2011 to December 2012, newly diagnosed patients with active RA according to American College of Rheumatology criteria for at least 6 months who received standard dose regimen of methotrexate (7.5-15 mg/week) for a minimum of 3 months were included. The treatment for the patients also included combination regimen of sulfasalazine (1-2 g/day), hydroxychloroquine (400 mg/day) in addition to oral corticosteroids (≤ 10 mg/day of prednisone or similar equivalents). Supplemental therapy with folic acid (5 mg/day) or folinic acid (15 mg/day) was given to the patients as well. Exclusion criteria comprised patients with severe RA according to Disease Activity Score 28 (DAS28 > 5.1),

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history of hepatitis B or C infection, history of malignancies within the past 5 years, history of hepatic failure and recent treatment with non-steroidal anti-inflammatory drugs before inception of MTX therapy. Moreover, patients with hemoglobin level of less than 10 g/dL, platelet count below 150,000/mm^3, serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels higher than the upper limit of normal (ULN) based on gender, increased prothrombin time (PT) with respect to the reference laboratory (> 13.5 sec), reduced serum albumin level (< 3.4 g/dL) and increased serum creatinine (based on gender), prior to starting the MTX therapy were excluded. Serum levels of AST, ALT and albumin were assessed using standard kits. After receiving 3 months of MTX therapy (in the context of the combination regimen), the patients' samples were obtained in one occasion 3 days after the final dose. The patients were divided into two groups according to the MTX dose received: (a) low-dose group (≤ 7.5 mg/week) and (b) high-dose group (> 7.5 mg/week).

The study has been approved by the institutional review board and all patients gave informed consent before entering the study. Comparison of the prevalence of liver function abnormalities between the two MTX dosage groups was analyzed with chi-squared test and the relative risk (RR) is shown with 95% confidence interval (95% CI). Comparison of mean values of liver function parameters between the two groups was analyzed with Student's t-test. Probability values of less than 0.05 were considered significant.

RESULTS

General profile of patients

One-hundred RA patients with mean (± SD) age of 45.8 ± 7.5 years were studied. Most patients were women (64%). The patients were treated with mean MTX dose of 8.1 ± 1.3 mg per week. Eighty patients (80%) received low-dose MTX and the rest received high-dose MTX.

Mean levels of liver function markers including AST, ALT, serum albumin and PT were 29.1 ± 18.9 IU/L, 35.3 ± 25.8 IU/L, 3.6 ± 0.4 g/dL and 14.0 ± 0.9 sec, respectively. Increased AST was found in 16% of patients, increased ALT in 17% of patients, hypoalbuminemia in 22% of patients and increased PT in 16% of patients. AST and ALT elevations greater than twice the ULN was seen in 5% and 12% of patients, respectively.

Comparison of liver function parameters between study groups

Mean values of AST (P = 0.004), ALT (P = 0.001) and PT (P = 0.014) were significantly higher in patients receiving high-dose MTX compared with those who received low-dose MTX (Table 1). Moreover, mean serum albumin was significantly lower in high-dose MTX receiving patients (P = 0.014).

Elevated AST was significantly more common in high-dose MTX treated patients compared with low-dose treated patients (45% vs. 8.8%, P <0.001). Likewise, increased ALT was significantly more common in high-dose MTX treated patients (50% vs. 8.8%, P < 0.001). Furthermore, over two fold increase in AST and ALT levels were significantly more common in high-dose MTX group (P = 0.001, < 0.001, respectively). Hypoalbuminemia was more commonly seen in high-dose MTX group (P = 0.030). Although increased PT was more frequent in high-dose MTX treated patients, the difference between the two groups was not statistically significant and it was only close to the level of significance (Table 2).

After discontinuation of MTX in patients with liver function abnormalities, the liver function parameters restored gradually to normal limits within 4-6 weeks.

DISCUSSION

In this study, we found that MTX doses over 7.5 mg per week were associated with higher risks for liver function abnormalities. Moreover, mean values of liver transaminases and PT were more significantly higher and mean level of serum albumin was significantly lower in patients treated with over 7.5 mg/week MTX compared to patients treated with lower than this dose.

MTX is a well-known cause of hepatic enzyme elevations (6). It has been ascertained that chronic low to moderate dose of MTX therapy can lead to liver enzyme abnormalities in 15 to 50% of patients (6,7,11-14). Fournier et al in a retrospective study on inflammatory bowel disease (IBD) patients, found that 24% of the patients with previously normal baseline aminotransferases developed abnormal hepatic aminotransferases after starting MTX therapy. In addition, they observed exacerbation of these abnormalities in patients with abnormal baseline aminotransferases (12).

Table 1. Analysis of mean levels of liver parameters according to study groups

	Total	Methotrexate dose		P value*
		High dose	Low dose	
AST (IU/L); mean ± SD	29.1 ± 18.9	46.4 ± 28.9	24.8 ± 12.2	0.004
ALT (IU/L); mean ± SD	35.3 ± 25.8	63.1 ± 38.4	28.5 ± 15.4	0.001
Serum albumin (g/dL); mean ± SD	3.6 ± 0.4	3.4 ± 0.5	3.6 ± 0.3	0.014
PT (sec); mean ± SD	14.0 ± 0.9	14.7 ± 1.3	13.9 ± 0.7	0.014

AST: Aspartate aminotransferase
ALT: Alanine aminotransferase
PT: Prothrombin time
* Analyzed with Student's t-test

Table 2. Analysis of frequency of impaired liver parameters according to study groups

	Total	Methotrexate dose		RR (CI 95%)	P value*
		High dose (n = 20)	Low dose (n = 80)		
Increased AST; n (%)	16 (16.0)	9 (45.0)	7 (8.8)	4.3 (2.1-8.7)	< 0.001
Increased AST > 2 × ULN; n (%)	5 (5.0)	4 (20.0)	1 (1.3)	4.1 (1.9-8.5)	0.001
Increased ALT; n (%)	17 (17.0)	10 (50.0)	7 (8.8)	4.9 (2.4-9.9)	< 0.001
Increased ALT > 2 × ULN; n (%)	12 (12.0)	10 (50.0)	2 (2.5)	7.3 (3.9-13.9)	< 0.001
Hypoalbuminemia; n (%)	22 (22.0)	8 (40.0)	14 (17.5)	2.3 (1.1-4.7)	0.030
Increased PT; n (%)	16 (16.0)	6 (30.0)	10 (12.5)	2.4 (1.0-5.8)	0.056

AST: Aspartate aminotransferase
ALT: Alanine aminotransferase
ULN: Upper limit of normal
PT: Prothrombin time
* Analyzed with chi-squared test

Te et al showed 30% of IBD patients treated with MTX had liver enzymes elevations (13). In another study, Sotoudehmanesh et al found transaminitis in 23.7% of 286 RA patients treated with over 7.5 mg MTX for an average of 3.5 years (14). Besides, according to different estimates and reports, 1-5% of patients treated with MTX may develop liver enzymes elevations twice the ULN (6,7,11). Similarly, in the present study, more than two-fold increase in liver transaminases (both AST and ALT) was seen in 5% of patients.

In addition to liver enzymes, other liver function parameters including serum albumin and coagulation factors can be affected by MTX-induced hepatotoxicity (15,16). In the present study, hypoalbuminemia was significantly more common among patients treated with higher doses of MTX. Clegg et al similarly reported this complication in long term MTX treatment (17). We also found that increased PT was more frequent in patients treated with higher doses of MTX. Totan et al, likewise, showed impairment in coagulation cascade (prolonged prothrombin time and activated partial thromboplastin time and decreased fibrinogen) and coagulation inhibitors in 20 patients treated with high dose MTX (16).

The question of what is the exact underlying mechanism for MTX-induced hepatotoxicity is still unanswered. Some tentative hypotheses have been suggested in this regard. In one theory, the direct effect of MTX, especially polyglutamated forms of MTX, which inhibit DNA synthesis in all cells including normal liver cells, has been proposed to trigger hepatic cell damage and degeneration (6,18). In another theory, prolonged MTX-induced activation of Ito cells has been suggested to result in transformation of these cells to myelofibroblasts and consequently produce hepatic fibrosis in the long run (6,18). Nonetheless, in several studies, liver biopsies of MTX treated patients revealed mild or non-significant hepatocellular changes (6,15,19-21), a fact that weakens the latter theory.

The good news for MTX users is that liver function abnormalities are mostly self-limiting especially in case of discontinuation of the drug or reduction of the dose (6,7,11,22). Our findings confirm this fact. Moreover, folate supplementation markedly diminishes liver toxicity as evidenced in several studies (22-24). Nonetheless, the treating physician should always be cautious about the potential threat of acute hepatic insufficiency and irreversible liver damages in their RA patients, and so, as directed by international guidelines, folate supplementation and regular monitoring of liver function status should be considered for all patients under treatment of MTX (25). Accordingly, liver transaminase profile should be monitored every 2-4 weeks for the first 3 months after initiation (or increasing the dose) of MTX, and for the next 3 months should be monitored every 8-12 weeks and beyond the first 6 months of therapy should be monitored every 12 weeks (25).

LIMITATIONS

The relatively small sample size of this study can be a limitation of this study. Moreover, in our analysis, the contributing effects of other drugs in the combination regimen given to our patients (i.e. sulfasalazine, hydroxychloroquine and low-dose prednisolone) could not be controlled. Liver injuries due to hydroxychlorquine and prednisolone are very rare and only reported in isolated cases (4,26,27). Although sulfasalazine has been recognized for causing liver injury, the incidence rate of sulfasalazine-induced liver injury is relatively low (1 per 1000 users) (28). Hence, the contributing role of sulfasalazine to the liver abnormalities of our patients is perhaps limited.

In the present study, newly diagnosed mild to moderate (DAS28 $\leq$ 5.1) RA patients were included. It should be noted that very chronic uncontrolled RA patients may develop liver damages by the disease itself or as a result of amyloidosis secondary to RA (29). Hence, we can assume that the liver function abnormalities detected in our patients can be majorly attributed to the MTX.

CONCLUSION

MTX therapy especially in doses higher than 7.5 mg/week can be associated with increased risk for hepatotoxic effects. Regular monitoring for patients under MTX treatment is necessary.

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REFERENCES

1. Picerno V, Ferro F, Adinolfi A, Valentini E, Tani C, Alunno A. One year in review: the pathogenesis of rheumatoid arthritis. Clin Exp Rheumatol 2015;33:551-8.
2. Mirfeizi Z, Noubakht Z, Rezaie AE, Jokar MH, Sarabi ZS. Plasma levels of leptin and visfatin in rheumatoid arthritis patients; is there any relationship with joint damage? Iran J Basic Med Sci 2014;17:662-6.
3. Davatchi F. Rheumatic diseases in the APLAR region. APLAR J Rheumatol 2006;9:5-10.
4. Smolen JS, Landewé R, Breedveld FC, Buch M, Burmester G, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. Ann Rheum Dis 2014;73:492-509.
5. Salliot C, van der Heijde D. Long-term safety of methotrexate monotherapy in patients with rheumatoid arthritis: a systematic literature research. Ann Rheum Dis 2009;68:1100-4.
6. Bath RK, Brar NK, Forouhar FA, Wu GY. A review of methotrexate-associated hepatotoxicity. J Dig Dis. 2014;15:517-24.
7. Curtis JR, Beukelman T, Onofrei A, Cassell S, Greenberg JD, Kavanaugh A, et al. Elevated liver enzyme tests among patients with rheumatoid arthritis or psoriatic arthritis treated with methotrexate and/or leflunomide. Ann Rheum Dis 2010;69:43-7.
8. Tornero Molina J, Ballina García FJ, Calvo Alén J, Caracuel Ruiz MÁ, Carbonell Abelló J, López Meseguer A, et al. Recommendations for the use of methotrexate in rheumatoid arthritis: up and down scaling of the dose and administration routes. Reumatol Clin 2015;11:3-8.
9. Haustein UF, Rytter M. Methotrexate in psoriasis: 26 years' experience with low-dose long-term treatment. J Eur Acad Dermatol Venereol 2000;14:382-8.
10. Weinblatt ME. Methotrexate in rheumatoid arthritis: a quarter century of development. Trans Am Clin Climatol Assoc 2013;124:16-25.
11. LiverTox, US National Institutes of Health. Methotrexate [Internet]. 2013 [Updated 2013 Apr 8, Cited 2015 May 2]. Available from: http://livertox.nih.gov/Methotrexate.htm
12. Fournier MR, Klein J, Minuk GY, Bernstein CN. Changes in liver biochemistry during methotrexate use for inflammatory bowel disease. Am J Gastroenterol 2010;105:1620-6.
13. Te HS, Schiano TD, Kuan SF, Hanauer SB, Conjeevaram HS, Baker AL. Hepatic effects of long-term methotrexate use in the treatment of inflammatory bowel disease. Am J Gastroenterol 2000;95:3150-6.
14. Sotoudehmanesh R, Anvari B, Akhlaghi M, Shahraeeni S, Kolahdoozan S. Methotrexate hepatotoxicity in patients with rheumatoid arthritis. Middle East J Dig Dis 2010;2:104-9.
15. Tolman KG, Clegg DO, Lee RG, Ward JR. Methotrexate and the liver. J Rheumatol Suppl 1985;12:29-34.
16. Totan M, Dagdemir A, Ak AR, Albayrak D, Kucukoduk S. Effects of high-dose methotrexate on the hemostatic system in childhood acute lymphoblastic leukemia. Med Pediatr Oncol 2001;36:429-33.
17. Clegg DO, Furst DE, Tolman KG, Pogue R. Acute, reversible hepatic failure associated with methotrexate treatment of rheumatoid arthritis. J Rheumatol 1989;16:1123-6.
18. Budzik GP1, Colletti LM, Faltynek CR. Effects of methotrexate on nucleotide pools in normal human T cells and the CEM T cell line. Life Sci 2000;66:2297-307.
19. Berends MA, Snoek , de Jong EM, van de Kerkhof PC, van Oijen MG, van Krieken JH, Drenth JP. Liver injury in long-term methotrexate treatment in psoriasis is relatively infrequent. Aliment Pharmacol Ther 2006;24:805-11.
20. Quintin E, Scoazec JY, Marotte H, Miossec P. Rare incidence of methotrexate-specific lesions in liver biopsy of patients with arthritis and elevated liver enzymes. Arthritis Res Ther 2010;12:R143.
21. MacDonald A, Burden AD. Noninvasive monitoring for methotrexate hepatotoxicity. Br J Dermatol 2005;152:405-8.
22. Hoekstra M, van Ede AE, Haagsma CJ, van de Laar MA, Huizinga TW, Kruijsen MW, et al. Factors associated with toxicity, final dose, and efficacy of methotrexate in patients with rheumatoid arthritis. Ann Rheum Dis 2003;62:423-6.
23. Strober BE, Menon K. Folate supplementation during methotrexate therapy for patients with psoriasis. J Am Acad Dermatol 2005;53:652-9.
24. Ortiz Z, Shea B, Suarez-Almazor ME, Moher D, Wells GA, Tugwell P. The efficacy of folic acid and folinic acid in reducing methotrexate gastrointestinal toxicity in rheumatoid arthritis. A metaanalysis of randomized controlled trials. J Rheumatol 1998;25:36-43.
25. Saag KG, Teng GG, Patkar NM, Anuntiyo J, Finney C, Curtis JR, et al. American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. Arthritis Rheum 2008;59:762-84.
26. Rodriguez-Caruncho C, Bielsa Marsol I. Antimalarials in dermatology: mechanism of action, indications, and side effects. Actas Dermosifiliogr 2014;105:243-52.
27. National Collaborating Centre for Chronic Conditions. Rheumatoid arthritis: national clinical guideline for management and treatment in adults. London: Royal College of Physicians; 2009.
28. de Abajo FJ, Montero D, Madurga M, García Rodríguez LA. Acute and clinically relevant drug-induced liver injury: a population based case-control study. Br J Clin Pharmacol 2004;58:71-80.
29. Ebert EC, Hagspiel KD. Gastrointestinal and hepatic manifestations of rheumatoid arthritis. Dig Dis Sci 2011;56:295-302.