Original article

J Nepal Health Res Counc 2020 Jul-Sep;18(48): 360-5

DOI: https://doi.org/10.33314/jnhrc.v18i3.2743

Adverse Events Profile of Low-dose Methotrexate in Nepalese Patients with Rheumatoid Arthritis: an Observational Study

Shweta Nakarmi,[1] Kalpana Pudasaini,[1] Bhojraj Adhikari,[2] Binit Vaidya[1]

[1]Department of Rheumatology, National Center for Rheumatic Diseases (NCRD), Ratopul, Gaushala, Kathmandu, Nepal, [2]Department of Internal Medicine, Bharatpur Hospital, Bharatpur, Chitwan, Nepal.

ABSTRACT

Background: Methotrexate is considered as the anchor drug for the treatment of rheumatoid arthritis. However, various adverse effects limit its use leading to frequent discontinuation of treatment. This study aimed to evaluate the common adverse effects of methotrexate in patients with rheumatoid arthritis.

Methods: A prospective observational study was conducted at National Center for Rheumatic Diseases from June 2018 to May 2019 among patients with rheumatoid arthritis using methotrexate monotherapy. Laboratory tests like liver function tests, renal function tests, complete blood count, C-reactive protein, erythrocyte sedimentation rate were done at baseline and every 3 months. Data on patients' comorbidities, disease activity and side effects of drug were collected on every follow- up. Statistical analysis was carried out with the help of SPSS 23.0.

Results: Out of 232 patients experiencing at least one adverse effect while on methotrexate monotherapy, 87.5% were female and mean age was 46.9±10.8 years. The mean dose of methotrexate was 16.6 ± 3.9 mg/week with the most frequently used dose of 20mg/week. Among the variety of adverse reaction observed, the most common was transaminitis (75.0%) with approximately 50.0% as isolated liver function abnormality, followed by nausea (19.4%), anorexia (12.9%), leukopenia (12.5%), oral ulcer (8.2%) and psychological intolerance (4.7%). Multiple regression analysis showed significant predictive value of body mass index for transaminitis (p-value 0.007).

Conclusions: Asymptomatic liver function test derangement was the most frequent adverse-effect of methotrexate observed, whereas nausea and anorexia were the most common patient reported events. The frequent dose associated with side-effects in Nepalese patients was around 20mg/week.

Keywords: Adverse events; methotrexate; Nepal; rheumatoid arthritis

INTRODUCTION

Methotrexate (MTX) is considered as the anchor immunosuppressant for rheumatoid arthritis (RA) because of its efficacy, cost-effectiveness, and acceptable toxicity profile.[1] It is used both as monotherapy or in combination with other DMARDs.[2] It is a folate antagonist, primarily metabolized in liver and mostly eliminated as unchanged drug by the kidneys.

The safety profile of MTX has been studied over several years and, adverse effects have been noted leading to discontinuation of MTX.[3] Possible toxicity ranges from mild to severe systemic side-effects involving gastrointestinal, renal, hepatic, pulmonary and hematopoietic systems.[4,5] With recent advances in genetic technology, studies have suggested the role of genetic variation in MTX transporter system in causing MTX toxicity and such association is distinct in different racial groups.[6]

This study aimed to evaluate adverse effects of MTX in Nepalese population and the frequently used dose of MTX associated with adverse effects.

METHODS

This was a prospective, observational, cohort study conducted at National Center for Rheumatic Diseases (NCRD), Kathmandu, Nepal from June 2018 to May 2019.

Written informed consent from each patient was obtained and ethical approval was obtained from Nepal Health Research Council, Nepal (Registration number

Correspondence: Dr Shweta Nakarmi, Department of Rheumatology, National Center for Rheumatic Diseases, Ratopul, Gaushala, Kathmandu, Nepal. Email: sweedie.shweta@gmail.com, Phone: +97714464288.

345/2018).

RA patients diagnosed on the basis of ACR/ European League against Rheumatism (EULAR) 2010 criteria[7]and who experienced any adverse effect with methotrexate monotherapy were included in the study. Patients with clinical diagnosis other than RA, under combination therapy with 2 or more DMARDs and those with pre-existing liver disease, impaired renal function, lung abnormalities on chest X-ray, and history of excessive alcohol intake were excluded from the study.

Socio-demographic data were recorded at the time of registration by a trained research officer in a pre-designed excel-sheet. Data were obtained on MTX dose, duration and use of concomitant medications at the baseline and 3 monthly follow- ups subsequently. Laboratory tests like liver function tests (LFT) which included serum glutamic pyruvic transaminase (SGPT); serum glutamic oxaloacetic transaminase (SGOT), renal function tests (RFT) which included urea and creatinine, complete blood count (CBC), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) were done at baseline and every 3months. Patients' co-morbidities, self-reported adverse-effects and disease activity were collected on every follow-up. Adverse effects of MTX were identified by patient interview (including self-report), laboratory abnormalities and file review. A dedicated mobile number carried by the research officer was provided to the patients to report any adverse events.

Abnormal liver function test was classified as more than 1- time the upper normal limit (UNL) for transaminases (SGPT: Serum glutamic pyruvic transaminase; SGOT: Serum glutamic oxaloacetic transaminase). World Health Organization (WHO) cutoff values of hemoglobin< 12 g/L for female and <13 g/L for male were used for the diagnosis of anemia[8] and total leukocyte count (TLC) <4000/ $mm^3$was considered as leukopenia. Thrombocytopenia was defined as platelet count <100,000/ mm^3.[9] Patients complaining of abdominal pain, nausea, vomiting and/or behavioral symptoms while on MTX were considered as MTX intolerants.[10]Psychological intolerance was defined as anticipatory nausea with methotrexate before actual intake of medicine.

Body mass index (BMI) was calculated using the formula [weight(kg)/height(m^2)]. CBC was performed using hematology analyzer (Elite 3 Erba version 2.1). ESR was done by Westergren's method. Serum electrolytes like sodium and potassium were done by direct ISE method and Jaffe's kinetic method was used for serum creatinine. Blood sugar was measured using glucose oxidase-peroxidase (GOD-POD) method. CRP was qualitatively measured by turbidimetry method using an automated analyzer (XL 200 Erba Mannheim). Liver function indexes like SGOT and SGPT were measured by International Federation of Clinical Chemistry (IFCC) with pyruvate dehydrogenous phosphatase (PDP), alkaline phosphatase (ALP) by IFCC with AMP (Adenosine monophosphate) buffer and bilirubin by Diazo method (Walter and Gerarde).

Statistical analysis was carried out with the help of SPSS software version (23.0 system for Windows (SPSS Chicago IL)). Quantitative variables were expressed in mean and standard deviation, and qualitative variables in frequency and percentage. Independent t-test was done to observe difference in mean MTX dose, age, BMI between groups with and without the particular adverse event. Chi-squared test was done where applicable. Multiple regression analysis was done to observe the predictive value of different variables for transaminitis. p-value of ≤ 0.05 was considered significant.

RESULTS

Out of 756 patients under MTX monotherapy, 232 (30.6%) patients experienced at least one adverse event. Of the 232 patients, majority were females (87.5%) with the mean age of 46.9±10.8 years. The average body mass index (BMI) of enrolled patients was 25.4±4.2kg/m^2. The most frequently used dose of MTX at which any adverse event was 20mg/week. The route of administration of MTX was oral in all the patients. Other demographic parameters are shown in table 1.

Table 1. Demographic profile of the study participants (n= 232).

Parameters	Frequency (%) or Mean ± SD
Age (years)	46.9 ± 10.8
Gender	Female 203 (87.5) Male 29 (12.5)
BMI (kg/m^2)	25.4 ± 4.2
Disease duration (months)	71.7 ± 62.6 (Median: 48.0)
Education	
Illiterate	49 (21.1)
Can sign only	45 (19.4)
Primary	13 (5.6)
Secondary	67 (28.9)
Higher secondary	28 (12.1)
Graduate	18 (7.8)
Post-graduate	12 (5.1)

Occupation	
Home-maker	162 (69.8)
Unemployed	3 (1.3)
Service holder	22 (9.5)
Business	11 (4.7)
Farmer	5 (2.2)
Others	29 (12.5)
Ethnicity	
Brahmin	72 (31.0)
Chhetri	55 (23.7)
Newar	69 (29.7)
Gurung	7 (3.0)
Madhesi	13 (5.6)
Others	16 (7.0)

BMI: body mass index; kg/m^2: kilogram per meter squared; %: percentage; SD: standard deviation

The mean DAS-28 score was 2.3±0.8. Other clinical profiles are shown in table 2. The most frequently observed patient reported adverse-events were gastrointestinal (nausea and vomiting) accounting for 25.0% of all. Psychological intolerance was reported in 4.7%.

Table 2.Clinical and laboratory parameters of the study participants (n=232).

Parameters	Frequency (%) or Mean ± SD	Normal values
RF	226 (97.3)	
ACPA	176 (75.8)	
Hb (gm/dL)	11.9 ± 1.5	12 - 16
TC (per cumm)	6158.6 ± 2387.5	4000 - 11000
Platelets (hundred thousand per cumm)	2.31 ± 0.79	1.5 - 4.5
SGPT (IU/L)	71.4 ± 60.2	5- 40
SGOT (IU/L)	57.0 ± 44.3	5 - 37
ESR (mm in 1st hour)	33.8 ± 14.0	0 - 20
CRP (mg/L)	8.6 ± 16.6	0 - 6
DAS 28	2.3 ± 0.8	
MTX dose (mg/ week)	Mean: 16.6 ± 3.9 Mode: 20.0	

RF- Rheumatoid Factor, ACPA- Anti-citrullinated Peptide Antibodies, HB- hemoglobin, TC- Total count, DAS- Disease activity Score

Leukopenia (12.5%) was the most common hematological adverse event noted. Other hematological abnormalities are mentioned in table 3.

Among the variety of laboratory adverse events observed, the most common was altered LFT (increased levels of SGOT and/or SGPT by more than 1- time the upper normal limit) accounting for 75.0% and approximately 50.0% had isolated liver function abnormality, commonly transaminitis of<3 times UNL. The frequencies of other adverse effects are shown in table 3.

Table 3. Adverse event profile of the study participants (n=232).

Adverse events	Frequency (%)
GI symptoms	
Nausea	45 (19.4)
Vomiting	13 (5.6)
Anorexia	30 (12.9)
Diarrhea	6 (2.6)
Oral ulcer	19 (8.2)
Hematological	
Anemia	1 (0.4)
Leukopenia	29 (12.5)
Thrombocytopenia	13 (5.6)
Hepatic	
Any Transaminitis	174 (75.0)
<3 times	149 (85.6)
>3 times	25 (14.3)
Psychological intolerance	11 (4.7)
Excess Hair fall	6 (2.6)

The mean age of patients with transaminitis and those with normal transaminases were 47.9±9.9 years and 40.9±14.9 years, respectively (p-value: 0.036). The mean BMI in patients with transaminitis and those with normal transaminases were 26.2±4.8 kg/m^2 and 22.9±3.2 kg/m^2, respectively (p-value <0.001) (table 4). When multiple regression analysis was done for age, BMI and dose of MTX, only BMI had significant predictive value for transaminitis (p-value 0.007).

Table 4. Comparison of baseline parameters between groups with normal versus raised transaminases.

Parameters	Transaminases: normal	Any transaminitis	p-value*
Age	40.9 ± 14.9	47.9 ± 9.9	0.036
BMI	22.9 ± 3.2	26.2 ± 4.8	<0.001
DAS 28	2.3 ± 0.8	2.4 ± 0.9	0.746
MTX dose	16.9 ± 3.6	16.0 ± 3.6	0.325
*Independent t-test			

Other adverse events did not correlate with the baseline parameters or dose of MTX. The mean values of age (p-value: 0.522), disease duration (p-value: 0.937), DAS 28 score (p-value: 0.701) or MTX dose (p-value: 0.706) did not differ between groups with and without leukopenia. The psychological intolerance did not correlate with gender (p-value: 0.726), and patients without transaminitis had psychological intolerance in comparison to those with deranged LFT (p-value: < 0.001). The mean values of age (p-value: 0.515) and MTX dose (p-value: 0.458) did not differ in patients with and without GI symptoms. GI symptoms did not show association with gender (p-value: 0.188).

DISCUSSION

RA, in the absence of treatment can lead to articular damage and bone erosions and may progress to more severe form that require aggressive and long-term treatment.[11] MTX, an anti-metabolite medication, is incontestably being used for several decades as an anchor drug for RA either as a monotherapy or in combination with other DMARDs and is considered to be the most accepted drug for a long- term therapy. Despite its efficacy, toxicity is a major concern that may lead to drug withdrawal.[12]

Various studies have observed the adverse effects of MTX monotherapy involving many organ systems ranging from mild gastrointestinal distress like nausea and vomiting to severe hepatotoxicity and bone marrow suppression.[13] Among many serious adverse effects attributed to MTX, liver related adverse reactions varying from asymptomatic transaminitis to fatal hepatic necrosis have been reported.[14] Sotoudenmanesh et al found 23.7% of patients on MTX with transaminitis.[15]Our study showed comparable results with 30.6% patients having any adverse-event while on MTX monotherapy, of which, transaminitis accounted for 75.0%; with mild transaminitis (< 3- times UNL) being the commonest (85.6%). Although exact mechanism is complex, the possible toxic effect of MTX on hepatocytes is thought to be due to reduced hepatic folate stores leading to elevated transaminases.[16]

GI side effects like nausea and vomiting are very common with the use of oral MTX.[17] Our study observed nausea (19.4%), vomiting (5.6%) and anorexia (12.9%) as the most common patient reported GI side effects. The frequencies noted for GI problems in our study were comparable with the study by Calasan et al. where 32.0% and 6.5% of the patients had nausea and vomiting, respectively after MTX administration.[10] A study on adolescents and young adults with inflammatory arthritis on MTX therapy showed higher frequencies for gastrointestinal symptoms ranging from 30.0 to 52.0%.[18] In contrast to a study by Lily et. al, where anemia (34.8%) was most common hematological side effect followed by leukopenia (4.4%), we observed 12.5% patients with leukopenia while anemia accounted for only 0.4%.[19] Since MTX-induced folate deficiency anemia is common[20], the concomitant use of folic acid with MTX in our patients is believed to have protective effect on anemia.

Psychological factors have long been recognized as an important predictor of MTX adherence in RA.[21] In a study by Calasanet. al, psychological intolerance of oral MTX was seen in 8.6% which is comparable to this study.[10] MTX inhibits deamination of adenosine, a purine-nucleoside and potentiates the vasodilator effect of adenosine. Adenosine, for its pathophysiological role in gastric acid secretion and its role as a modulator of neurotransmitter release, is believed to cause GI symptoms as well as leads to psychological intolerance due its cerebral accumulation in patients using MTX.[22]

Age and BMI were found to have correlation with transaminitis in this study. There are evidences of synergy between obesity and autoimmune disease where higher BMI is linked to higher liver dysfunction leading to MTX discontinuation.[23] Mean BMI in our patients were on overweight rangewith a greater proportion in those with transaminitis. Steatohepatitis could have contributed to deranged LFT in these patients. Since the prevalence of overweight population among Nepalese adults (women > men) is substantially rising, this factor was likely to cause higher rate of transaminitis in patients under MTX in this study.[24] Asians have a relatively lower BMI compared to Europeans and the most frequent dose of MTX at which adverse effects are seen can vary among those ethnical groups.[25]

This is a single-center study, thus the data may not represent the whole nation. Also, the authors did not quantify certain adverse events like nausea, vomiting, or MTX intolerance.

CONCLUSIONS

Asymptomatic liver function abnormalities and GI intolerance were the most common adverse events associated with MTX and the mean dose of MTX being used was 16.6 ± 3.9 mg/week. Thus, frequent monitoring should be exercised Nepalese patients on MTX therapy.

CONFLICT OF INTEREST

The authors do not have any conflict of interest to declare.

ACKNOWLEDGEMENT

The authors would like to acknowledge Dr. Jayanti Rai, Dr. Manisha Bhochhibhoya and Mr. Sanjay Gurung for their cooperation in patient care. We also thank Ms. Rakshya Joshi, research officer for helping with data collection and storage.

REFERENCES

1. Visser K, van der Heijde D. Optimal dosage and route of administration of methotrexate in rheumatoid arthritis: a systematic review of the literature. Ann Rheum Dis. 2009;68(7):1094-9.[PubMed | Full Text | DOI]
2. Emery P, Sebba A, Huizinga TW. Biologic and oral disease-modifying antirheumatic drug monotherapy in rheumatoid arthritis. Ann Rheum Dis. 2013;72(12):1897-904. [PubMed | Full Text | DOI]
3. Wang W, Zhou H, Liu L. Side effects of methotrexate therapy for rheumatoid arthritis: A systematic review. Eur J Med Chem. 2018;158:502-16. [PuMed | DOI]
4. Al-Niaimi F, Cox NH. Methotrexate safety: from prescribing to labelling. Br J Dermatol. 2009;160(6):1345-6. [Full Text]
5. Shen DD, Azarnoff DL. Clinical pharmacokinetics of methotrexate. Clin Pharmacokinet. 1978;3(1):1-13. [DOI]
6. Ranganathan P, Culverhouse R, Marsh S, Mody A, Scott-Horton TJ, Brasington R, et al. Methotrexate (MTX) pathway gene polymorphisms and their effects on MTX toxicity in Caucasian and African American patients with rheumatoid arthritis. J Rheumatol. 2008;35(4):572-9. [PubMed | Full Text]
7. Jonathan Kay, Katherine S. Upchurch, ACR/EULAR 2010 rheumatoid arthritis classification criteria, Rheumatology, Volume 51, Issue suppl_6, 1 December 2012, Pages vi5–vi9, https://doi.org/10.1093/rheumatology/kes279 [Full text]
8. Beutler E, Waalen J. The definition of anemia: what is the lower limit of normal of the blood hemoglobin concentration? Blood. 2006;107(5):1747-50. [Full Text |
9. Gayathri BN, Rao KS. Pancytopenia: a clinico hematological study. J Lab Physicians. 2011;3(1):15-20. [Full Text]
10. Calasan MB, van den Bosch OF, Creemers MC, Custers M, Heurkens AH, van Woerkom JM, et al. Prevalence of methotrexate intolerance in rheumatoid arthritis and psoriatic arthritis. Arthritis Res Ther. 2013;15(6):R217. [PubMed | Full Text |
11. Birch JT, Jr., Bhattacharya S. Emerging trends in diagnosis and treatment of rheumatoid arthritis. Prim Care. 2010;37(4):779-792. [PubMed | DOI]
12. Singh JA, Furst DE, Bharat A, Curtis JR, Kavanaugh AF, Kremer JM,et al. 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. Arthritis Care Res (Hoboken). 2012;64(5):625-39. [Full Text | DOI]
13. Shea B, Swinden MV, Tanjong Ghogomu E, Ortiz Z, Katchamart W, Rader T, et al. Folic Acid and Folinic Acid for Reducing Side Effects inPatients Receiving Methotrexate for RheumatoidArthritis. Cochrane Database Syst Rev. 2013;41(6). [PubMed | Full Text|
14. Visser K, van der Heijde DM. Risk and management of liver toxicity during methotrexate treatment in rheumatoid and psoriatic arthritis: a systematic review of the literature. Clin Exp Rheumatol. 2009;27(6):1017-25. [PubMed | Full Text]
15. Sotoudehmanesh R, Anvari B, Akhlaghi M, Shahraeeni S, Kolahdoozan S. Methotrexate hepatotoxicity in patients with rheumatoid arthritis. Middle East J Dig Dis. 2010;2(2):104-9. [Full Text]
16. van Ede AE, Laan RF, Rood MJ, Huizinga TW, van de Laar MA, van Denderen CJ, et al. Effect of folic or folinic acid supplementation on the toxicity and efficacy of methotrexate in rheumatoid arthritis: a forty-eight week, multicenter, randomized, double-blind, placebo-controlled study. Arthritis Rheum. 2001;44(7):1515-24. [PubMed | Full Text |DOI]
17. van Jaarsveld CH, Jahangier ZN, Jacobs JW, Blaauw AA, van Albada-Kuipers GA, ter Borg EJ, et al. Toxicity of anti-rheumatic drugs in a randomized clinical trial of early rheumatoid arthritis. Rheumatology (Oxford). 2000;39(12):1374-82. [PubMed | Full Text |DOI]
18. Patil P, Parker RA, Rawcliffe C, Olaleye A, Moore S, Daly et al. Methotrexate-induced nausea and vomiting in adolescent and young adult patients. Clin Rheumatol. 2014;33(3):403-407. doi:10.1007/s10067-013-2389-x [Full Text]
19. Dubey L, Chatterjee S, Ghosh A. Hepatic and hematological adverse effects of long-term low-dose methotrexate therapy in rheumatoid arthritis: An observational study. Indian J Pharmacol. 2016 Se;48(5):591-4. [PubMed | Full Text |DOI]

20. Casserly CM, Stange KC, Chren MM. Severe megaloblastic anemia in a patient receiving low-dose methotrexate for psoriasis. J Am Acad Dermatol. 1993;29(3):477-80. [PubMed]

21. Salt E, Frazier SK. Predictors of medication adherence in patients with rheumatoid arthritis. Drug Dev Res. 2011;72(8):756-63. [PubMed | Full Text]

22. Riksen NP, Barrera P, van den Broek PH, van Riel PL, Smits P, Rongen GA. Methotrexate modulates the kinetics of adenosine in humans in vivo. Ann Rheum Dis. 2006;65(4):465-70. [PubMed | Full Text | DOI]

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

24. Rawal LB, Kanda K, Mahumud RA, Joshi D, Mehata S, Shrestha N, et al. Prevalence of underweight, overweight and obesity and their associated risk factors in Nepalese adults: Data from a Nationwide Survey, 2016. PLoS One. 2018;13(11):e0205912. [PubMed | Full Text | DOI]

25. Wang D, LiY, Lee SG, Wang L, Fan J, Zhang G, et al. Ethnic differences in body composition and obesity related risk factors: study in Chinese and white males living in China. PLoS One. 2011;6(5):e19835. [PubMed | Full Text | DOI]