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BRIEF REPORT

Frequency of methotrexate intolerance in rheumatoid arthritis patients using methotrexate intolerance severity score (MISS questionnaire)

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Abstract The objective of the study was to determine the frequency of methotrexate intolerance in rheumatoid arthritis (RA) patients by applying the methotrexate intolerance severity score (MISS) questionnaire and to see the effect of dose and concomitant use of other disease-modifying antirheumatic drugs (DMARDS) on methotrexate (MTX) intolerance. For the descriptive study, non-probability sampling was carried out in the Female Rheumatology Department of Fauji Foundation Hospital (FFH), Rawalpindi, Pakistan. One hundred and fifty diagnosed cases of RA using oral MTX were selected. The MISS questionnaire embodies five elements: abdominal pain, nausea, vomiting, fatigue and behavioural symptoms. The amplitude of each element was ranked from 0 to 3 being no complaint (0 points), mild (1 point), moderate (2 points) and severe (3 points). A cut-off score of 6 and above ascertained intolerance by the physicians. A total of 33.3 % of the subjects exhibited MTX intolerance according to the MISS questionnaire. Out of which, the most recurring symptom of all was behavioural with a value of 44 % whereas vomiting was least noticeable with a figure of 11 %. About 6.6 % of the women with intolerance were consuming DMARDs in conjunction with MTX. Those using the highest weekly dose of MTX (20 mg) had supreme intolerance with prevalence in 46.2 % of the patients. The frequency of intolerance decreased with a decrease in weekly dose to a minimum of 20 % with 7.5 mg of MTX. MTX intolerance has moderate prevalence in RA patients and if left undetected, the compliance to use of MTX as a first-line therapy will decrease. Methotrexate intolerance is directly proportional to the dose of MTX taken. Also, there is no upstroke seen in intolerance with the use of other disease-modifying agents.

Keywords Concomitant DMARD therapy · Methotrexate · Methotrexate dose · Methotrexate intolerance severity score · Rheumatoid arthritis

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Introduction

Rheumatoid arthritis (RA) is an autoimmune disease that is caused by chronic inflammation of the joints or the synovial membrane surrounding the joints [1]. Chronic inflammation can also lead to cardiovascular and pulmonary complications [2]. RA affects between 0.5 and 1 % of adults in the developed world of all ages, but typically targets those between 20 and 45 years of age [3, 4]. Women are three times more likely to develop RA as compared to men [5]. Genetic factors are also involved in the pathogenesis of RA [6].

To acquire substantial clinical remission, it is mandatory to start drug therapy soon after the diagnosis and to enhance the treatment with the disease activity [7, 8]. The Treat-to-Target Recommendations are meant to outline the strategies to reach optimal outcomes of RA [9–11].

In countries like Pakistan, most of the RA patients have access to oral methotrexate (MTX) drug therapy only. It is

therefore imperative to study the development of intolerance to MTX among RA patients and its effects on drug compliance.

In the treatment of RA, the two main classes of medications are analgesics such as NSAIDs and disease-modifying anti rheumatic drugs (DMARDs). DMARDs are classified as synthetic DMARDs, e.g. methotrexate, sulfasalazine and leflunomide and newer biologic DMARDs [12].

MTX is the most important and useful DMARD, hence is usually the first-line treatment as it slows or halts the progress of the disease [13]. It must be remembered that MTX has certain side effects which can impair the quality of life [14]. Most common side effects are pertaining to gastrointestinal (GI) tract which are reduced with folic acid supplementation. Anticipatory and associative symptoms can hamper with compliance of the patient to long-term treatment. There are two main mechanisms which play a role in MTX-related GI intolerance. The epithelial cells located in the oral cavity and in the intestine are sensitive to MTX irrespective of folate deficiency. The gastrointestinal epithelium becomes more sensitive with the passage of time due to more and more accumulation of MTX [15]. The second mechanism of MTX intolerance is through stimulation of chemotactic trigger zone (CTZ).

The MISS questionnaire is used as a tool for early detection of MTX intolerance and change of treatment at an early stage to prevent progression of RA.

Materials and methods

One hundred fifty adult females suffering from RA were selected through non-probability sampling for the descriptive study in the Female Rheumatology Department Fauji Foundation Hospital, Rawalpindi, Pakistan, in 2014. All the subjects were diagnosed cases of RA according to the 1987 ACR criterion [16]. All were taking oral MTX as per protocol. Exclusive history was taken to rule out any current or previous drug intolerance [17]. Written/informed consent was taken from all patients. Demographic data constituting of name, sge and duration of MTX use was acquired. Information was secured about the weekly dose of MTX utilized along with parallel use of DMARDs, glucocorticoids, NSAIDs, COX 2 inhibitors, gastroprotective agents and any other medication the patient was taking [18]. All the subjects were using folic acid supplementation with oral MTX.

The MISS questionnaire is a validated tool supported by the American College of Rheumatology and published in 2011 [19]. The MISS Questionnaire embodies five elements: abdominal pain, nausea, vomiting, fatigue and behavioural symptoms. Each symptom is evaluated after intake of MTX, several hours to 1 day before taking MTX (anticipatory) and on thinking about MTX (associative). Behavioural symptoms constitute of restlessness, crying and irritability on taking MTX advancing on to refusal to take MTX [20]. The amplitude of each element was ranked from 0 to 3 being no complaint, mild, moderate and severe respectively. A cut-off score of 6 and above ascertained intolerance. Data collected was entered in SPSS version 21 and analysed. The frequency and percentage for the respective symptoms and the severity of each symptom with respect to MISS score was calculated and tabulated. Confidence interval was kept at 95 %. Null hypothesis was streamlined, accepted and rejected with relation to the results deduced from chi-square test, correlation, statistical significance and correlation coefficient.

Results

Out of the 150 subjects, 50 had MTX intolerance with a MISS score of 6 or above. Thus, the percentage of intolerance came out to be 33.3 % (Fig. 1). The symptoms were then individually analysed to scrutinize their respective potential prevalence and contribution to the intolerance. The results unfolded 44 % of the subjects to have behavioural symptoms followed by abdominal pain 34.66 %, nausea 34 % and fatigue 31.1 %. Only 11.33 % of the subjects had complaint of vomiting (Fig. 2). Frequency and percentage of each element according to severity were calculated as concluded in Table 1.

About 6.6 % of the patients were using DMARDS along with MTX. The effect of use of leflunomide and sulfasalazine on MTX intolerance along with statistics of those patients who

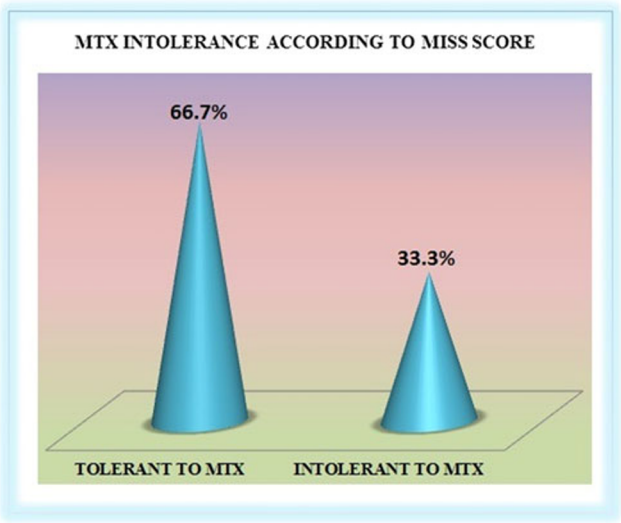

Fig. 1 Percentage of MTX tolerance and intolerance in RA subjects. Intolerance is calculated with patients having a MISS score of 6 or above in the study sample

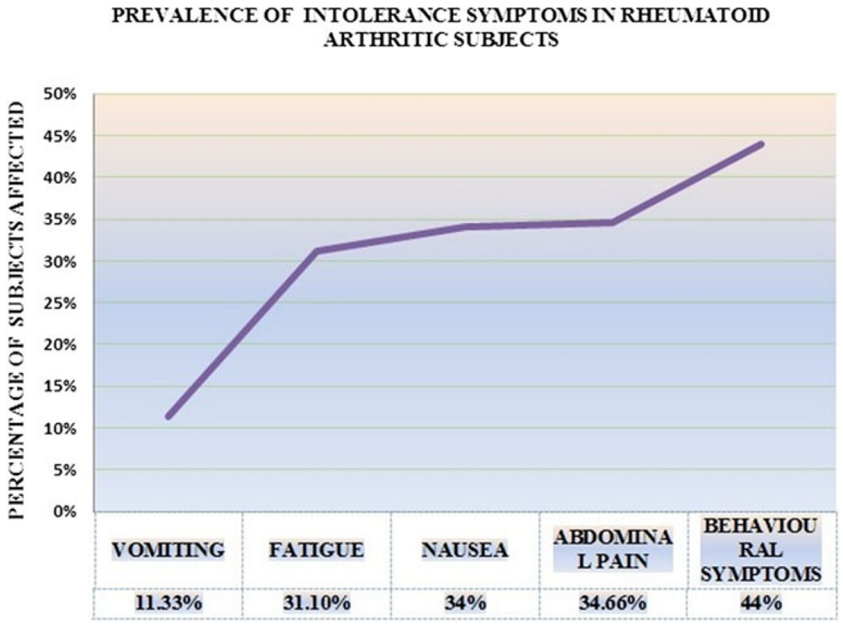

Fig. 2 Prevalence of intolerance symptoms in RA patients. Figure shows quota of subjects with each symptom diagnostic of intolerance to MTX

were not using any DMARDs other than MTX is shown in Fig. 3.

The subjects under study were using four different weekly strengths of oral MTX. Those using the highest weekly dose of MTX (20 mg) had supreme intolerance prevailing in 46.2 %. The frequency of intolerance decreased with a decrease in weekly dose being a minimum of 20 % with 7.5 mg (Fig. 4).

Table 1 Frequency of symptoms prevalent in rheumatoid arthritis subjects graded in the order of severity

Variation of symptoms in R.A subjects in concordance with MISS scoring criteria				
Behavioural symptoms	No complaint	Mild symptoms	Moderate symptoms	Severe symptoms
Restlessness	100	23	13	14
Crying	128	8	6	8
Irritability	108	9	9	24
Refusal to take MTX	127	8	6	9
Abdominal pain				
After MTX	98	14	19	19
Anticipatory	149	1	–	–
Associative	150	–	–	–
Nausea				
After MTX	102	22	15	11
Anticipatory	146	1	–	3
Associative	140	2	1	7
Fatigue				
After MTX	103	17	14	16
Anticipatory	148	1	–	1
Associative	148	1	–	1
Vomiting				
After MTX	132	12	2	4
Anticipatory	148	1	1	–
Associative	149	–	–	1

Behavioural symptoms constitute restlessness, crying and irritability on taking methotrexate (MTX) advancing on to refusal to take MTX. Rest of the symptoms is evaluated for after intake of MTX, several hours to 1 day before taking MTX and on thinking about MTX

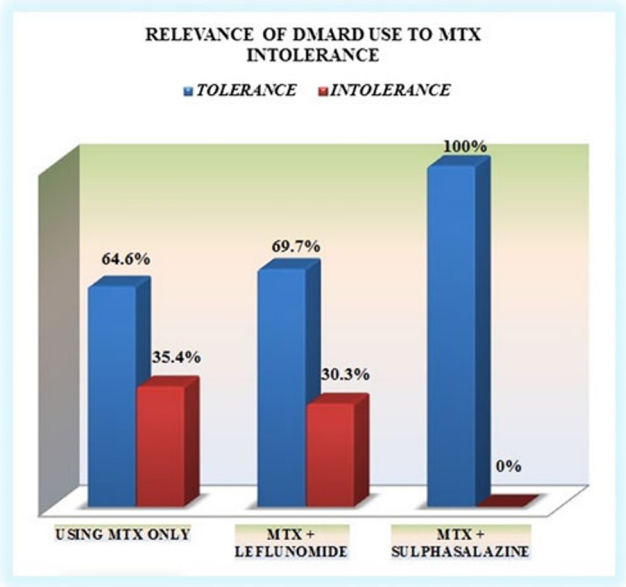

Fig. 3 Effect of concurrent use of other DMARDS with MTX on MTX intolerance. $p = 0.18$ by chi-square test

Discussion

RA is an irreversible disease, so the main focus of management is to improve the quality of life [21]. The first line of treatment used in RA is MTX.

In developing countries like Pakistan, most of the biologics are not accessible to the general population. So most of the rheumatologists as well as general practitioners stick to conventional DMARDs only. Among them, MTX is the most commonly used. As MTX is easily available, has good tolerance and is relatively inexpensive, its common GI side effects are being neglected. The treat to target approach for RA does not aim for remission or low disease activity only but also for improvement of quality of life. If common side effects are not monitored, patients either stop the medicine themselves without consulting their physicians or start taking complementary and alternative medicine (CAM). So early detection of these side effects is mandatory.

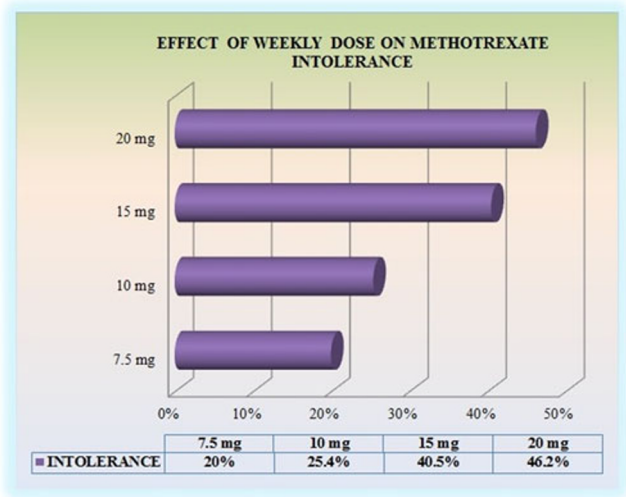

Fig. 4 Correlation of MTX intolerance with weekly dose utilized to be directly proportional. $p = 0.01$ by chi-square test with positive correlation coefficient

To overcome this hazard and to estimate the level of intolerance in a patient using MTX, MISS has been formulated and validated to assess the prevalence of this intolerance in RA patients [19].

This questionnaire was validated for juvenile idiopathic arthritis patients (JIA). In this study, MTX intolerance was found to be 50.5 % by using the MISS questionnaire.

A similar study carried out among rheumatoid and psoriatic arthritis patients showed 11 % of the patients to be intolerant to MTX out of which 81.3 % had behavioural symptoms, 56.3 % had nausea, 46.9 % had abdominal pain and 31.3 % had vomiting [22].

We used this questionnaire in adult RA patients who were taking MTX in order to assess their type of intolerance. Nevertheless, the MISS questionnaire should be validated for RA patients as well. Once validated, it can be used in routine practice.

This is the first study being done in Pakistan using a standard questionnaire to assess MTX intolerance in RA patients. A similar study was done in the Rheumatology Department of Pakistan Institute of Medical Sciences Hospital, Islamabad, using the same questionnaire in JIA patients showing MTX intolerance of 40 % [23]. Our evaluation points out that 33.3 % of the subjects visiting the Female Rheumatology Department exhibited MTX intolerance according to the MISS questionnaire. Out of which, the most recurring symptom was behavioural, i.e. 44 %, and least noticeable being vomiting, i.e. 11 %. This indicates that one third of the patients using MTX suffer from intolerance. Further stressing on the point, one third of the RA patients using MTX are prone to become non-compliant. In clinical practice, the anticipatory and associative symptoms are usually not asked for. These symptoms if severe can affect the patient's quality of life or make them abandon the proper treatment. Therefore, all patients using MTX should be monitored and inquired about any symptoms pertaining to intolerance [24].

The study has also brought to our notice that the use of other DMARDs has no effect on the MTX intolerance. A total of 6.6 % of the women with intolerance were consuming DMARDs in conjunction with MTX. The verdict goes in favour of null hypothesis affirming no association of MTX intolerance to the collateral use of DMARDs ($p = 0.18$).

Those using the highest weekly dose of MTX (20 mg) had supreme intolerance prevailing in 46.2 %. The frequency of intolerance decreased with a decrease in weekly dose being a minimum of 20 % with 7.5 mg. The result goes against null hypothesis corroborating a directly proportional association of MTX intolerance to the weekly dose taken ($p = 0.013$).

Our study had certain limitations. It was performed on a small sample size of 150 patients in the Female Rheumatology Department of Fauji Foundation Hospital. Therefore, no statistical data to reveal the prevalence of intolerance in male counterparts is available. All patients were using oral MTX so a comparative analysis of intolerance between oral and parenteral use of MTX could not be observed. As all the patients in the study sample were using folic acid, thus the increased level of intolerance due to folic acid deficiency could not be registered. As the patients were not inquired about the relation of symptoms with meal, hence a correlation of MTX intolerance before and after intake of meal was not seen.

To summarize, one can conclude that MTX intolerance has moderate prevalence in RA patients and if left untreated and undetected, it can reduce the compliance for MTX. Counselling should be inculcated in practice for intolerance to MTX as the most prevalent symptom is associative and apt rehabilitation should be done for it. The prescribing dose of MTX should be a matter of concern as higher dosage leads to more intolerance.

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Compliance with ethical standards

Disclosures None.

References

1. Walker BR, Colledge NR, Ralston SH, Penman I (2014) Davidson's principles and practice of medicine. Elsevier—Health Sciences Division
2. Ajeganova S, Andersson ML, Frostegard J, Hafstrom I (2013) Disease factors in early rheumatoid arthritis are associated with differential risks for cardiovascular events and mortality depending on age at onset: a 10-year observational cohort study. J Rheumatol 40(12):1958–1966. doi:10.3899/jrheum.130365
3. Scott DL, Wolfe F, Huizinga TW (2010) Rheumatoid arthritis. Lancet 376(9746):1094–1108. doi:10.1016/S0140-6736(10)60826-4
4. Yamanaka H, Sugiyama N, Inoue E, Taniguchi A, Momohara S (2014) Estimates of the prevalence of and current treatment practices for rheumatoid arthritis in Japan using reimbursement data from health insurance societies and the IORRA cohort (I). Mod Rheumatol 24(1):33–40. doi:10.3109/14397595.2013.854059
5. Kvien TK, Uhlig T, Odegard S, Heiberg MS (2006) Epidemiological aspects of rheumatoid arthritis: the sex ratio. Ann N Y Acad Sci 1069:212–222. doi:10.1196/annals.1351.019
6. Silman AJ, Pearson JE (2002) Epidemiology and genetics of rheumatoid arthritis. Arthritis Res 4(Suppl 3):S265–S272
7. Gramling A, O'Dell JR (2012) Initial management of rheumatoid arthritis. Rheum Dis Clin N Am 38(2):311–325. doi:10.1016/j.rdc.2012.05.003
8. Majithia V, Geraci SA (2007) Rheumatoid arthritis: diagnosis and management. Am J Med 120(11):936–939. doi:10.1016/j.amjmed.2007.04.005
9. Ruderman EM, Nola KM, Ferrell S, Sapir T, Cameron DR (2012) Incorporating the treat-to-target concept in rheumatoid arthritis. J Manag Care Pharm 18(9):1–18
10. Smolen JS, Aletaha D, Bijlsma JW, Breedveld FC, Boumpas D, Burmester G, Combe B, Cutolo M, de Wit M, Dougados M, Emery P, Gibofsky A, Gomez-Reino JJ, Haraoui B, Kalden J, Keystone EC, Kvien TK, McInnes I, Martin-Mola E, Montecucco C, Schoels M, van der Heijde D (2010) Treating rheumatoid arthritis to target: recommendations of an international task force. Ann Rheum Dis 69(4):631–637. doi:10.1136/ard.2009.123919
11. Axelsen MB, Eshed I, Horslev-Petersen K, Stengaard-Pedersen K, Hetland ML, Moller J, Junker P, Podenphant J, Schlemmer A, Ellingsen T, Ahlquist P, Lindegaard H, Linauskas A, Dam MY, Hansen I, Horn HC, Ammitzboll CG, Jorgensen A, Krintel SB, Raun J, Krogh NS, Johansen JS, Ostergaard M, group Os (2014) A treat-to-target strategy with methotrexate and intra-articular triamcinolone with or without adalimumab effectively reduces MRI synovitis, osteitis and tenosynovitis and halts structural damage progression in early rheumatoid arthritis: results from the OPERA randomised controlled trial. Ann Rheum Dis. doi:10.1136/annrheumdis-2013-204537
12. Wasserman AM (2011) Diagnosis and management of rheumatoid arthritis. Am Fam Physician 84(11):1245–1252
13. Fiehn C (2009) Methotrexate in rheumatology. Z Rheumatol 68(9):747–756. doi:10.1007/s00393-009-0535-2, quiz 757
14. Weekly oral methotrexate therapy: raise awareness of fatal dosing errors (2013). Prescrire international 22 (138):126
15. Chan ES, Cronstein BN (2013) Mechanisms of action of methotrexate. Bull Hosp Jt Dis 71(Suppl 1):S5–S8
16. MacGregor AJ (1995) Classification criteria for rheumatoid arthritis. Baillieres Clin Rheumatol 9(2):287–304
17. Bagatini F, Blatt CR, Maliska G, Trespash GV, Pereira IA, Zimmermann AF, Storb BH, Farias MR (2011) Potential drug interactions in patients with rheumatoid arthritis. Rev Bras Reumatol 51(1):20–39
18. Braun J (2011) Methotrexate: optimizing the efficacy in rheumatoid arthritis. Therapeutic advances in musculoskeletal disease 3(3):151–158. doi:10.1177/1759720X11408635
19. Bulatovic M, Heijstek MW, Verkaaik M, van Dijkhuizen EH, Armbrust W, Hoppenreijs EP, Kamphuis S, Kuis W, Egberts TC, Sinnema G, Rademaker CM, Wulffraat NM (2011) High prevalence of methotrexate intolerance in juvenile idiopathic arthritis: development and validation of a methotrexate intolerance severity score. Arthritis Rheum 63(7):2007–2013. doi:10.1002/art.30367
20. Vezmar S, Becker A, Bode U, Jaehde U (2003) Biochemical and clinical aspects of methotrexate neurotoxicity. Chemotherapy 49(1–2):92–104
21. Smolen JS, Aletaha D (2010) The assessment of disease activity in rheumatoid arthritis. Clin Exp Rheumatol 28(3 Suppl 59):S18–S27
22. Calasan MB, van den Bosch OF, Creemers MC, Custers M, Heurkens AH, van Woerkom JM, Wulffraat NM (2013) Prevalence of methotrexate intolerance in rheumatoid arthritis and psoriatic arthritis. Arthritis Res Ther 15(6):R217. doi:10.1186/ar4413
23. Babur Salim SA, Bhatti Raza A (2013) Frequency of methotrexate intolerance in juvenile idiopathic arthritis patients (JIA): an experience using methotrexate intolerance severity score (MISS). US Armed Forces Med J
24. Agarwal S, Zaman T, Handa R (2009) Retention rates of disease-modifying anti-rheumatic drugs in patients with rheumatoid arthritis. Singap Med J 50(7):686–692