



ORIGINAL ARTICLE

## Assessment of methotrexate intolerance through methotrexate intolerance severity score (MISS questionnaire) in patients of Rheumatoid Arthritis.

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**Article Citation:** Asghar MA, Hashmat M, Wagon AA, Zafar ZA, Atta-ur-Rehman, Pirzada AR. Assessment of methotrexate intolerance through methotrexate intolerance severity score (MISS questionnaire) in patients of Rheumatoid Arthritis. Professional Med J 2023; 30(06):736-740. <https://doi.org/10.29309/TPMJ/2023.30.06.7505>

**ABSTRACT... Objective:** To assess the frequency of methotrexate intolerance in patients with rheumatoid arthritis by using methotrexate intolerance severity scale. **Study Design:** Cross Sectional study. **Setting:** Sahiwal Teaching Hospital Sahiwal. **Period:** November 2021 – April 2022. **Material & Methods:** Sample of 178 cases were selected through non-probability consecutive sampling. Patients of age 20-80 years, either gender, diagnosed with rheumatoid arthritis were enrolled. The MISS questionnaire was used to note the information and intolerance was noted. Data analysis was done in SPSS version 25.0. **Results:** In this study, the mean age of patients was  $35.12 \pm 11.16$  years. Out of 178 patients, 24 (13.5%) were males and 154 (86.5%) were females. The mean duration of disease was  $31.22 \pm 23.94$  months. Mean duration of using methotrexate was  $12.03 \pm 12.61$  months. About 33.7% patients had mild to moderate complaint of abdominal pain after taking methotrexate, abdominal pain anticipatory was absent in 98.9% patients and abdominal pain associative was also absent in 96.6% cases. Restlessness was mild in 20 (11.2%) cases, moderate in 22 (12.4%) and severe in 4 (2.2%) cases. Irritability was mild in 22 (12.4%) cases, moderate in 20 (11.2%) and severe in 4 (2.2%) cases. Overall refusal of methotrexate was noted in 38 (21.3%) cases. The mean MISS score attained by patients was  $2.93 \pm 3.82$ . Out of 178 patients, 44 (24.7%) had intolerance against methotrexate use for rheumatoid arthritis. **Conclusion:** The frequency of intolerance against methotrexate in patients of rheumatoid arthritis is high and cannot be ignored. Further trials should be done and treatment alterations must be done to improve the tolerance and outcome of treatment.

**Key words:** Abdominal Pain, Intolerance, Irritability, Methotrexate, Nausea, Rheumatoid Arthritis, Refusal.

### INTRODUCTION

Rheumatoid arthritis is chronic autoimmune polyarthritis of synovial joints and also has various extra skeletal manifestations.<sup>1</sup> It is one of the most common inflammatory arthropathy and prevalence is about 0.5% - 1% in general population.<sup>2</sup> It can lead to permanent joint damage and deformities.<sup>3</sup> Main aim of the treatment is to achieve remission or low disease activity which has shown to prevent rheumatoid related joint damage.<sup>4</sup> Poor compliance with treatment is one the important factor of failure to achieve remission or low disease activity.<sup>5</sup>

Treatment of rheumatoid arthritis includes use of conventional synthetic DMARDs, biological DMARDs and symptomatic therapy with low dose

steroids and NSAIDs. Many guidelines including ACR and EULAR Guidelines recommend Methotrexate as first line DMARD because of good safety and efficacy profile.<sup>6,7</sup> Folic acid antagonist “methotrexate” is frequently prescribed to treat neoplastic diseases. Through interacting with dihydrofolate reductase, methotrexate prevents the formation of deoxyribonucleic acid, ribonucleic acid, and proteins. Now a days, one of the most often prescribed medications for the treatment of rheumatoid arthritis is methotrexate.<sup>8</sup> Major side effects of Methotrexate are hepatotoxicity, pulmonary toxicity, bone marrow suppression are fortunately rare but gastrointestinal symptoms including nausea, vomiting, diarrhea, abdominal pain are common and usually prevented by folic acid supplementation but still patients suffer

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**Article received on:** 20/02/2023  
**Accepted for publication:** 26/04/2023

from these symptoms. Many patients also have anticipatory symptoms which occur prior to methotrexate intake.<sup>9</sup>

Methotrexate intolerance remains a significant and a bit ignored problem in our clinical practice which can lead to poor compliance and poor disease control.<sup>10</sup> Data on this topic is scarce in Pakistan and one study done in 2016 showed prevalence of Methotrexate intolerance around 33%.<sup>11</sup> The Methotrexate Intolerance Severity Score (MISS) was created because there were no particular measures available to evaluate the side effects of using methotrexate.<sup>12</sup> Currently, this is the only questionnaire that formally assesses methotrexate intolerance while taking into account the side effects that are most common as well as behavioural, associative, and anticipatory symptoms, all of which are crucial in the detection of intolerance. This tool was created and tested on juvenile idiopathic arthritis patients, and it has also been approved for use in French-speaking juvenile idiopathic arthritis patients.<sup>13</sup> Moreover, the prevalence of methotrexate intolerance in people with RA and psoriatic arthritis has been studied in numerous nations using the MISS questionnaire.<sup>13,14</sup>

Aim of this study is to determine the frequency of methotrexate intolerance in patients with rheumatoid arthritis by using methotrexate intolerance severity scale and factors associated with it in patients with rheumatoid arthritis.

## MATERIAL & METHODS

It was a descriptive, Cross-Sectional study that was conducted at DHQ Teaching Hospital Sahiwal during 6 months i.e. November 2021 – April 2022 after approval from institutional ethical committee. Sample size of 178 cases was calculated with 95% confidence level, 7% margin of error and prevalence of Methotrexate intolerance around 33%.<sup>11</sup> One hundred seventy eight adult patients suffering from rheumatoid arthritis were selected through non-probability consecutive sampling. Patients of age 20-80 years, either gender, diagnosed with rheumatoid arthritis were enrolled. All the subjects were diagnosed cases of rheumatoid arthritis according to the 1987

ACR/ 2010 ACR/EULAR Classification Criteria of Rheumatoid Arthritis.

Exclusive history was taken to check for any current or previous drug intolerance. Informed consent was taken after explaining pros and cons of research. Demographic data constituting of name, age, gender, BMI, duration of rheumatoid arthritis, family history of rheumatoid arthritis and duration of methotrexate use was acquired. The American College of Rheumatology has validated the MISS questionnaire, which was released in 2011. Five components make up the MISS Questionnaire: gastrointestinal discomfort, motion sickness, exhaustion, and behavioural problems. Each symptom is assessed after taking methotrexate, several hours to a day prior (anticipatory), and when contemplating taking methotrexate (associative). When taking methotrexate, behavioural symptoms include agitation, weeping, and impatience that eventually lead to refusal. Each element's intensity was graded on a scale of 0 to 3, with 0 representing no complaints, mild, moderate, and severe, respectively. The threshold score of 6 or higher indicated the intolerance against methotrexate. Data analysis was done using SPSS version 25.0.

## RESULTS

In this study, the mean age of patients was  $35.12 \pm 11.16$  years. Out of 178 patients, 24 (13.5%) were males and 154 (86.5%) were females. The male-to-female ratio was observed as 1:6.5. About 20 (11.2%) had primary education, 68 (38.2%) were matric or below matric, 50 (28.1%) were intermediate pass, 16 (9.0%) had bachelor degree and 24 (13.5%) patients had master's degree. The mean duration of disease was  $31.22 \pm 23.94$  months. Mean dose was  $37.68 \pm 183.60$  mg and mean duration of using methotrexate was  $12.03 \pm 12.61$  months. Diabetes was also present in 4 (2.2%) cases while hypertension was present in 4 (2.2%) cases. Table-I

About 33.7% patients had mild to moderate complaint of abdominal pain after taking methotrexate, abdominal pain anticipatory was absent in 98.9% patients and abdominal pain associative was also absent in 96.6% cases. After

taking methotrexate, mild nausea was reported in 50 (28.1%) cases, moderate in 14 (7.9%) cases and 2 (1.1%) patients had severe nausea. Mild anticipatory nausea was reported in 10 (5.6%) cases, moderate in 6 (3.4%), but no patient had severe anticipatory nausea. Mild associative nausea was reported in 8 (4.5%) cases, moderate in 4 (2.2%), but no patient had severe associative nausea. Vomiting was reported in 18 (10.1%) cases after taking methotrexate and mild to moderate anticipatory vomiting was reported in 8 (4.5%) cases. Restlessness was mild in 20 (11.2%) cases, moderate in 22 (12.4%) and severe in 4 (2.2%) cases. Irritability was mild in 22 (12.4%) cases, moderate in 20 (11.2%) and severe in 4 (2.2%) cases. Overall refusal of methotrexate was noted in 38 (21.3%) cases. The mean MISS score attained by patients was  $2.93 \pm 3.82$ . Table-II

Out of 178 patients, 44 (24.7%) had intolerance against methotrexate use for rheumatoid arthritis. Figure-1

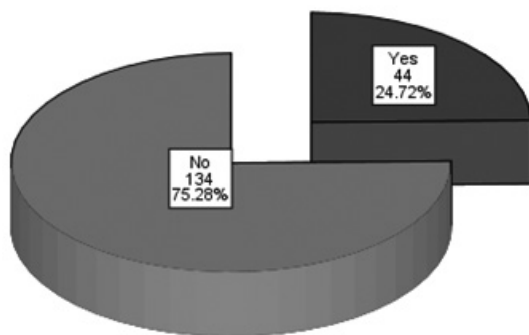


Figure-1. Intolerance against methotrexate

	Nil	Mild	Moderate	Severe
Abdominal Pain after methotrexate	118 (66.3%)	44 (24.7%)	16 (9.0%)	0 (0%)
Abdominal Pain Anticipatory	176 (98.9%)	2 (1.1%)	0 (0%)	0 (0%)
Abdominal pain Associative	172 (96.6%)	6 (3.4%)	0 (0%)	0 (0%)
Nausea after methotrexate	112 (62.9%)	50 (28.1%)	14 (7.9%)	2 (1.1%)
Nausea Anticipatory	162 (91.0%)	10 (5.6%)	6 (3.4%)	0 (0%)
Nausea associative	166 (93.3%)	8 (4.5%)	4 (2.2%)	0 (0%)
Vomiting after methotrexate	160 (89.9%)	10 (5.6%)	6 (3.4%)	2 (1.1%)
Vomiting Anticipatory	170 (95.5%)	6 (3.4%)	2 (1.1%)	0 (0%)
Restlessness	132 (74.2%)	20 (11.2%)	22 (12.4%)	4 (2.2%)
Crying	132 (74.2%)	24 (13.5%)	18 (10.1%)	4 (2.2%)
Irritability	132 (74.2%)	22 (12.4%)	20 (11.2%)	4 (2.2%)
Refusal of methotrexate	140 (78.7%)	22 (12.4%)	14 (7.9%)	2 (1.1%)
MISS score obtained	$2.93 \pm 3.82$			

Table-II. Causes of methotrexate intolerance

	F (%), mean $\pm$ SD
n	178
Age (in years)	35.12 $\pm$ 11.16
Sex	
Male	24 (13.5%)
Female	154 (86.5%)
Level of education	
Primary	20 (11.2%)
Matric	68 (38.2%)
Intermediate	50 (28.1%)
Bachelors	16 (9.0%)
Masters	24 (13.5%)
Duration of Disease in months	31.22 $\pm$ 23.94
Dose of methotrexate in mg	37.68 $\pm$ 183.60
Duration of methotrexate in months	12.03 $\pm$ 12.61
Co Morbidities	
None	160 (89.9%)
Diabetes	4 (2.2%)
Hypertension	18 (10.1%)

Table-1. Basic characteristics of patients

### DISCUSSION

Unknown causes contribute to the systemic, chronic inflammation of rheumatoid arthritis. Synovial proliferation, symmetric erosive arthritis, and systemic involvement are possible clinical presentations.<sup>8</sup> Patients with rheumatoid arthritis, as well as those with a number of other inflammatory arthritic conditions and autoimmune diseases, are frequently treated with methotrexate. After being created in the late 1940s as a chemotherapeutic drug for cancer, it was initially used in 1951 to treat rheumatoid arthritis and psoriasis.

However, until case series documenting usage in RA were published in the early 1980s, it garnered little attention in the treatment of rheumatic disorders.<sup>15</sup>

These side effects are a response to prior symptoms that patients taking methotrexate had, and because they are frequently not clinically obvious, they are frequently not appropriately handled.<sup>12</sup> Amaral et al., conducted a similar study on 120 patients and found that there was 85.8% were female, as we also observed rheumatoid in 86% females in our study.<sup>16</sup>

In our study, the frequency of methotrexate intolerance was observed in 24.7% cases. Amaral et al., also found that the frequency of methotrexate intolerance was 21.6%.<sup>16</sup> In our study, nausea was observed in 37.1% cases, abdominal pain in 33.7%, vomiting in 10.1% and behavioral symptoms in 25.8% cases. But Amaral et al., reported that the most frequent symptoms reported after the use of methotrexate were nausea (92.3%), abdominal pain (46.1%), and vomiting (30.7%). Behavioral symptoms occurred in 96.1% of patients with methotrexate intolerance, the most frequent being restlessness and irritability.<sup>16</sup>

Last but not least, a recent Saudi Arabian study of rheumatoid arthritis patients who had been on methotrexate for at least three months discovered that 39.5% of them had a positive MISS questionnaire result for methotrexate intolerance.<sup>17</sup> The most frequent side effects of methotrexate use reported by our patients were comparable to those from the Dutch trial, where 100% of patients reported nausea, 46.9% reported abdominal discomfort, and 31.3% reported vomiting.<sup>18</sup> Tekaya et al., also discovered that 36% of patients may develop methotrexate intolerance. The most frequent symptom, abdominal discomfort, was experienced by 55% of patients, followed by nausea (51%), and vomiting (16%). A total of 72.2% and 69.4% of intolerant individuals experienced anticipatory and associated stomach pain, respectively. There were 58.3% and 59% of intolerant patients who experienced anticipatory and associated

nausea, respectively. Intolerant patients who were expecting to vomit did so 16.6% of the time. About 75% of intolerant patients experienced behavioural problems overall, with 19.4% of these patients refusing methotrexate.<sup>19</sup>

## CONCLUSION

The frequency of intolerance against methotrexate in patients of rheumatoid arthritis is high and cannot be ignored. Further trials should be done at adjust dose and alterations must be done to improve the tolerance and outcome of treatment.






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## REFERENCES

1. Smolen JS, Aletaha D, McInnes IB. **Rheumatoid arthritis**. *Lancet*. 2016; 388(10055):2023-38.
2. Naqvi AA, Hassali MA, Aftab MT, Naqvi SBS, Zehra F, Ahmad R, et al. **Development of evidence-based disease education literature for pakistani rheumatoid arthritis patients**. *Diseases*. 2017; 5(4):27.
3. Ostrowska M, Maśliński W, Prochorec-Sobieszek M, Nieciecki M, Sudoł-Szopińska I. **Cartilage and bone damage in rheumatoid arthritis**. *Reumatologia/Rheumatology*. 2018; 56(2):111-20.
4. Bullock J, Rizvi SA, Saleh AM, Ahmed SS, Do DP, Ansari RA, et al. **Rheumatoid arthritis: A brief overview of the treatment**. *Medical Principles and Practice*. 2018; 27(6):501-7.
5. Sharp LA. **A medical anthropologist's view on posttransplant compliance: the underground economy of medical survival**. In *Transplantation proceedings* 1999 Jun (Vol. 31, No. 4A, pp. 31S-33S).
6. Smolen JS, Landewé RB, Bijlsma JW, Burmester GR, Dougados M, Kerschbaumer A, et al. **EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update**. *Annals of the rheumatic diseases*. 2020; 79(6):685-99.
7. Singh JA, Saag KG, Bridges SL, Jr., Akl EA, Bannuru RR, Sullivan MC, et al. **2015 American College of rheumatology guideline for the treatment of rheumatoid arthritis**. *Arthritis care & research*. 2016; 68(1):1-25.
8. Lopez-Olivo MA, Siddhanamatha HR, Shea B, Tugwell P, Wells GA, Suarez-Almazor ME. **Methotrexate for treating rheumatoid arthritis**. *The Cochrane database of systematic reviews*. 2014; 2014(6):Cd000957.

9. Wang W, Zhou H, Liu L. **Side effects of methotrexate therapy for rheumatoid arthritis: A systematic review.** European journal of medicinal chemistry. 2018; 158:502-16.
10. Viridi P, Singh B, Singh R. **Role of methotrexate intolerance severity score (miss) in rheumatoid arthritis to know methotrexate intolerance: A 2-year prospective study.** Int J Adv Res. 2017; 5:2542-8.
11. Fatimah N, Salim B, Nasim A, Hussain K, Gul H, Niazi S. **Frequency of methotrexate intolerance in rheumatoid arthritis patients using methotrexate intolerance severity score (MISS questionnaire).** Clinical rheumatology. 2016; 35(5):1341-5.
12. Bulatović M, Heijstek MW, Verkaaik M, van Dijkhuizen EH, Armbrust W, Hoppenreijns EP, et al. **High prevalence of methotrexate intolerance in juvenile idiopathic arthritis: Development and validation of a methotrexate intolerance severity score.** Arthritis and rheumatism. 2011; 63(7):2007-13.
13. Chausset A, Fargeix T, Pereira B, Echaubard S, Duquesne A, Desjonquères M, et al. **MISS questionnaire in French version: A good tool for children and parents to assess methotrexate intolerance.** Clinical rheumatology. 2017; 36(6):1281-8.
14. Fatimah N, Salim B, Nasim A, Hussain K, Gul H, Niazi S. **Frequency of methotrexate intolerance in rheumatoid arthritis patients using methotrexate intolerance severity score (MISS questionnaire).** Clinical rheumatology. 2016; 35(5):1341-5.
15. Kremer JM. **Use of methotrexate in the treatment of rheumatoid arthritis.** UpToDate: Walters Kluwer, Waltham (MA); 2019.
16. Amaral JM, Brito MJM, Kakehasi AM. **High frequency of methotrexate intolerance in longstanding rheumatoid arthritis: Using the methotrexate intolerance severity score (MISS).** Advances in rheumatology (London, England). 2020; 60(1):43.
17. Albaqami J, Alshalhoub R, Almalag H, Dessougi M, Al Harthi A, Bedaiwi MK, et al. **Prevalence of methotrexate intolerance among patients with rheumatoid arthritis using the Arabic version of the methotrexate intolerance severity score.** International journal of rheumatic diseases. 2019; 22(8):1572-7.
18. 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 research & therapy. 2013; 15(6):R217.
19. Tekaya R, Triki W, Tekaya AB, Saidane O, Mahmoud I, Abdelmoula L. **AB0352 High prevalence fo anticipatory and associative symptoms of methotrexate intolerance in patients with rheumatoid arthritis.** Ann Rheum Dis. 2019; 78(Suppl 2):1632-.

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2	Masooma Hashmat	Data collection, analysis, Manuscript writing, Proof reading.	
3	Abrar Ahmed Wagan	Data collection, analysis, Manuscript writing, Proof reading.	
4	Zafar Ali Zafar	Data analysis, Manuscript writing proof reading.	
5	Atta-ur-Rehman	Data analysis, Manuscript writing, Proof reading.	
6	Ali Rukh Pirzada	Data collection, analysis, Manuscript writing, Proof reading.	