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Prevalence of Methotrexate Intolerance in Patients with Rheumatoid Arthritis, Psoriatic Arthritis and Juvenile Idiopathic Arthritis

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ABSTRACT

Methotrexate intolerance is frequently encountered, however, seldom studied scientifically in a low-resource setting. Hence, the study was planned to look for the areas for possible early interventions that may assist in decreasing or preventing intolerance, and its early identification may impact treatment, leading to timely changes in medication that may promote patient compliance and better control of the disease. **Objectives:** To determine the prevalence of methotrexate intolerance in patients with rheumatoid arthritis, psoriatic arthritis and juvenile idiopathic arthritis. **Methods:** This descriptive comparative study was carried out at the Department of Rheumatology, Khyber Teaching Hospital, Peshawar, during the period 12th February 2025 to 31st May 2025. Male and female patients aged 10 to 70 years diagnosed with rheumatoid arthritis, psoriatic arthritis and juvenile rheumatoid arthritis were enrolled and evaluated for methotrexate intolerance using the MISS questionnaire, taking a score ≥6 as a cut-off for the presence of intolerance. **Results:** Mean age was 38.85 ± 17.31 years, and the majority of participants had an age of more than 40 years (n=81, 53.6%), while 91 patients (60.3%) were male. Rheumatoid arthritis was the most common clinical diagnosis (n=91, 60.3%). Overall, methotrexate intolerance was observed in 58 (38.4%) patients. Methotrexate intolerance was most common in rheumatoid arthritis patients (n=38, 41.8%) (p-value=0.323). **Conclusions:** Though methotrexate intolerance is fairly common among patients with rheumatic disorders, no statistically significant association was observed between intolerance and background disease or baseline parameters such as route of administration.

INTRODUCTION

Persistent arthritic conditions are a hallmark of autoimmune diseases such as psoriasis-associated arthritis (PsA) and rheumatoid arthritis (RA) [1]. Methotrexate (MTX) remains the primary disease-modifying anti-rheumatic medication (DMARD) for treating RA and PsA because of its affordability, effectiveness, and tolerable safety record [2]. Despite many beneficial effects, MTX use has been linked to various adverse events such as GI distress (abdominal pain, nausea and vomiting), cytopenias and hepatic enzymes derangements [3]. GI adverse events like nausea and abdominal pain were reported by 85.5% and 59.4% respectively, in a cross-sectional study. Overall, MTX intolerance was reported by 34.5% patients [4]. The greatest rate of methotrexate intolerance was seen in JIA/uveitis patients. The sole predictor of intolerance risk was the subcutaneous injection method [5]. MTX intolerance was found in a significant proportion of rheumatoid arthritis patients [6]. Patients with juvenile idiopathic arthritis (JIA) experienced a wide range of gastrointestinal adverse reactions before and following taking MTX (anticipatory and associative). Following the use of MTX, the latter complaints develop as a conventional conditioning reaction to digestive issues [7]. As a result, MTX-induced gastrointestinal side effects, commonly labelled MTX intolerance, are complicated and may make it much harder to take a medication that might

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usually work. Although gastrointestinal complications from MTX are common in RA and PsA, the nature and extent of these side effects, particularly their presence, have not been evaluated [8]. Methotrexate is a cornerstone of therapy in autoimmune diseases, a valuable chemotherapeutic agent and a potent immunosuppressant in organ transplant patients. Among autoimmune diseases, methotrexate holds a central role in the management of rheumatoid arthritis, psoriatic arthritis and juvenile idiopathic arthritis because of its therapeutic effect and cost effectiveness [9]. Despite an acceptable safety profile, a major limitation to its use is intolerance to the drug. Serious adverse effects such as pulmonary toxicity, hepatotoxicity and bone marrow suppression are rare or transient if MTX is stopped. Drug intolerance leads to discontinuation of therapy and the need for novel agents, resulting in more health care and societal costs [10]. The frequency of MTX intolerance in rheumatism has been evaluated in a number of studies. A significantly elevated proportion of MTX intolerance, 50.5%, was noted in the population of 297 patients in a research study in which the MISS score was verified. A greater likelihood of intolerance was linked to a somewhat greater MTX dose, most likely as a result of an elevated plasma level of medication. Additionally, individuals taking parenteral MTX had a 23% greater rate of MTX intolerance [11]. Adult individuals with psoriatic and rheumatoid arthritis were examined for MTX intolerance in a cross-sectional study. In a sample of 291 patients, GI adverse events were reported by 123 patients (42.3%); however, MTX intolerance was shown to be 11% prevalent. Patients receiving parenteral MTX had a greater rate of MTX intolerance (20.6%) compared to those receiving oral MTX (6.2%) [12]. A total of 138 patients with JIA were evaluated for methotrexate intolerance using the MISS questionnaire. Taking a score of 6 as a cut, the prevalence of intolerance was 62.3% [13]. Prompt recognition of intolerance could have a direct effect on treatment, resulting in timely adjustments to medications that could improve adherence by patients and alleviate symptoms.

Although methotrexate (MTX) remains the cornerstone therapy for rheumatoid arthritis, psoriatic arthritis, and juvenile idiopathic arthritis, intolerance to the drug frequently compromises treatment adherence and clinical outcomes. Most available evidence on MTX intolerance originates from high-income countries, with limited data from resource-limited settings such as Khyber Pakhtunkhwa, Pakistan. Furthermore, variations in demographic characteristics, route of administration, and disease profiles may influence intolerance patterns, yet local comparative data across RA, JIA, and PsA populations remain scarce. This gap underscores the need to determine the prevalence and associated factors of MTX intolerance in our setting to guide early identification and intervention strategies. This study aims to determine the prevalence of methotrexate intolerance in patients with RA, JIA, and PsA who presented to a tertiary care resource-limited setting in Khyber Pakhtunkhwa. To identify potential early measures that could help reduce or prevent intolerance.

METHODS

This descriptive comparative study was carried out at the Department of Rheumatology, Khyber Teaching Hospital, Peshawar, during the period 12th February 2025 to 31st May 2025, after taking permission from the hospital IRB vide no: 138/DME/KMC. Male and female patients aged 10 to 70 years diagnosed with rheumatoid arthritis, psoriatic arthritis and juvenile rheumatoid arthritis were enrolled. Patients with endoscopically proven peptic ulcer disease, pregnant patients, psychiatric illnesses such as eating disorders, a history of bowel surgery and patients with cytopenias were excluded. Rheumatoid arthritis was confirmed with ACR criteria by the presence of at least four among morning stiffness, soft tissue swelling, small joint arthritis, symmetrical distribution of joint swelling, subcutaneous nodules, raised inflammatory markers such as RA factors and ESR/CRP. Juvenile rheumatoid arthritis was confirmed with similar criteria, with the addition of symptoms in patients aged less than 16 years. Psoriatic arthritis was confirmed with CASPAR criteria scoring 3 or above. CASPAR criteria included clinical presence of psoriasis, psoriatic nail dystrophy, seronegativity, dactylitis and radiologic evidence of bone erosions. Intolerance was confirmed with MISS (Methotrexate Intolerance Severity Score), which comprised four parameters including abdominal pain, nausea, vomiting and behavioural symptoms occurring upon, before (anticipatory) and when thinking of MTX (associative). MTX intolerance was defined as ≥6 on the MISS with ≥1 point on anticipatory and/or associative and/or behavioural items. Sample size was 151, calculated using the WHO sample size calculator using 11% anticipated proportion of methotrexate intolerance, with 5% margin of error and 95% confidence level [12]. Participants were recruited using a nonprobability consecutive sampling technique. Informed consent was taken from enrolled patients before initiating the study. Baseline information like age, gender, body mass index (BMI), smoking history, residence, education and SE status were recorded. Clinical information gathered included diagnosis, mode of methotrexate administration (oral/subcutaneous), drug duration (weeks), disease activity, concomitant disease and medications. An interview was arranged with all patients after comfortably seating them in a quiet room in a chair. History was taken based on the MISS questionnaire about methotrexate related events, including abdominal pain, nausea, vomiting

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and behavioural symptoms. The score was calculated, and a score ≥6 was noted. Data analysis was carried out using IBM SPSS version 26.0. Descriptive statistics were carried out for reporting baseline demographic and clinical parameters. Continuous data like age, BMI, disease duration and MISS score were reported as means and standard deviations and categorical data like gender, family history, residence, education, profession, smoking, comorbidities, disease activity and methotrexate intolerance were presented as frequencies and percentages. Effect modifiers were controlled through stratification. Post-stratification chi-square test was applied at 5% significance level.

RESULTS

The mean age of participants was 38.85 years, with a standard deviation of 17.311, the mean BMI was 25.179 ± 0.978kg/m^2, and the Mean MISS score was 5.059 ± 1.87 as reported in table 1.

Table 1: Descriptive Statistics of Study Participants (n=151)

Parameters	Mean ± SD
Age (Years)	38.9 ± 17.3
BMI (kg/m^2)	25.1 ± 1.0
Duration (Months)	8.2 ± 2.9
MISS	5.06 ± 1.9

The majority of study participants were more than 40 years (n = 81, 53.6%), while 91 patients (60.3%) were male. 81 patients (53.6%) belonged to rural areas. 39 (25.8%) patients had a family history of rheumatic disease, and 42 patients (27.8%) were smokers. 130 patients (86.1%) were taking methotrexate orally, and 59 (39.1%) had severe disease activity. Rheumatoid arthritis was the most common recorded in 91 patients (60.3%), as shown in Table 2.

Table 2: Baseline Clinical and Demographic Information of Study Participants (n=151)

Parameters	Subgroups	Frequency (%)
Age (Years)	Below 17	32 (21.2%)
	17-40	38 (25.2%)
	Above 40	81 (53.6%)
Gender	Male	91 (60.3%)
	Female	60 (39.7%)
BMI (kg/m^2)	24.0 or Below	23 (15.2%)
	More Than 24.0	128 (84.8%)
Disease Duration (Months)	6 or Below	46 (30.5%)
	More Than 6	105 (69.5%)
Residence	Rural	81 (53.6%)
	Urban	70 (46.4%)
Education	No Formal Schooling	42 (27.8%)
	Matric or Below	77 (51.0%)
	Above Matric	32 (21.2%)
Family Hx	Yes	39 (25.8%)
	No	112 (74.2%)
Smoking	Yes	42 (27.8%)
	No	109 (72.2%)
Comorbidities	Yes	30 (19.9%)
	No	121 (80.1%)
Route	Oral	130 (86.1%)
	SC	21 (13.9%)
Disease Activity	Mild	42 (27.8%)
	Moderate	59 (39.1%)
	Severe	50 (33.1%)
Diagnosis	RA	91 (60.3%)
	JIA	36 (23.8%)
	PA	24 (15.9%)

32 patients (100.0%) had juvenile rheumatoid arthritis and were aged 16 years or below, while 04 patients (10.5%) with JRA were in the aging more than 16 years or older. 59 patients (64.8%) with rheumatoid arthritis were male compared to 32 (53.3%) female. 28 patients (71.8%) with rheumatoid arthritis had a family history of RA. Moderate disease activity was recorded in 31 RA patients (61.0%), 14 (23.7%) JRA and 09 (15.3%) with psoriatic arthritis, as reported in table 3.

Table 3: Patient Distribution with Respect to Diagnosis (n=151)

Parameters		Diagnosis			Total
		RA (n=91)	JRA (n=36)	PA (n=24)	
Age (Years)	16 and Below	0 (0.0%)	32 (100.0%)	0 (0.0%)	32 (100.0%)
	17 to 40	22 (57.9%)	4 (10.5%)	12 (31.6%)	38 (100.0%)
	More than 40	69 (85.2%)	0 (0.0%)	12 (14.8%)	81 (100.0%)
Gender	Male	59 (64.8%)	16 (17.6%)	16 (17.6%)	91 (100.0%)
	Female	32 (53.3%)	20 (33.3%)	8 (13.3%)	60 (100.0%)
BMI (kg/m^2)	≤24.0	19 (82.6%)	4 (17.4%)	0 (0.0%)	23 (100.0%)
	>24.0	72 (56.3%)	32 (25.0%)	24 (18.8%)	128 (100.0%)
Smoking	Yes	33 (78.6%)	4 (9.5%)	5 (11.5%)	42 (100.0%)
	No	58 (53.2%)	32 (29.4%)	19 (17.4%)	109 (100.0%)
Family History	Yes	28 (71.8%)	4 (10.3%)	7 (17.9%)	39 (100.0%)
	No	63 (56.3%)	32 (28.6%)	17 (15.2%)	112 (100.0%)
Route	Oral	79 (60.8%)	31 (23.8%)	20 (15.4%)	130 (100.0%)
	SC	12 (57.1%)	5 (23.8%)	4 (19.0%)	21 (100.0%)
Disease Activity	Mild	25 (59.5%)	10 (23.8%)	7 (16.7%)	42 (100.0%)
	Moderate	36 (61.0%)	14 (23.7%)	9 (15.3%)	59 (100.0%)
	Severe	30 (60.0%)	12 (24.0%)	8 (16.0%)	50 (100.0%)
Duration (Months)	6 or Below	27 (58.7%)	14 (30.4%)	5 (10.9%)	46 (100.0%)
	More Than 6	64 (61.0%)	22 (21.0%)	19 (18.1%)	105 (100.0%)
Joints	Right	33 (67.3%)	8 (16.3%)	8 (16.3%)	49 (100.0%)
	Left	29 (56.9%)	12 (23.5%)	10 (19.6%)	51 (100.0%)
	Bilateral	29 (56.9%)	16 (31.4%)	6 (11.8%)	51 (100.0%)
Comor-bidities	Yes	17 (56.7%)	4 (13.3%)	9 (30.0%)	30 (100.0%)
	No	74 (61.2%)	32 (26.4%)	15 (12.4%)	121 (100.0%)

Methotrexate intolerance was observed in 58 (38.4%) patients, while 58 (38.4%) were methotrexate tolerate, as reported in figure 1.

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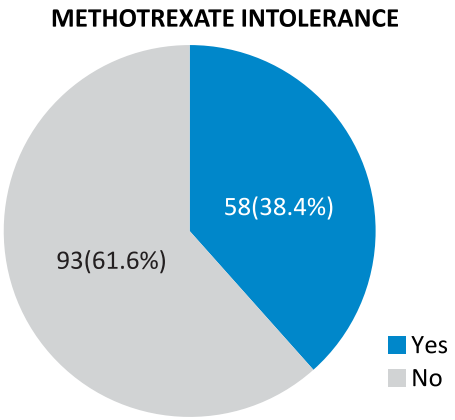

Figure 1: Methotrexate Intolerance among Study Participants (n=151)

38 patients (41.8%) with rheumatoid arthritis were intolerant to methotrexate compared to 14 (38.9%) with JIA and 6 (25.0%) with psoriatic arthritis (p-value=0.323), as reported in table 4.

Table 4: Subgroup Analysis of Methotrexate Intolerance with Background Diagnosis (n=151)

Parameters		Intolerance		Total	p-Value
		No	Yes		
Diagnosis	RA	53 (58.2%)	38 (41.8%)	91 (100.0%)	0.323
	JIA	22 (61.1%)	14 (38.9%)	36 (100.0%)	
	PA	18 (75.0%)	6 (25.0%)	24 (100.0%)	
Total		93 (61.6%)	58 (38.4%)	151 (100.0%)	

22 patients (64.7%) in the age group (21-40 years) were intolerant to methotrexate compared to 14 (38.9%) and 22 (27.2%) in the age groups 20 or below and more than 40 years respectively (p value 0.001. No other statistically significant association was recorded with other parameters, as reported in table 5.

Table 5: Demographic Information of Intolerance

Parameters		Intolerance		Total	p-Value
		No	Yes		
Age (Years)	Below 17	20 (62.5%)	12 (37.5%)	32 (100.0%)	0.001
	17 to 40	14 (36.8%)	24 (63.2%)	38 (100.0%)	
	Above 40	59 (72.8%)	22 (27.2%)	81 (100.0%)	
Gender	Male	58 (63.7%)	33 (36.3%)	91 (100.0%)	0.504
	Female	35 (58.3%)	25 (41.7%)	60 (100.0%)	
BMI (kg/m^2)	24.0 or Below	17 (73.9%)	6 (26.1%)	23 (100.0%)	0.187
	More than 24.0	76 (59.4%)	52 (40.6%)	128 (100.0%)	
Route	Oral	83 (63.8%)	47 (36.2%)	130 (100.0%)	0.156
	SC	10 (47.6%)	11 (52.4%)	21 (100.0%)	
Disease Activity	Mild	25 (59.5%)	17 (40.5%)	42 (100.0%)	0.849
	Moderate	38 (64.4%)	21 (35.6%)	59 (100.0%)	
	Severe	30 (60.0%)	20 (40.0%)	50 (100.0%)	
Comorbidities	Yes	19 (63.3%)	11 (36.7%)	30 (100.0%)	0.826
	No	74 (61.2%)	47 (38.8%)	121 (100.0%)	
Disease Duration (Months)	6 or Below	27 (58.7%)	19 (41.3%)	46 (100.0%)	0.628
	More Than 6	66 (62.9%)	39 (37.1%)	105 (100.0%)	
Smoking History	Yes	24 (57.1%)	18 (42.9%)	42 (100.0%)	0.486
	No	69 (63.3%)	40 (36.7%)	109 (100.0%)	
Family History	Yes	20 (51.3%)	19 (48.7%)	39 (100.0%)	0.124
	No	73 (65.2%)	39 (34.8%)	112 (100.0%)	

DISCUSSION

In addition to the widely recognized abdominal discomfort that MTX causes, investigators reported that patients with RA, JIA and PA additionally experienced anticipated and associated digestive and behavioural manifestations. These complaints are all referred to as MTX intolerance. 38.4% of our study cohort had MTX intolerance. Equivalent Intolerant rates comparable to our study have been reported in RA studies [11, 12]. Gastrointestinal toxicity is the primary dose-limiting concern for MTX usage. Intestinal mucositis caused by MTX poses a significant challenge to patients. It can impact the whole alimentary tract and is frequently accompanied by cramps, nausea, and pain in the stomach [14]. The frequency of MTX intolerance in RA was slightly higher compared to JIA and psoriatic arthritis. Our findings demonstrated a higher prevalence of MTX intolerance in adult rheumatoid arthritis (RA) patients compared to adolescents, but the difference was statistically significant (p-value=0.323). Methotrexate intolerance is a complex phenomenon. Three fundamental concepts comprise the complicated belief system associated with methotrexate intolerance: beliefs on the dangers of RA, the advantages of methotrexate, and the risk of methotrexate [15]. In this study, we also found that MTX intolerance was more common in patients receiving parenteral MTX (52.4%) compared to oral MTX (36.8%); however, this difference in intolerance did not reach statistical significance. More behavioural problems in the parenteral group were the reason for this discrepancy. Apart from the route of administration, there are also concerns about the dosing with high doses attributed to severe complications such as malignancies [16]. Given their prior oral MTX complaints, individuals who shifted could have become more likely to experience gastrointestinal and behavioural side effects when taking parenteral MTX, which would have increased the incidence of MTX intolerance in the injectable category. MTX intolerance was substantially correlated with age; specifically, patients in the age group 20 to 40 years had a higher likelihood of having MTX intolerance than those in the extreme ages. MTX-related gastrointestinal and additional problems were not linked to younger or older ages in earlier research [17]. To ascertain if younger age is an independent risk contributor to MTX intolerance, confirmatory research is necessary. In addition to impeding the administration of MTX, intolerance can undermine patients' standard of living [1]. However, strictly speaking, these indications do not seem particularly

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noticeable. As a result, they are difficult to identify by medical evaluation alone, but the MISS can identify them [8]. Thus, it is beneficial to use the MISS as it enables early symptom diagnosis. This could open up an area of possibility for prompt MTX intolerance therapy along with prompt physiological relief of symptoms, which might stop conditioned reactions and MTX intolerance from developing. Reducing the MTX dosage, moving to parenteral MTX, initiating behavioural therapy, or using antiemetics like ondansetron are all possible treatments for (physical) symptoms [18, 19]. Using an established questionnaire, the current research is the initial attempt to show the proportion of patients affected by MTX intolerance. Intolerance was more prevalent in those receiving parenteral (subcutaneous) than oral MTX. Considering the primary explanation for stopping MTX is continuous gastrointestinal issues, intolerant patients may be more inclined to quit taking MTX altogether or switch to costlier biological therapies or (less potent) DMARDs [20]. The MISS can be used in regular clinical settings to closely observe patients and promptly assist by employing the aforementioned strategies to avoid or mitigate the detrimental effects of MTX intolerance on patients' daily activities, adherence, and ability to continue receiving successful therapy.

This study was limited by its single-center design and non-probability consecutive sampling, which may restrict the generalizability of findings to the broader rheumatology population. Additionally, the cross-sectional nature of the study precludes assessment of causal relationships and long-term treatment outcomes related to methotrexate intolerance. Future multicenter longitudinal studies with larger sample sizes are recommended to evaluate predictors of intolerance, assess the impact on treatment adherence and disease control, and explore targeted preventive strategies to optimize methotrexate therapy in patients with rheumatic diseases.

CONCLUSIONS

The study demonstrated via the internationally accepted MISS assessment that the prevalence of MTX intolerance was 38.4%, and it was more common in patients on parenteral MTX than in those on oral MTX, and it continued after switching from parenteral to oral MTX. Moreover, patients in the third and fourth decades of life were more often intolerant to MTX. Because persistent MTX intolerance can negatively affect a patient's quality of life and interfere with MTX use, RA, JIA and PA patients on MTX, it is recommended to observe them using the MISS for early identification of MTX intolerance.

Authors' Contribution

Conceptualization: UA
Methodology: IUD, HA, MI, AZ
Formal analysis: MI
Writing and Drafting: UA, AA, IUD, HA, AZ
Review and Editing: UA, AA, IUD, HA, AZ, MI

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

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