Original Article

Frequency of Methotrexate Intolerance in Juvenile Idiopathic Arthritis Patients Using Methotrexate Intolerance Severity Score

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Abstract

Background: The Methotrexate Intolerance Severity Score (MISS) is a comprehensive scoring system used to assess methotrexate intolerance.

Objective: The study aims to determine the frequency of methotrexate intolerance in JIA patients using MISS and its association with demographic factors, subtypes of JIA, duration of illness, and MTX intake.

Methods: This cross-sectional study was conducted at the Department of Rheumatology, UCHS and The Children's Hospital, Lahore. All patients having JIA and taking MTX for at least 3 months were enrolled. Demographic data, including age, gender, subtype of JIA, duration of the disease, and MTX dosage and duration, were collected. The MISS score has four elements: abdominal pain, nausea, vomiting, and behavioral symptoms. A cutoff value of 6 or above was considered indicative of MTX intolerance. Data was analyzed into SPSS version 22.

Results: Out of 96 JIA patients, 60.4% were female and the mean age was 9.92 ± 4.11 years. Polyarticular seronegative JIA was present in 56.3% of patients. Among all patients, 22.9% had MTX intolerance according to the MISS score. Nausea was found in 58.3%, followed by behavioral symptoms in 44.8%. All MTX-intolerant patients experienced nausea and behavioral symptoms, with vomiting occurring in 59.1% and abdominal pain in 45.4%. MTX intolerance was significantly linked with increasing age in JIA patients but was not related to gender, subtype of JIA, duration of disease, and MTX intake, or MTX dose.

Conclusion: About one-third of all JIA patients were methotrexate intolerant having nausea and behavioral symptoms. MTX intolerance was significantly linked with increasing age in JIA patients taking MTX.

Received: 07-09-2024 | **1st Revision:** 04-04-2025 | **2nd Revision:** 23-07-2025 | **Accepted:** 10-10-2025

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Keywords | Juvenile idiopathic arthritis, Methotrexate, intolerance Methotrexate intolerance severity score, MISS

How to cite: Naz S, Ashfaq S, Qamar S, Jabeen F. Frequency of Methotrexate Intolerance in Juvenile Idiopathic Arthritis Patients Using Methotrexate Intolerance Severity Score. Ann King Edw Med Univ.2025;31i4:

Introduction

Juvenile idiopathic arthritis (JIA) is the most common rheumatic illness in children. It refers to a spectrum of illnesses characterized by chronic arthritis and is the primary cause of both short and long-term disability. Between 0.8 to 22.6 cases of JIA are reported per million kids worldwide each year. The primary method of diagnosing JIA is clinical; laboratory tests are required to confirm the diagnosis and rule out alternative causes of pediatric arthritis.[1] Joint abnormalities including leg length discrepancy, joint contractures, or vision loss from chronic uveitis are among the severe morbidities that

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https://doi.org/10.21649/akemu.v31i4.5687

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can result from JIA if accurate and early aggressive treatment is not provided.[1,2]

Methotrexate (MTX) is the commonly used first-line disease-modifying anti-rheumatic drug (DMARD) for the treatment of JIA.[3] Studies indicate that treatment with either oral or parenteral MTX results in comparable improvement in JIA patients. MTX is typically administered at a dose of 10-15 mg/m² per week, with oral administration preferred for children. The most common adverse effects of MTX are gastrointestinal, including nausea, abdominal pain, vomiting, or diarrhea. Despite its availability, good tolerance, and relatively low cost, these common GI side effects are often overlooked. Hepatotoxicity and bone marrow suppression are generally infrequent and transient if MTX is discontinued.[3,4]

In addition to these side effects, JIA patients may develop gastrointestinal symptoms before or around MTX intake (anticipatory), when thinking about MTX (associative), as well as behavioral symptoms such as restlessness, crying, or even refusal to take MTX. These side effects result from a conditioned response to the physical symptoms experienced after MTX intake.[5] Research supports the protective effect of folic or folinic acid supplementation in significantly reducing GI effects; however, some patients still experience these troubling side effects despite folic acid use.[6]

Methotrexate Intolerance Severity Score (MISS) is a recently developed tool, validated by a study conducted in the Netherlands and supported by the American College of Rheumatology.[5] According to the MISS questionnaire, the prevalence of MTX-related GI and behavioral side effects, termed MTX intolerance, was as high as 50.5% in JIA patients. In contrast, the prevalence was considerably lower in patients with RA and psoriatic arthritis, at 11%.[7,8] A study conducted in Pakistan reported a frequency of MTX intolerance at 40%.[9] These unpleasant side effects may have a negative impact on the child's health-related quality of life (HRQoL) and treatment compliance.[10] Non-compliance can lead to the early discontinuation of an otherwise effective treatment. By using the MISS score, we can identify such patients earlier, which allows for timely management of intolerance through strategies such as folate supplementation, switching from oral to subcutaneous methotrexate, using antiemetic medications, and implementing behavioral therapies like eye movement desensitization and reprocessing (EMDR), cognitive behavioral therapy (CBT), and alternative therapies to MTX. These measures can help prevent JIA progression.[11,12] An alternative treatment option could be a combination of MTX with other DMARDs, such as Leflunomide, which is safe and effective for patient's intolerant to oral MTX.[13,14] Early detections will aid in making informed decisions about further treatment options, ultimately leading to improved outcomes for JIA patients. This study aims to assess the frequency of methotrexate intolerance in JIA patients using the MISS and to examine its association with demographic factors, subtypes of JIA, duration of illness, and MTX intake duration.

Methods

This cross-sectional study was conducted at the Rheumatology outpatient department of The Children's Hospital and University of Child Health Sciences, Lahore. Ethical approval was taken from local institutional review board. Both male and female patients under the age of 16 who met the ILAR criteria for JIA were enrolled. Eligible patients were those taking oral MTX for at least 3 months with good compliance (defined as not missing any dose or missing fewer than 2 doses in the last 3 months) and presenting for follow-up of JIA. Patients were excluded if they were taking concomitant treatments such as other DMARDs (e.g., Sulfasalazine or Leflunomide), or had discontinued MTX earlier due to side effects, were receiving subcutaneous MTX, or refused to participate in the study. Written informed consent was obtained from the patients/parents. Demographic data, including age, gender, subtype of JIA, duration of disease, and MTX dosage and duration, were collected. The data were recorded on a structured proforma. The MISS questionnaire, a validated tool supported by the American College of Rheumatology was used.[7] The MISS score includes four elements: abdominal pain, nausea, vomiting, and behavioral symptoms. Each symptom was evaluated after MTX intake, several hours to 1 day before taking MTX (anticipatory), and when thinking about MTX (associative). Behavioral symptoms include restlessness, crying, grumpiness, or irritability, progressing to refusal to take MTX. The severity of each element was ranked from 0 to 3, with 0 indicating no complaint, 1 indicating mild, 2 indicating moderate, and 3 indicating severe. Vomiting and behavioral symptoms were classified as mild (1-2 times per month), moderate (3-4 times per month), and severe (>4 times per month). A cutoff score of 6 or above was considered indicative of MTX intolerance (range 0-36).

Data were analyzed using into SPSS V.25. The Mean and Standard deviation (SD) of numerical variables including patient age, duration of disease at presentation, dose, and duration of MTX intake were calculated. For categorical variables like gender, subtype of JIA, and presence of MTX intolerance (patients scoring 6 or

more points on the MISS), were calculated as frequencies and percentages. Results were calculated and described as tables. Stratification of data were done as age, gender, duration of disease, subtype of JIA, and MTX dosage and duration to address effect modifiers. A post-stratification chi-square test was applied, with a p-value ≤ 0.05 considered statistically significant.

Results

Total 96 patients with JIA who were undergoing MTX therapy were recruited in this study. The mean age was 9.92 ± 4.11 years, with 57.3% of patients being over 10 years of age (n=55). Females comprised 60.4% of the cohort (n=58), yielding a female-to-male ratio of 1.5:1. The average age at diagnosis was 7.23 ± 3.66 years, and the mean duration of the disease at presentation was 2.68 ± 2.21 years. Patients were enrolled when MTX had been administered for more than 3 months, with the mean duration of MTX use being 1.63 ± 1.54 years, and the mean dose was 8.67 ± 2.64 mg.

Poly-articular seronegative JIA affected 56.3% of patients (n=54), followed by systemic JIA (sJIA) at 28.1% (n=27), poly-articular seropositive JIA at 8.3% (n=8), and oligoarticular JIA at 7.3% (n=7). In addition to MTX, all patients were taking NSAIDs, and 65% of the patients (n=54) were also receiving steroids.

Among all patients, 22.9% (n=22) exhibited methotrexate intolerance as indicated by a MISS score greater than 6. Specifically, 3.1% of patients had a MISS score between 7 and 10, 14.6% had a score between 11 and 15, and 5.2% had a score exceeding 15. The most frequent symptom among all patients was nausea, reported by 58.3% (n=56), followed by behavioral symptoms in 44.8% (n=43), abdominal pain in 38.5% (n=37), and vomiting in 27.1% (n=26). The frequency of symptoms according to their severity, as per the MISS score, is detailed in Table 1. This table shows that none of the patients experienced severe symptoms in the domain of abdominal pain.

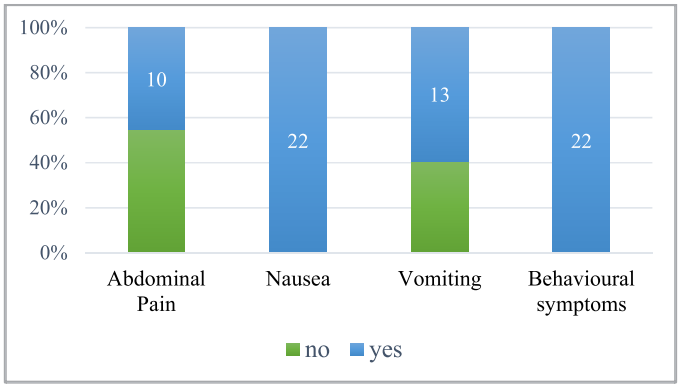

Figure-1: *Frequency of symptoms in Methotrexate intolerant group*

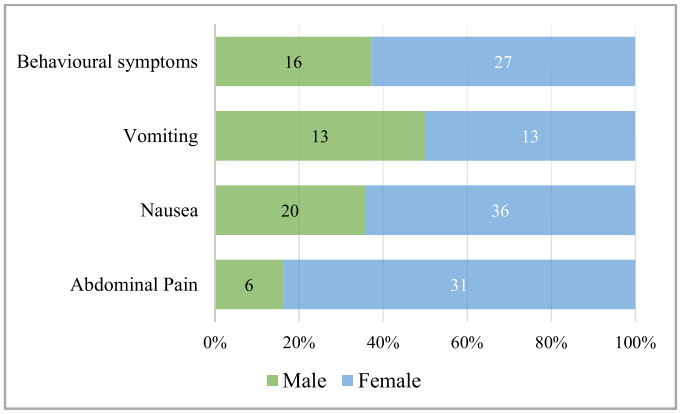

Figure-2: *Relationship of symptoms of MISS score with gender*

All patients intolerant to methotrexate (100%) had nausea and behavioral symptoms, with vomiting reported by 59.1% and abdominal pain by 45.4% [Figure 1]. Abdominal pain and nausea were more common after taking MTX, while irritability was the most common

Table 1: *Frequency of severity of symptoms in JIA patients as per MISS score (n=96)*

Domains		No complaint	Mild complaint	Moderatecomplaint	Severe complaint
Abdominal pain	After taking MTX	61 (63.5%)	23 (24%)	12 (12.5%)	0
	Anticipatory	85 (88.5%)	7 (7.3%)	4 (4.2%)	0
	Associative	95 (99.0%)	1 (1.0%)	0	0
Nausea	After taking MTX	40 (41.7%)	14 (14.6%)	39 (40.6)	3 (3.1%)
	Anticipatory	76 (79.2%)	9 (9.4%)	8 (8.3%)	3 (3.1%)
	Associative	75 (78.1%)	9 (9.4%)	9 (9.4%)	3 (3.1%)
Vomiting	After taking MTX	70 (72.9%)	16 (16.7%)	9 (9.4%)	1 (1.0%)
	Anticipatory	92 (95.8%)	2 (2.1%)	1 (1.0%)	1 (1.0%)
Behavioural symptoms	Restless	62 (64.6%)	13 (13.5%)	17 (17.7%)	4 (4.2%)
	Crying	73 (76.0%)	13 (13.5%)	7 (7.3%)	3 (3.1%)
	Irritability	53 (55.2%)	27 (28.1%)	12 (12.5%)	4 (4.2%)
	Refusal to take MTX	78 (81.3%)	3 (3.1%)	11 (11.5%)	4 (4.2%)

behavioral symptom. Symptoms were generally more prevalent among females, except for vomiting, which had an equal gender distribution [Figure 2]. Four patients experienced severe symptoms in one or more domains (nausea, vomiting, and behavioral symptoms) [Figure 3], leading to refusal of MTX treatment and poor outcomes.

Table 2: *Relationship of various parameters in JIA patients with MTX intolerance*

	MTX Intolerance			
	No	Yes	Total	p-value
Gender				
Male	28 (73.7%)	10 (26.3%)	38 (100%)	0.521
Female	46 (79.3%)	12 (20.7%)	58 (100%)	
Age				
Up to 5 years	14 (93.3%)	1 (6.7%)	15 (100%)	0.014
5 to 10 years	15 (57.7%)	11 (42.3%)	26 (100%)	
More than 10 years	45 (81.8%)	10 (18.2%)	55 (100%)	
JIA subtype				
Oligo-articular JIA	5 (71.4%)	2 (28.6%)	7 (100%)	
Polyarticular RF+ JIA	6 (75%)	2 (25%)	8 (100%)	0.699
Polyarticular RF- JIA	40 (74.1%)	14 (25.9%)	54 (100%)	
Systemic onset JIA	23 (85.2%)	4 (14.8%)	27 (100%)	
Duration of illness				
< 3 months	2 (100%)	0 (0%)	2 (100%)	0.692
3 to 6 months	8 (88.9%)	1 (11.1%)	9 (100%)	
6 to 12 months	12 (75%)	4 (25%)	16 (100%)	
>1 year	52 (75.4%)	17 (24.6%)	69 (100%)	
Duration of MTX intake				
< 3 months	6 (100%)	0 (0%)	6 (100%)	
3 to 6 months	14 (82.4%)	3 (17.6%)	17(100%)	0.457
6 to 12 months	17 (73.9%)	6 (26.1%)	23 (100%)	
>1 year	35 (72.9%)	13 (27.1%)	48 (100%)	
Dose of MTX				
5-10mg/m2/week	71 (76.3%)	22 (23.7%)	93 (100%)	0.337
>10mg/m2/week	3 (100%)	0 (0%)	3 (100%)	

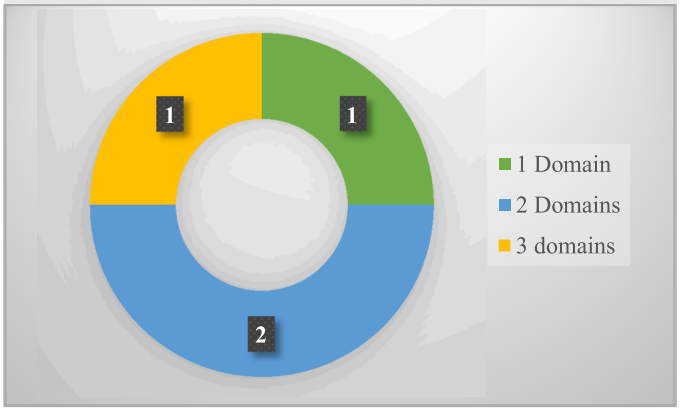

Figure-3: *Severity of symptoms in different domains*

There was no significant relationship between MTX intolerance to JIA subtype, gender, duration of illness and MTX intake, or dose of MTX. However, a significant relationship was observed with age (p=0.014), with children older than 5 years being more likely to experience MTX intolerance [Table 2].

Discussion

In children, the most prevalent rheumatic illness is juvenile idiopathic arthritis (JIA).[1] Methotrexate is the most used first-line Disease Modifying Anti-Rheumatic Drug (DMARD) for treating JIA.[3] In low-income nations like Pakistan, where most biologics are not available to the public, pediatric rheumatologists frequently rely on conventional DMARDs like MTX.[3,7]

In our study, 57.3% of patients were older than 10 years (n=55). Salim et al. (2013) reported a similar higher proportion in these age groups: 11-14 years (47%) and 6-10 years (35%) among JIA patients.[3] Similarly, 60.4% of patients in our study were female, resulting in a female-to-male ratio of 1.5:1. This female predominance is similar with findings reported by Salim et al. in 2013 (1:1.3) and Bulatovic et al. in 2011 (1:2.2) among JIA patients.[5,9] Another study conducted by Ćalasan et al. in 2013 reported a similar ratio (1:1.6) among RA patients.[7] A Common type of JIA in our study was poly-arcticular seronegative JIA, affecting 56.3% of patients, which aligns with findings from a study conducted in the Netherlands as well as other studies conducted in Pakistan.[1,2,5]

Methotrexate intolerance was found in 22.9% of patients according to the MISS score. The most common symptom was nausea, followed by behavioral symptoms. A relatively higher frequency of methotrexate intolerance has been reported by Bulatovic et al. in the Netherlands, who observed an intolerance rate of 50.5%, and by Ekici Tekin Z et al. in Turkey, where the rate was 41.4% among JIA patients.[15,16] Moreover, nausea and behavioral symptoms were the most common, which is similar to our study, and these symptoms were reported after taking MTX, also consistent with our findings. Another study conducted by Salim et al. reported 40.0% methotrexate intolerance among JIA patients. This study also reported anticipatory symptoms in almost half of the patients.[9]

Fatimah et al. reported methotrexate intolerance rates of 24.7% at Sahiwal Teaching Hospital, Sahiwal, and 33.3% at Fauji Foundation Hospital, Rawalpindi, among RA patients.[17] In contrast, Calasan MB et al. reported a higher frequency of methotrexate intolerance (42.3%) among patients with RA and psoriatic arthritis.[7] A study conducted by Amaral JM et al. in Brazil focused on RA patients, found a methotrexate intolerance rate of

21.6%.[18] Nausea (92.3%) and behavioral symptoms (96.1% of individuals with methotrexate intolerance) were the most common post-medication symptoms reported. The most common behavioral symptoms were restlessness and irritability, which are comparable to our results. Our study showed that all methotrexate intolerant patients (100%) experienced nausea and behavioral symptoms, with irritability being the most common among the behavioral symptoms.

In our study, there was no significant relationship between methotrexate intolerance and subtype of JIA, gender, duration of illness, and MTX intake, or MTX dose. Similar results were observed by Ekici Tekin Z et al. in Turkey, who found no significant relationship with gender ($p = 0.238$), a subtype of JIA ($p = 0.378$), MTX intake duration ($p = 0.165$), and MTX dosage ($p = 0.962$).16 However, Ekici Tekin Z et al. also found no significant relationship with the age of patients ($p = 0.31$), which contrasts with our study where we found a significant relationship with age ($p = 0.014$).16 Similar results were described by Amaral JM in Brazil, where a reduced incidence of methotrexate intolerance was slightly correlated with increasing age ($p = 0.059$).[18]

Some studies also document a relationship with the oral and subcutaneous doses of methotrexate.[19,20] In the current study, patients who were taking subcutaneous methotrexate, were excluded, so intolerance in these patients was not assessed. Additional research is required to ascertain methotrexate intolerance in patients taking both oral and subcutaneous forms. Hence forth, longer follow-up with a larger number of JIA patients is needed to assess long-term tolerance and to evaluate the need for discontinuation of methotrexate due to adverse events.

The MISS questionnaire should be employed to evaluate the type and severity of methotrexate intolerance. If undetected, it may result in insufficient compliance with MTX, which, in turn, results in poor outcomes for JIA patients. Early identification of patients intolerant to MTX can help with the addition of adjuvant treatments such as anti-emetics or psychotherapy. Counseling and appropriate interventions can improve compliance and overall treatment outcomes.

Conclusion

The MISS questionnaire is an effective tool for detecting methotrexate intolerance in JIA patients. Using this tool, methotrexate intolerance was found in about one-third of JIA patients taking MTX. Nausea and behavioral symptoms were experienced by all patients. Methotrexate intolerance was significantly associated with increasing age among JIA patients taking MTX. Early detection using this tool, particularly in older patients on MTX, would help improve compliance and outcomes for these patients.

Ethical Approval: The Institutional Review Board (IRB), The Children's Hospital & The Institute of Child Health, Lahore approved this study vide letter #. 2020-119-CHICH.

Conflict of Interest: The authors declare no conflict of interest.

Funding Source: None

Authors' Contribution:

SN: Conception & design, analysis & interpretation of data, drafting of article, critical revision for important intellectual content, final approval

SN & SQ: Critical revision for important intellectual content, final approval

SN & SA: Analysis & interpretation of data,

SA & FJ: Acquisition of data

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