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Prevalence of Methotrexate Toxicity and Intolerance in Juvenile Idiopathic Arthritis and Possible Risk Factors for Methotrexate Intolerance: A Tertiary Center Experience

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Abstract

Methotrexate has a safe and inexpensive profile and is the first choice of juvenile idiopathic arthritis treatment. Nevertheless, gastrointestinal symptoms are not serious but are common side effects of methotrexate. Sometimes patients may have nausea by thinking of methotrexate and even refuse methotrexate use. In this study, we aimed to define the prevalence of methotrexate side effects in juvenile idiopathic arthritis and the possible risk factors for methotrexate intolerance. Methotrexate intolerance severity score showed a severity of gastrointestinal symptoms. Eighty-seven patients accepted to join the study and answered the questions. The prevalence of adverse events of methotrexate was 64.4% and the rate of gastrointestinal symptoms was 55.2%. Nausea (27.6%) was the most common gastrointestinal symptom. The median methotrexate intolerance severity score was 14.5 (interquartile range: 10-18). However, there was no significant difference in main parameters between tolerant and intolerant groups and no risk factor was observed for methotrexate intolerance. In a conclusion, we observed methotrexate toxicity and intolerance commonly but no associative factors were defined, and, prospective larger studies are necessary to understand and prevent the occurrence of gastrointestinal symptoms.

Keywords: Juvenile idiopathic arthritis, intolerance, methotrexate, nausea

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Introduction

Methotrexate (MTX) has a broad usage in pediatric rheumatic diseases because of its effective, safe, and affordable profile. It is the most commonly selected medication in pediatric rheumatology practice.[1,2] Additionally, MTX is the first and main choice of disease-modifying anti-rheumatic drug (DMARD) for juvenile idiopathic arthritis (JIA).[2] JIA is the most frequent rheumatic disease in childhood and is characterized by arthritis with unknown etiology that is constant for at least 6 weeks in children under 16 years.[3] Despite its many advantages, low dose MTX may lead to adverse effects such as gastrointestinal (GI) symptoms (abdominal pain, nausea, vomiting), hepatotoxicity, rash, and bone marrow suppression. While gastrointestinal symptoms occur frequently, the other symptoms are rare.[1,4-6] MTX toxicity is the occurrence of adverse effects after MTX administration.[4,7] GI symptoms (nausea, vomiting) or fatigue are observed circa 4-36 hours after MTX administration.

Highlights

- There is no prominent risk factor for MTX intolerance in JIA.
- The preventions for MTX intolerance were not enough effective.
- MISS is a practical and easy applicable tool to show MTX intolerance.
- Self-discontinuation due to MTX intolerance is a main reason to interrupt of therapy.

Furthermore, JIA patients meet anticipatory and associative adverse effects of MTX. The anticipatory symptoms occur before MTX administration, such as nausea or abdominal pain by seeing syringe or hospital. The associative symptoms (nausea, vomiting, abdominal pain) happen by thinking, smell, or color of MTX.[7] These anticipatory and associative symptoms are termed MTX intolerance. There is a validated questionnaire for evaluating MTX intolerance in JIA patients. The Methotrexate Intolerance Severity Score (MISS) includes 12 items consisting of abdominal pain, nausea, vomiting, and behavioral changes.[7]

In this study, we aimed primarily to define the prevalence of MTX intolerance and toxicity in JIA patients. The second aim is to identify risk factors for MTX intolerance by comparing JIA patients with and without MTX intolerance.

Materials and Method

Study Population and Design

A cross-sectional descriptive study included JIA patients who were treated with MTX for at least 6 months. One hundred fifty-five patients were listed and the data of patients were collected from electronic files. Three patients did not fulfill the inclusion criteria and the data of ten patients were missing.

For MISS questionnaire, 142 patients were telephoned of which parents of 87 patients accepted the conversation and completed the MISS questionnaire.

The demographic, clinic and laboratory findings at diagnosis [C-reactive Protein (CRP), erythrocyte sedimentation rate (ESR), alanine aminotransferase (ALT)], disease activity, MTX dose, folic acid dose, MTX duration, adverse effects of MTX (abdominal pain, nausea, vomiting, behavioral symptoms, liver enzymes elevation, cytopenia, rash, oral ulcer), accompanying GI disease were collected retrospectively. Juvenile arthritis disease activity score (JADAS) was used to score disease activity. JADAS includes 4 items; the joint count, the physician and the patient's/parent's global assessment, and the inflammatory marker (ESR or CRP).[8] The ethics committee of Ankara City Hospital approved this study. All procedures were conducted according to the principles of the Declaration of Helsinki, and human and animal rights.

Definition of MTX Intolerance

Methotrexate intolerance severity score is used to determine MTX intolerance. MISS is a questionnaire that was developed for MTX intolerance in JIA and includes four components.7 The first three components categorize the abdominal pain, nausea, and vomiting as; after MTX use, anticipatory (before MTX), and associative (reminding of MTX) and the last part consists of behavioral symptoms (restlessness, crying, irritability, refusing) due to MTX induced GI symptoms. The patient should define the severity of symptoms by scoring 1 (mild), 2 (moderate), or 3 (severe). The MISS value ≥6 (maximum score: 36) and at least 1 anticipatory, associative or behavioral symptom showed MTX intolerance.7

Statistical Analysis

Data of the present study were assessed using SPSS (Version 22.0). In this study, quantitative variables were evaluated using the Kolmogorov-Smirnov test, detrended Normal Q-Q Plot, and histogram to define whether they were normally distributed. Normally distributed data were expressed as mean, and standard deviation (SD). Non-normally distributed data were presented as median, interquartile range (IQR). The categorical data were expressed in count and percentage.

A parametric test (Student -t) was used to compare normally distributed independent quantitative variables. If a parametric test was not provided for quantitative parameters, the Mann-Whitney U test was used to compare the independent groups. Differences between categorical data were analyzed using the Chi-square test. P values <0.05 with a 95% confidence interval were considered significant.

Results

Main Characteristics of Patients

Of 87 JIA patients, 61 (70.1%) were female and the median age was 13 (9-17) years. The most common form of JIA was oligoarticular JIA (59.8%) and the median follow-up was 49 (22-73) months. The median duration of MTX use was 24 (16-34) months and the main findings are in **Table 1**.

Table 1
Baseline characteristics of participants

Female, n (%)	61 (70.1%)
JIA subtypes, n (%)	
Oligoarticular JIA	52 (59.8%)
Polyarticular JIA	21 (24.1%)
Systemic onset polyarticular JIA	2 (2.3%)
Enthesitis-related JIA	12 (13.8%)
Age at diagnosis, median (IQR)	7 (3-12) years
JADAS at diagnosis, median (IQR)	21 (18-25)
Age at MTX onset, median (IQR)	9 (4-13) years
Duration of MTX use, median (IQR)	24 (16-34) months
Dose of MTX, median (IQR)	12.5 (10-15) mg/week
Administration of MTX, n (%)	
Oral	19 (21.8%)
Subcutaneous	48 (55.2%)
First oral later subcutaneous	20 (23%)
Folic acid, n (%)	
No	3 (3.4%)
3.75-7.5 mg/week (3 days/week)	75 (86.2%)
7.5-15 mg/week (6 days/week)	9 (10.3%)
Biologic therapy, n (%)	26 (29.9%)
Additional rheumatologic disease, n (%)	4 (4.6%)

JIA: juvenile idiopathic arthritis, JADAS: juvenile arthritis disease activity score, MTX: methotrexate, IQR: interquartile range

Prevalence of MTX Toxicity and Intolerance

In this study, 56 (64.4%) patients had MTX side effects. Of 56 patients, 20 (23%) had purely MTX toxicity, 8 (9.2%) had purely MTX intolerance and 28 (32.2%) had both of them together. GI toxicity occurred in 39 (44.8%) patients after MTX administration and nausea was the most common adverse effect (**Table 2**). MTX intolerance was observed in 36 patients who had MISS ≥6 and, all of them had GI symptoms and nausea as the most frequent symptom (27.6%) (**Table 2**). The median value of the MISS questionnaire was 14.5 (10-18) and detailed results of the MISS questionnaire are summarized in **Table 3**. We observed MTX intolerance in the first 6 months of treatment (**Figure 1**). The MTX reminders such as a syringe, yellow color, and thinking or talking about MTX might cause intolerance. The thinking of MTX was the most common trigger of symptoms (**Table 2**). Self- discontinuation of MTX occurred in 14 (16.1%) patients due to MTX intolerance. In some cases, we tried to prevent intolerance by changing the dose or administration way. Use of folic acid or anti-emetics were other preventions (**Table 2**).

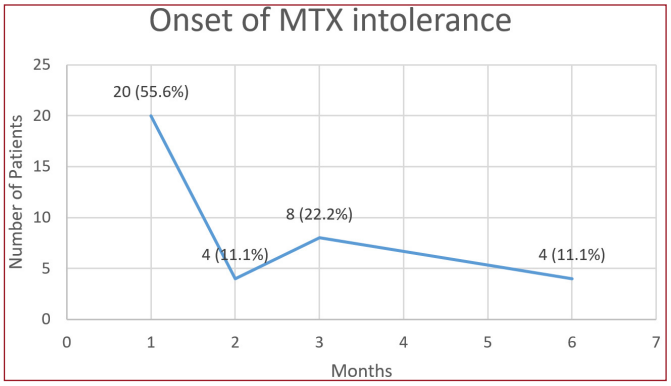

Figure 1. Distribution of MTX intolerance onset
MTX, methotrexate

Table 2
The prevalence of MTX toxicity and intolerance, the results of the MISS questionnaire

MTX toxicity, n (%) (after MTX)	**48 (55.2%)**
GI symptoms	39 (44.8%)
Abdominal pain	3 (3.4%)
Nausea	38 (43.7%)
Vomiting	23 (26.4%)
Liver enzymes elevation	16 (18.4%)
Oral ulcers	4 (4.6%)
Cytopenia	3 (3.4%)
MTX intolerance, n (%) (before MTX)	**36 (41.4%)**
Abdominal pain	0
Nausea	24 (27.6%)
Vomiting	11 (12.6%)
Fatigue	4 (4.6%)
MISS (Range: 0-36), n (%)	
MISS (0)	38 (43.7%)
MISS (1-5)	13 (14.9%)
MISS (6-36)	36 (41.4%)
Triggers of MTX intolerance, n (%)	**30 (34.5%)**
Doctor office	6 (6.9%)
Syringe/tablet	18 (20.7%)
Yellow color	9 (10.3%)
Talking about MTX	20 (23%)
Thinking about MTX	25 (28.7%)
Preventions of MTX intolerance, n (%)	**24 (27.6%)**
Reducing MTX dose	4 (4.6%)
Changing route of MTX administration	12 (13.7%)
Stopping MTX	3 (3.4%)
Elevation of folic acid	3 (3.4%)
Antiemetic drugs	2 (2.3%)

MTX, methotrexate; GI, gastrointestinal; MISS, methotrexate intolerance severity score

Table 3
The prevalence and severity of gastrointestinal and behavioral symptoms due to MTX intolerance

	No symptom	Mild symptom	Moderate symptom	Severe symptom
Abdominal pain, n (%)				
after MTX	84 (97.3%)	-	2 (2.3%)	1 (1.1%)
anticipatory	87 (100%)	-	-	-
associative	87 (100%)	-	-	-
Nausea, n (%)				
after MTX	51 (58.6%)	6 (6.9%)	13 (14.9%)	17 (19.5%)
anticipatory	65 (74.7%)	-	12 (13.8%)	10 (11.5%)
associative	78 (89.6%)	-	3 (3.4%)	6 (6.9%)
Vomiting, n (%)				
after MTX	65 (74.7%)	3 (3.4%)	5 (5.7%)	14 (16.1%)
anticipatory	76 (87.4%)	2 (2.3%)	5 (5.7%)	4 (4.6%)
Behavioral symptoms, n (%)				
restlessness	55 (63.2%)	3 (3.4%)	13 (14.9%)	16 (18.4%)
crying	64 (73.6%)	3 (3.4%)	6 (6.9%)	14 (16.1%)
irritability	67 (77%)	2 (2.3%)	3 (3.4%)	15 (17.2%)
refusal of MTX	54 (62.1%)	3 (3.4%)	8 (9.2%)	22 (25.3%)

MTX, methotrexate

Evaluating Risk Factors for MTX Intolerance

The main characteristics of tolerant and intolerant patients were compared to define probable factors that might cause MTX intolerance. There was no significant relation between MTX intolerance and gender, JIA subgroups, laboratory parameters at diagnosis (AST, ALT, CRP, ESR, CBC), JADAS at onset, age at diagnosis, age at MTX onset, the dose of MTX and duration of MTX use. There was no significant difference in the main parameters for tolerant and intolerant groups (**Table 4**).

Table 4
Comparing tolerant and intolerant patients to define risk factors

	MTX tolerant	MTX intolerant	p value
Gender, n (%)			0.238*
Girls	33 (37.9%)	28 (32.2%)	
Boys	18 (20.7%)	8 (9.2%)	
JIA subtypes, n (%)			0.378*
Oligoarticular JIA	28 (32.2%)	24 (27.6%)	
Polyarticular JIA	14 (16.1%)	9 (10.3%)	
Enthesitis-related JIA	3 (3.4%)	9 (10.3%)	
Age at diagnosis, median (IQR)	7 (2-12)	8 (5-13)	0.31**
JADAS at diagnosis, median (IQR)	17.4 (20.9-25.2)	18.4 (21.1-24.6)	0.67**
Age at MTX onset, median (IQR)	8 (3-12)	9 (5.25-13.75)	0.286**
Duration of MTX use, median (IQR)	23 (16-29)	27.5 (15-48)	0.165**
Dose of MTX, median (IQR)	13.2 (10-15)	12.5 (10-18.75)	0.962**
Administration of MTX, n (%)			0.151*
Oral	14 (16.1%)	5 (5.7%)	
Subcutaneous	31 (35.6%)	17 (19.5%)	
Oral → subcutaneous	6 (6.9%)	14 (16.1%)	
Folic acid, n (%)			0.389*
No	1 (1.1%)	2 (2.3%)	
3.75-7.5 mg/week (3 days/week)	46 (52.9%)	29 (33.3%)	
7.5-15 mg/week (6 days/week)	4 (4.6%)	5 (5.7%)	
Biologic therapy, n (%)	16 (18.4%)	10 (11.5%)	0.814*

MTX, methotrexate; JIA, juvenile idiopathic arthritis; JADAS, juvenile arthritis disease activity score; IQR, interquartile range, *Chi-Square test, **Mann Whitney U test

Discussion

In the current study, we focused on the prevalence of MTX toxicity and intolerance in JIA, the results of the MISS questionnaire, and the probable risk factors for MTX intolerance. Among 87 JIA patients, we found that 55.2% had MTX toxicity and 41.4% had MTX intolerance with MISS of 6 and over. Nausea was the most common symptom before and after MTX. The remembering or thinking of MTX was the most frequent trigger of MTX intolerance. Additionally, we observed no significant association between MTX intolerance and other parameters.

Juvenile idiopathic arthritis is the most common rheumatic disease in childhood and might have devastating results without effective treatment. MTX is a central point of medical therapy of JIA because of its safety and effectiveness.[1,2,5] Nevertheless, MTX can have rarely serious side effects like bone marrow suppression or elevation of liver enzymes. On the other hand, MTX-induced GI symptoms were quite common in clinical practice.[4,7] The clinicians usually ignore GI symptoms of MTX, because there are not many DMARDs options for children.

In this study, 48 (55.2%) patients had MTX-induced GI symptoms; 9 (10.3%) patients suffered from GI problems before MTX, 12 (13.8%) patients had problems after MTX and 27 (31.1%) patients had GI symptoms both before and after MTX. We observed MTX intolerance in 36 (41.4%) patients. In adult studies, the prevalence of MTX intolerance was between 11 and 39.5%.[9-12] Two studies about JIA reported MTX intolerance of 51% and 42%.[7,13] A current study that compared MTX intolerance between adults and children reported MTX intolerance of 64% in children and 10% in adults.[14] All our patients with MTX intolerance had nausea (41.4%). Among the patients, 12.6% had vomiting and nobody reported abdominal pain before MTX. The rate of MTX-induced nausea in JIA was reported between 21-73%.[7,15] MTX-induced nausea was the most common reason for self-discontinuation. In our study, 14 (16.1%) of 36 patients with MTX intolerance discontinued MTX. The self-discontinuation due to MTX intolerance was reported between 10-67% in studies.[15-17] Because of the different methods and populations of studies, the range of self-discontinuation was broad.

Methotrexate intolerance severity score was a beneficial tool to show MTX intolerance and all participants of this study readily completed the questionnaire. The MISS questionnaire provided gradual MTX intolerance objectively and we found that the median score of the MISS questionnaire was 14.5 (IQR: 10-18).

In this study, all MTX intolerance cases occurred in the first 6 months of MTX treatment and 20 (55.6%) of 36 patients had symptoms in the first month. According to studies, it occurred within the first year of treatment.[7,13] A current study reported MTX intolerance of 25% within 6 months and 30% within the first year.[18]

The rare and serious side effects of MTX were persistent cytopenias and elevations of liver enzymes. These adverse events were reported in 5-9%.[19,20] We observed an 18.4% elevation of liver enzymes, and 3.4% cytopenia. None of them was persistent and the laboratory parameters were normalized after a pause of MTX dose for a few weeks. In studies, recommendations for MTX intolerance were focused on preventing nausea before its occurrence and early use of anti-emetics was suggested.[15,20] The known countermeasures were not enough to prevent MTX intolerance, such as folic acid and changing the dose of MTX. Current studies investigated the effects of acupressure points, coffee/dark chocolate, and behavioral treatments.[20] We observed no decrease in nausea after folic acid or dose changing.

The causes and pathogenesis of MTX intolerance are still unknown and a few studies reported no prominent risk factors for MTX intolerance like ALT, thrombocyte, and creatinine.[21] Franova et al.[18] defined no potential predictors for MTX intolerance. In this study, we found no difference in clinical and laboratory parameters of tolerant and intolerant patients and, we observed no distinctive demographic, clinical, and laboratory findings that might be associated with MTX intolerance.

A cross-sectional design, single-center experience, relatively small number of patients, and filling MISS questionnaire were the main limitations of this study.

Conclusion

The predictive possible risk factors of MTX intolerance and prevention of MTX intolerance before occurrence in JIA are not available. The MISS questionnaire is suitable for defining MTX intolerance objectively. MTX intolerance is an important reason for self-discontinuation. There is no effective solution for MTX intolerance. However, MTX is still the first option for DMARDs in JIA and it is necessary for prospective studies on a larger number of patients to impede MTX intolerance.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

Conflict of Interest: There are no conflicts of interest in connection with this paper, and the material described is not under publication or consideration for publication elsewhere.

Ethics Committee Approval: This study was performed in line with the principles of the Declaration of Helsinki. The Ethics Committee of Ankara City Hospital (Date 08.06.2022/E2-22-1928) granted approval.

Financial Disclosure: The authors have no conflicts of interest to declare.

Informed Consent: Informed consent was obtained from the parents of the patients.

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