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ORIGINAL ARTICLES

Prevalence and clinical risk factors for methotrexate intolerance in patients with juvenile idiopathic arthritis

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ABSTRACT

Aims: Methotrexate (MTX) is a basic therapy for juvenile idiopathic arthritis (JIA). MTX intolerance can significantly impact quality of life, treatment adherence and outcomes. We aimed to assess the prevalence of MTX intolerance and to identify clinical factors associated with intolerance in children and adolescents with JIA.

Methods: This cross-sectional study was conducted at a large pediatric rheumatology referral center between July 2019 and July 2021. It included 94 patients with JIA, aged up to 19 years, who had been treated with MTX (oral or subcutaneous) for at least three months. Patients with systemic JIA and those exhibiting toxic MTX effects were excluded. Demographic and clinical data were collected, and MTX intolerance was assessed using the Methotrexate Intolerance Severity Score (MISS) questionnaire. MTX intolerance was defined as a total MISS score of ≥6, including at least one anticipatory, associative, or behavioral symptom. Statistical analyses were performed to compare MTX-tolerant and MTX-intolerant groups.

Results: The median patient age was 9.9 years (range 2.3–18.5 years), and 69 (73.4%) were female. The median age at disease onset was 3.7 years, and the median duration of MTX therapy was 2.3 years. The prevalence of MTX intolerance was 24.5%. The most common symptom was nausea after MTX intake (38.3%), followed by behavioral problems such as irritability or restlessness. Intolerant patients were significantly older at disease onset and MTX initiation (U=577.0, p=0.04 and U=555.5, p=0.02, respectively), and MTX as first-line therapy was more frequent in this group (X^2=5.78, p=0.02). There was a strong positive correlation between age at disease onset and MTX initiation (r=0.9, p<0.001).

Conclusions: MTX intolerance is relatively common in pediatric patients with JIA and is associated with older age at disease onset and MTX initiation, as well as the use of MTX as first-line therapy.

Keywords: Juvenile idiopathic arthritis; Metxotrexate; Drug tolerance; Surveys and questionnaires.

KEY MESSAGES

- MTX intolerance affects nearly 1 in 4 pediatric JIA patients, emphasizing its clinical relevance in routine care.
- Older age at disease onset and MTX start are associated with intolerance in this population.
- First-line MTX use is significantly associated with intolerance, supporting the need for tailored treatment strategies in JIA.

INTRODUCTION

Juvenile Idiopathic Arthritis (JIA) refers to a group of inflammatory rheumatic diseases that begin in childhood, whose etiology is not fully understood, and whose common feature is chronic joint inflammation[1]. JIA is considered a rare disease, with an incidence ranging from 1.6 to 23 per 100,000 children per year and a prevalence from 3.8 to 400 per 100,000 children[2].

There have been several attempts to classify JIA, but the International League of Associations for Rheumatology (ILAR) classification is the most commonly used in

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clinical practice[3].

JIA is a chronic disease characterized by periods of remission and exacerbation. The goal of JIA treatment is to achieve and maintain remission or minimal disease activity in order to prevent joint damage, functional limitations, and growth disorders[4,5]. Pharmacological treatment of JIA includes the use of nonsteroidal anti-inflammatory drugs (NSAIDs), intra-articular and systemic corticosteroids, conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), and biologic disease-modifying antirheumatic drugs (bDMARDs)[6-10].

According to recommendations from the American College of Rheumatology (ACR), the pharmacological approach to treating JIA depends on the clinical characteristics of the patient (disease subtype, disease activity, indicators of poor prognosis, previous therapy, and associated extra-articular manifestations such as psoriasis or uveitis), rather than on the subtype of the disease according to ILAR classification[7-11]. Methotrexate (MTX) is the most commonly used csDMARD due to its good efficacy and safety profile[12]. Although a stepwise approach is generally recommended in JIA treatment, in certain cases (e.g., patients with polyarthritis, high disease activity, poor prognostic indicators, or associated uveitis), early initiation of MTX therapy or use of MTX as the first-line drug is advised[7-11]. On the other hand, MTX is not the drug of choice in active sacroiliitis and is not recommended for treating systemic manifestations in the systemic form of JIA[7-10]. MTX has both cytotoxic and anti-inflammatory effects. It can be administered orally or parenterally (subcutaneously, intramuscularly, or intravenously), with subcutaneous injection being the most common parenteral route[12]. The route of administration affects the drug's bioavailability. It is believed that bioavailability after oral administration is 11–15% lower than after subcutaneous administration[13-14]. This is due to saturation of absorption during oral intake (nonlinear pharmacokinetics), unlike parenteral routes[14]. There are significant differences in clinical practice regarding the preferred route of MTX administration. If oral administration is the initial method, parenteral therapy is considered in cases of poor compliance due to gastrointestinal side effects or the need for higher doses to achieve a therapeutic effect[15].

MTX intolerance refers to a range of subjective, adverse symptoms that occur during MTX treatment, even in the absence of measurable toxicity (e.g., abnormal laboratory results)[16,17]. These symptoms may occur during drug use, but also anticipatorily (before taking the drug) or associatively (at the thought of the drug)[17,18]. To recognize and quantify the severity of physical and psychological symptoms related to MTX use, the Methotrexate Intolerance Severity Score (MISS) questionnaire was developed[17]. Since MTX is one of the most widely used medications in JIA treatment, MTX intolerance represents a significant issue in clinical practice. However, the risk factors for the development of MTX intolerance are still not well understood.

We aimed to assess the prevalence of methotrexate (MTX) intolerance using the MISS questionnaire, as well as to identify clinical factors that may be associated with intolerance to MTX therapy in children and adolescents with juvenile idiopathic arthritis (JIA).

PATIENTS AND METHODS

Study Design and Patient Selection

The research was conducted as a cross-sectional study at the Institute of Rheumatology, during the period from July 2019 to July 2021.

The study included children and adolescents up to 19 years of age diagnosed with JIA according to the ILAR classification, who had been on a stable dose of methotrexate (either oral or subcutaneous) for at least three months. The following were exclusion criteria: treatment with methotrexate for less than three months; measurable toxic effects of methotrexate (e.g., elevated transaminases or cytopenias), as these may reflect objective organ damage rather than intolerance, which is inherently more subjective; the systemic form of JIA, due to its distinct etiopathogenesis and the small number of such patients receiving methotrexate; and incomplete or unreliable data.

The study protocol was approved by the Ethics Committee of the Institute of Rheumatology (approval number: 29/1-35). Written informed consent was obtained from the parents of all participants.

Data collection

To assess methotrexate (MTX) intolerance, all participants and/or their parents completed the MISS questionnaire, which had been previously adapted for the Serbian-speaking population[17]. The questionnaire consists of 12 questions divided into four domains: abdominal pain, nausea, vomiting, and behavioral symptoms. The first three domains refer to symptoms occurring after taking MTX, before taking MTX (anticipatory symptoms), or when thinking of MTX (associative symptoms), while the fourth domain addresses behavioral problems such as restlessness, crying, irritability, and refusal to take MTX. Each question is scored as 0 (no symptoms), 1 (mild symptoms), 2 (moderate symptoms), or 3 (severe symptoms). The total score, obtained by summing scores from all domains, ranges from 0 to 36. MTX intolerance is defined as a total score of ≥6, including at least one anticipatory or associative symptom or behavioral problem[17].

If a patient had switched from oral to subcutaneous MTX therapy less than six weeks prior to completing the questionnaire, the responses referred to oral therapy.

Similarly, if the switch was from subcutaneous to oral MTX within the previous six weeks, the responses referred to subcutaneous therapy.

In addition to the MISS questionnaire, demographic and clinical data were collected, including age, sex, JIA subtype, age at disease onset, disease duration, number of swollen joints, number of joints with limited range of motion, presence of uveitis (active or in remission), erythrocyte sedimentation rate (ESR), levels of C-reactive protein (CRP), presence of antinuclear antibodies (ANA), rheumatoid factor (RF), and HLA-B27 antigen. The global assessment of disease activity by the parent or patient was also recorded, as well as the age at initiation of MTX therapy, disease duration prior to MTX initiation, duration of MTX treatment, whether MTX was the first line of treatment, whether MTX therapy was restarted due to disease relapse, the route of administration (oral or parenteral), MTX dose, and whether MTX was used in combination with biological therapy. The ANA test was considered positive if the ANA titer was greater than 1:80, as determined by indirect immunofluorescence using a HEp-2 cell substrate.

Statistical analysis

Numerical data were presented as medians with ranges or interquartile ranges, while categorical data were presented as frequencies and percentages. To test for the presence of statistically significant differences in demographic and clinical factors between patients who tolerate MTX and those who do not, the Mann-Whitney U test was used for numerical data, and the chi-square (χ^2) test or Fisher's exact test was used for categorical data.

To assess the association between age at disease onset and age at initiation of MTX therapy, Pearson's correlation coefficient was used.

A p-value of <0.05 was considered statistically significant. Statistical analysis was performed using IBM SPSS Statistics, version 23.0.

RESULTS

Demographic data and clinical characteristics of the patients

Out of 121 patients diagnosed with JIA who were receiving MTX therapy during the study period, 101 were considered potential candidates for inclusion in the study. Of these, seven were excluded due to incomplete or unreliable data, resulting in a final sample of 94 patients (Figure 1). Among the eight patients who developed measurable toxic effects from MTX, five had elevations in transaminase levels exceeding twice the upper limit of normal, two developed neutropenia, and one patient exhibited both elevated transaminase levels and neutropenia.

The demographic and clinical characteristics of the patients included in the study are presented in the table (Table I). The median age of all participants was 9.9 years (range 2.3–18.5 years). Of them, 69 (73.4%) were female. The majority of patients (42.6%) had RF-negative polyarticular JIA, while 29 (30.9%) had oligoarticular or extended oligoarticular JIA. Undifferentiated JIA was diagnosed in 12 patients (12.8%), enthesitis-related arthritis (ERA) in 7 (7.4%), RF-positive polyarticular JIA

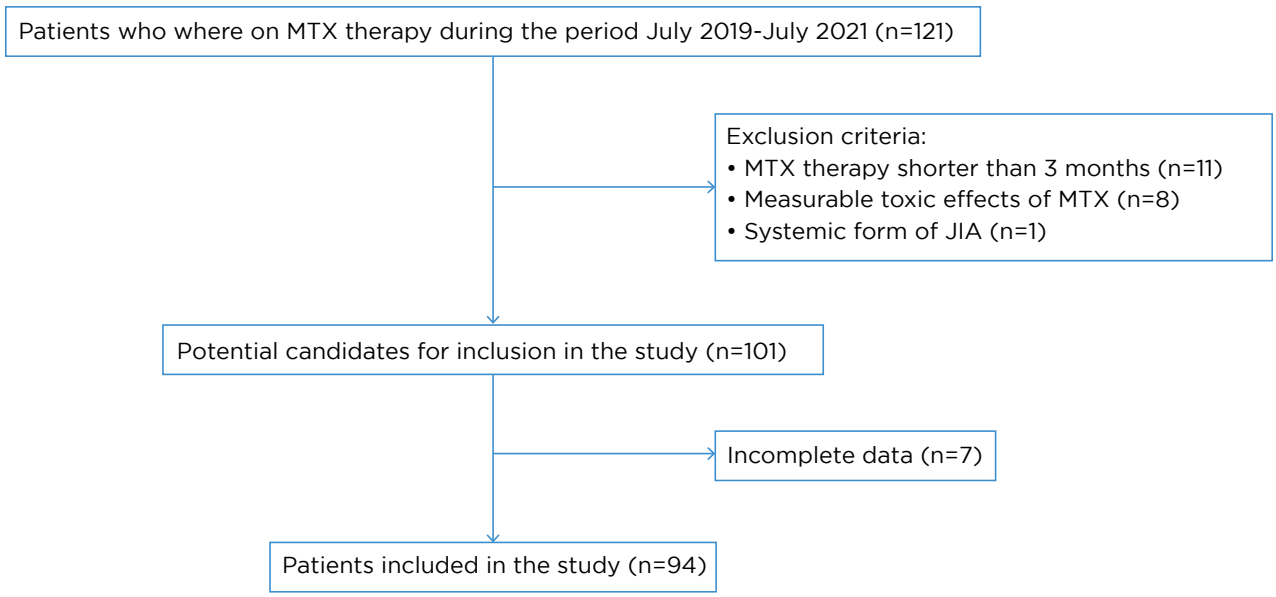

Figure 1. A flowchart showing the inclusion of patients in the study. MTX: methotrexate; JIA: juvenile idiopathic arthritis.

TABLE I. Demographic and clinical characteristics of patients who tolerate and do not tolerate methotrexate (MTX) in oral or subcutaneous form. Values are presented as median (interquartile range) or as frequencies (percentages). Statistically significant p-values are highlighted in bold.

Characteristic	MTX tolerant N=71 (75.5%)	MTX intolerant N=23 (24.5%)	Statistical significance
Age	8.9 (5.6-13.7)	11.0 (8.9-14.5)	U=598.5, p=0.06
Sex			
Male	18 (25.4%)	7 (30.4%)	X^2=0.23, p=0.63
Female	53 (74.6%)	16 (69.6%)	
Type of JIA			
Oligoarticular (persistent or extended)	23 (32.4%)	6 (26.1%)	X^2=0.32, p=0.57
Polyarticular (RF negative or RF positive)	32 (45.1%)	12 (52.2%)	X^2=0.35, p=0.55
Psoriatic arthritis, enthesitis-related arthritis, and undifferentiated JIA	16 (22.5%)	5 (21.7%)	X^2=0.01, p=0.94
Disease characteristics			
Age at disease onset (years)	3.5 (2.4-7.8)	6.9 (3.1-9.9)	U=577.0, **p=0.04**
Duration of disease (years)	3.5 (1.7-6.7)	3.6 (3.1-6.1)	U=751.0, p=0.57
Number of swollen joints	0 (0-0)	0 (0-0)	U=794.0, p=0.76
Number of joints with limited range of motion	0 (0-1)	0 (0-1)	U=756.0, p=0.49
Associated uveitis	14 (19.7%)	3 (13.0%)	p=0.55
ESR (mm/h)	8 (5-12)	8 (5-18)	U=788.5, p=0.81
CRP (mg/L)	1.5 (0.6-2.7)	2 (0.9-3.2)	U=696.5, p=0.29
ANA positivity	35 (49.3%)	12 (52.2%)	X^2=0.58, p=0.81
RF positivity	2 (2.8%)	2 (8.7%)	p=0.25
HLA-B27 antigen	9 (12.7%)	2 (8.7%)	p=1.00
Parent's or patient's global assessment of disease activity	0 (0-1)	0 (0-2)	U=751.0, p=0.48

JIA: juvenile idiopathic arthritis; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

in 4 (4.3%), and psoriatic arthritis in 2 patients (2.1%). In patients with ERA, MTX was used to treat peripheral arthritis.

The median age at disease onset was 3.7 years (range 0.8–16.4 years), while the median disease duration was 3.6 years (range 0.6–14 years). The median number of swollen joints at the time of completing the questionnaire was 0 (range 0–13). Similarly, the median number of joints with limited mobility was 0 (range 0–15). Seventeen patients (18.1%) had associated anterior uveitis, which was in remission in all cases.

Ten patients (10.6%) had increased ESR levels, and 9 (9.6%) had increased CRP levels. Half of the patients tested positive for antinuclear antibodies (ANA), rheumatoid factor (RF) was positive in 4 patients (4.3%), and 11 patients (11.7%) were positive for the HLA-B27 antigen.

The median global assessment of disease activity by parents or patients was 0 (range 0–9).

Methotrexate Therapy and Methotrexate Intolerance

In the entire study population, the median age at the start of MTX therapy was 5.5 years (range 1.5–16.8 years) (Table II). The median duration of disease before starting MTX therapy was 0.6 years (range 0–10.4 years), while the median length of MTX treatment was 2.3 years (range 0.3–11.2 years).

MTX was the first-choice medication for 43.6% of patients, the majority of whom (58.5%) had RF-negative polyarticular JIA, followed by undifferentiated JIA (17.1%), oligoarticular JIA (12.2%), RF-positive polyarticular JIA (7.3%), and psoriatic arthritis (4.9%). MTX was reintroduced in the treatment of 11 patients due to disease relapse after remission had been achieved.

Oral MTX was administered to 87.2% of patients, while 12.8% received MTX parenterally (subcutaneously). The median age of patients receiving oral MTX was 9.0 years (range 2.3–18.3 years), and13.6 years (range 6.5–18.3 years) for those receiving parenteral MTX. Patients treated with oral MTX were statistically significantly younger than those receiving parenteral MTX (U=244.0, p=0.005). Four patients did not tolerate MTX in either oral or subcutaneous form. Three of these patients initially received oral MTX, then switched to subcutaneous, while one patient first received subcutaneous MTX and later switched to oral.

TABLE II. Data related to methotrexate (MTX) therapy for participants divided into two groups: those who tolerate MTX and those who do not tolerate MTX. Values are presented as median (interquartile range) or as frequencies (percentages). Statistically significant p-values are highlighted in bold.

Characteristic	MTX tolerant N=71 (75.5%)	MTX intolerant N=23 (24.5%)	Statistical significance
Age at the start of MTX therapy (years)	5.0 (3.1-10.0)	8.4 (5.0-12.1)	U=555.5, **p=0.02**
Duration of disease before starting MTX therapy (years)	0.6 (0.3-1.3)	0.7 (0.3-1.7)	U=751.5, p=0.57
Length of MTX treatment (years)	2.6 (0.9-4.7)	2.3 (1.3-3.8)	U=769.0, p=0.68
MTX as first-line therapy	26 (36.6%)	15 (65.2%)	X^2=5.78, **p=0.02**
Reinitiation of MTX therapy	8 (11.3%)	3 (13.0%)	p=1.0
Oral administration of the drug	66 (93.0%)	16 (69.6%)	p=0.09*
Subcutaneous administration of the drug	5 (7.0%)	7 (30.4%)	
Drug dose (mg/m²/week)	10.0 (9.3-10.9)	10.7 (9.9-11.6)	U=532.0, p=0.09
Use of MTX in monotherapy	31 (43.7%)	11 (47.8%)	X^2=0.12, p=0.73

*Four patients who did not tolerate MTX in either oral or subcutaneous form were excluded to allow for meaningful analysis of route-specific tolerance.

The median MTX dose was 10.0 mg/m²/week (range 6–15 mg/m²/week). All patients received folic acid at a dose of 5 mg weekly and vitamin D (cholecalciferol) at a dose of 1500–2000 IU daily. Additionally, 42 patients (44.7%) were concurrently treated with biological therapy: 21 (50%) received adalimumab, 20 (47.6%) etanercept, and 1 patient (2.4%) received intravenous tocilizumab. Corticosteroids were given only as bridging therapy until the effect of MTX was observed. No patient was concurrently treated with MTX and nonsteroidal anti-inflammatory drugs (NSAIDs) as regular therapy or other csDMARDs. Thirteen patients (13.8%) received antiemetics due to nausea associated with MTX use.

The median MISS score was 1.5 (range 0–25), with the prevalence of MTX intolerance in the entire study population being 24.5%. The most common complaint related to MTX intake was nausea after taking MTX (38.3% of all patients), followed by irritability (33.0%), abdominal pain after taking MTX (30.9%), restlessness (28.7%), nausea when thinking of of MTX and refusal of MTX (27.7%), vomiting after taking MTX (18.1%), crying (13.8%), abdominal pain when thinking of MTX (12.8%), nausea several hours to one day before taking MTX (11.7%), abdominal pain several hours to one day before taking MTX (8.5%), and the least frequent complaint was vomiting several hours to one day before taking MTX (2.1%) (Table III). Among patients who did not tolerate MTX, all experienced nausea and behavioral problems, 87.0% had abdominal pain, and 60.9% had vomiting. Almost all complaints, except for vomiting several hours to one day before taking MTX, were significantly more frequent in patients intolerant to MTX (Table III).

Regarding severity, complaints rated as severe (score of 3) included nausea after taking MTX (in 9.6% of cases), abdominal pain after taking MTX and irritability (6.4% of cases), vomiting after taking MTX, restlessness, and refusal of MTX (4.3% of cases), crying (3.2% of cases), and abdominal pain and nausea when thinking of MTX (2.1% of cases).

Older age at disease onset and at the start of MTX therapy, as well as the use of MTX as first-line treatment, were significantly more common in patients who did not tolerate MTX (Tables I and II). There was a strong positive correlation between age at disease onset and age at the start of MTX therapy ($r = 0.9$, $p < 0.001$).

DISCUSSION

Methotrexate intolerance affects quality of life, compliance, and treatment outcomes. For this reason, great attention is given not only to the direct toxic effects of MTX but also to neuropsychological symptoms that cannot be explained by the drug's neurotoxicity. These neuropsychological symptoms—primarily anticipatory and associative symptoms—are believed to represent a classic example of Pavlovian conditioning[17].

In our study, every fourth patient did not tolerate MTX, and each of them experienced nausea and behav-

TABLE III. Comparison of the frequency of symptoms (mild, moderate, and severe) related to methotrexate (MTX) intake (items from the Methotrexate Intolerance Severity Score) between patients who tolerate and those who do not tolerate methotrexate in oral or subcutaneous form. Statistically significant p-values are highlighted in bold.

Characteristic	MTX tolerant N=71 (75.5%)	MTX intolerant N=23 (24.5%)	Statistical significance
Abdominal pain			
After taking MTX	9 (12.7%)	20 (87.0%)	**p<0.01**
Several hours to one day before taking MTX (anticipatory pain)	1 (1.4%)	7 (30.4%)	**p<0.01**
When thinking of MTX (associative pain)	1 (1.4%)	11 (47.8%)	**p<0.01**
Nausea			
After taking MTX	17 (23.9%)	19 (82.6%)	**p<0.01**
Several hours to one day before taking MTX (anticipatory nausea)	2 (2.8%)	9 (39.1%)	**p<0.01**
When thinking of MTX (associative nausea)	8 (11.3%)	18 (78.3%)	**p<0.01**
Vomiting			
After taking MTX	4 (5.6%)	13 (56.5%)	**p<0.01**
Several hours to one day before taking MTX (anticipatory vomiting)	0 (0%)	2 (8.7%)	p=0.06
Behavioral symptoms			
Restlessness	10 (14.1%)	17 (73.9%)	**p<0.01**
Crying	3 (4.2%)	10 (43.5%)	**p<0.01**
Irritability	13 (18.3%)	18 (78.3%)	X^2=28.25, **p<0.01**
Refusal to take MTX	6 (8.5%)	16 (69.6%)	X^2=36.20, **p<0.01**

ioral symptoms. Additionally, anticipatory vomiting was observed only in patients who did not tolerate MTX. In cross-sectional studies that used the MISS questionnaire to assess MTX intolerance in patients with JIA, the prevalence of MTX intolerance ranged from 41.4% to 60.8%[17,19-21]. However, it is difficult to compare the results of these studies because they differ in the number and selection of participants, disease duration, use of MTX in oral and parenteral forms, and length of MTX treatment. For example, in a study by Dutch authors, the prevalence of MTX intolerance among 297 patients with a mean age of 10.9 years (range 2–18 years) was 50.5%[17]. Of them, 74.1% took MTX orally, while the median duration of therapy was 1.6 years (interquartile range 0.6–3.6 years). Among those who were intolerant to MTX, 91.3% experienced nausea, and 88.7% exhibited behavioral symptoms[17]. Anticipatory vomiting was also observed only in patients who did not tolerate MTX, but its prevalence was higher than in our study (18.7% compared to 8.7%)[17]. In a study by Danish authors, which included 120 patients with JIA with a mean age of 13.3 years (range 9.1–17.4 years), the prevalence of MTX intolerance was as high as 60.8%[19]. Of these, 37.5% were receiving MTX orally, and 62.5% subcutaneously, while the median duration of MTX therapy was 11.1 months (interquartile range 4.7–25.1 months)[19]. Similar to our study, the most common symptom related to MTX intake was nausea after taking MTX (in as many as 73% of patients), but a high prevalence of anticipatory and associative symptoms, as well as behavioral problems, was also observed[19]. In the study by Tekin and colleagues, which included 87 patients with JIA with a mean age of 13 years (range 9–17 years), the prevalence of MTX intolerance was 41.4%[20]. Among them, 21.8% received MTX orally, 55.2% subcutaneously, and 23% initially received MTX orally and then switched to subcutaneous administration. The median duration of MTX therapy was 24 months (range 16–34 months). In patients who did not tolerate MTX, the most common symptoms were nausea and gastrointestinal complaints (in 27.6% of patients)[20]. In a study by German authors that included 196 patients with JIA, with an average age of 9.67 ± 4.42 years and an average disease duration of 4.14 ± 3.54 years, the prevalence of MTX intolerance was 46%[21]. Among them, 44.6% received MTX in the subcutaneous form. In addition to the mentioned studies, a high prevalence of MTX intolerance (64%) was reported in a study by Turkish authors that included 100 patients with an average age of 11.9 ± 3.7 years[22]. However, only 72% of these patients had a diagnosis of JIA, while the diagnoses of the remain-

ing pediatric patients were not specified[22].

The slightly lower prevalence of MTX intolerance in our group of patients with JIA could be explained by the exclusion of patients with measurable toxic effects of MTX (e.g., elevated transaminases and cytopenias), as well as the fact that our patients were younger compared to those in some other studies[20,21]. Our results are most consistent with the findings of a study by Dutch authors who investigated risk factors for MTX intolerance in patients aged 1–18 years with JIA[23]. In that study, the prevalence of MTX intolerance at 3, 6, and 12 months after initiating MTX therapy was 15.7%, 24.1%, and 23.3%, respectively[23]. Additionally, in a prospective study by Czech authors, the prevalence of MTX intolerance after 6 and 12 months of therapy was 25.5% and 30.6%, respectively[16]. However, during the one-year follow-up period, as many as 45.5% of patients experienced MTX intolerance at some point[16]. The study included 55 patients with JIA, with a median age of 5.3 years (interquartile range 2.8–10.6 years) and a median disease duration of 3.8 months. The majority of patients received MTX in parenteral form (81.8%). All patients in the study who were intolerant to MTX exhibited some form of behavioral disorder; 78.6% experienced abdominal pain, and 71.4% reported nausea[16].

In our study, patients who were intolerant to MTX were significantly older at disease onset and at the initiation of MTX therapy. Similarly, in the study by Czech and German authors, the likelihood of developing MTX intolerance increased with age[16,21]. One possible explanation for this finding is the increase in psychological distress with age. On the other hand, in the study by Turkish authors, there was no statistically significant association between age at diagnosis or age at the initiation of MTX therapy and MTX intolerance[20]. In the study by German authors, patients who tolerated MTX received significantly higher doses of MTX (per square meter of body surface area)[21]. Higher doses of MTX are usually required for younger children because they metabolize the drug faster, which may suggest that younger children tolerate MTX better. On the other hand, our results show that patients who were intolerant to MTX received slightly higher doses, although this difference was not statistically significant. Similarly, in the study by Dutch authors, patients receiving higher doses of MTX had increased odds of MTX intolerance[17]. However, other studies have not shown a statistically significant difference in MTX dosage between patients who tolerate MTX and those who do not[16,19,20].

In our study, there was no statistically significant difference in the prevalence of MTX intolerance between patients receiving the drug orally and those receiving it subcutaneously, although a slightly higher frequency of MTX intolerance was observed with parenteral administration. One possible explanation for the slighlty higher frequency of drug intolerance among patients receiving subcutaneous MTX might be its greater bioavailability (and consequently higher blood concentrations) compared with oral MTX at the same dose. However, age should also be considered as a potential confounding factor, as patients receiving MTX parenterally were significantly older than those receiving it orally. Some authors have also found no significant association between MTX intolerance and the route of drug administration (oral versus parenteral)[19,23]. On the other hand, a study by Dutch authors showed that parenteral administration of MTX was significantly more common in patients who were intolerant to MTX[17]. Additionally, in the study by Londe AC *et al.,* conducted on a convenient (non-representative) sample of pediatric patients with JIA, MTX intolerance was significantly more common among patients receiving MTX via the parenteral route[24]. However, the conclusions of these studies[17,19,23,24] may be biased, as the statistical analyses did not account for changes in the route of drug administration (from oral to subcutaneous or vice versa).

One way to overcome MTX intolerance is to change the route of drug administration. For example, if a patient does not tolerate the drug orally, parenteral administration is usually attempted, which may increase the prevalence of MTX intolerance in the group receiving MTX parenterally. Therefore, in our analysis, we included patients who switched from one form of therapy to another but excluded those who were intolerant to MTX in both oral and parenteral forms. Secondly, if a higher dose of MTX is needed, the drug is given parenterally due to better bioavailability; however, this may increase the risk of intolerance due to dose-dependent adverse effects. Accordingly, the results from the Dutch authors indicate that patients on parenteral therapy received slightly higher doses of MTX, which may explain the increased prevalence of MTX intolerance in this patient group[17]. Van Dijkhuizen and colleagues compared MTX intolerance between patients receiving MTX exclusively orally and those receiving it exclusively parenterally, finding no statistically significant difference in the drug dose between these two groups[25]. The authors concluded that patients on parenteral therapy were significantly more likely to be intolerant to MTX, primarily reflected in a higher prevalence of behavioral disorders. However, it is difficult to establish a causal relationship since the study was cross-sectional, and the influence of confounding factors, such as needle phobia, cannot be excluded[25].

We also found the use of MTX as a first-line drug as a risk factor for MTX intolerance. One possible explanation for this is that MTX is recommended as first-line therapy for polyarthritis or oligoarthritis with high disease activity and poor prognostic factors[7-10]. Additional-

ly, the duration of MTX therapy is longer in patients for whom MTX is the first-line drug. However, there was no statistically significant difference between patients who tolerated MTX and those who did not in terms of the frequency of polyarticular JIA (a typical indication for first-line MTX therapy), associated uveitis, or the duration of MTX treatment. In the study by van Dijkhuizen and colleagues, the prevalence of the polyarticular form was actually lower in patients who were intolerant to MTX[25]. On the other hand, in a study by Czech authors, patients with the polyarticular form of JIA had a 1.43 times higher odds of MTX intolerance[16]. Furthermore, data from some studies indicate that patients who were intolerant to MTX had a longer duration of MTX therapy[17,21,25], although this trend was not observed in a study by Danish authors[19].

Disease duration has also been reported in the literature as a potentially significant factor for the development of MTX intolerance[17,21,25,26]. However, in both our study and the study by Danish authors[19], MTX intolerance was not associated with disease duration.

This study has several limitations. First, the research was conducted as a cross-sectional study, which has its limitations, the most important of which is the inability to establish causal relationships. Therefore, we were able to identify associations, but not to confirm whether a potential risk factor preceded and caused MTX intolerance. Second, the study included only patients with JIA treated at a single tertiary care center, which may affect the generalizability of the study's conclusions. Third, the sample was heterogeneous in terms of age, disease duration, length of MTX therapy, and other examined factors. Finally, while the outcomes may have been influenced by interventions aimed at preventing MTX intolerance (e.g., antiemetics), these measures are limited and often ineffective[26,27]. Therefore, we believe they did not significantly impact the results of our study.

CONCLUSIONS

Methotrexate intolerance represents a significant problem in patients with JIA, as it can lead to poor compliance and premature discontinuation of therapy. The prevalence of methotrexate intolerance in our patients with JIA was relatively high (24.5%). Although the most common symptom was nausea after taking the medication, various behavioral symptoms were also significantly present. Older age at disease onset and at the start of methotrexate therapy, as well as the use of methotrexate as first-line treatment, are potential clinical risk factors for methotrexate intolerance.

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