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THERAPY IN PRACTICE

Methotrexate Intolerance in Juvenile Idiopathic Arthritis: Definition, Risks, and Management

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Abstract

Juvenile idiopathic arthritis is the most common rheumatic disorder in childhood and adolescence posing a significant threat of short-term and long-term disability if left untreated. Methotrexate is a folic acid analog with various immunomodulatory properties. It has demonstrated significant efficacy for the treatment of juvenile idiopathic arthritis, often considered the preferred first-line disease-modifying anti-rheumatic drug given as monotherapy or in combination with biological drugs. Despite this, there is a considerable risk for treatment disruptions owing to the high prevalence of methotrexate intolerance, with symptoms such as nausea, stomach ache, vomiting, and behavioral symptoms. Many different risk factors for the intolerance have been proposed including gender, age, disease activity, treatment duration, dosing and administration, and genetic and psychological factors. As the studies have shown contradictory results, many questions are left unanswered. Therefore, a consensus regarding outcome measures and reporting is crucial. In this review, we describe the identification and assessment of methotrexate intolerance and evaluate potential risk factors, genetic associations as well as management strategies.

Key Points

Methotrexate-induced intolerance, such as nausea, affects up to 73% of children with juvenile idiopathic arthritis.

The Methotrexate Intolerance Severity Score provides a simple and standardized method for assessing and documenting methotrexate intolerance.

Evidence regarding the management of methotrexate intolerance, which includes adjusting the dose or administration method, behavioral strategies, and the use of anti-emetics and folate supplementation, is still scarce.

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1 Introduction

Juvenile idiopathic arthritis (JIA) is one of the most common chronic diseases in childhood and adolescence affecting one out of a thousand below the age of 16 years and is a major cause of short-term and long-term disability. Juvenile idiopathic arthritis comprises a group of heterogeneous forms of arthritis characterized by joint inflammation for more than 6 weeks, occurring before the age of 16 years, and with an unknown cause [1]. Juvenile idiopathic arthritis covers seven mutually exclusive categories according to the International League of Associations for Rheumatology classification criteria, namely systemic arthritis, oligoarthritis, rheumatoid factor-positive polyarthritis, rheumatoid factor-negative polyarthritis, psoriatic arthritis, enthesitis-related arthritis, and undifferentiated arthritis [1].

The aim of modern treatment of JIA is to induce rapid disease control to minimize pain, regain physical function, prevent joint damage, and achieve a normal lifestyle. Pharmacological therapies for the treatment of JIA include conventional synthetic disease-modifying antirheumatic drugs, among which methotrexate (MTX) is the most prescribed [2]. Even after the advent of biological disease-modifying antirheumatic drugs, MTX has been recommended as the first-line disease-modifying antirheumatic drug. In addition, MTX improves outcomes when used as combination

therapy [3, 4]. Methotrexate is also used in other rheumatic diseases such as juvenile dermatomyositis [5] and localized scleroderma [6].

Although studies have shown that MTX treatment resulted in significant efficacy in 65–89% of children with polyarticular JIA [7–9], more than half of the children reported problems taking the medicine, primarily because of nausea, vomiting, and abnormalities in liver function tests [10, 11]. Hence, the focus of this review is on MTX intolerance, specifically the identification and assessment hereof, potential risk factors and genetic associations, as well as management strategies for patients with JIA with MTX intolerance.

2 The Role of MTX for the Management of JIA

The management of JIA in the last two decades has seen a continuous evolution of new agents and approaches to effectively manage the disease [12]. Over a span of more than 50 years, the primary treatments for JIA have included non-steroid anti-inflammatory drugs, corticosteroids, gold, penicillamine, hydroxychloroquine, and sulfasalazine but most studies did not find the drugs to be significantly effective [13–19].

Methotrexate demonstrates a high level of efficacy and has an acceptable safety profile [7, 20]. The initial controlled trial of MTX in JIA [21] paved the way for its widespread usage in pediatric rheumatology. However, the exact mechanism of action by which MTX effectively treats arthritis remains not fully comprehended [22, 23]. However, multiple mechanisms potentially contribute to the anti-inflammatory actions, with enhancement of adenosine signaling carrying the most robust data [22]. Compared with high-dose therapy as used in oncology, low-dose MTX scarcely inhibits cell division [22].

Despite the limited understanding of its mode of action, MTX remains an anchor drug even in the most recent treatment guidelines from 2019 and 2021 [24, 25]. Based on these guidelines, treatment should be intensified in a step-by-step manner with MTX as the initial agent for non-systemic JIA unless sacroiliac or temporomandibular joints are involved [24, 25]. An alternative strategy suggests that initiating an aggressive therapy early with MTX plus a tumor necrosis factor inhibitor may exploit the "window of opportunity" and potentially modify the course of the disease, resulting in better long-term outcomes. However, the data to confirm the best initial treatment strategy are still pending [26].

A recent randomized controlled trial (RCT) by Rezaieyazdi et al. of 19 patients with JIA documented that combining MTX with leflunomide did not improve the outcome but increased the side effects [27]. In contrast, the combination of MTX and a tumor necrosis factor inhibitor has been shown to enhance the efficacy of treatment for polyarticular JIA without significantly compromising safety [28]. The combination therapy continues to be significant in the management of JIA and the addition of biologics have played a groundbreaking role in the 21st century, greatly transforming outcomes for children, adolescents and extending well into adulthood. However, some patients do not respond to these modern agents, or they experience a loss of efficacy over time possibly because of the presence of antidrug antibodies (ADAs) [29]. There is growing evidence that combining MTX and biologic agents may prevent or diminish the development of ADAs, thereby improving the response [30–32]. However, the optimal strategy regarding dosing of MTX as an ADA inhibitor in JIA and the most treatment-effective strategy on how to manage ADAs are still unknown [33, 34].

3 Patterns of Symptoms and Challenges Presented by MTX Intolerance: Risk Factors for Developing Intolerance?

Gastrointestinal side effects related to MTX are frequently encountered by patients, with a reported prevalence from 25 to 73%. However, it is crucial to discriminate the events of MTX toxicity from MTX intolerance, when discussing these gastrointestinal events. Methotrexate toxicity refers to the direct side effects of MTX such as nausea, vomiting, and elevation of liver enzymes such as alanine transaminase (ALT). However, MTX intolerance not only encompasses vomiting, stomach ache and nausea after MTX intake, which are indicative of toxicity, but also if these symptoms occur when thinking of MTX (associative) and/or prior to MTX intake (anticipatory) as well as behavioral symptoms (i.e., crying) when taking MTX [35].

These symptoms pose one of the greatest challenges of MTX intolerance. Behavioral symptoms may negatively affect patients' quality of life, hinder successful treatment, and increase the risk of MTX discontinuation, which makes them of great importance to notice and address [10, 11, 25, 36–43]. Additionally, children describe MTX intolerance as extremely challenging, forcing them to change their daily routines to avoid interference with key activities, causing anxiety attacks, and making it difficult to do homework or participate in sports. This makes it of key interest to physicians and care providers to gain more knowledge within this field [44].

For healthcare professionals, it is crucial to have awareness of the considerable risk of MTX intolerance when discussing and recommending treatment options. The prevalence of MTX intolerance shows inter-study variability that

ranges from 20% to more than 60% of study populations [10, 36–39, 45–51]. A large contributor to this inter-study variability is most likely the differing manners of reporting and collecting information on MTX intolerance as some studies report MTX toxicity as MTX intolerance. Notably, the studies with the highest prevalence [10, 37, 38, 46, 47, 50] measured MTX intolerance using the Methotrexate Intolerance Severity Score (MISS) [discussed below].

Symptoms of MTX intolerance show a characteristic pattern, with prospective studies finding a steady increase in the number of prevalent cases over time, although the specific affected patients differed from timepoint to timepoint [37, 50, 51]. In particular, behavioral symptoms such as crying are often present in MTX intolerance with a reported prevalence from 61.1 to 88.7% [10, 37, 50]. Fráňová et al. also reported elevated levels of behavioral symptoms even in children who did not meet the criteria for MTX intolerance as determined by the MISS (47.5%) [50]. The frequencies of anticipatory/associative vomiting are surprisingly similar in studies (13–18.7%), whereas the rates of anticipatory or associative nausea and/or stomach ache vary more when comparing studies (39–59% and 18–56.7%, respectively) [10, 37, 52].

Many parameters have been proposed as potentially predisposing to developing MTX intolerance. An overview of potential risk factors and studies investigating them can be found in Table 1.

3.1 Gender

Most studies conclude that gender is not an independent risk factor for MTX intolerance [37, 46, 47, 50]. However, Weitzman et al. found that more girls than boys were MTX intolerant [38]. A similar result was found in a study including children with inflammatory bowel disease [53].

3.2 Laboratory Values

Van Dijkhuizen et al. found that a baseline ALT level below 12 U/L was a risk factor for developing MTX intolerance [51]. In contrast, we have previously shown no difference in median ALT levels between MTX-intolerant and MTX-tolerant children. However, we did find that only MTX-intolerant girls, but not MTX-intolerant boys, had elevated ALT-levels [54]. van Dijkhuizen et al. further described baseline creatinine above 50 μmol/L as a risk factor for developing MTX intolerance and noted that age was correlated with creatinine. Thus, creatinine may be interpreted as a proxy for age [51]. Last, they also found baseline thrombocytes above 350×10^9/L and baseline positive antinuclear antibody to be potential risk factors [51, 55].

3.3 MTX Dose

The evidence in this area is very contradictory, as some studies find that MTX-intolerant children receive higher MTX doses [10, 37], while others have not been able to confirm this association [50]. Mulligan et al. found that the MTX dose was a risk factor in a univariate analysis, but when taking into account multiple risk factors the association became non-significant. In pediatric inflammatory bowel disease, higher MTX doses were associated with MTX intolerance [53]. However, it should be noted that a potential effect of MTX dose might be subject to channeling bias, i.e., that patients with higher disease activity receive higher doses of MTX and hence that the effect of dose on MTX intolerance might be due to disease activity instead.

3.4 Treatment and Disease Duration

Most studies find that MTX treatment duration is not significantly associated with MTX intolerance [39, 54]. However, Bulatović et al. found that the MTX-intolerant children had received longer MTX treatment than the MTX-tolerant children and had a longer disease duration [10].

3.5 Age

The effect of age on the risk of MTX intolerance is highly debatable. Some find a higher age to be a risk factor [39, 48, 51], some find no association [50], and others find that the younger the child, the higher the risk [10, 37]. One could speculate that different sets of side effects vary with age; however, this would need further investigation.

3.6 Disease Subtype

Kearsley-Fleet et al. [48] found that children with polyarticular arthritis had a lower risk of developing MTX intolerance, which contradicts the findings of van Dijkhuizen et al. In this study, oligoarticular JIA had the lowest risk of MTX intolerance and polyarticular JIA had the highest risk of MTX intolerance [51]. They do, however, note that there was a significant interaction between disease subtype and age, where polyarthritis primarily was a risk factor in younger patients. Others have found no significant effect of disease subtype on the risk of MTX intolerance [10, 50, 56].

3.7 Disease Activity

In a multivariable analysis, Mulligan et al. found high disease activity to be associated with MTX intolerance, whereas van Dijkhuizen et al. found that high disease activity lowered the risk of developing MTX intolerance [39, 51]. Other studies within JIA have not found any association

Table 1 Studies investigating risk factors for MTX intolerance[a]

Risk factor	Study	Study design[b]	Study size	Measurement/statistics[c]	Results	Conclusion	Comments
Sex	Akca et al. [37]	Cross-sectional	200	Univariate logistic regression [OR (95% CI)]	Female gender 1.165 (0.638–2.127)	Not a risk	100 pediatric and 100 adult patients receiving MTX for any rheumatological disease. Most common diagnosis in the pediatric population was JIA (72%) and in the adult population was RA (70%)
	Weitzman et al. [38]	Cross-sectional	90	Proportion of MTX-intolerant girls and boys	48.5% MTX-intolerant girls 22.7% MTX-intolerant boys $p = 0.0332$	Female sex a risk	
	McColl et al. [46]	Cross-sectional	48	OR (95% CI)	Female sex Unadjusted: 4.68 (0.53–41.07) Adjusted: 3.4 (0.27–41.86)	Not a risk	Patients with both morphea, atopic dermatitis and JIA/uveitis
	Kyvsgaard et al. [47]	Cross-sectional	121	Number of MTX-tolerant and MTX-intolerant girls and boys	MTX intolerant: 50 girls, 23 boys MTX tolerant: 31 girls, 16 boys $\chi^2 = 0.08$; $p = 0.77$	Not a risk	
	Franova et al. [50]	Prospective	55	OR (95% CI)	Male 0.70 (0.22–2.22)	Not a risk	
	Dupont-Lucas et al. [53]	Cross-sectional	102	Multivariate model [OR (95% CI)]	Female sex 4.31 (1.37–13.60)	Female sex a risk	Patients with inflammatory bowel disease
Laboratory values	Dijkhuizen et al. [51]	Prospective	152	Multivariate model [OR (95% CI)]. The seven parameters with the lowest p value from the univariate model were included	Baseline ALT > 12 U/L: 0.39 (0.16–0.96) Baseline creatinine > 50 µmol/L: 1.37 (0.33–5.67) Baseline thrombocytes > 350×10^9/L: 1.27 (0.49–3.27) Baseline positive ANA: 1.98 (0.83–4.68)	Baseline ALT < 12 U/L a risk Baseline creatinine > 50 µmol/L a risk Baseline thrombocytes > 350×10^9/L a risk Baseline positive ANA a risk	

Table 1 (continued)

Risk factor	Study	Study design[b]	Study size	Measurement/statistics[c]	Results	Conclusion	Comments
	Wibrand et al. [54]	Cross-sectional	121	Comparing proportion of MTX-intolerant children with and without ALT elevation as well as comparing median ALT levels	ALT elevation in MTX-intolerant children (12.5%) and MTX-tolerant (10.9%) children ($p = 1.00$) ALT levels in MTX-intolerant children (17.0) and MTX-tolerant (20.5) children ($p = 0.17$)	ALT not a risk factor	
MTX dose	Bulatovic et al. [10]	Cross-sectional	297	Multivariate logistic regression [OR (95% CI)]	Higher dose 1.08 (1.00–1.16)	High-MTX dose a risk	
	Akca et al. [37]	Cross-sectional	200	Univariate analysis [OR (95% CI]	Higher dose 1.418 (1.245–1.616)	High-MTX dose a risk	100 pediatric and 100 adult patients receiving MTX for any rheumatological disease. Most common diagnosis in the pediatric population was JIA (72%) and in the adult population was RA (70%)
	Mulligan et al. [39]	Cross-sectional	171	Univariate and multivariate model for feeling sick before taking MTX [OR (95% CI)]	High dose, univariate: 1.10 (1.02–1.19) High dose, multivariate: 1.06 (0.95–1.19)	High-MTX dose a risk	High-MTX dose a risk in the univariate analysis, but not in the multivariate analysis
	Dupont-Lucas et al. [53]	Cross-sectional	102	Multivariate model [OR (95% CI)]	Receiving a dose of MTX higher than 20 mg/week: 4.06 (1.30–12.70)	High-MTX dose a risk	Patients with inflammatory bowel disease
	Franova et al. [50]	Prospective	55	OR (95% CI)	Mean MTX dose in MTX-intolerant vs MTX-tolerant patients: 1.15 (0.94–1.40)	Not a risk	
Treatment and disease duration	Bulatovic et al. [10]	Cross-sectional	297	Comparing treatment and disease duration between MTX-intolerant and MTX-tolerant patients	Disease duration: 4.3 years vs 3.0 years ($p = 0.026$) Treatment duration: 2.0 years vs 1.2 years ($p = 0.001$)	Longer MTX treatment and disease duration a risk	
	Mulligan et al. [39]	Cross-sectional	171	Univariate and multivariate model for feeling sick before taking MTX [OR (95% CI)]	Univariate: 1.02 (1.01–1.03) Multivariate: 1.01 (0.99–1.03)	Treatment duration not a risk	Treatment duration a risk in the univariate analysis, but not in the multivariate analysis

Table 1 (continued)

Risk factor	Study	Study design[b]	Study size	Measurement/statistics[c]	Results	Conclusion	Comments
	Wibrand et al. [54]	Cross-sectional	121	Comparing treatment duration between MTX-intolerant and MTX-tolerant patients	MTX intolerant: 335 days, MTX tolerant 261.5 ($p = 0.40$)	Not a risk	
Age	Bulatovic et al. [10]	Cross-sectional	297	Comparing age between MTX-intolerant and tolerant patients	Median age 11 vs 12 years ($p = 0.001$)	Lower age a risk	
	Akca et al. [37]	Cross-sectional	200	Multivariate analysis [OR (95% CI)]	0.929 (0.901–0.958)	Lower age a risk	100 pediatric and 100 adult patients receiving MTX for any rheumatological disease. Most common diagnosis in the pediatric population was JIA (72%) and in the adult population was RA (70%)
	Mulligan et al. [39]	Cross-sectional	171	Univariate and multivariate model for feeling sick before taking MTX [OR (95% CI)]	Univariate: 1.10 (1.01–1.19) Multivariate: 1.06 (0.92–1.22)	Higher age a risk	Higher age a risk in the univariate analysis, but not in the multivariate analysis
	Kearsley-Fleet et al. [48]	Prospective	577	OR (95% CI) for every year increase in age for experiencing a gastrointestinal adverse reaction	1.1 (1.0–1.2)	Higher age a risk	
	Franova et al. [50]	Prospective	55	Logistic regression [OR (95% CI)]	High age at MTX start: 1.48 (0.48–4.47)	Not a risk	
	Dijkhuizen et al. [51]	Prospective	152	Multivariate model [OR (95% CI)]. The seven parameters with the lowest *p*-value from the univariate model included	Baseline creatinine > 50 µmol/L: 1.37 (0.33–5.67)	Higher age a risk	Creatinine and age were correlated and the authors suggest creatine as a surrogate measure
Disease subtype	Bulatovic et al. [10]	Cross-sectional	297	Unknown	Unknown	Not a risk	Written in text that the JIA subtype did not differ significantly between MTX-intolerant and MTX-tolerant patients
	Kearsley-Fleet et al. [48]	Prospective	577	OR (95% CI)	0.4 (0.2–0.9)	Polyarticular arthritis RF-positive a low risk	Compared to polyarticular arthritis RF negative
	Franova et al. [50]	Prospective	55	Logistic regression [OR (95% CI)]	Polyarticular JIA: 1.43 (0.36–5.78)	Not a risk	

Table 1 (continued)

Risk factor	Study	Study design[b]	Study size	Measurement/statistics[c]	Results	Conclusion	Comments
	Dijkhuizen et al. [51]	Prospective	152	Multivariate model [OR (95% CI)]. The seven parameters with the lowest *p*-value from the univariate model were included	Polyarticular: 4.99 (1.36–18.34)	Polyarticular arthritis a high risk Oligoarticular arthritis a low risk	Using oligoarticular as a reference
	Raab et al. [56]	Prospective	1058	Discontinuation (%) because of intolerability	Persistent oligoarticular JIA: 23.2 Extended oligoarticular JIA: 31.6 Polyarticular JIA, RF negative: 32.8	Not a risk	
Disease activity	Bulatovic et al. [10]	Cross-sectional	297	Unknown	Unknown	Not a risk	Written in text that the JIA subtype did not differ significantly between MTX-intolerant and MTX-tolerant patients
	Mulligan et al. [39]	Cross-sectional	171	Univariate and multivariate model for feeling sick before taking MTX [OR (95% CI)]	Univariate: 1.24 (1.06–1.44) Multivariate: 1.29 (1.05–1.60)	High-disease activity a risk	Measured as number of active joints
	Franova et al. [50]	Prospective	55	Logistic regression [OR (95% CI)]	JADAS-71 (10 points): 1.12 (0.68–1.82)	Not a risk	
	Dijkhuizen et al. [51]	Prospective	152	Multivariate model [OR (95% CI)]. The seven parameters with the lowest *p*-value from the univariate model were included	JADAS-27 5–15: 0.35 (0.08–1.56) JADAS-27 > 15: 0.77 (0.14–4.32)	Low-disease activity a risk	Compared to JADAS-27 < 5
	Dupont-Lucas et al. [53]	Cross-sectional	102	Multivariate analysis [OR (95% CI]	3.44 (1.15–10.26)	High-disease activity a risk	Patients with inflammatory bowel disease Measured using the physician's global assessment
SLCO1B1 gene	Kyvsgaard et al. [57]	Cross-sectional	121	Association between phenotype and SNP genotypes using the chi-squared test/Fisher's exact test	rs4149056: $p = 0.86$ rs4149081: $p = 0.86$	rs4149056 and rs4149081 not a risk	
	Roskiewicz et al. [59]	Prospective	100	OR (95% CI) for MTX gastrointestinal side effects	4.55 (1.37–15.13)	rs4149056 a risk	

Table 1 (continued)

Risk factor	Study	Study design[b]	Study size	Measurement/statistics[c]	Results	Conclusion	Comments
	Lima et al. [60]	Cross-sectional	233	Association with MTX gastrointestinal toxicity OR (95% CI)	0.32 (0.11–0.96) and 0.34 (0.13–0.88)	rs4149056 a risk	Patients with RA ORs for CC homozygotes and carriers, respectively
	Mehta et al. [64]	Cross-sectional	278	Frequency of nausea	$p = 0.0234$	rs2306283 and rs4149056 risks	Patients with inflammatory bowel disease
SLC19A1 gene	Lima et al. [60]	Cross-sectional	233	Association with MTX gastrointestinal toxicity OR (95% CI)	Rs7499 A homozygous: 0.18 (0.05–0.69) Rs7499 A carrier: 0.43 (0.19–0.98) Rs1051266 A homozygous: 0.33 (0.12–0.92) Rs2838956 G homozygous: 0.31 (0.10–1.00)	rs7499, rs1051266, and rs2838956 risks	Patients with RA
	Kishi et al. [61]	Cross-sectional	240	Gastrointestinal toxicity OR (95% CI)	Consolidation phase: 10.4 (1.35–80.4) Continuation phase: 2.01 (1.06–4.11)	rs1051266 a risk	Patients with ALL. AA or AG vs GG
MTHFR gene	Dijkhuizen et al. [51]	Prospective	152	OR (95% CI)	rs1801133: 0.60 (0.21–1.69) rs1801131: 1.65 (0.76–3.62)	rs1801133 and rs1801131 not risks	
	Kyvsgaard et al. [57]	Cross-sectional	121	Association between phenotype and SNP genotypes using the chi-squared test/Fisher's exact test	rs1801133: $p = 0.02$ rs1801131: $p = 0.63$	rs1801133 a risk rs1801131 not a risk	
	Tukova et al. [65]	Cross-sectional	69	Overall side effects [OR (95% CI)]	55.5 (2.9–1080)	rs1801133 a risk	TT vs CC
	Scheuren et al. [66]	Cross-sectional	196	Proportion of MTX intolerance compared to homozygous wild-type patients	$p = 0.285$	rs1801133 not a risk	
ATIC gene	Becker et al. [62]	Cross-sectional	104	OR (95% CI)	18.5 (3.7–93.2)	rs4673990 a risk	In combination with *ADORA2a* (rs3761422) found to elevated MTX polyglutamate levels, which were found to be elevated in patients with JIA experiencing MTX intolerance

Table 1 (continued)

Risk factor	Study	Study design[b]	Study size	Measurement/statistics[c]	Results	Conclusion	Comments
ADORA2a gene	Becker et al. [62]	Cross-sectional	104	OR (95% CI)	18.5 (3.7–93.2)	rs3761422 a risk	In combination with *ATIC* (rs4673990) found to elevate MTX-polyglutamate levels, which were found to be elevated in patients with JIA experiencing MTX intolerance
	Roskiewicz et al. [63]	Prospective	100	OR (95% CI) for gastrointestinal side effects	3.59 (1.15–11.22)	rs2236624 a risk	
AMDP1 gene	Dijkhuizen et al. [51]	Prospective	152	OR (95% CI)	1.46 (0.70–3.05)	rs17602729 not a risk	
	Avramovic et al. [67]	Retrospective	119	Multivariate analysis for time to first gastrointestinal adverse event (HR)	1.61	rs17602729 associated with the time to develop gastrointestinal adverse effects	
MTHFD1 gene	Avramovic et al. [67]	Retrospective	119	Multivariate analysis for time to first gastrointestinal adverse event (HR)	1.55	rs2236225 associated with the time to develop gastrointestinal adverse effects	
Psychological properties	Kyvsgaard et al [47]	Cross-sectional	121	Wilcoxon rank-sum test	$p = 0.0118$	Coping strategy internalizing/catastrophizing more used among the MTX-intolerant patients No difference in anxiety levels	
Route of administration	Kyvsgaard et al. [73]	Cross-sectional	121	Proportion of children receiving treatment orally or subcutaneously divided by MTX intolerance	$p = 0.09$	Not a risk	

ALL acute lymphoblastic leukemia, *ALT* alanine transaminase, *ANA antinuclear antibody* , *CI* confidence interval, *HR hazard ratio* , *JIA* juvenile idiopathic arthritis, *MTX* methotrexate, *OR* odds ratio, *RA* rheumatoid arthritis, *RF* rheumatoid factor, *SNP* single nucleotide polymorphism

[a]Patients were children with JIA unless otherwise indicated in the "Comments" column

[b]Prospective studies were observational

[c]Analyses are comparing MTX-intolerant to MTX-tolerant patients unless otherwise noted

between disease activity and MTX intolerance [10, 50]. In inflammatory bowel disease, higher disease activity was associated with a higher risk of MTX intolerance [53].

Other potential risk factors include genetic factors, route of administration, psychological properties, and folate levels. These will be explored in detail below as some require more in-depth explanations and others because they have been investigated in studies trying to avoid or treat MTX intolerance [10, 47, 57, 58].

In conclusion, the evidence of risk factors for MTX intolerance is highly variable and sometimes even contradictory. This might in part be due to the heterogeneity of the investigated populations, small sample sizes, and the differences in measuring MTX intolerance. Larger rigorous studies are needed to truly pinpoint risk factors.

4 Genetic Association with MTX Intolerance

Because of the desire to understand the mechanism behind MTX intolerance and personalize therapy, genetic factors related to MTX adverse effects have become an area of significant research interest. Discovering biomarkers in this field could potentially make it possible to individualize therapy further; however, studies on genetic factors in MTX intolerance, measured using the MISS, within JIA, are still scarce. Relevant findings may be deduced from studies investigating MTX gastrointestinal adverse effects in general, studies including children with other diagnoses than JIA, and studies including adults. The focus has almost entirely been on investigating genetic factors, such as single nucleotide polymorphisms (SNPs), within MTX transporter proteins and enzymes in the MTX metabolic pathway [57, 59–67]. Single nucleotide polymorphisms are common variations of a single nucleotide in a specific position within the DNA, uniquely labeled with rs- followed by an ID number (e.g., rs4149056) [68].

The MTX transporter proteins most often investigated are involved in the enterohepatic circulation of MTX, hence in the intestinal cells and liver cells. In the study by Roszkiewicz et al. [59] rs4149056 in the gene *SLCO1B1* was associated with a higher odds of gastrointestinal side effects in patients with JIA. However, Kyvsgaard et al. [57] found no significant association between rs4149056 and MTX intolerance (assessed by the MISS) in patients with JIA. The role of *SCLO1B1* is maintained by Mehta et al. [64] in their study within pediatric inflammatory bowel disease. They found that having an SLCO1*15 allele (rs2306283 and rs4149056) was associated with a higher frequency of MTX-induced nausea. Furthermore, Lima et al. [60] found rs4149056 was associated with gastrointestinal toxicity in patients with rheumatoid arthritis.

Lima et al. [60] further discovered that SNPs (rs7499, rs1051266, rs2838956) in the gene *SLC19A1* were associated with gastrointestinal toxicity in patients with rheumatoid arthritis. Similarly, Kishi et al. found that rs1051266 in *SLC19A1* was associated with gastrointestinal toxicity in children with acute lymphoblastic leukemia. To our knowledge, no statistically significant association between MTX intolerance and SLC19A1 in a JIA population has been discovered, nor between MTX intolerance (assessed by the MISS) and the remaining MTX transporter proteins involved in the enterohepatic circulation in a JIA population.

Within the MTX metabolic pathway, methylenetetrahydrofolate reductase is a frequently investigated enzyme, but often with differing results. Tuková et al. [65] discovered rs1801133, in the gene encoding methylenetetrahydrofolate reductase, was associated with a higher probability of any adverse effect to MTX in JIA. This was supported by Kyvsgaard et al. [57] where rs1801133 was significantly associated with MTX intolerance (evaluated by the MISS) in patients with JIA. However, neither Scheuern et al. [69] nor van Dijkhuizen et al. [51] found this association in their study populations.

Other enzymes in the MTX metabolic pathway have been investigated. Becker et al. [62] investigated genetic factors influencing the level of MTX polyglutamates, and the role of MTX polyglutamates in relation to treatment efficacy and adverse effects within JIA. They discovered that a combination of SNPs in the genes *ATIC* (rs4673990) and *ADORA2a* (rs3761422) was associated with the level of MTX glutamates$_{3\text{-}5}$. Furthermore, they found higher concentrations of MTX glutamates$_{3\text{-}5}$ in children with JIA who experienced gastrointestinal adverse effects. Roskiewicz et al. [63] similarly found a SNP (rs2236624) in *ADORA2A* was associated with a 3.5 times higher odds of gastrointestinal side effects in patients with JIA.

Zajc Avramovic et al. [67] discovered rs17602729 in the gene *AMPD1* and rs2236225 in the gene *MTHFD1* were associated with the time to develop MTX-induced gastrointestinal adverse effects in JIA. However, van Dijkhuizen et al. [51] did not find a significant association between rs17602729 in *AMPD1* and MTX intolerance (assessed by the MISS) within JIA.

In summary, an association between MTX intolerance and a SNP in a MTX relevant gene may exist, and *SLCO1B1* seems to be a strong candidate gene. However, studies in large populations with standardized tools to assess MTX intolerance are needed to cement the association. The current differing results could indicate a more complex genetic mechanism or that non-genetic factors are involved as elaborated on in this review.

5 The MISS, A Tool to Identify and Assess MTX Intolerance: What Have we Learnt?

Although MTX intolerance, as described above, is highly prevalent in JIA during MTX treatment, reports of MTX intolerance including symptoms, severity, and a timely correlation to MTX intake, have varied greatly from study to study, making inter-study comparisons cumbersome and difficult. Thus, Bulatović et al. decided to develop and validate an MTX intolerance questionnaire, the MISS [10]. The tool addresses gastrointestinal symptoms and the highly relevant behavioral symptoms of MTX intolerance. In the MISS questionnaire, four categories (abdominal pain, nausea, vomiting, and behavioral complaints) give way to 12 questions. The questionnaire addresses if symptoms of abdominal pain, nausea, and vomiting occur after taking MTX, before taking MTX (anticipatory symptoms), and/or when thinking about taking MTX (associative symptoms, vomiting excluded). As for behavioral symptoms, the questionnaire inquires whether the child exhibits restlessness, irritability, or crying when taking MTX, and/or if they refuse to take MTX. Each question is assigned a score from zero to three that ranges from "No complaints" to "Severe complaints," giving the MISS a total score range from 0 to 36. A child is defined as MTX intolerant if the total score is 6 or more and has at least 1 point from an anticipatory, associative, or behavioral symptom. The MISS has shown usefulness across languages [70–73], when being answered by either a parent and/or the child itself [70], in other pediatric diseases than JIA [53, 73] and in the adult population as well [72, 74–76]. Notably, the MISS is not heavily influenced by cultural differences, suggesting that it could be easily adaptable all over the world [70].

Often when creating a scoring system, a cut-off value is introduced to separate patients into groups, in the case of the MISS, with the goal of separating patients into MTX tolerant or MTX intolerant. The original cut-off value established by Bulatović et al. [10] has been disputed by Chausset et al. [70], as they found the highest specificity and sensitivity at a score of 3. This could be due to differences in the gold standard used for measuring MTX intolerance (i.e., physician's opinion or patient-reported visual analog scale from 0 to 10). However, it can be debated whether a dichotomous cut-off value or the continuous value of the MISS is of greatest significance. One could argue that the continuous value offers more information into, i.e., variability and patterns, and allows for ongoing monitoring of the individual patient. It has further been questioned whether the original four categories within the MISS truly provide separate psychometric entities, as some find high inter-question correlations between different categories and low inter-question correlations within categories [70]. However, the categories remain clinically relevant and separable, and some studies differ in which aspect of the MISS is more prevalent in their study population. For example, in the study by Kaya Akca et al., behavioral symptoms were the most prevalent and the MISS is hence a tool to shed light on these symptoms that may otherwise go unnoticed in busy everyday clinical practice [37]. This underlines the potential role of the MISS to monitor symptoms of MTX intolerance in the clinic to create targeted personalized treatment options for MTX intolerance based on affected categories. Hence, studies are needed comparing different treatment options (i.e., antiemetics, dose splitting, psychological therapy) for not only different levels of MTX intolerance, but also for different patterns of MTX intolerance based on the MISS.

One could worry whether continuous monitoring of MTX intolerance per se could induce MTX intolerance in children. However, when van Dijkhuizen et al. [51] prospectively collected MISS data on patients they did not find a higher prevalence of MTX intolerance in their cohort (41.5%) as compared to what they have previously reported (50.5%) [77], making it unlikely that monitoring will induce MTX intolerance.

Using the MISS in other pediatric diseases has led to interesting findings. For example, Kyvsgaard et al. found that children with acute lymphoblastic leukemia treated with low-dose MTX had significantly lower MISS scores than children with JIA also treated with MTX despite the patients with acute lymphoblastic leukemia having a higher dose of MTX intake [73]. So far, only speculations about this discrepancy have been offered, but pediatric rheumatology might have valuable lessons to learn from pediatric oncology in terms of MTX intolerance and conditioned responses to treatment.

Until 2021, the MISS was the only questionnaire for MTX intolerance, but Vijaykumar and colleagues developed the Methotrexate Intolerance and Severity Assessment, which addresses oral sores after MTX, dose skipping, or a reduction, and the use of anti-emetics or other drugs because of intolerance. The Methotrexate Intolerance and Severity Assessment showed a higher area under the curve than the MISS in rheumatoid arthritis but has yet to be used and validated in a pediatric study population [78].

Conclusively, the MISS has proved a possible valuable tool in not only research but in clinical practice, paving the way for comparable studies, clinical monitoring, and personalized efforts in the treatment of MTX intolerance.

6 Management Strategies

To manage MTX intolerance, current recommendations include adjusting the dose or administration method, a team member teaching a behavioral technique, using folic acid, or prescribing antiemetics before or after MTX

administration. However, there is very little evidence and no studies have compared these strategies, including the preventative use of anti-emetics [35, 79]. Additionally, there is no evidence to determine the efficiency of changing the route of administration from oral to subcutaneous or vice versa [80]. An overview of studies investigating management strategies can be found in Table 2.

6.1 Behavioral Strategies

Discovering that a conditional response is regarded a main factor in the development of MTX intolerance, especially for the associative and anticipatory symptoms, has caused behavioral strategies and psychological interventions to be of key interest. However, the evidence is still scarce [80].

Methotrexate intolerance is thought to be partially a negative psychological conditioning mechanism, by which side effects (i.e., nausea and stomach ache) occur even without the stimulus (MTX). In other research areas, i.e., immunological agent positive pharmacological conditioning, in which patients receive part placebo part true drug, have led to fewer side effects and a lower treatment dose with the same clinical effect [81]. However, this field has not yet been explored in JIA. Hence, this was suggested by Smits et al. [82] as a potential future research area for JIA and MTX intolerance. The authors propose a study that should first include 6 months of positive conditioning, meaning that all patients should receive MTX in standard doses until disease remission. In this period, the focus should be on the therapeutic effects of MTX without exaggerating the potential side effects to help build a positive conditional response. After 6 months, patients should be randomized to receive either standard MTX doses or lower MTX doses mixed with placebo. This is innovative but raises many questions if it were to be used in standard clinical practice. First, because of its proven efficacy, blinded treatment with MTX is not ethically acceptable for the treatment of JIA, nor is it acceptable to prescribe sub-therapeutic doses of medicine. Second, would the placebo be effective if the patients were aware that they were receiving placebo? It should be noted, however, that this exact phenomenon has been demonstrated in other diseases [83–85]. Third, how do we make sure that the negative conditioning of side effects does not occur in the first 6 months of treatment?

Different non-medical treatment interventions toward MTX intolerance have been suggested and tested. van der Meer and colleagues performed a small pilot study investigating the effect of behavioral therapy on children referred to a psychologist because of MTX intolerance [86]. The children were treated with either systemic desensitization or cognitive behavioral therapy depending on the age of the child. Ten patients were included. The behavioral therapy was effective in five patients and moderately effective in another two patients. Scheuern et al. concluded in their observational study of 196 patients with JIA with a minimum MTX treatment duration of 3 months that neither covert dosing nor taste masking instituted by parents lowered MTX intolerance assessed by the MISS [69]. Eye movement desensitization and reprocessing has shown potential for treating MTX intolerance [87]. Eye movement desensitization and reprocessing is most known from the treatment of post-traumatic stress disorder but has also been used in stress-related psychological disorders. Hence, Höfel et al. speculated whether eye movement desensitization and reprocessing could play a role in the treatment of MTX intolerance in JIA based on the hypothesis that MTX intolerance is a repetitive stressful event [87]. A statistically significant reduction in the MISS was seen in the included 18 patients after a course of therapy consisting of eight sessions as per an institutional protocol. The median MISS before therapy was a staggering 16.5 falling to 1 after therapy, with no patients scoring 6 or more and thus no longer showing MTX intolerance. After 4 months, without any additional sessions, the median had risen to 6.5 and 50% of the patients were MTX intolerant as evaluated by the MISS. The authors highlighted that parental expectations of recurrence of MTX intolerance seemed to play an important role. This underlines the significance of parental involvement and psychoeducation in the treatment. Collectively, these studies suggest that behavioral therapy could constitute a way of handling MTX intolerance, albeit larger confirmatory studies are required.

Coping mechanisms dictate how we handle stressors and adverse events and thus could possibly play a part in the development of MTX intolerance. Kyvsgaard et al. investigated whether anxiety and/or specific coping strategies were associated with MTX intolerance in a cross-sectional study including children with JIA [47]. They discovered that the coping strategy internalizing/catastrophizing was used more frequently in the MTX-intolerant group compared with the MTX-tolerant group, whereas no difference in anxiety levels could be detected. Hence, it could be proposed that patients should be screened for problematic coping strategies before starting MTX treatment, to be able to guide applicable children to more appropriate coping strategies. However, this requires larger prospective studies investigating whether baseline coping mechanisms differ between those who develop MTX intolerance and those who do not. Identifying the most effective coping strategies and determining which children would benefit from an intervention is essential.

Finally, other types of behavioral therapies could be considered for MTX intolerance in JIA. These could include hypnosis, biofeedback, imagery, or different relaxation methods, which have proven to reduce anticipatory nausea and vomiting in patients with cancer [88, 89]. However, it is

Table 2 Studies investigating management strategies for MTX intolerance[a]

Strategy	Study	Study design[b]	Study size	Measurement	Results	Conclusion	Comments
Systemic desensitization or cognitive behavioral therapy	Van der Meer et al [86]	Case study	10			Effective (MTX side effects fully abolished) in 5, moderately effective (MTX side effects decreased in severity) in 2	
Covert dosing by parents	Scheuren et al. [69]	Prospective	196	Change in mean MISS	11.0 vs 12.5 (p = 0.779)	Not effective	
Taste masking instituted by parents	Scheuren et al. [69]	Prospective	196	Change in mean MISS	9.0 vs 12.0 (p = 0.581)	Not effective	
Eye movement desensitization and reprocessing	Höfel et al. [87]	Prospective	18	Change in median MISS	Before therapy: 16.5 Directly after therapy: 1 (p > 0.001) Four months after therapy: 6.5 (p = 0.001)	Effective	No intolerant patients after initial therapy, 50% intolerant after 4 months
Folic acid	Martini et al. [90]	Prospective	21	Complete remission gastrointestinal complaints (proportion)	T1: 61.9% (13/21) T2: 85.7% (18/21) T3: 95% (20/21) T4: 85.7% (12/14) T5: 100% (7/7)	Effective	Taken 48 hours before and again 48 hours after MTX Non-controlled Follow-up every 3–4 months
	Shea et al. [91]	Cochrane review		Reduction in gastrointestinal side effects [RR (95% CI)]	0.74 (0.59–0.92)	Effective	Adult patients with rheumatoid arthritis
Anti-emetics	Scheuren et al. [69]	Prospective	57	Difference in mean MISS	11.0 vs 12.5 (p = 0.779)	Not effective	MTX intolerance was already present
	Kempinska et al. [93]	Retrospective case-control	60	Proportion of patients developing nausea	2.0% (1/50) vs 60.0% (6/10) [p < 0.001]	Effective	Pediatric patients with Crohn's disease Anti-emetics as premedication
	Saif et al. [94]	Prospective	48	Change in median MISS	Baseline: 12.0 1 month: 3 2 months: 2 3 months: 2	Effective	Interventional. Patients reporting nausea and vomiting were prescribed ondansetron
Split dosage (twice or three times a week compared to once a week)	Ashgar et al. [96]	Quasi-experimental	246	Proportion of patients experiencing nausea	51.2% vs 35.8% (p = 0.018)	Effective	Adult patients with rheumatoid arthritis
	Dhaon et al. [97]	Randomized	135	Proportion of patients experiencing gastrointestinal adverse events	18% (split) vs 33% (oral once a week) vs 24% (i.m. once a week	Not effective	Adult patients with rheumatoid arthritis

Table 2 (continued)

Strategy	Study	Study design[b]	Study size	Measurement	Results	Conclusion	Comments
Route of administration	Zuber et al. [49]	Prospective	20	Proportion of patients experiencing adverse drug reactions after switching from oral to subcutaneous treatment because of MTX intolerance	9.4%	Effective	
	Alsufyani et al. [102]	Retrospective	11	Proportion of patients experiencing complete relief from nausea after switching from oral to subcutaneous treatment because of nausea	82%	Effective	

CI confidence interval, *i.m.* intramuscular, *MISS* Methotrexate Intolerance Severity Score, *MTX* methotrexate, *RR* relative risk

[a]Patients were children with JIA unless otherwise indicated in the "Comments" column

[b]Prospective studies were observational unless otherwise indicated in the "Comments" column

highly recommended to primarily focus on preventing acute and delayed MTX-induced nausea, as this is an independent risk factor for anticipatory nausea and vomiting [89].

6.2 Evidence and Efficacy of the Use of Anti-Emetics and Folic Acid Supplementation

Currently, potential approaches for managing MTX intolerance include the addition of folic acid, adjusting the MTX dosage, changing the administration, and using anti-emetics before or after the MTX administration. In 2023, the first prospective study has been published reporting on the efficacy of levofolinic acid in reducing MTX-related gastrointestinal complaints in 21 patients with JIA [90]. Levofolinic acid taken 48 hours before and again 48 hours after MTX significantly reduced the gastrointestinal side effects; however, the study was non-controlled.

In rheumatoid arthritis, a Cochrane review revealed that patients who were given folic or folinic acid supplements while taking MTX experienced a 26% reduction in the relative risk (9% in absolute risk) of gastrointestinal side effects such as nausea, vomiting, or abdominal pain, which supports the protective effect [91].

In a British prescriber survey by Amin et al., about MTX-related nausea in JIA, 21% of the 84 respondents started anti-emetic treatment > 50% of the time [80]. Nevertheless, there is weak evidence to support the use of counteragents, such as anti-emetics, and the potential use of anti-emetics as symptomatic treatment or as preventative treatment when starting MTX therapy is a topic of ongoing debate [92]. In children with Crohn's disease, a retrospective case-control study of 50 patients compared children who received ondansetron pre-medication with the first dose of subcutaneous MTX to those who did not receive ondansetron pre-medication initially. Among the 50 patients who received ondansetron pre-medication, only 2% experienced nausea in the 3 months following MTX start, while 60% of the ten children who did not receive ondansetron pre-medication experienced nausea ($p < 0.001$) [93]. A prospective JIA study by Scheuern et al. [69], showed that in eight out of 57 patients with MTX intolerance, anti-emetics were started and the MISS score did not decrease significantly ($p = 0.779$). However, the patients were enrolled at different timepoints in their MTX treatment duration and the specific regimen for anti-emetic treatment was not provided.

Recently, Saif et al. reported a significant reduction in MISS in 48 MTX-intolerant patients with arthritis aged 14–60 years. [94] Ondansetron was used in symptomatic patients 1 hour before taking MTX and repeated after 8 hours. There was a notable decrease in the median MISS score over the subsequent 2 months ($p < 0.05$), but by the third month, the median did not exhibit further reduction

compared to the second month ($p = 0.12$). However, this was an observational study without a control group.

In summary, there is little evidence to support that folic acid reduces MTX intolerance. While anti-emetics are commonly used in JIA, there is contradictory evidence regarding their effectiveness. The study designs, outcome measures, and study populations are heterogeneous, hampering comparisons. To establish definitive conclusions on their overall efficacy and preventive capabilities, RCTs are essential.

6.3 Treatment Regimens and Route of Administration: Relation to Intolerance?

6.3.1 Dosage

Which MTX dosage should be recommended? The first RCT investigating MTX by Giannini et al. [21] forms the basis of the current use of MTX in JIA. This was a 6-month trial showing that an MTX dose of 10 mg/m^2/week had efficacy in 63% compared with 32% of the group receiving 5 mg/m^2/week and 36% in the placebo group. Currently, MTX therapy is generally started at a dose of 10–15 mg/m^2/week or 0.3–0.6 mg/kg/week [25, 95]. A multinational RCT compared a high dose (30 mg/m^2/week) to a medium dose (15 mg/m^2/week) in children with polyarticular JIA who did not respond significantly on the conventional dose of 10 mg/m^2/week. There was a significant improvement in the non-responders in both arms, but the 30-mg/m^2/week dose was not better than the 15-mg/m^2/week dose [7].

A recent study on 246 patients with rheumatoid arthritis found that a split dosage of oral MTX into two halves on alternate days (half dose on Sundays and half dose on Tuesdays) improved gastritis, nausea, appetite, and hepatotoxicity compared with a dosage of oral MTX once weekly [96]. The pain analog scale, patient activity scales, and the number of tender joints showed no difference when comparing the alternate-day regimen with the conventional dosage [96]. Another study on 135 adults with rheumatoid arthritis investigated a split dosage twice or three times weekly versus oral or subcutaneous MTX once weekly [97]. They found no difference in the Simplified Disease Activity Score between a split dosage and subcutaneous MTX at 24 weeks. Adherence to treatment was best in the group with a split dosage. Nevertheless, they found no clinically significant difference in gastrointestinal adverse events between split and weekly dosages. To our knowledge, no studies on a split dosage in children have been performed so no evidence on compliance or adverse events in children with a split dosage can be provided.

6.3.2 Route of Administration

For the use in JIA, the route of administration can be either oral or parenteral (usually subcutaneous). The decision as to which route to use is based on several factors. Because of the saturation of the transporters in the intestines, the pharmacokinetic profile of orally administered MTX is non-linear compared to parenteral administration. As a result, administration of doses ≥ 15 mg shows reduced relative bioavailability when given orally compared with parenteral administration [98]. In JIA, oral reference products have shown reduced systemic bioavailability of approximately 10–27% when compared to reference subcutaneous products [99]. As such, patients who have an inadequate response to an oral dose can show benefit at the same dose administered parenterally [100]. Therefore, it is recommended for patients on doses ≥ 15 mg to be prescribed a parenteral route of administration. However, studies on the relative effectiveness of these two routes have shown conflicting conclusions. Some studies have reported better efficacy with subcutaneous administration, whereas others have found no significant difference between the two methods [8, 28, 101]. In a questionnaire-based study by Żuber et al. [49], 20 patients changed from oral to subcutaneous MTX after median 14 months because of MTX intolerance. After 6 months on a subcutaneous formula, 91% did not report adverse drug reactions. In addition, Alsufyani et al. [102] published a retrospective study of 61 patients with JIA of whom 11 patients experienced nausea. Out of these 11 patients, nine (82%) indicated complete relief from nausea after transitioning to subcutaneous MTX, indicating that altering the administration route could be advantageous. However, the conclusions from these two studies are drawn from series of a few cases, highlighting the necessity for a RCT to provide definitive recommendations. Furthermore, particularly in pediatric populations, parenteral administration adds an additional burden to patients and their families in addition to side effects above those related solely to the MTX in the form of needle phobias, pain at the injection site, and behavioral issues [47, 52, 103, 104].

For patients with JIA receiving the same MTX dose either subcutaneously or orally, Kyvsgaard et al. [73] found that the median MISS was slightly higher in the subcutaneous group compared with those receiving MTX orally, both prescribed once weekly. However, they found no significant difference between the proportion of MTX-intolerant children in the group treated subcutaneously compared to those given MTX orally [73].

In conclusion, there is little evidence supporting the split dosage of MTX in adults with no studies available in JIA. Contradictory evidence exists regarding the route of administration and treatment intolerance. One study comparing MISS scores in children treated orally and subcutaneously showed no discernable difference. Case series suggest that switching from oral to subcutaneous administration can be beneficial for children intolerant to MTX.

7 Conclusions

Since the first RCT investigating MTX in JIA, it has been a cornerstone in the treatment regimen. However, MTX intolerance and thereby nausea, stomach ache, vomiting, and behavioral symptoms pose a considerable risk, affecting up to 73% of MTX-treated children with JIA. Many different risk factors have been proposed and investigated including gender, age, disease activity, disease and treatment duration, MTX dose and administration route, and genetic and psychological factors. The studies have provided contradictory results, and it remains to be fully elucidated as to which factors predispose to the development of MTX intolerance. This demands a uniform approach to measuring and reporting MTX intolerance. The MISS, with its simplicity, adaptability, and range of measured symptoms, provides an excellent means of accomplishing such an alignment. Yet, the need is not only to understand the development and measure the severity of MTX intolerance to prevent it. It is equally important to be able to treat it once present. Several strategies have been suggested, including behavioral strategies (e.g., coping mechanisms, eye movement desensitization and reprocessing, and cognitive behavioral therapy), the use of anti-emetics and folate supplementation, and last by changing the route of administration. However, the evidence is still scarce, the studies small, and the conclusions uncertain. As such, future studies are indeed required to fully understand not only the complexity of MTX intolerance but also how to best handle it in everyday clinical practice.

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