JPPT | Single Center Cross-Sectional Study

Evaluation of Methotrexate Intolerance in Children With Morphea

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OBJECTIVE Methotrexate is an immunosuppressant commonly used in dermatology. The prevalence of intolerance using the Methotrexate Intolerance Severity Score (MISS) in pediatric juvenile idiopathic arthritis (JIA) ranges from 25% to 75%, but studies in morphea patients are lacking. We sought to determine the prevalence and predictors of methotrexate intolerance in children with morphea compared with children with inflammatory skin diseases and JIA/uveitis.

METHODS Eligible patients were ages 2 to 18 years and were taking methotrexate for at least 3 months to treat morphea, inflammatory skin disease, or uveitis/JIA. Methotrexate intolerance was calculated using the MISS. A 1-way analysis of variance compared absolute intolerance scores. Multivariate regression analysis was used to compare MISS across diseases and covariates.

RESULTS Of 48 participants (mean ± SD age, 11.3 ± 4.1 years, 70.8% female), 15 had morphea, 16 had JIA/uveitis, and 17 had inflammatory skin diseases. The overall prevalence of intolerance was 20.8%. Age, sex, duration, and dose did not correlate with overall MISS. The MISS mean ± SD total for oral dosing was 2.5 ± 3.4, compared with 6.78 ± 6.8 for subcutaneous dosing. Patients with JIA/uveitis had the highest prevalence of intolerance (37.5%, n = 6), followed by morphea patients (20%, n = 3) and inflammatory skin disease patients (5.9%, n = 1). The OR of intolerance according to route of administration was 11.2 (95% CI, 2.03–61.89).

CONCLUSIONS Methotrexate intolerance was highest among patients with JIA/uveitis. The only predictor for risk of intolerance was subcutaneous route of administration. Future work could examine disease activity correlations and interventions designed to minimize intolerance.

ABBREVIATIONS GI, gastrointestinal; JDM, juvenile dermatomyositis; JIA, juvenile idiopathic arthritis; MISS, Methotrexate Intolerance Severity Score; MTX, methotrexate

KEYWORDS intolerance; JIA; methotrexate; morphea; uveitis

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Introduction

Methotrexate (MTX) is a systemic immunosuppressant used to treat many inflammatory diseases in children, including morphea (localized scleroderma), juvenile idiopathic arthritis (JIA), uveitis, juvenile dermatomyositis (JDM), psoriasis, and atopic dermatitis. It is typically administered weekly in 1 dose or 2 divided doses either subcutaneously or orally. Adverse effects, including nausea and vomiting, and anticipatory anxiety are commonly reported. Patients experiencing side effects may skip doses or discontinue medication, leading to suboptimal treatment. Intolerance to MTX has been associated with decreased quality of life in children with JIA.[1]

The prevalence of intolerance using the Methotrexate Intolerance Severity Score (MISS) in children with JIA ranges from 25% to 75%, and intolerance in this population has been associated with larger doses and younger ages.[2–5] The prevalence of intolerance measured by the MISS in children with acute leukemia was lower, at 17%, despite the use of larger doses than for JIA.[4]

In our experience, patients taking MTX for morphea seem to report intolerance more often than patients taking it for other indications, but this has not been demonstrated in a comparative study to date. These are ideal comparator groups given that children with inflammatory skin disease and JIA are commonly given MTX by the same providers who use it to treat morphea. We hypothesized that children with morphea would have a higher prevalence of MTX intolerance.

To help answer these questions, we studied the prevalence of MTX intolerance in children with morphea, compared with children with inflammatory skin diseases (eczema, psoriasis, alopecia areata) and JIA/uveitis. Our primary objective was to determine the prevalence of MTX intolerance among the 3 cohorts.

Our secondary objective was to determine any predictors for risk of intolerance.

Methods

In this single-center cross-sectional study, we recruited patients ages 2 to 18 years who were taking MTX at a stable dose for 3 months to treat morphea, inflammatory skin diseases (alopecia areata, eczema, psoriasis), JIA, and/or uveitis. Patients were recruited consecutively during routine morphea and rheumatology clinic appointments at The Hospital for Sick Children, a tertiary/quaternary referral center for the province of Ontario (population 12 million), Canada, from April to July 2021. Participants were excluded if 1) the patient or parent/legal guardian was unable to speak and/or understand English or 2) the patient had cognitive impairment and was unable to communicate symptoms such as nausea. Informed consent was obtained from all participants.

Methotrexate intolerance was assessed using the MISS administered by a study team member (Supplemental Appendices S1 and S2). The MISS was developed to assess for MTX intolerance in children ages 2 to 18 years with JIA, and it is calculated using a validated questionnaire.[2] The questionnaire consists of 16 questions across 4 domains (abdominal pain, nausea, vomiting, and behavioral symptoms). Each item is ranked on a severity scale from zero to 3, with a total possible score of 36 (Supplemental Appendixes S1 and S2). Intolerance is defined by a score of 6 or more. It can be completed by patients or their caregivers. Patients were also asked how many doses of MTX and folic acid were missed in the previous 3 months.

Data including disease duration, starting dose of MTX, current dose, folic acid administration, and route changes were obtained from the medical record to capture regimen characteristics that may affect MTX tolerance.

Prevalence of MTX intolerance was assessed using a χ^2 test to analyze whether a statistical difference exists in the proportion of patients deemed to be intolerant to MTX with morphea compared with other disease states. A 1-way analysis of variance was used to compare the absolute intolerance scores. The odds of MTX intolerance (MISS defined as a score of ≥6) were assessed using a multivariate logistic regression. The covariates in this model included age, sex, duration of disease, duration of MTX therapy, dose and route of MTX, and folate dose. An OR with 95% CI was presented for any covariate that had an association. We used STATA version 13.1 (2013) to perform statistical analysis.

Results

All 48 individuals who were approached to participate provided informed written consent. Patient characteristics are summarized in Table 1. Most participants were female (70.8%), with a mean ± SD age of 11.3 ± 4.1 years. This study included 15 individuals with morphea. The current mean ± SD MTX dose for morphea was 0.46 ± 0.12 mg/kg/dose. There were 17 patients with inflammatory skin disease on a current

Table 1. Patient Demographics

	All Patients (N = 48)	Morphea (n = 15)	Atopic Dermatitis/ Alopecia/Psoriasis (n = 17)	JIA/Uveitis (n = 16)	Significance Level (p value)
Current age, mean ± SD, yr	11.3 ± 4.1	11.7 ± 3.9	12.1 ± 4.9	10.1 ± 3.0	NS
Age at diagnosis, mean ± SD, yr	6.8 ± 4.4	8.6 ± 4.6	6.4	5.7 ± 3.4	NS
Sex, n (%)					NS
Female	34 (70.8)	13 (27)	9 (18.8)	12 (25)	
Male	14 (29)	2 (4.1)	8 (16.7)	4 (8.3)	
Current MTX dose, mean ± SD, mg/kg/dose	0.41 ± 0.13	0.46 ± 0.12	0.33 ± 0.08	0.43 ± 0.14	0.004
Initial MTX dose, mean ± SD, mg/kg/dose	0.45 ± 0.14	0.50 ± 0.11	0.41 ± 0.13	0.31 ± 0.09	<0.001
MTX dose route, n (%)					0.004
sc	18 (37.5)	7 (14.6)	1 (2.1)	9 (18.8)	
po	30 (62.5)	8 (16.7)	16 (33.3)	7 (14.6)	
Duration of MTX, mean ± SD, mo	22.3 ± 19.1	21.0 ± 15.8	10.6 ± 8.1	35.2 ± 22.2	0.001
Systemic manifestations, n (%)	ND	3 (20%)	ND	ND	NA

JIA, juvenile idiopathic arthritis; MTX, methotrexate; NS, not significant (p > 0.05) ND, not done

mean ± SD MTX dose of 0.33 ± 0.08 mg/kg/dose and 16 participants with JIA/uveitis with a current mean ± SD MTX dose of 0.43 ± 0.14 mg/kg/dose. There was a significant difference in current mean MTX doses (p = 0.004) among groups. One patient with morphea and 1 patient with JIA/uveitis were taking an antiemetic, and 3 patients with JIA/uveitis were taking nonsteroidal anti-inflammatory drugs.

Ten patients were intolerant to MTX (Table 2). The OR of intolerance according to route of administration was 11.2 (95% CI, 2.03–61.89; p < 0.05). Age, sex, duration of disease, and dose of MTX were not associated with increased odds of intolerance (Table 3). Three patients with morphea and 3 patients with JIA/uveitis changed route of MTX administration: 2 from subcutaneous to oral dosing and 1 from oral to subcutaneous dosing in each disease cohort. One patient with inflammatory skin disease changed from oral dosing to subcutaneous dosing.

The proportion of patients with intolerance and subcutaneous dosing was 37.5% (3 of 8) for morphea patients, 44% (4 of 9) for JIA, and 100% (1 of 1) for patients with inflammatory skin diseases. The OR for intolerance according to subcutaneous route versus oral route was 2 (0.24–16.4, p = 0.5) in the JIA/uveitis group. The ORs for intolerance according to route could not be calculated for the morphea and inflammatory skin disease cohorts because there were no patients on oral dosing who were intolerant.

Overall mean ± SD MISS was 4.1 ± 5.2. The JIA/uveitis patients had the highest mean ± SD total MISS at 6.3 ± 7.1, followed by morphea patients at 3.7 ± 4.0, and inflammatory skin disease patients at 2.2 ± 2.8 (Table 2 and Figures 1 through 3). The MISS mean ± SD total for oral dosing was 2.5 ± 3.4, with a range of zero to 13, compared with 6.78 ± 6.8 for subcutaneous dosing (Table 1). A total of 16 of the 17 patients with inflammatory skin disease were treated with oral dosing. The route of administration did significantly correlate with MISS GI and behavioral scores (p = 0.01).

Mean ± SD weekly folic acid dosing was 6.1 ± 3.6 mg. Dosing regimens varied, with 30 patients taking 1 mg daily 6 days a week, 17 taking 5 mg once a week, and 1 patient taking 5 mg 6 days a week. The average ± SD number of forgotten folate doses was 2.5 ± 5.5 per

Table 2. Methotrexate Intolerance Scores

	All patients	Morphea	Atopic Dermatitis/ Alopecia/Psoriasis	JIA/ Uveitis	Significance Level (p value)
Intolerant, n (%)*	10 (20.8)	3 (20)	1 ± 5.9)	6 (37.5)	NS
Total MISS, mean ± SD	4.1 ± 5.2	3.7 ± 4.0	2.2 ± 2.8	6.3 ± 7.1	0.05
GI score, mean ± SD	0.3 ± 0.7	0.2 ± 0.6	0.2 ± 0.6	0.4 ± 0.8	NS
Behavioral score, mean ± SD	0.5 ± 0.8	0.4 ± 0.7	0.2 ± 0.5	0.8 ± 1.0	0.02

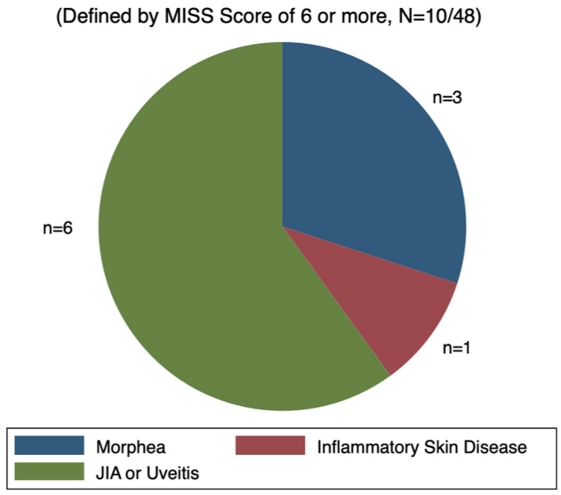
JIA, juvenile idiopathic arthritis; MISS, Methotrexate Intolerance Severity Score; NS, not significant (p > 0.05)
*Intolerant defined by MISS >6.

Table 3. ORs for Intolerance According to Patient and Clinical Characteristics

Variable	Unadjusted, OR (95% CI)	Adjusted for Route, OR (95% CI)
Subcutaneous route	11.2 (2.03–61.89), p = 0.006	~
Age (current)	1.04 (0.87–1.24), p = 0.64	1.04 (0.85–1.28), p = 0.70
Age (at diagnosis)	1.11 (0.95–1.29), p = 0.193	1.10 (0.92–1.3), p = 0.31
Female sex	4.68 (0.53–41.07), p = 0.164	3.4 (0.27–41.86), p = 0.31
Duration of disease	1.00 (0.97–1.04), p = 0.164	0.99 (0.95–1.02), p = 0.65
Dose of methotrexate (at MISS evaluation)	5.36 (0.02–1302.56), p = 0.55	0.96 (0.86–1.06), p = 0.42
Dose of methotrexate (initial)	4.33 (0.03–608.37), p = 0.561	0.54 (0.00–153.32), p = 0.83
Morphea diagnosis	0.93 (0.20–4.22), p = 0.924	0.45 (0.06–3.11), p = 0.40
JIA/uveitis	4.2 (0.98–18.0), p = 0.05	2.40 (0.5–9.75), p = 0.21
Inflammatory skin disease	0.15 (0.01–1.33), p = 0.90	0.52 (0.06–4.57), p = 0.55

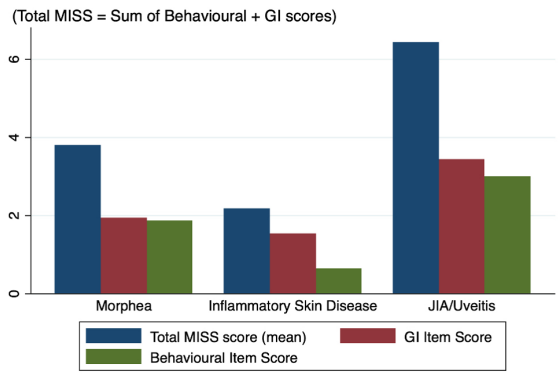
JIA, juvenile idiopathic arthritis; MISS, Methotrexate Intolerance Severity Score

Figure 1. Patients with methotrexate (MTX) intolerance.



JIA, juvenile idiopathic arthritis; MISS, Methotrexate Intolerance Severity Score

Figure 2. Mean Methotrexate Intolerance Severity Score (MISS).



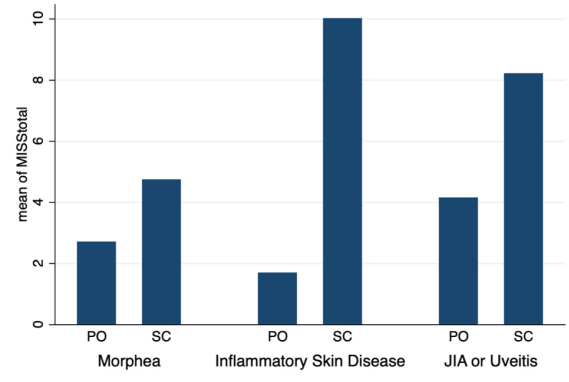
GI, gastrointestinal; JIA, juvenile idiopathic arthritis

month, compared with 0.4 ± 0.9 MTX doses. Patients with morphea on average (± SD) forgot 4.1 ± 7.4 doses of folic acid compared with 1.3 ± 3.7 for individuals with JIA/uveitis and 2.2 ± 5 for patients with inflammatory skin disease. There was no correlation between number of forgotten folate doses and total MISS. Those with MTX intolerance missed on average (±SD) 5.5 ± 8.80 doses per month compared with 1.73 ± 4.1 for those who tolerated MTX (Table 4). Two patients (1 with morphea and 1 with JIA) took ondansetron to treat MTX-associated nausea.

Discussion

In this study, MTX intolerance was higher in JIA/uveitis patients compared with the morphea and inflammatory skin disease cohorts. The only predictor for risk of intolerance was subcutaneous route of administration.

Figure 3. Methotrexate Intolerance Severity Score (MISS) totals according to route.



JIA, juvenile idiopathic arthritis

Individuals with morphea and inflammatory skin disease were treated with oral dosing more than JIA/uveitis patients, which may explain why they had overall less intolerance. This raises the question, given the prevalence of intolerance with subcutaneous dosing, of whether patients should be treated solely using an oral route. The overall mean MISS intolerance score was 6.3 in the JIA/uveitis cohort. Previous literature demonstrated lower intestinal absorption with oral MTX, limiting the bioavailability and efficacy with standard doses used to treat JIA.[6] Other studies have reported greater intolerance in those who took MTX subcutaneously compared with oral.[2,3] Clinicians must weigh the risks and benefits of dosing route and consider the potential risk of medication nonadherence secondary to intolerance with the subcutaneous route. Methotrexate intolerance may impact health-related quality of life, and some countermeasures, such as antiemetics, covert dosing, and taste masking, are often not effective.[1,7] There is promising evidence that eye movement desensitization and reprocessing has short-term efficacy in decreasing MTX intolerance.[8]

Understanding the magnitude and predictors for MTX intolerance has several benefits. Preventative and early treatment options for select patients could minimize the impact of intolerance on quality of life and minimize the severity of associated side effects and risk of MTX discontinuation. Strategies reported to date include the use of antiemetics, psychotherapy, behavioral therapy, and reprocessing.[8,9] Recently, a protocol was proposed that delivers anticipatory guidance and treats physical and emotional symptoms of intolerance to prevent progression and conditioned responses.[10]

We did not find any predictors for intolerance other than route of administration. This is in contrast to the findings of Franova et al,[3] who studied children with JIA and reported increased odds for MTX intolerance with older age at MTX start and female sex. Dose did not correlate

Table 4. Characteristics of Patients Who Were Intolerant to Methotrexate (MTX) Compared With Those Who Were Not

	MTX Tolerant (n = 38)	MTX Intolerant (n = 10)	Significance Level (p value)
Female, % (n)	66 (25 of 38)	90 (9 of 10)	NS (0.134)
Age at MISS, mean ± SD, yr	11.13 ± 4.26	11.80 ± 3.26	NS (0.65)
Duration of disease, mean ± SD, yr	21.86 ± 2.97	23.80 ± 7.23	NS (0.78)
MTX dose (current), mean ± SD, mg/kg	0.40 ± 0.13	0.43 ± 0.11	NS (0.55)
sc route, % (n)	74 (10 of 38)	80 (8 of 10)	0.002
MTX initial dose, mean ± SD, mg/kg	0.45 ± 0.14	0.48 ± 0.15	NS (0.56)
Diagnosis, % (n)			NS (0.08)
Morphea	31.6 (12 of 38)	30 (3 of 10)	
Inflammatory skin disease	42.1 (16 of 38)	10 (1 of 10)	
JIA or uveitis	26.3 (10 of 38)	60 (6 of 10)	
Missed folate doses, mean ± SD	1.73 ± 4.1	5.5 ± 8.8	0.054
Missed MTX doses, mean ± SD	0.34 ± 0.75	0.90 ± 1.10	NS (0.07)

JIA, juvenile idiopathic arthritis; MISS, Methotrexate Intolerance Severity Score; NS, not significant (p > 0.05)

with intolerance in our cohort, which could be explained by the relatively small doses of MTX used in inflammatory arthritis compared with those used to treat malignancies.[4] Yet, similarly to our study, children with JIA had greater MTX intolerance compared with children with acute lymphoblastic leukemia requiring anti emetic adjunct therapy.[4] Perhaps unknown underlying disease factors in JIA/uveitis contribute to MTX intolerance.

The prevalence of MTX intolerance in participants with JIA/uveitis in this study falls within reported ranges in the literature of 25% to 75%.[2–4] Franova et al[3] found 25% of patients at 6 months of treatment and 30% of patients at 12 months of treatment had a MISS of 6 or greater.[4] Mean behavior scores were higher than GI scores across groups except in the inflammatory skin disease cohort. Route did correlate with GI intolerance and behavior scores with greater intolerance to subcutaneous dosing. The inflammatory skin disease group was treated primarily with oral dosing, which may explain why there were lower GI and behavior scores in this set of patients. It has been well established that needle phobia is prevalent in JIA patients, with nearly a third of patients experiencing it at least sometimes.[11] This likely contributes to the behavioral symptoms in particular: feeling restless, crying, irritability, and medication refusal. Methotrexate itself is also thought to contribute because these features can be present in patients on oral dosing as well. Behavioral conditioning is thought to play a role with anticipatory nausea, abdominal pain, and emesis.[2]

Patients with morphea on average forgot more doses of folic acid but had less intolerance than those with JIA/uveitis. There is some evidence that folic acid can decrease GI side effects of MTX without an impact on efficacy.[11] This discordance may be secondary to poor patient recall of forgotten doses of folic acid in the JIA/uveitis group or dosing frequency differences. When comparing all disease cohorts together, those who were tolerant of MTX had fewer missed folate doses per month than those who were MTX intolerant.

Our conclusions must be interpreted in light of several limitations. The design of the study selected for tolerance because patients had to be taking MTX for a minimum of 3 months. We did not capture patients who stopped the medication secondary to intolerance, which would provide useful information. The sample size was limited by the number of patients with morphea who fulfilled the eligibility criteria, which was 15. This was a single-center study, and our results may not be reflective of the larger morphea population. We did not collect data on other potential cofactors, including disease severity, socioeconomic status, genetics, or race. Previous work has found SCLO1B1 rs4149056 CT/CC variant was associated with higher OR of MTX GI side effects.[12] To our knowledge this is the first study examining MTX intolerance in patients with morphea. The prevalence of methotrexate intolerance in patients with JIA/uveitis was similar to other studies.[2–5]

Conclusion

Methotrexate intolerance was highest among JIA/uveitis patients. The only predictor for risk of intolerance was subcutaneous route of administration. Future

work could examine MTX intolerance and disease activity over time, and the efficacy of interventions designed to minimize intolerance.

Article Information

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Ethical Approval and Informed Consent. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation and have been approved by the approved by the appropriate committees at our institution. All patients and/or parents/caregivers provided written informed consent and/or assent at enrollment.

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