Methotrexate intolerance in oral and subcutaneous administration in patients with juvenile idiopathic arthritis: a cross-sectional, observational study

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Abstract

Objective

Methotrexate (MTX) is the cornerstone disease-modifying anti-rheumatic drug (DMARD) in juvenile idiopathic arthritis (JIA). In Dutch patients, MTX intolerance occurred frequently and was associated with subcutaneous (SC) administration. The aim of this study was to assess the prevalence of MTX intolerance and its association with the route of administration in a German cohort of JIA patients.

Methods

A cross-sectional study of JIA patients on MTX was performed. Primary outcome was MTX intolerance, which was determined using the validated Methotrexate Intolerance Severity Score (MISS) questionnaire. The prevalence of gastrointestinal adverse effects and MTX intolerance was compared between patients on MTX SC and MTX administered orally (PO).

Results

Of 179 JIA patients on MTX, 73 (40.8%) were intolerant. The odds of MTX intolerance were higher in patients using MTX exclusively SC compared to exclusively PO (adjusted odds ratio 3.37 [95% confidence interval 1.19–10.0]). There was strong evidence that the former experienced more behavioural complaints (76.1% vs. 47.4%, p=0.001) and weak evidence that they experienced more abdominal pain after MTX intake (43.5% vs. 27.4%, p=0.056).

Conclusion

The prevalence of MTX intolerance was high and exclusively SC administration of MTX was associated with MTX intolerance and behavioural adverse effects. The prevalence of gastrointestinal adverse effects was at least as high as in patients on MTX PO. The frequently held assumption that SC causes fewer side effects than PO seems unwarranted. Definite answers about the differences between SC and PO administration with respect to safety and efficacy should be obtained by randomised trials.

Key words

juvenile idiopathic arthritis, methotrexate, adverse effects, route of administration, subcutaneous injections

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Introduction

Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease in childhood with a prevalence between 16 and 150 per 100,000 (1). It is defined as chronic joint inflammation of unknown aetiology, lasting at least 6 weeks, with the onset before 16 years of age. In JIA, methotrexate (MTX) is the most frequently used disease-modifying anti-rheumatic drug (DMARD) (2, 3) because it is beneficial in around 70% of the patients (2, 4), safe and relatively inexpensive (5, 6). It is usually administered orally (PO) or subcutaneously (SC) in a dose of 10–20 mg/m^2/week (2, 7). MTX can give rise to adverse effects including gastrointestinal complaints, such as abdominal pain, nausea and vomiting (3, 8-12). It is thought that these originate from intestinal serotonin release or by stimulation of the chemoreceptor trigger zone (CTZ). This zone is located in the medulla oblongata and communicates with the area postrema (the vomiting centre) in the medulla. However, the exact mechanism remains unknown (13, 14).

These gastrointestinal complaints after MTX intake in turn can lead to complaints occurring prior to MTX intake (anticipatory complaints) or when thinking of MTX (associative complaints), via what is thought to be a classical conditioning response (3, 10, 11, 15). These symptoms, occurring not only after but also before MTX intake, are termed MTX intolerance. It has been observed in about 50% of the JIA patients on MTX (15). MTX intolerance influences the quality of life of JIA patients negatively (16). Moreover, up to three-quarters of MTX intolerant patients are reluctant to take MTX, potentially leading to non-compliance, inefficacy and switch to costly biologicals (11, 15, 17).

Previously it has been assumed that MTX SC causes fewer adverse effects (8, 10, 18). Furthermore, because MTX SC has a higher drug bioavailability and a greater absorption (18-21), it has been supposed that it is more efficacious, compared to MTX PO (10, 21). However, both assumptions have been challenged recently. Firstly, in a Dutch cohort, the prevalence of MTX intolerance in patients receiving MTX SC exceeded the prevalence in patients on MTX PO significantly (67.5% *vs.* 44.5%, p=0.001) (15). Secondly, in a German observational cohort, no differences between MTX PO and SC were found in terms of efficacy or toxicity. Furthermore, MTX SC was significantly more frequently discontinued because of adverse effects (22). MTX SC may therefore not be superior to MTX PO regarding adverse effects and efficacy. These findings are clinically relevant, since they may guide physicians in their choice of the route of administration of MTX and may spare JIA patients unnecessary injections.

To date, the prevalence of MTX intolerance and its related factors have only been assessed in Dutch patients. Furthermore, the finding that MTX intolerance was more frequent in patients taking MTX SC was quite unexpected. Consequently, the question of what route of administration to choose when starting MTX in daily clinical practice has not yet been settled unequivocally. The aim of this study was to determine the prevalence of MTX intolerance in a cohort of German JIA patients and to determine whether this prevalence was associated with the route of administration of MTX, to aid physicians in the choice of route of administration.

Patients and methods

Study design and population

We performed a cross-sectional multicentre study in five hospitals in Germany that have paediatric rheumatology departments (Garmisch-Partenkirchen, Sendenhorst, Tübingen, Sankt Augustin and Münster). Centres were gradually added, as the number of participants remained low. In one centre (Sankt Augustin), patients of one paediatric rheumatologist were enrolled (GH). The case mix of patients among rheumatologists in this centre was comparable. The study was approved by the local medical ethics committees, and it was performed according to good clinical practice regulations and the declaration of Helsinki. Written informed consent was obtained from all the patients and/or their parents.

All patients with a confirmed JIA diagnosis according to ILAR criteria (23),

aged between 2 and 18 years and using MTX for at least three months, either orally or subcutaneously, were eligible. The cohort contained 190 patients, who were included between August 2009 and April 2013.

MTX intolerance

To determine whether the patients experienced intolerance, they completed the validated Methotrexate Intolerance Severity Score (MISS) questionnaire, either at the outpatient clinic, or at home (Sendenhorst) (15). The MISS consists of 12 questions distributed over four domains, being abdominal pain, nausea, vomiting and behavioural symptoms. The first three domains each assess experiencing symptoms after intake of MTX, anticipatory (before intake) and/or associative (when thinking of MTX) complaints. The behavioural domain assesses crying, irritability, restlessness and refusal to take MTX. The items can be assigned 0 (no symptoms), 1 (mild), 2 (moderate) or 3 (severe) points. The MISS was calculated as the sum of the questionnaire, while blank questions were assigned 0 points. The score could range from 0 to 36. A patient was considered intolerant if she had a score above the validated cut point of 6 points in concert with at least one associative, anticipatory or behavioural symptom (15).

Data collection

Patient characteristics were collected from the medical records at the time of completion of the questionnaire (Table I). For five patients, the dose of MTX in mg/wk. was converted to mg/m^2/wk. using the mean body surface area for their age and gender. The juvenile arthritis disease activity score (JADAS)-10 was calculated from the number of active joints, PGA, ESR and the parent/patient assessment of wellbeing (24).

Statistical analysis

To determine factors associated with intolerance, the patient characteristics were tested in a univariate analysis for differences between intolerant and tolerant patients. Route of administration was categorised as exclusively PO, exclusively SC, switch from PO to SC and switch from SC to PO, and differences of patient characteristics between the exclusively PO and exclusively SC groups were tested. Differences between the two groups who switched route of administration and the other two groups were not tested, since the reason and date of switch were not known. The crude odds ratio (OR) of the effect of route of administration on MTX intolerance was calculated using logistic regression. Other patient characteristics, such as age, gender, dosage and duration of MTX use and concomitant medication (especially NSAIDs), were subsequently added one by one and the change in OR was observed to detect potential confounding of the effect.

Finally, the prevalence of MTX adverse effects, according to the responses on the MISS questionnaire, was evaluated for differences between the tolerant and intolerant patients and between the exclusively PO and exclusively SC patients. We used the chi-square (χ^2), Mann-Whitney U (M-W U) or Kruskal-Wallis (KW) tests for

Table I. Baseline characteristics by MTX intolerance.

Characteristics	Tolerant n=106 (59.2)	Intolerant n=73 (40.8)	*p*-value*
Sex, female	69 (65.1)	49 (67.1)	0.78
Age (years), mean ± SD	10.3 ± 4.8	11.0 ± 4.1	0.30†
JIA subtype			
Oligoarticular, persistent	24 (22.6)	20 (27.4)	0.47
Oligoarticular, extended	14 (13.2)	18 (24.7)	0.049
Polyarticular	41 (38.7)	19 (26.0)	0.08
Systemic	3 (2.8)	2 (2.7)	0.99#
Enthesitis-related	12 (11.3)	5 (6.8)	0.44#
Psoriatic arthritis	8 (7.5)	5 (6.8)	0.99#
Undifferentiated	4 (3.8)	4 (5.5)	0.72#
Disease characteristics			
ANA positive	65 (61.9)	42 (61.8)	0.95
RF positive	7 (8.4)	2 (3.4)	0.31#
HLA-B27 positive	17 (17.5)	9 (15.0)	0.83#
Disease duration (years), mean ± SD	3.2 ± 3.3	5.2 ± 4.1	<0.001†
AJC, median (IQR)	0.0 (0.0-1.0)	0.0 (0.0-2.0)	0.078
JLM, median (IQR)	1.0 (0.0-2.0)	1.5 (0.0-3.0)	0.034
ESR (mm/h), median (IQR)	8.0 (4.0-14.0)	6.0 (4.0-12.0)	0.22
PGA, median (IQR)	1.0 (0.0-3.0)	2.0 (1.0-3.0)	0.32
Parent/patient global assessment, median (IQR)	2.0 (0.0-3.0)	2.0 (0.0-3.0)	0.79
JADAS-10, median (IQR)	4.0 (2.0-9.0)	4.0 (1.6-7.5)	0.91
MTX use			
Route of administration, exclusively PO	67 (63.2)	28 (38.4)	0.001
Route of administration, exclusively SC	26 (24.5)	20 (27.4)	0.67
Duration use (months), median (IQR)	14.5 (6.0-23.0)	21.0 (10.0-31.0)	0.006
Dose (mg/m^2/wk.), median (IQR)	12.0 (10.0-14.0)	11.4 (9.8-13.2)	0.30
Additional medication			
Steroids	15 (21.7)	4 (10.3)	0.19#
NSAIDs	33 (47.8)	18 (46.2)	0.87
Folic acid	39 (56.5)	21 (53.8)	0.79
Other DMARDs	14 (20.3)	12 (30.8)	0.22
MTX intolerance: MISS, median (IQR)	1.0 (0.0-3.0)	11.0 (8.0-16.0)	<0.001

AJC: active joint count; ANA: antinuclear antibodies; RF: rheumatoid factor; DMARDs: disease-modifying anti-rheumatic drugs; ESR: erythrocyte sedimentation rate; HLA-B27: human leukocyte antigen type B27; SD: standard deviation; IQR: interquartile range; JADAS: juvenile arthritis disease activity score; JIA: juvenile idiopathic arthritis; JLM: joints limited in movement; MISS: Methotrexate Intolerance Severity Score; MTX: methotrexate; NSAIDs: non-steroidal anti-inflammatory drugs; PGA: physician global assessment; PO: oral administration; SC: subcutaneous administration.

Values are the number (%) of patients of non-missing data, except where indicated otherwise. ANA status was determined in 174 patients, RF in 141, HLA-B27 in 157, AJC in 174, JLM in 161, ESR in 147, PGA in 122, Parent/patient global assessment in 89, JADAS-10 in 87 and additional medication in 108 patients.

*Continuous variables were tested with the Mann-Whitney U-test and categorical variables with Pearson's chi-square test, except where indicated otherwise. # Fisher's exact test. † Student's *t*-test.

Table II. Baseline characteristics by route of administration.

Characteristics	Exclusively PO n=95 (53.1)	Exclusively SC n=46 (25.7)	*p*-value*
Sex, female	66 (69.5)	25 (54.3)	0.08
Age (years), mean ± SD	11.6 ± 4.4	9 ± 4.7	0.003†
JIA subtype			
Oligoarticular, persistent	17 (17.9)	18 (39.1)	0.006
Oligoarticular, extended	14 (14.7)	11 (23.9)	0.18
Polyarticular	38 (40.0)	10 (21.7)	0.03
Systemic	2 (2.1)	2 (4.3)	0.60#
Enthesitis-related	12 (12.6)	3 (6.5)	0.39
Psoriatic arthritis	10 (10.5)	0 (0.0)	0.03
Undifferentiated	2 (2.1)	2 (4.3)	0.60
Disease characteristics			
ANA positive	52 (57.1)	30 (66.7)	0.29
RF positive	5 (7.2)	3 (7.5)	0.99#
HLA-B27 positive	16 (19.5)	5 (12.8)	0.45#
Disease duration (years), mean ± SD	4 ± 3.9	3.6 ± 3.7	0.54†
AJC, median (IQR)	0.0 (0.0-2.0)	0.0 (0.0-0.1)	0.17
JLM, median (IQR)	1.0 (0.0-3.0)	1.0 (0.0-3.0)	0.68
ESR (mm/h), median (IQR)	8.0 (5.0-16.0)	7.0 (5.0-12.5)	0.29
PGA, median (IQR)	2.0 (1.0-3.0)	1.0 (1.0-2.0)	0.11
Parent/patient global assessment, median (IQR)	2.0 (0.0-3.0)	1.0 (0.0-2.0)	0.19
JADAS-10, median (IQR)	5.0 (2.0-10.0)	3.0 (1.0-5.0)	0.12
MTX use			
Duration use (months), median (IQR)	13.0 (6.0-26.0)	17.0 (8.0-26.0)	0.30
Dose (mg/m^2/wk.), median (IQR)	11.8 (10.0-13.6)	11.6 (9.7-13.2)	0.43
Additional medication			
Steroids	14 (19.7)	3 (11.5)	0.55#
NSAIDs	39 (54.9)	9 (34.6)	0.08
Folic acid	41 (57.7)	13 (50.0)	0.50
Other DMARDs	19 (26.8)	5 (19.2)	0.45
MTX intolerance: MISS, median (IQR)	2.0 (0.0-7.0)	4.5 (3.0-11.0)	0.003

Values are the number (%) of patients of non-missing data, except where indicated otherwise.
For abbreviations and number of missing values, see Table I.
*Continuous variables were tested with the Mann-Whitney U-test and categorical variables with Pearson's chi-square test, except where indicated otherwise. # Fisher's exact test. † Student's *t*-test.

Table III. Multivariate analysis of MTX intolerance.

Variable	OR (95% CI)	*p*-value
Route of administration		
PO	Reference	
Switch PO to SC	4.9 (1.4-18.1)	0.01
Switch SC to PO	4.0 (1.1-15.0)	0.03
SC	3.4 (1.2-10.0)	0.02
Age, years	1.0 (0.9-1.1)	0.94
Disease duration, years	1.2 (1.1-1.4)	<0.001
PGA	1.1 (0.9-1.4)	0.36

CI: confidence interval; OR: odds ratio; PGA: physician's global assessment; PO: oral administration; SC: subcutaneous administration.

non-normally distributed variables and the independent sample *t*-test for normally distributed variables. Statistical analyses were performed with SPSS, version 20 (SPSS Inc., Chicago, USA) and R statistics v. 2.15.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results

In all centres combined, 216 patients were eligible, of whom 26 refused participation. Of 190 enrolled patients, four patients were excluded because they were older than 18 years, six because the route of administration was unknown and one because the MISS questionnaire was missing, leaving 179 patients for analysis. Table I shows the baseline characteristics, subdivided by MTX intolerance, at the time of completing the MISS questionnaire. MTX intolerance (score ≥6 and at least one anticipatory, associative or behavioural symptom) was present in 73 (40.8%) patients. The mean age was 10.6 years and the majority was female (65.9%). Of all patients, 26 used additional DMARDs, next to MTX (etanercept: n=11; sulfasalazine: n=10; adalimumab: n=3; hydroxychloroquine: n=2).

Differences between tolerant and intolerant patients in univariate analysis

There was strong evidence that intolerant patients had a longer disease duration, a longer history of MTX treatment and that they took MTX exclusively PO less frequently ($p \leq 0.001$, Table I). There was some evidence the prevalence of the extended oligoarticular subtype was higher in the intolerant group, whereas the prevalence of the polyarticular subtype was lower (*p*-value around 0.05, Table I). Furthermore, there was some evidence that intolerant patients had a higher number of active and limited joints. For all other variables tested, there was no evidence of differences between the two groups (Table I). Folic acid was administered in 56.5% of the tolerant patients and 53.8% of the intolerant patients ($p=0.79$). As expected, the median MISS score was higher in the intolerant group (median of 11.0 *vs.* 1.0 points, $p<0.001$).

Differences between patients with different routes of administration in univariate analysis

The oral group was older than the subcutaneous group (mean age 11.6 *vs.* 9 years, $p=0.003$, Table II). Persistent oligoarticular JIA was more common in the subcutaneous group (39.1% *vs.* 17.9%, $p=0.006$), whereas polyarticular arthritis was more common in the oral group (40.0% *vs.* 21.7%, $p=0.03$). Psoriatic JIA had a prevalence of 10.5% in the oral group and was absent in the subcutaneous group. The median MISS scores per group were the following: PO: 2.0, SC: 4.5, PO >SC: 8.0 and SC

>PO: 8.0. There was strong evidence these four groups differed (KW test: p=0.002) and that the median MISS score of the exclusively SC group was higher than the median score of the exclusively PO group (M-W U test: p=0.003). There was no evidence of other differences between the PO and SC groups (Table II).

Effect of subcutaneous route of administration on MTX intolerance

The crude OR for MTX intolerance of taking MTX exclusively SC was 1.84 (95% CI 0.88–3.83) showing no evidence of increased odds. However, this effect was confounded by age, disease duration, PGA, NSAID use and folic acid use, as indicated by a substantial change in the OR after adjustment for these parameters. After adjustment for age, disease duration and PGA the OR for MTX intolerance of MTX SC changed to 3.37 (95% CI 1.19–10.0, p=0.02, Table III). Additionally, longer disease duration was associated with MTX intolerance (OR 1.2 [95% CI 1.1–1.4], p<0.001). Inclusion of NSAID and folic acid use in this model yielded an unstable model due to paucity of data regarding additional medication, showing an OR of 10.1 (95% CI 1.79-77.6, p=0.01). Interestingly, MTX dosage and duration of MTX use were no confounders, since inclusion of these variables in the model did not change the OR of route of administration.

Prevalence of MTX intolerance, gastrointestinal and behavioural symptoms

Table IV contains the prevalence of gastrointestinal and behavioural symptoms, by MTX intolerance and route of administration. As expected, the intolerant patients showed a significantly higher prevalence for each item of the questionnaire.

Notably, there was strong evidence that behavioural symptoms (restlessness, crying, irritability and MTX refusal combined) were more frequent among children taking MTX SC (p=0.001). Furthermore, there was weak evidence of a higher prevalence of abdominal pain after administration of MTX in the SC group (43.5% *vs*. 27.4%, p=0.056).

Table IV. Prevalence of items on the MISS per intolerance and route of administration.

Number of patients	Tolerant 106	Intolerant[b] 73	PO 95	SC 46	p-value*
MTX intolerance[a]	0 (0)	73 (100)	28 (29)	20 (43)	0.10
Abdominal pain	28 (26)	50 (68)	33 (35)	23 (50)	0.08
After MTX	23 (22)	43 (59)	26 (27)	20 (43)	0.06
Anticipatory	4 (4)	15 (21)	10 (11)	4 (9)	0.99#
Associative	3 (3)	26 (36)	9 (9)	6 (13)	0.57#
Nausea	34 (32)	69 (95)	48 (51)	30 (65)	0.10
After MTX	29 (27)	61 (84)	43 (45)	24 (52)	0.44
Anticipatory	4 (4)	31 (42)	14 (15)	8 (17)	0.81#
Associative	13 (12)	51 (70)	26 (27)	18 (39)	0.16
Vomiting	4 (4)	33 (45)	17 (18)	9 (20)	0.82#
After MTX	3 (3)	31 (42)	15 (16)	8 (17)	0.81#
Anticipatory	0 (0)	9 (12)	5 (5)	1 (2)	0.66#
Behavioural	39 (37)	71 (97)	45 (47)	35 (76)	0.001
Restlessness	21 (20)	56 (77)	30 (32)	24 (52)	0.02
Crying	12 (11)	34 (47)	16 (17)	18 (39)	0.003
Irritability	14 (13)	57 (78)	29 (31)	25 (54)	0.006
MTX refusal	9 (8)	30 (41)	9 (9)	11 (24)	0.037#

MISS: methotrexate intolerance severity score; MTX: methotrexate; PO: exclusively orally administered MTX; SC: exclusively subcutaneous.

Values are the number (%) of patients within the groups of (in)tolerance and within the groups of different routes of administration. The groups who switched route of administration were left out of this table, because of potential biases.

[a]Intolerance to methotrexate was defined as a score of ≥6 on the MISS and at least one associative, anticipatory or behavioural symptom.

*p-value of the null hypothesis of no differences between the PO and the SC group, using Pearson's chi square test, except where indicated otherwise. #Fisher's exact test.

The same held true for any symptom of the abdominal pain domain (after MTX, anticipatory and associatively), which was more common in the SC group (50.0% *vs*. 34.7%, p=0.082). There was no evidence of other differences between the PO and SC groups.

Discussion

In this cross-sectional, multicentre study, 40.8% of 179 JIA patients receiving MTX were intolerant to the therapy. There was evidence that receiving MTX exclusively subcutaneously as compared to exclusively orally increased the odds of MTX intolerance (adjusted OR: 3.37 [95% CI 1.19–10.0]). There was strong evidence that the median MISS score was higher in the MTX SC group than in the MTX PO group and that patients taking subcutaneous MTX showed more often behavioural complaints, such as crying, restlessness, irritability and refusal to take MTX. Finally, there was some evidence that they experienced more abdominal pain after MTX administration. Taken together, the odds of MTX intolerance were higher in patients taking MTX SC and they experienced more gastrointestinal and behavioural adverse effects than patients taking MTX PO did.

Some other factors were significantly associated with MTX intolerance (Table I), most notably the duration of MTX use. When analysing these factors together with route of administration in multivariate analysis, these associations were not maintained (data not shown). Patients with persistent oligoarthritis used MTX SC more often (Table II), probably because these patients tend to be younger and are therefore unable to swallow MTX PO. Another possible explanation is that MTX in these patients is frequently started because of uveitis. Treatment in these cases is performed in cooperation with the ophthalmologist, potentially leading to a different approach.

MTX intolerance is thought to arise as a classical conditioning response, as follows (11, 15). In MTX therapy, many potential conditioned stimuli are present, such as the yellow color of the drug. Unconditioned gastrointestinal adverse effects may occur after the intake of MTX. Over the course of weeks, the potential conditioned stimuli can elicit the unconditioned stimuli due

to stimulation of the central nervous system, giving rise to the so-called anticipatory and associative complaints. (15, 25). Why MTX intolerance would occur more often in the MTX SC group is unknown. It could be speculated that the higher prevalence of behavioural complaints in the MTX SC group may be explained by a fear of needles and the negative experience with injections, leading to stress and subsequently to crying, irritability and refusal to take the drug. In turn, these negative experiences could incline patients to value any gastrointestinal side effect more negatively, thus contributing to the high prevalence of the latter in the MTX SC group. These gastrointestinal side effects may also arise due to triggering of the chemoreceptor trigger zone in the medulla oblongata (13, 14), folic acid depletion (10, 26) or as of yet unknown mechanisms. These mechanisms might be triggered more often in the case of MTX SC, because of its higher bioavailability (18-21). Finally, the subcutaneous route of administration was shown to be associated with a higher concentration of long chain MTX polyglutamates (MTX-PGs) (27), potentially contributing to the higher prevalence of adverse effects. However, an association between MTX-PGs and the frequency of adverse events could not be demonstrated in a longitudinal study in JIA (28) or RA (29).

Two accepted and widely used approaches to counter the side effects of MTX are the supplementation of folic or folinic acid 24 hours after MTX administration and the administration of anti-emetics (3, 10, 15, 18, 26). Some recent studies state there is lack of convincing evidence for these strategies (7, 30). In our cohort, 55.6% of all patients used folic acid supplementation, which was comparable for the tolerant and intolerant group (p=0.79) and for the SC and PO group (p=0.50). We could not reliably assess the use of anti-emetics.

Previously, we studied a Dutch cohort, in which the prevalence of MTX intolerance was 50.5%. There was strong evidence of an increased frequency in SC patients (67.5% *vs*. 44.5%, p=0.001) (15). Likewise, the occurrence of behavioural complaints was more frequent in the SC group. These results were partly confirmed by the current study. Of note, there were methodological differences between the two studies; the most important being that the Dutch paper assessed patients who switched route of administration together with patients who remained on the same route from the start of MTX. In the current study, patients who switched were excluded from the analyses, because it was suspected that many of these patients switched because of side effects, causing a high prevalence of intolerance in these groups (63.2% and 68.4%, respectively). Furthermore, they might have switched shortly before completing the questionnaire, making the results of the MISS more applicable to the route of administration before the switch.

In a recent British study, a slightly different questionnaire than ours was used to assess the frequency of MTX-induced nausea and vomiting in adolescents and adults (31). Nausea and vomiting were reported in 73% and 43% of adolescents respectively. In this study, too, SC administration of MTX was associated with nausea in a multivariate analysis. In addition, in another German study, MTX SC was discontinued more frequently than MTX PO, due to adverse effects. No differences were observed between MTX SC and MTX PO with respect to efficacy or toxicity (22). Finally, in RA patients MTX SC administration was found to be associated with a higher prevalence of MTX intolerance as well (32).

In our study, we used a self-reporting method to assess the frequency of MTX intolerance. This could potentially lead to overestimation of the prevalence of MTX intolerance. In one centre (Sendenhorst), the questionnaire was sent home, potentially causing mainly MTX intolerant patients to complete and return it, thus overestimating the prevalence of MTX intolerance. However, the prevalence of MTX intolerance at Sendenhorst was in range with the other centres (41.5%). Next, due to missing data, we could not calculate the JADAS or determine the use of additional medication in a sufficient number of patients to include these as covariates in the multivariate analysis. Neither did we know the prevalence of uveitis in our sample. Patients who stopped MTX in the past because of intolerance were not included in the study and questions of the MISS who were left blank, were assigned 0 points, potentially causing the prevalence of MTX intolerance to have been underestimated. Finally, the aim of this study was to investigate the prevalence of MTX intolerance. Therefore, liver toxicity was not taken into account, since it is a well-known side effect of MTX, which is easily dealt with by suspending the drug.

In conclusion, in this cross-sectional study of a German sample of JIA patients, the prevalence of MTX intolerance was high. The odds of MTX intolerance were higher in patients taking MTX SC, they experienced more behavioural adverse effects than patients taking MTX PO did and at least as many gastrointestinal adverse effects as patients on MTX PO, thereby disconfirming the frequently held belief that SC causes fewer side effects (8, 10, 18), and confirming our previous findings (15). However, given the cross-sectional design of the study, results need to be interpreted with caution. Randomised controlled trials are necessary to obtain definite answers about the differences between SC and PO administration of MTX in terms of safety and efficacy.

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