Translation and validation in Italian of the methotrexate intolerance severity score for children and adults with arthritis

G. Tarantino[1], R. Nicolai[1], A. Aquilani[1], A. Tomasini[2], A. Celano[2], A. Pucacco[1], S. Magni-Manzoni[1], F. De Benedetti[1], E. Marasco[1]

[1]Division of Rheumatology, Department of Paediatrics, IRCCS Bambino Gesù Children's Hospital, Rome, Italy; [2]Associazione Nazionale Persone con Malattie Reumatologie e Rare - APMARR, Lecce, Italy.

Abstract

Objective

Methotrexate (MTX) is the most used drug to treat children and adults with arthritis and its use is burdened by adverse effects. The MTX intolerance severity score (MISS) was developed in English to identify patients who are intolerant to MTX. The aim of this study was to translate and validate the MISS in Italian.

Methods

The Italian version of the MISS was developed following the "guidelines for process of cross-cultural adaptation of self-reported measures". The Italian version of the MISS was validated in 125 patients with juvenile idiopathic arthritis (JIA) followed at the Rheumatology Unit of Bambino Gesù Children Hospital. We assessed the construct validity and calculated the internal consistency of the Italian MISS. We performed ROC analysis to assess the overall performance of the Italian MISS.

Results

We translated and adapted the MISS to the Italian language. The Italian MISS showed a very good internal consistency as shown by a Cronbach α of 0.87 (95% CI, 0.84–0.90) and a composite reliability of 0.89 (95% CI, 0.83–0.91). The Cohen's κ was 0.81 (95% CI, 0.71–0.91), suggesting a very good construct validity. The ROC analysis showed an area under the curve (AUC) of 0.97 (95% CI, 0.93–0.99). A threshold of 6 to define intolerant patients, showed a sensitivity of 98.3% and specificity of 81.2%.

Conclusion

We developed the Italian version of the MISS and showed its validity and reliability to identify patients intolerant to MTX in clinical practice and in a research setting.

Key words

methotrexate, juvenile idiopathic arthritis, intolerance, questionnaire translation, conditioning

Giusyda Tarantino, MD
Rebecca Nicolai, MD
Angela Aquilani, MD
Andrea Tomasini
Antonella Celano
Aurora Pucacco, RN
Silvia Magni-Manzoni, MD
Fabrizio De Benedetti, MD, PhD
Emiliano Marasco, MD

Please address correspondence to:
Silvia Magni-Manzoni
Division of Rheumatology,
Ospedale Pediatrico Bambino Gesù - IRCCS,
Piazza S. Onofrio 4,
00165 Rome, Italy
E-mail: silvia.magnimanzoni@opbg.net

Received on October 19, 2023; accepted in revised form on February 21, 2024.

Competing interests: F. De Benedetti has recieved research grants from Abbvie, Novimmune, Pfizer, Roche, Sanofi, and consulting fees from Novartis and SOBI. The other authors have declared no competing interests.

Introduction

Juvenile idiopathic arthritis (JIA) is the most common rheumatological disease in children. JIA is defined as the presence of arthritis that begins before the age of 16 and persists for at least 6 weeks (1). According to International League of Associations for Rheumatology (ILAR) criteria, JIA encompasses various subtypes with involvement of both joint structures and extraarticular domains (*i.e.* eyes, skin and internal organs) (2).

Methotrexate (MTX) is the conventional synthetic disease-modifying anti-rheumatic drug (cDMARD) of first choice in the management of JIA because of its safety, efficacy and low cost (3). Although new biological DMARDS have been developed (*i.e.* TNF-inhibitors, IL6-inhibitors, etc.), MTX remains the anchor DMARD for JIA treatment. Indeed, over 70% of all children with JIA in the Childhood Arthritis and Rheumatology Research Alliance (CARRA) registry had ever received MTX (4).

Although MTX may have significant side effects, long-term follow-up of both children and adults showed an adequate safety profile. Severe side effects, such as bone marrow suppression and hepatotoxicity, are rare and usually self-limiting after stopping MTX and can be reduced by adequate folate supplementation (5, 6). The most common adverse effects after MTX administration are gastrointestinal symptoms (*i.e.* abdominal pain, nausea, vomiting and diarrhea) (7). Many patients on MTX also develop anticipatory and associative gastrointestinal symptoms that occur before MTX administration or even when thinking of MTX. These symptoms have a psychological component, being present before MTX is administered, and it is hypothesised that they are part of a conditional response to the aforementioned gastrointestinal side effects occurring after MTX administration (8). Moreover, as part of the conditioned response, patients also experience behavioural complaints, such as asthenia, crying, irritability and refusal to take the drug (8). All these side effects have a significant impact both on the quality of life of patients and their care-givers and on adherence to therapy (9-11). This causes MTX discontinuation with a frequency as high as 35% (12). Few tools were available to assess MTX-related adverse events, which only focused on the gastrointestinal side effects, without taking in consideration the full spectrum of the conditional response. Bulatović and colleagues developed and validated a questionnaire, the Methotrexate Intolerance Severity Score (MISS), to identify patients intolerant to MTX (13). The MISS integrates the conditional responses and behavioural changes in response to MTX, contrary to other tools that only consider gastrointestinal side effects (7). Using this screening tool, the prevalence of MTX intolerance was estimated at approximately 50% in patients with JIA (13) and around 20–40% in adult patients with rheumatoid arthritis (RA) (14-16). The MISS questionnaire has been used in several studies (17, 18) and validated in other languages (14, 15, 19). As there is no validated tool in the Italian language to assess intolerance to MTX objectively and in a standardised fashion in paediatric and adult patients, the aim of the current study was to translate and validate the MISS questionnaire in Italian for both groups of patients.

Materials and methods

Study design

This methodological study was performed at the Division of Rheumatology of Bambino Gesù Children Hospital in Rome. The MISS was translated into Italian following the published guidelines for the process of translation and cross-cultural adaptation of self-report measures (20, 21). The main stages of translation and validation of MISS were:

1. Authorisation by the authors: authorisation for translation was granted by the authors of the original instrument (13).
2. Forward translation: translation of the English version of the MISS into Italian by three Italian bilingual translators: two had medical training and familiarity with the terminology, and one had no medical training, but experience as an English professor. The translations were performed independently. The items of MISS were also adapted from children to adults by changing "my child" with "I".

3. Synthesis of translations: the three Italian versions of the MISS for children and adults were compared and differences were reconciled to obtain a first Italian version of the MISS for children and adults.
4. Back translation: the Italian versions of the MISS for children and adults were back translated into English by two bilingual translators, one with biomedical experience and one lay person. Both translators had no access to the original version of MISS.
5. Expert committee meeting: a panel of eight individuals (four paediatric rheumatologists, one paediatric rheumatologist with methodology experience, one rheumatologist, one nurse with experience in paediatric rheumatology, one patient representative) was formed to evaluate the translations and the back translations. The panel evaluated the different versions of the MISS and compared them with the original, assessing the equivalency of the versions. All conflicts and ambiguous expressions were discussed and resolved. All members agreed on the final versions of the MISS for children and adults, establishing the prefinal version of the instrument.
6. Pretest: the questionnaire was administered to twenty randomly selected patients with JIA (ten children and ten adults) in order to verify the clarity, comprehension, acceptability and adequacy of the questionnaire. Any unclear items were reworded and agreed by the Expert committee.
7. Final Italian version: the final versions of the questionnaire were tested.

Ethics

The project was approved by the Ethical Committee of the Children Hospital Bambino Gesù (protocol no. 2333_OPBG_2020).

Population

Care-givers and/or patients were invited to participate during routine rheumatology consultation (n=125). We enrolled patients with a diagnosis of JIA (excluding patients with systemic JIA) according to the ILAR classification criteria (2) and on treatment with MTX (oral or parenteral administration, with a dosage raging between 5 and 15 mg/m^2/week). Participation in the study was not proposed if MTX had been started less than three months prior to time of inclusion. We included only those patients who demonstrated good adherence to MTX treatment by taking more than 87% of the prescribed doses (*e.g.* missing no more than 2 doses in a 4 month period). The paediatric version of the MISS was administered to patients younger than 18 years and was filled out by care-givers (n=101). We administered the adult version of MISS to patients older than 18 years (n=24).

Table I. Demographical and clinical features of the study population.

	n=125
Female subjects, n (%)	104 (83)
JIA ILAR classification, n (%)	
Persistent oligoarthritis	50 (40)
Extendend oligoartrhitis	21 (17)
Rheumatoid factor positive polyarthritis	4 (3.2)
Rheumatoid factor negative polyarthritis	43 (34.4)
Enthesitis-related arthritis	4 (3.2)
Psoriatic arthritis	3 (2.4)
Disease characteristics, n (%)	
Chronic uveitis (ever)	37 (29.6)
Antinuclear antibody (ANA) positive	72 (57.6)
Rheumatoid factor positive	4 (3.2)
HLA-B27 positive	3 (2.4)
Age at JIA onset (yrs), median (IQR)	4 (2.4-9.1)
JIA duration (yrs), median (IQR)	6.0 (3.3-10.5)
Age at MISS (yrs), median (IQR)	12.7 (7.9 -17.2)
Disease activity	
Physician's Global Assessment of disease activity (VAS 0-10), mean (±SD)	0.7 (±1.5)
c-JADAS10 (range 0-30), mean (±SD)	2.4 (±4.1)
Inactive, n (%)	81 (64.8)
Low activity, n (%)	10 (8.0)
Moderate activity, n (%)	16 (12.8)
High activity, n (%)	18 (14.4)
Treatment	
MTX usage duration (yrs), median (range)	4.6 (2.4-7.2)
MTX dosage (mg/mq/w), mean (±SD)	14.5 (±4.5)
MTX route administration, n (%)	
oral	2 (1.6)
subcutaneous	123 (98.4)
Folic/folinic acid, n (%)	
3.75 mg	15 (12.0)
5 mg	11 (8.8)
7.5 mg	99 (79.2)
NSAIDs, n (%)	7 (5.6)
Oral glucocorticoids, n (%)	7 (5.6)
Proton-pump inhibitors (PPI), n (%)	5 (4.0)
Antiemetics, n (%)	48 (38.4)
Biological DMARDs, n (%)	
Etanercept	52 (41.6)
Adalimumab	37 (29.6)
Infliximab	1 (0.8)
Golimumab	1 (0.8)
Tocilizumab	2 (1.6)
Upadacitinib	1 (0.8)
Switch biological DMARDs, n (%)	28 (22.4)
Biological DMARDs treatment (yrs), median (range)	2.7 (1.4-4.3)

c-JADAS10: clinical juvenile arthritis disease activity score up to 10 active joints; NSAIDs: non steroidal anti-inflammatory drugs.

Data collection

The following data were collected: demographics, clinical parameter (*i.e.* ILAR JIA subtype, age at JIA onset, presence of uveitis, ANA-FR positivity, clinical JADAS), MTX treatment (*i.e.* MTX starting date, MTX dose/

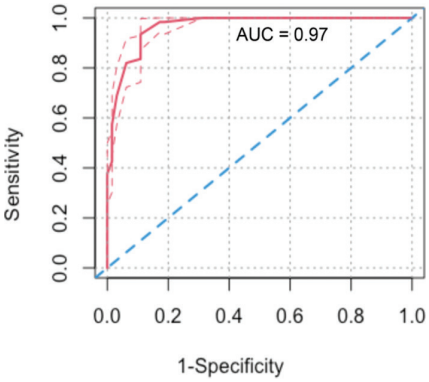

Fig. 1. Receiver-operating characteristic (ROC) analysis for the Italian version of the MISS in predicting MTX intolerance against the medical evaluation of drug intolerance. The dashed red lines indicate 95% confidence intervals of the ROC curve, the dashed blue line indicates the random classifier. The area under the ROC curve (AUC) is shown.

route), concomitant treatments (*i.e.* biological DMARDs, folic/folinic acid, antiemetics, etc.). The evaluating physician, blinded to the result of the MISS, determined whether the patient was intolerant to MTX as previously described (13). The opinion of the evaluating physician was considered the gold standard to define MTX intolerance.

Statistical analysis

Descriptive statistics were used to describe demographics, disease activity, functional disability and MISS scores. Quantitative variables were expressed as means (±SD; standard deviation) or as median (±IQR; interquartile range) when appropriate. Questionnaire reliability was evaluated using Cronbach α and the composite reliability calculated with the factor loadings from a confirmatory factor analysis (22). The concordance between the MISS results and the medical evaluation, considered as the standard criterion, was evaluated with the Cohen's κ coefficient.

To confirm the best cut-off point for MTX intolerance, the receiver operating characteristic (ROC) curve was constructed considering sensitivity and specificity. Face validity and content validity were assessed by three independent rheumatologists and then discussed together with the Expert Committee. Statistical analysis was performed using R, R Core Team (2022).

Table II. Internal consistency of the Italian version of the MISS questionnaire.

Item	Mean	SD	Item-test correlation (total score)	Item-test correlation (excluding the item)	Mean inter-item correlation	Standardised Cronbach α (if item is excluded)
Question 1	0.70	1.02	0.62	0.53	0.36	0.86
Question 2	0.22	0.56	0.53	0.47	0.37	0.87
Question 3	0.55	0.93	0.68	0.60	0.36	0.86
Question 4	1.39	1.16	0.68	0.59	0.36	0.86
Question 5	0.49	0.88	0.57	0.49	0.37	0.87
Question 6	1.16	1.17	0.66	0.57	0.36	0.86
Question 7	0.56	0.89	0.63	0.56	0.36	0.86
Question 8	0.18	0.57	0.41	0.35	0.39	0.87
Question 9	0.96	1.10	0.72	0.64	0.35	0.86
Question 10	0.79	1.11	0.67	0.58	0.36	0.86
Question 11	1.02	1.16	0.79	0.72	0.34	0.85
Question 12	1.12	1.22	0.73	0.64	0.35	0.86

MISS questions: question 1 = My child has/I have a stomachache after taking MTX; question 2 =; My child has/I have a stomachache several hours to one day before taking MTX; question 3 = My child has/I have a stomachache when thinking of MTX; question 4=My child is/ I am nauseous after taking MTX; question 5=My child is/I am nauseous several hours to one day before taking MTX; question 6=My child is/ I am nauseous when thinking of MTX; question 7=My child vomits/I vomit after taking MTX; question 8=My child vomits/I vomit hours to one day before taking MTX; question 9=My child is/ I am restless when taking MTX; question 10=My child cries/I cry when taking MTX; question 11=My child is/ I am irritable when taking MTX; question 12=My child refuses/ I refuse to take MTX.

Results

Translation results

The Italian translators produced three very similar Italian versions of the MISS questionnaire for children and three similar versions for adults. The only differences regarded the words "complaints" and "irritable". Translators reported no difficulties and ambiguity neither doubt in the translation. No cultural adaptation was required and only minor vocabulary changes were needed to obtain the first draft. The English translators produced two English versions of the MISS for children and two versions for adults: the two English translations retained the meaning of the original version; only minor vocabulary changes were observed. The pre-test phase with twenty patients did not show any ambiguity in the sentences; around 30% of patients reported not to be familiar with the acronym "MTX'. For this reason, "MTX" was substituted with the full-length name "Methotrexate". The expert panel agreed on the final questionnaire after discussing minor lexical conflicts (Supplementary Fig. S1).

Descriptive data

A total of 125 subjects were recruited and included in the study. About 83% were females, 71 (57%) had oligoarthritis, 43 (34%) RF-negative polyarthritis, 4 (3.2%) enthesitis-related arthritis (ERA) and 3 (2.4%) psoriatic arthritis. Chronic uveitis occurred in about 30% of patients (Table I). The median (±IQR) age at diagnosis was 4.4 (2.4–9.1). Disease duration at MISS questionnaire was 6 years (IQR 3.3-10.5). The mean score (±SD) of physician's global assessment of disease activity (VAS) and clinical-JADAS score were 0.7 (±1.5) and 2.4 (±4.1) respectively, with 65% of patients in inactive disease (Table I). The majority (98%) of patients received MTX subcutaneously. The median duration of MTX use was about 4.6 (2.4–7.2) years. The mean (±SD) doses of MTX and folic/folinic acid were 14.5±4.5 mg and 6.4±1.3 mg, respectively (Table I). Concomitant drugs included antiemetics (38.4%), non-steroidal anti-inflammatory drugs (NSAIDs) (5.6%), oral glucocorticoids (5.6%) and proton-pump inhibitors (4%). Thirty-one (24.8%) patients were biological DMARDs naive at enrolment, whereas 72.8% were on a TNF inhibitor, 1.6% were on tocilizumab and 0.8% on upadacitinib (Table I).

Internal consistency

The standardised Cronbach α was 0.87 (95% CI, 0.84–0.90), suggesting a good

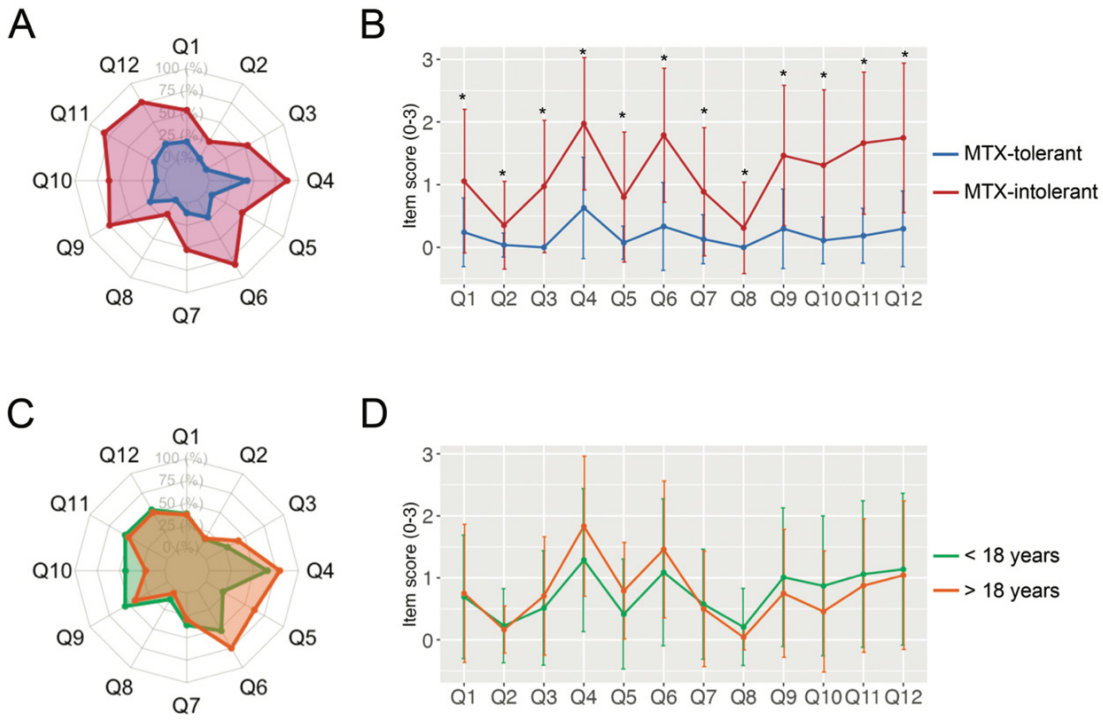

Fig. 2. Prevalence of MTX intolerance in patients with JIA.
A: Radar chart showing the frequency of a positive score (item score >0) for each of the 12 questions of MISS in tolerant and intolerant patients.
B: Item score (mean ±SD) for each of the 12 questions of MISS for tolerant and intolerant patients. **C**: Radar chart showing the frequency of a positive score (item score >0) for each of the 12 questions of the MISS in paediatric (<18 years of age) and adult patients (>18 years of age).
D: Item score (mean ±SD) for each of the 12 questions of the MISS for paediatric (<18 years of age) and adult patients (>18 years of age).
Radar chart MISS questions: question 1 = My child has/I have a stomachache after taking MTX; question 2 = My child has/I have a stomachache several hours to one day before taking MTX; question 3 = My child has/I have a stomachache when thinking of MTX; question 4 = My child is/ I am nauseous after taking MTX; question 5 = My child is/I am nauseous several hours to one day before taking MTX; question 6 = My child is/ I am nauseous when thinking of MTX; question 7 = My child vomits/I vomit after taking MTX; question 8 = My child vomits/I vomit hours to one day before taking MTX; question 9 = My child is/ I am restless when taking MTX; question 10 = My child cries/I cry when taking MTX; question 11 = My child is/ I am irritable when taking MTX; question 12 = My child refuses/ I refuse to take MTX.

internal consistency. Table II shows mean and SD of each item, together with item-test correlation, inter-item correlation and standardised Cronbach α if item were excluded. The mean inter-item correlations were good (0.34–0.39). There was no significant gain or reduction after excluding any of the 12 items (data not shown).

To further confirm the internal consistency of the MISS, we calculated the composite reliability of the Italian version of the MISS from the factor loadings of a confirmatory factor analysis. We first checked the appropriateness of the data for factorial analysis: the Kaiser-Meyer-Olkin adequacy test (KMO factor adequacy 0.74) and the Bartlett sphericity test (c^2 =729, p<0.001) showed the data were appropriate for factorial analysis. The composite reliability calculated from the factorial analysis was 0.89 (95% CI, 0.83–0.91), confirming a good internal consistency.

Construct validity

The concordance of the MISS questionnaire with the medical evaluation (considered as the standard criterion) was evaluated with the Cohen's κ coefficient: the κ coefficient was 0.81 (95% CI 0.71–0.91) (p-value<0.001).

Receiver-operating characteristic (ROC) analysis

The area under the ROC curve (AUC) was 0.97 (95% CI 0.93–0.99), and it was significantly greater 0.5 (p-value <0.001) (Fig. 1). The threshold of 6, as suggested by the authors of MISS (13), resulted in a sensitivity of 98.3% and specificity of 81.2%, a positive predictive value (PPV) of 83.4% and a negative predictive value (NPV) of 98.1%.

Prevalence of MTX intolerance in patients with JIA

Seventy-one (56.8%) patients scored ³6 on the Italian version of the MISS, with at least 1 point on anticipatory and/or associative and/or behavioural symptoms and thus were defined to be intolerant to MTX (*13*). Among the intolerant patients, the most frequent complaint was nausea after taking MTX (87.3%), followed by nausea when thinking of MTX (83.1%) (associative symptoms), and behavioural symptoms (restlessness 74.6%, crying 61.9%, irritability 81.6% and refusal of MTX 76.0%) (Fig. 2A). The lest frequent symptoms were anticipatory stomachache and anticipatory vomiting (respectively, 25.3% and 18.3%). Of note, the frequency of the different complaints among the tolerant patients had a similar distribution as in the intolerant patients, although with a lower prevalence and a significantly lesser intensity (Fig. 2A). Specifically, nausea after taking MTX was the most frequent complaint among tolerant patients (42.6%), followed by nausea when thinking of MTX (22.2%), stom-

achache after taking MTX (18.5%) and behavioural symptoms (restlessness 22.2%, crying 9.3%, irritability 16.7% and refusal of MTX 22.2%) (Fig. 2A). All item scores were significantly higher in intolerant patients than in tolerant patients (Fig. 2B).

We analysed the differences between patients younger (paediatric group, n=101) and older (young adult group, n=24) than 18 years of age. The frequency of intolerant patients was similar in the two groups: 56.4% of intolerant patients in the paediatric group and 58.3% in the young adult group (c^2 =0.028, p=1) (Fig. 2C). The average MISS (±SD) score was 9.0 (±7.8) in the paediatric group and 9.4 (±7.4) in the young adult group (p=0.81). Interestingly, the frequency of a positive complaint (score >0) for each item was similar between paediatric and adult patients except for the anticipatory complaint of nausea before MTX administration (paediatric group 21.8%, adult group 62.5%), which was significantly more frequent in adults (c^2 =15.42, p<0.001) (Fig. 2C). The behavioural complaint crying was more frequent in paediatric patients than adults, although the difference was not statistically significant (p=0.061).

Discussion

The aim of our study was to develop the Italian version of the MISS, in order to have a standardised and validated tool to assess intolerance to MTX in children and young adults with arthritis. We followed the published guidelines to perform the translation and cultural adaptation of the MISS questionnaire (20, 21). The original version of the MISS was developed for children and items were formulated referring to care-givers. We decided to also adapt the MISS for adults as it had already been done in Portuguese and Arabic (14, 15). To this end, we developed a version of the MISS in Italian where items were addressed directly to the patients and not to their care-givers. The process of translation was straightforward, no major issues were reported and incongruencies were promptly resolved. No significant cross-cultural adaptation was required as the items posed simple and unambiguous questions in Italian. A major difference from the original version was to substitute the acronym MTX with the molecule name "methotrexate", as a significant fraction of patients were not familiar with the acronym.

The Italian version of the MISS showed a very good internal consistency, with a Cronbach α of 0.87, confirmed by a composite reliability of 0.89 calculated from the factorial analysis. The single item analysis showed good homogeneity, justifying the retention of the 12 items in the questionnaire. Using a threshold of 6 as suggested by the authors who developed the MISS (13), we calculated a sensitivity of 98.3% and specificity of 81.2%, a PPV of 83.4% and a NPV of 98.1%. These results are better than those reported in the original validation of the MISS (sensitivity 88%, specificity 80%, PPV 65% and NPV 94%) (13).

In our cohort of patients with JIA, 56.8% of patients were intolerant to MTX, a frequency that is similar to that reported by Bulatović *et al*. (50.5%). The most frequent complaints among intolerant patients were nausea after taking MTX (87.3%) and nausea when thinking of MTX (83.1%) followed by the behavioural symptoms (restlessness 74.6%, crying 61.9%, irritability 81.6% and refusal of MTX 76.0%). The frequency of symptoms is similar to that reported by Bulatović and colleagues, who also observed a high frequency of nausea and behavioural symptoms. These figures, in line with the work of Bulatović, are higher than what had been reported in previous studies on gastrointestinal adverse effect to MTX in patients with JIA (23, 24). As highlighted by Bulatović, the MISS incorporate the associative, anticipatory and behavioural symptoms induced by MTX administration that contribute to the intolerance to MTX. Thus, the establishment of MTX intolerance is complex and goes beyond the proposed biological toxic effect of MTX (for example, direct mucosal injury or stimulation of the chemoreceptor trigger zone), it also involves psychological and conditioning mechanisms. Interestingly, Albaqami and colleagues reported that in an adult cohort of patients with RA from Saudi Arabia, the most frequent symptoms were behavioural complaints, specifically restlessness and refusal to take MTX (15). The authors explain this observation with the fact that MTX, regardless of its use as a DMARD or for leukaemia treatment, is labelled as a chemotherapeutic agent, causing a negative psychological impact. In our cohort of patients with JIA, both adult (more than 18 years of age at the time of MISS administration) and paediatric patients (less than 18 years of age at the time of MISS administration) were included. We observed a similar proportion of intolerant patients in the two groups: 56.4% of intolerant patients in the paediatric group and 58.3% in the young adult group. Interestingly, the main differences between the two groups were that young adult patients reported significantly more often nausea before MTX administration (anticipatory symptom), whereas crying was more frequent in children. All in all, we can conclude that social-demographic factors concur in the establishment of MTX intolerance.

Our study has several limitations. First, we did not assess agreement between care-givers and children. We administered the Italian paediatric version of the MISS to care-givers of patients under the age of 18 years, and the Italian adult version of the MISS to patients older than 18 years. In the age range of 8 to 18 years, it would be possible to administer the questionnaire separately to patients and care-givers and assess agreement and differences between the two. We are planning to investigate this in future studies. We did not assess stability over time because of the difficulty of re-testing at the appropriate time (25). This matter was only addressed in the French translation of the MISS, that showed very high test-re-test agreement (19). Finally, we could not assess differences between patients on oral and parenteral MTX in our cohort: only two patients were on oral MTX.

Conclusions

In conclusion, we translated and adapted the MISS questionnaire in Italian and showed it has good reliability and

validity. We also adapted it for adults, making it available for studies in adult cohorts. We observed that, in our cohort of patients with JIA, the frequency of MTX intolerance was high, with a considerable proportion of patients reporting anticipatory, associative and behavioural symptoms. The MISS can be used in clinical practice and also in clinical research to identify patients intolerant to MTX, both in the adult and paediatric setting. The availability of MISS in Italian will allow to investigate the mechanisms underlying the development of MTX intolerance in children and adults with arthritis.

Acknowledgement

This work was supported by the Italian Ministry of Health with "Current Research funds".

References

1. RAVELLI A, MARTINI A: Juvenile idiopathic arthritis. *Lancet* 2007; 369: 767-78. https://doi.org/10.1016/s0140-6736(07)60363-8
2. PETTY RE, SOUTHWOOD TR, MANNERS P *et al*.: International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. *J Rheumatol* 2004; 31: 390-392.
3. MURRAY KJ, LOVELL DJ: Advanced therapy for juvenile arthritis. *Best Pract Res Clin Rheumatol* 2002; 16: 361-78.
4. BEUKELMAN T, RINGOLD S, DAVIS TE *et al*.: Disease-modifying antirheumatic drug use in the treatment of juvenile idiopathic arthritis: a cross-sectional analysis of the CARRA Registry. *J Rheumatol* 2012; 39: 1867-74. https://doi.org/10.3899/jrheum.120110
5. ORTIZ-ALVAREZ O, MORISHITA K, AVERY G *et al*.: Guidelines for blood test monitoring of methotrexate toxicity in juvenile idiopathic arthritis. *J Rheumatol* 2004; 31: 2501-6.
6. NIEHUES T, HORNEFF G, MICHELS H *et al*.: Evidence-based use of methotrexate in children with rheumatic diseases: a consensus statement of the Working Groups Pediatric Rheumatology Germany (AGKJR) and Pediatric Rheumatology Austria. *Rheumatol Int* 2005; 25: 169-78. https://doi.org/10.1007/s00296-004-0537-y
7. BRUNNER HI, JOHNSON AL, BARRON AC *et al*.: Gastrointestinal symptoms and their association with health-related quality of life of children with juvenile rheumatoid arthritis: validation of a gastrointestinal symptom questionnaire. *J Clin Rheumatol* 2005; 11: 194-204. https://doi.org/10.1097/01.rhu.0000173616.81928.44
8. VAN DER MEER A, WULFFRAAT NM, PRAKKEN BJ *et al*.: Psychological side effects of MTX treatment in juvenile idiopathic arthritis: a pilot study. *Clin Exp Rheumatol* 2007; 25: 480-85.
9. MULLIGAN K, KASSOUMERI L, ETHERIDGE A *et al*.: Mothers' reports of the difficulties that their children experience in taking methotrexate for Juvenile Idiopathic Arthritis and how these impact on quality of life. *Pediatr Rheumatol Online J* 2013; 11(1): 23. https://doi.org/10.1186/1546-0096-11-23
10. MULLIGAN K, WEDDERBURN LR, NEWMAN S: The experience of taking methotrexate for juvenile idiopathic arthritis: results of a cross-sectional survey with children and young people. *Pediatr Rheumatol Online J* 2015; 13: 58. https://doi.org/10.1186/s12969-015-0052-6
11. RAVELLI A, MIGLIAVACCA D, VIOLA S *et al*.: Efficacy of folinic acid in reducing methotrexate toxicity in juvenile idiopathic arthritis. *Clin Exp Rheumatol* 1999; 17: 625-27.
12. SHEA B, SWINDEN MV, GHOGOMU ET *et al*.: Folic acid and folinic acid for reducing side effects in patients receiving methotrexate for rheumatoid arthritis. *J Rheumatol* 2014; 41: 1049-60. https://doi.org/10.3899/jrheum.130738
13. BULATOVIĆ M, HEIJSTEK MW, VERKAAIK M *et al*.: High prevalence of methotrexate intolerance in juvenile idiopathic arthritis: development and validation of a methotrexate intolerance severity score. *Arthritis Rheum* 2011; 63: 2007-13. https://doi.org/10.1002/art.30367
14. AMARAL JM, BRITO MJM, KAKEHASI AM: Cultural adaptation and validation of the Methotrexate Intolerance Severity Score in Brazilian Portuguese for adults with rheumatoid arthritis. *J Clin Rheumatol* 2021; 27: S168-72. https://doi.org/10.1097/rhu.0000000000001221
15. ALBAQAMI J, ALSHALHOUB R, ALMALAG H *et al*.: Prevalence of methotrexate intolerance among patients with rheumatoid arthritis using the Arabic version of the methotrexate intolerance severity score. *Int J Rheum Dis* 2019; 22: 1572-77. https://doi.org/10.1111/1756-185x.13637
16. AMARAL JM, BRITO MJM, KAKEHASI AM: High frequency of methotrexate intolerance in longstanding rheumatoid arthritis: using the methotrexate intolerance severity score (MISS). *Adv Rheumatol* 2020; 60(1): 43. https://doi.org/10.1186/s42358-020-00145-5
17. VAN DIJKHUIZEN EH, WULFFRAAT NM: Early predictors of prognosis in juvenile idiopathic arthritis: a systematic literature review. *Ann Rheum Dis* 2015; 74: 1996-2005. https://doi.org/10.1136/annrheumdis-2014-205265
18. VAN DIJKHUIZEN EH, BULATOVIĆ ĆALASAN M, PLUIJM SM *et al*.: Prediction of methotrexate intolerance in juvenile idiopathic arthritis: a prospective, observational cohort study. *Pediatr Rheumatol Online J* 2015; 13: 5. https://doi.org/10.1186/s12969-015-0002-3
19. CHAUSSET A, FARGEIX T, PEREIRA B *et al*.: MISS questionnaire in French version: a good tool for children and parents to assess methotrexate intolerance. *Clin Rheumatol* 2017; 36: 1281-88. https://doi.org/10.1007/s10067-017-3638-1
20. BEATON DE, BOMBARDIER C, GUILLEMIN F *et al*.: Guidelines for the process of cross-cultural adaptation of self-report measures. *Spine* 2000; 25(24): 3186-3191. https://doi.org/10.1097/00007632-200012150-00014
21. WILD D, GROVE A, MARTIN M *et al*.: Principles of good practice for the Translation and Cultural Adaptation Process for Patient-Reported Outcomes (PRO) Measures: report of the ISPOR Task Force for Translation and Cultural Adaptation. *Value Health* 2005; 8: 94-104. https://doi.org/10.1111/j.1524-4733.2005.04054.x
22. ROSSEEL Y: lavaan: An R Package for Structural Equation Modeling. *Journal of Statistical Software* 2012; 48: 1-36. https://doi.org/10.18637/jss.v048.i02
23. RUPERTO N, MURRAY KJ, GERLONI V *et al*.: A randomized trial of parenteral methotrexate comparing an intermediate dose with a higher dose in children with juvenile idiopathic arthritis who failed to respond to standard doses of methotrexate. *Arthritis Rheum* 2004; 50: 2191-2201. https://doi.org/10.1002/art.20288
24. ALSUFYANI K, ORTIZ-ALVAREZ O, CABRAL DA *et al*.: The role of subcutaneous administration of methotrexate in children with juvenile idiopathic arthritis who have failed oral methotrexate. *J Rheumatol* 2004; 31: 179-82.
25. SOUZA AC, ALEXANDRE NMC, GUIRARDELLO EB: Psychometric properties in instruments evaluation of reliability and validity. *Epidemiol Serv Saude* 2017; 26: 649-59. https://doi.org/10.5123/s1679-49742017000300022