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RESEARCH

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Validation of Methotrexate Intolerance Severity Score (MISS) questionnaire to measure methotrexate intolerance among rheumatoid arthritis Egyptian patients

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Abstract

Background Rheumatoid arthritis (RA) is a systemic autoimmune chronic inflammatory disease, causing progressive disability. Methotrexate (MTX) is the gold standard drug treatment for RA. Long-term use of MTX is associated with intolerance including gastrointestinal effects. In addition, anticipatory, associative, and behavioral symptoms such as anxiety and irritability are also observed which are often inadequately managed, leading to discontinuation of treatment. Methotrexate Intolerance Severity Score (MISS) questionnaire designed to measure MTX intolerance. The work aims to validate the MISS questionnaire Arabic version for the detection of MTX intolerance among Egyptian RA patients to halt the progression of the disease.

Results A total of 80 patients were involved in this study. Of those, 67 (83.8%) were females with a mean disease duration of 6.9 ± 6.1 years. Forty-eight patients (60%) were intolerant to MTX and 32 patients (40%) were tolerant. Comparison between the tolerant group ($n = 32$) to MTX and the intolerant group ($n = 48$) revealed a statistically significant difference between them regarding the DAS28 score and HAQ score. Behavioral intolerance is the predominant factor that directs MTX intolerance.

Conclusion The MISS questionnaire has a good predictive ability to detect MTX intolerance among Egyptian RA patients. Due to its good reliability, serves as an invaluable tool as it detects anticipatory and associative symptoms.

Keywords Rheumatoid arthritis, Methotrexate, Methotrexate Intolerance Severity Score (MISS) questionnaire, Disease activity score 28 (DAS28)

Background

Rheumatoid arthritis (RA) is a chronic autoimmune disease with a detrimental effect on quality of life due to irreversible joint damage [1]. Methotrexate (MTX) is the gold standard prescribed conventional synthetic (CS) Disease-modifying anti-rheumatic drugs (DMARDs) based on their efficacy, safety, and route of administration. It is endorsed as an initial treatment, as an "anchor drug" in combination with csDMARD, biological DMARD, or targeted synthetic DMARD [2].

MTX inhibits dihydrofolate reductase which is the enzyme required for purine and pyrimidine synthesis [3] causing uncoupling of nitric oxide synthase which increases apoptosis of T cells [4, 5]. It employs anti-inflammatory effects by inhibiting transmethylation

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reactions required for cellular functions with diminished synovial damage and enhances adenosine release causing inhibition of neutrophil recruitment [6].

The half-life of MTX is short about 6 h [6]. Its adverse effects that could limit its use [7] include nausea, vomiting, stomachache, dizziness, and headache termed "MTX intolerance" as occurred in juvenile idiopathic arthritis, psoriatic arthritis, and inflammatory bowel disease [8]. Thus, evaluating MTX intolerance to improve patient tolerability is critical [9].

Symptoms may be anticipatory prior to intake, associative when thinking about consuming the drug, or behavioral as anxiety and irritability arising as a conditioned response may develop [10].

MTX Intolerance Severity Score (MISS) questionnaire considers the patient intolerant if the score is ≥ 6 [9]. The Arabic version was validated in Saudi Arabian RA patients [11].

Our objective was to validate the MISS questionnaire Arabic version for the detection of MTX intolerance among Egyptian RA patients to halt the progression of the disease.

Material and methods

A cross-sectional study was conducted on 80 adult RA patients who were diagnosed according to the 2010 American College of Rheumatology/European League Against Rheumatism classification criteria (ACR/EULAR) criteria [12] and were on regular use of MTX therapy for at least 3 months.

The study was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki), the study was approved by the Ethics Committee of the hospital and informed written consent was obtained from participants in the study.

Exclusion criteria

Patients suffered from gastrointestinal diseases (such as malignancy or celiac disease), and psychiatric illnesses and were unable to fully understand or unwilling to complete the MISS questionnaire.

Clinical evaluation

Full medical history taking with special concern about MTX dose, duration, route of administration, folic acid dose, other DMARDs, steroids dose, and antiemetic drug.

Thorough clinical examination using disease activity score 28(DAS28) [13]. Laboratory investigations: complete blood count with differential count (CBC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor (RF), anti-citrullinated protein antibodies (ACPA), liver function test (AST and ALT), and renal function tests (serum urea, creatinine).

Health Assessment Questionnaire (HAQ) for daily activities of living

Which comprises 20 questions grouped into 8 subscales and the question's highest score determines the score for the subscale [14].

Methotrexate Intolerance Severity Score (MISS) questionnaire (Arabic version)

It is a 12-item questionnaire constructed to assess MTX intolerance covering 4 aspects of intolerance: stomachache, nausea, vomiting, and behavioral complaints. Its score ranges from 0 to 36 and the patient is considered intolerant if the score is ≥ 6 points with at least 1 point in the anticipatory, associative, and/or behavioral symptoms [11].

Statistical analysis

Data were tabulated and statistically analyzed using SPSS, version 20 (SPSS Inc., Chicago, IL, USA). Quantitative data were described as mean and standard deviation/median and interquartile range. Independent *t* test was used to compare quantitative data between independent groups. Qualitative data were expressed as frequencies (*n*) and percentages (%). Fisher's exact test was used to the relation between qualitative variables. Pearson correlation coefficient (*r*) was used to correlate between parametric quantitative variables. Logistic regression analysis was done for the detection of variables independently affecting the occurrence of MTX intolerance. Reliability analysis was done by alpha (Cronbach's) coefficient. *P* value ≤ 0.05 was considered significant.

Results

Eighty patients were included, their age was [Mean ± SD (min–max)] 45 ± 11 (23–72) years, disease duration was 6.9 ± 6.1 (1–35) years, DAS28 was 4.72 ± 1.28 (2.16–7.6) as 3 (3.8%) were in remission, 6 (7.5%) were of low disease activity, 47 (58.8%) were of moderate disease activity and 24 (30.0%) were of high disease activity. HAQ score was 1.358 ± 0.658 (0.125–2.625). Demographic data can be found in Table 1 and laboratory data in Table 2.

MTX treatment duration was 5 ± 5 (1–23) years, the most common MTX route was subcutaneous (SC) 55(68.8%) followed by intramuscular (IM) then oral. Drug history among the studied RA patients (Table 3).

Forty-eight patients (60%) were intolerant to MTX, and 32 patients (40%) were tolerant. Intolerant patients were 41 (72.9%) female patients and 7 (27.08%) male patients. The most frequently occurring complaint was a refusal to take MTX detected in 56 patients (70%)

Table 1 Demographic data of patients

Items		*N* (%)
Sex	Male	13 (16.2%)
	Female	67 (83.8%)
Job	Unemployed	52 (65%)
	Employed	28 (35%)
Marital status	Single	2 (2.5%)
	Married	67 (83.8%)
	Divorced	4 (5.0%)
	Widow	7 (8.8%)
Menstrual history	Regular	30 (44.8%)
	Irregular	12 (17.9%)
	Menopause	25 (37.3%)
Smoking	Non-smoker	71 (88.8%)
	Smoker	9 (11.2%)
Education	Non-educated	6 (7.5%)
	Primary	20 (25%)
	Secondary	41 (51.2%)
	Tertiary	13 (16.2%)
Handedness	Right	79 (98.8%)
	Left	1 (1.2%)

Table 2 Laboratory data of patients

Items	[Mean ± SD (min–max)]
WBCs $10^{\wedge 3}$/µL	6.75 ± 2.43 (3.44 – 16.3)
RBCs $10^{\wedge 6}$/µL	4.5 ± 0.5 (3.4 – 6)
HGB g/dl	11.5 ± 1.7 (6.3 – 14.2)
PLTs $10^{\wedge 3}$/µL	322.6 ± 102 (125 – 753)
ESR mm/hr	35 ± 21.7 (8 – 90)
CRP mg/l	21.5 ± 37.3 (0.6–300)
RF U/mL	49.5 ± 86.3 (3 – 635.2)
ACPA U/ml	149.4 ± 156.2 (0.2 – 630)
SGPT U/L	20.4 ± 16.4 (5 – 141)
SGOT U/L	21.8 ± 15.3 (10 – 136)
Serum urea mg/dl	20.51 ± 7.77 (10 – 59)
Serum creatinine mg/dl	0.79 ± 0.38 (0.3 – 3.4)

WBCs white blood cell count, *RBC* red blood cell count, *HGB* hemoglobin concentration, *PLT* platelets, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *RF* rheumatoid factor, *ACPA* anti-citrullinated protein antibodies (ACPA), *SGPT* serum glutamic pyruvic transaminase, *SGOT* serum glutamic-oxaloacetic transaminase

and 45 patients complained of restlessness (56.3%) followed by nausea after taking MTX occurred in 39 patients (49.5%). Vomiting complaint was the least frequent symptom that occurred in 16 patients (20%) who had vomiting after taking MTX and 7 patients (8.8%) of them had anticipatory symptoms. Distribution of MISS items and scores among the studied RA patients (Table 4).

Table 3 Drug history among the studied RA patients

	Number (%)	
MTX route	SC	55(68.8%)
	IM	22(27.5%)
	Oral	3(3.8%)
MTX dose (mg)	7.5 mg	2(2.5%)
	12.5 mg	26(32.5%)
	15 mg	3(3.8%)
	17.5 mg	5(6.2%)
	18.75 mg	11(13.8%)
	20 mg	7(8.8%)
	25 mg	26(32.5%)
Corticosteroid dose (mg)	Prednisolone 5 mg	39(58.2%)
	Prednisolone 10 mg	19(28.4%)
	Prednisolone 15 mg	2(3.0%)
	Prednisolone 20 mg	4(6.0%)
	Betamethasone 5 mg	3(4.5%)
Hydroxychloroquine		49(61.2%)
Leflunomide		47(58.8%)
Sulfasalazine		4(5.0%)
Etanercept		4(5.0%)
Adalimumab		1(1.2%)
Folic acid		71(88.8%)
Gastroprotective		59(73.8%)
Analgesics		48(60.0%)
Antiemetic		2(2.5%)

MTX methotrexate, *SC* subcutaneous, *IM* intramuscular

Table 4 Distribution of MISS items and scores among the studied RA patients

		N (%)
Stomachache	After MTX	35 (43.80%)
	Anticipatory	13 (16.30%)
	Associative	18 (22.80%)
Nausea	After MTX	39 (49.50%)
	Anticipatory	13 (16.20%)
	Associative	15 (18.70%)
Vomiting	After MTX	16 (20%)
	Anticipatory	7 (8.80%)
Behavioral	Restlessness	45 (56.30%)
	Crying	37 (46.20%)
	Irritability	41 (51.30%)
	Refusal to take	56 (70%)

Score of ≥ 6 was considered intolerant. *MTX* methotrexate

A statistically significant positive correlation of the MISS questionnaire with the HAQ score was detected ($r = 0.298$, p value = 0.007), but no correlation was found with the DAS28 score ($r = 0.171$, p value = 0.130).

Comparison between the tolerant group ($n=32$) to MTX and the intolerant group ($n=48$) detected a statistically significant difference ($p<0.05$) between them regarding the DAS28 score and HAQ score. There was no statistical difference between the two groups regarding marital status, menstrual history, education, or job ($p>0.05$). Comparison between MTX tolerant and intolerant groups (Table 5).

Logistic regression detected that RF significantly ($p<0.05$) increases the risk of MTX intolerance by 0.024 times (Table 6). The reliability of the MISS questionnaire was 0.809 suggesting good internal consistency.

Discussion

Management of RA focuses on improving the quality of life as it is an irreversible disease [2]. So, early detection of MTX intolerance is essential and easy as the MISS is a simple and objective questionnaire [15].

If intolerance is due to gastrointestinal symptoms folic acid intake, dose splitting, and shift from oral to parenteral route is considered [16] and if it is due to behavioral symptoms, patient counseling is important [11].

In Egyptian RA patients, 60% of the participants were MTX-intolerant which was higher than the Albaqami et al. [11] study conducted on 185 Saudi Arabian RA and found that 39.5% of them were intolerant. Also, a study on 150 Brazilian RA patients found a prevalence of MTX intolerance of 21.6% [17].

Our findings could be due to a behavioral intolerance, as the MTX is categorized as a chemotherapeutic drug with a negative psychological impression which was supported by the findings in Albaqami et al. [11] as they identified a higher percentage of behavioral intolerance compared to gastrointestinal intolerance.

Also, the higher percentage of intolerance in our study may be due to anticipatory and associative gastrointestinal symptoms which were considered as a conditioned response [18] and could be explained by increased sensitivity of gastrointestinal epithelium due to the buildup of MTX causing nausea and vomiting [10, 19] and its stimulation to adenosine receptors in the central nervous system [20, 21] and chemoreceptor trigger zone (CTZ) leading to reflex vomiting [22, 23]. Contrary to Amaral et al. [17], all the patients reported nausea followed by abdominal pain, and then vomiting. Therefore, Cognitive behavioral therapy may benefit in the treatment [8].

Our study included more intolerant female patients than male patients. Similarly, Almalag et al. 2020 assumed that MTX intolerance was linked to the female gender [24] which could be explained by a lower average glomerular filtration rate in females than males. But

Table 5 Comparison between MTX tolerant and intolerant groups

		Tolerance *N*=32	Intolerance *N*=48	*P*
Age(Mean ± SD)**		45 ± 13	45 ± 10	0.228
Sex (female: male)		26: 6	41:7	0.043
MTX route !	Oral	2	1	0.144
	SC	21	34	
	IM	9	13	
MTX dose (mg) !	7.5	1	1	0.655
	12.5	11	15	
	15	1	2	
	17.5	2	3	
	18.75	7	4	
	20	2	5	
	25	8	18	
**MTX duration (year) **		4.318 ± 3.526	5.064 ± 5.305	0.483
Corticosteroid		25 (75.8%)	42 (89.4%)	0.104
Folic acid!		30 (90.9%)	41 (87.2%)	0.729
Analgesics		18 (54.5%)	30 (63.8%)	0.404
Gastroprotective		21 (63.6%)	38 (80.9%)	0.085
Caffeine		27 (45%)	33 (55%)	0.696
DAS28 (Mean ± SD)		4.569 ± 1.305	4.823 ± 1.258	0.036*
HAQ score (Mean ± SD)		1.123 ± 0.594	1.520 ± 0.658	0.007*

(**) Independent *t* test, and (!) Fisher exact test was used, *P* value < 0.05 is considered statistically significant (*). *MTX* methotrexate, *DAS28* disease activity score, *HAQ* Health assessment questionnaire

Table 6 Logistic regression for detection of independent variables associated with MTX intolerance

Items		*B*	*P*
Age		−.113	.155
Female		2.470	.349
Disease duration (years)		−.360	.088
ESR		−.078	.150
CRP		−.018	.335
Rheumatoid factor		.024	.036*
Anti-CCP		−.003	.583
MTX route	SC	34.973	.998
	IM	37.329	.998
MTX dose (mg)		−.395	.506
MTX duration **(year)**		.590	.106
Corticosteroid use		3.249	.204
Folic acid intake		−.198	.939
Analgesics use		2.249	.216
Gastroprotective use		2.326	.334
Caffeine intake		−1.593	.354
DAS28		.805	.357
HAQ		.498	.686
Constant		−19.678	.997

P value < 0.05 is considered statistically significant (*)

as the lower percentage of male gender was included in our study, therefore, results should be interpreted with caution. Also, Bulatović Ćalasan et al. [9] study included 291 RA and psoriatic arthritis (PsA) patients who reported more intolerance in females, but it was statistically insignificant.

Regarding caffeine, no association was detected between MTX intolerance and caffeine in our study. While El Nouby et al. [25] and Malaviya [26] reported that caffeine reduced the severe MTX intolerance symptoms which could be explained by that caffeine antagonizes the MTX activation of adenosine receptors in the central nervous system.

We noticed a significant difference in the DAS28 score between the intolerant group and the tolerant group as it was correlated with disease severity. Regarding HAQ, there was a significant positive correlation with MISS score which could be explained by increased level of non-adherence to MTX and missed doses by the patients due to its effect on behavior and gastrointestinal tract. Also, Sherbini et al. [27] noticed an increased risk of MTX cessation after 1-year follow-up due to adverse effects correlated with a high baseline HAQ [28].

In our study, the most common MTX route was SC followed by IM then oral and we noticed that patients on the SC route were more intolerant. Our findings were similar to Bulatovic et al. [8] and Bulatović Ćalasan et al. [29] who detected that more intolerance on parenteral than on oral MTX which could be due to hatred towards needles causing more behavioral symptoms in the parenteral group [30]. Albaqami et al. [11] and Almalag et al. [24] stated that oral intolerance was higher than the SC administration group.

Regarding MTX dose, patients treated with 20 or 25 mg MTX were more intolerant may be due to triggering the CTZ. Similarly, Fatimah et al. [15] noticed that the higher the dose, the more the intolerance.

In our study, there was a higher percentage of MTX intolerance associated with corticosteroid use. Similarly, Amaral et al. [17] stated that corticosteroids may have physiological gastroprotective and pathological proulcerogenic effects. The prolonged action of corticosteroids can be a significant factor in the gastric mucosa [31]. Also, Nalwa et al. [18] stated that the use of corticosteroid therapy is a predisposing factor for increased risk of MTX intolerance.

Regarding other drugs combined with MTX doses, there was no significant relation with MTX intolerance which corresponds with Almalag et al. [24] and Fatimah et al. [15]. Also, our study was in accordance with Amaral et al. [17] as MTX intolerance was not linked with folic acid deficiency.

Our finding was in accordance with Majorczyk et al. [32] suggested a predictive value of RF for the MTX treatment outcome. In our study, the internal consistency of the MISS questionnaire was similar to Albaqami et al. [11] suggesting its reliability.

Limitations of the study included a small number of patients and most of them were females so other studies are needed with a larger number of male and female patients and explore different parameters such as types of food and different ethnicities.

Conclusion

The MISS questionnaire has a good predictive ability to detect MTX intolerance among Egyptian RA patients. Due to its good reliability, serves as an invaluable tool as it detects anticipatory and associative symptoms.

Abbreviations

ACPA	Anti-citrullinated protein antibodies
CBC	Complete blood count
CRP	C-reactive protein
CS	Conventional synthetic
CTZ	Chemoreceptor trigger zone
DAS28	Disease Activity Score 28
DMARDs	Disease-modifying anti-rheumatic drugs
ESR	Erythrocyte sedimentation rate
HAQ	Health Assessment Questionnaire
MISS	MTX Intolerance Severity Score
MTX	Methotrexate
RA	Rheumatoid arthritis
RF	Rheumatoid factor

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Authors' contributions

HATK was responsible for the following tasks: provided an idea, data collection, writing the first draught, contributing to the work's design, clinical work, and data interpretation. NMS completed the following tasks: placed the study design, followed the patients, and revised the draught paper. MGE did the following: formal evaluation, data collection, editing and reviewing the draught, clinical work, data interpretation, and revising. MAN did the following: data collection, writing the first draught, editing, and reviewing it; contributing to the work's design; and participating in conceptualization, formal analysis, data interpretation, and revision. All authors read and approved the final manuscript.

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Availability of data and materials

All data are available on request.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Ain Shams University (FMASU MS 333/2022), and informed written consent was obtained from participants in the study.

Consent for publication

Not applicable.

Competing interests
The authors declare that they have no competing interests.

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