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PREVALENCE OF METHOTREXATE INTOLERANCE AMONG RHEUMATOID ARTHRITIS PATIENTS USING METHOTREXATE INTOLERANCE SEVERITY SCORE QUESTIONNAIRE

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ABSTRACT

Introduction: Methotrexate is the cornerstone in the treatment of Rheumatoid Arthritis. Methotrexate intolerance is frequent, the underlying cause and risk factors are not fully understood. Therefore, this study aimed to determine the prevalence of methotrexate intolerance and its associated risk factors, using the Arabic version of the Methotrexate Intolerance Severity Score Questionnaire. **Methods**: This cross-sectional study was performed between October 2021 and October 2022, included 105 patients with Rheumatoid Arthritis who were treated with methotrexate, and visited the clinic and division of musculoskeletal diseases at Tishreen University Hospital. Age, sex, smoking, dose, MTX use duration, route of administration and Disease Activity Score for 28joint data were collected. Patients also answered the MISS questionnaire after being explained. **Results**: Among 105 patients, the prevalence of methotrexate intolerance was 20%, behavioral symptoms were the most common (95%), followed by nausea (90.5%), abdominal pain (42.6%), and finally vomiting (28.6%). The proportion of those who used corticosteroids was greater in MTX intolerance group than in MTX tolerance one ($p = 0.001$). The risk of MTX intolerance increased with increasing the dose of corticosteroids (odds ratio = 3.4, 95% CI, 1.6–9.8, $p = 0.0001$). There was also a statistically significant association between higher DAS28 values and the increased risk of MTX intolerance (odds ratio = 2.8, 95% CI, 1.1–7.5, $p = 0.008$). **Conclusion**: Corticosteroids use increases the risk of developing MTX intolerance. Severe disease is also associated with MTX intolerance. We advised reducing the dose of corticosteroids as much as possible and controlling disease activity.

KEYWORDS: Rheumatoid arthritis, Methotrexate, Intolerance, Corticosteroids, Questionnaire, DAS-28.

1. INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease whose hallmark feature is a persistent symmetric polyarthritis (synovitis) that affects the hands and feet.[1]

Methotrexate, an analog and antagonist of folic acid[2], is currently the first-line disease-modifying anti-rheumatic drugs (DMARDs) in the treatment of rheumatoid arthritis (RA), juvenile idiopathic arthritis, and psoriasis, and is useful in inflammatory bowel diseases, vasculitis, systemic lupus erythematosus and other connective tissue diseases.[3]

MTX is associated with adverse effects that could limit its use. These complaints can take several forms, such as gastrointestinal symptoms, including abdominal pain, nausea and vomiting. Behavioral side effects may include anxiety and irritability. Moreover, it is not necessary that these symptoms occur after taking MTX .Patients may experience them when thinking about their MTX dose. Failure to recognize these symptoms can affect patients' quality of life and adherence to MTX therapy.[4]

There are two main mechanisms, which play a role in MTX related GI intolerance. The epithelial cells in the oral cavity and in the intestine are sensitive to MTX irrespective of folate deficiency. The gastrointestinal

epithelium becomes more sensitive with the passage of time due to accumulation of MTX.[5]

The second mechanism of MTX intolerance is through stimulation of chemotactic trigger zone (CTZ).[6]

An alternative explication could be a nocebo reaction, which represents a 'negative' drug reaction without an underlying pathophysiologic process, positing that patients susceptible to nocebo reactions are also likely to develop MTX intolerance. Enzymes of the dopamine metabolism can be associated with placebo and nocebo effects.[7]

The MISS questionnaire has been used to determine the prevalence of MTX intolerance in patients with RA and psoriatic arthritis in several countries.[8]

This questionnaire was validated to be used in juvenile idiopathic arthritis patients, and later in patients of other rheumatic diseases, including RA.[9]

More recently, the MISS questionnaire has also been validated in Arabic language for use in adults with RA.[4]

In countries like Syria, most of the RA patients have access to methotrexate (MTX) drug therapy only. Thus, this study aimed to identify the frequency of MTX intolerance using the Arabic version of the MISS questionnaire in patients with RA, as well as risk factors that may be associated with MTX intolerance.

2. METHODS

2.1 Study design

This cross-sectional study was performed in Tishreen University Hospital in Syria from October 2021 to October 2022.

2.2 Patient eligibility and assessment

One hundred and 5 patients diagnosed with RA according to the ACR/European League Against Rheumatism 2010 criteria[10], and in regular use of oral or subcutaneous MTX for at least 3 months, were invited to answer the MISS questionnaire. Patients who had psychiatric illnesses were excluded.

The MISS questionnaire comprises twelve items divided into four dimensions: abdominal pain (three questions), nausea (three questions), vomiting (two questions), and behavioral complaints (four questions). The symptoms appearing after MTX intake, before MTX intake (anticipatory symptoms) and/or when thinking of taking MTX (associative symptoms). The possible answers for each item are no complaints (0), mild complaints (1), moderate complaints (2), and severe complaints (3). Points are summed to give a score. The definition of MTX intolerance is given by a score of 6 or more points, with at least 1 point in the anticipatory, associative, or behavioral symptoms.[11]

Data was collected from all patients and included age, sex, disease duration, time of MTX use, route of administration, dose, concomitant medications, other comorbidities, smoking, and disease activity as assessed by Disease Activity Score in 28 joints (DAS28).[12]

2.3 Statistical analysis

The primary outcome of interest was MTX intolerance. Univariate analyses were performed to recognize the association of demographic and clinical variables with MTX intolerance; categorical variables were assessed using Pearson's Chi-Square test or Fisher's exact test, depending on the number of cases and categories. Quantitative variables were assessed using t-test. Variables in the univariate analyses with a p-value < 0.05 were inserted in a multivariate logistic regression model to define independent risk factors for MTX intolerance. Odds ratios (OR) from the multivariate analysis with values above 1.00 indicate an increased risk of MTX intolerance. Statistical significance was considered for p-values < 0.05.

Table 1

Baseline Characteristic	Tolerant	Intolerant	P-value
Age, mean (SD)	51.94±11.9	48.76±9.5	0.2
Gender, n (%) Female	 68(81%)	 18(85.7%)	 0.6
Smoker, n (%)	38(45.2%)	14(66.7%)	0.07
Comorbidities DM (%) HTN (%)	 8(9.5%) 19(22.6%)	 2(9.5%) 6(28.6%)	 1 0.5
Methotrexate dose (milligram/ week), mean (SD)	11.72±3.8	13.09±3.7	0.1
Route of administration, n (%) Oral Subcutaneous	 65(77.4%) 19(22.6%)	 15(71.4%) 6(28.6%)	 0.5 0.5
Mean MTX usage duration, months (SD)	50.3±45.51	56.42±49.8	0.3

Mean DAS28 (SD)	3.78±0.7	5.39±1.2	0.0001
Mean Corticosteroids dose (SD)	5.5±5.37	16.6±11.38	0.008
Folic acid Yes (%)	50(59.5%)	9(42.9%)	0.1

Table 2

Symptoms	**MTX- intolerant**	**MTX- tolerant**
Behaviour symptoms	20(95%)	0(0%)
Nausea		
After taking MTX	19(90.5%)	3(3.6%)
Anticipatory	13(61.9%)	2(2.4%)
Associative	17(80.9%)	1(1.2%)
Abdominal pain		
After taking MTX	9(42.6%)	3(3.6%)
Anticipatory	1(4.8%)	2(2.4%)
Associative	2(9.5%)	1(1.2%)
Vomiting		
After taking MTX	6(28.6%)	7(8.3%)
Anticipatory	1(4.8%)	1(1.2%)

Table 3

Variables	**OR (confidence interval 95%)**	**P-value**
Corticosteroids	3.4[1.6-9.8]	0.0001
DAS28-CRP	2.8[1.1-7.5]	0.008

3. RESULTS

3.1 Demographic and clinical characteristics

Among the 105 patients who participated in the study, 86 (81.9%) were female, the mean age was (51.3 ± 11.5) years, and the average dose of MTX was (12 ± 3.8) mg/week. These and other patient characteristics are shown in Table 1.

3.2 Frequency and characteristics of MTX intolerance

Considering all 105 patients, MTX intolerance was present in 21 of 105 patients (20%). The most frequent complain after MTX intake among patients with MTX intolerance was behavior symptoms, in 20 (95%) patients, followed by nausea, in 19 (90.5%) patients, and abdominal pain, in 9 (42.6%) patients. The least frequent symptom was vomiting in 6 (28.6%) patients. All 21 patients with MTX intolerance had symptoms in the nausea and abdominal pain domain either after taking MTX or as anticipatory or associative symptoms (Table 2).

3.3 Predictors of MTX intolerance

In univariate analyses, corticosteroids (p = 0.008), and DAS28 –CRP (p = 0.0001), were deemed associated with the presence of MTX intolerance, due to a p-value < 0.05, and thus carried forward to the multivariate analysis. This study did not detect association of MTX intolerance with other variables, such as subcutaneous or oral formulation, sex and comorbidities. Of these variables, only DAS28-CRP and use of corticosteroids were retained in the final logistic regression model, presented in Table 3. In this multivariate analysis, use of corticosteroid was significantly associated with MTX intolerance (OR = 3.4; 95% confidence interval [CI], 1.6 to 9.8; p = 0.0001). With regard to DAS28-CRP, moderate and severe disease was significantly associated with MTX intolerance (OR = 2.8; 95% confidence interval [CI], 1.1 to 7.5; p = 0.008).

4. DISCUSSION

In our study, we have found a frequency of 20% of MTX intolerance among RA patients. The most frequent symptoms reported after the use of MTX were nausea (90.5%), abdominal pain (42.6%), and vomiting (28.6%). Patients who used a prednisolone dose of 16.6±11.38 mg were nearly three times more likely to develop MTX intolerance than those using a dose of 5.5±5.37 mg. In addition, increasing disease activity score was associated with increasing risk of MTX intolerance by two times.

To our knowledge, this is the first study developed in Syria and the third one in Arab population using a validated questionnaire to assess MTX intolerance in patients with RA. The prevalence of MTX intolerance we found is within the range reported in studies using the MISS questionnaire. For example, a study performed in Utrecht, in the Netherlands, found a prevalence of MTX intolerance of 11% among patients with RA and psoriatic arthritis.[13]

In a study from Pakistan, this frequency was 33.3% among RA patients.[6] A recent study from Saudi Arabia among RA patients who used MTX for at least 3 months found that 39.5% of them had a positive score for MTX intolerance using the same questionnaire.[4] Almalage et

al observed MTX intolerance in (47%) of Arab patients.[9]

In a study conducted in Brazil, this frequency was 21.6% among RA patients.[8] The frequency of the most common symptoms reported by our patients after the use of MTX were similar to this study, in which 92.3% of the patients reported nausea, 46.1% abdominal pain, and 30.7% vomiting.[8]

In addition to experiencing gastrointestinal symptoms after receiving the drug, patients with MTX intolerance presented anticipatory, associative, and behavioral complaints. The occurrence of these symptoms before the ingestion of MTX supports the idea that classical conditioning processes play an important role in the development of MTX intolerance.[11]

Our findings suggest that patients who used higher dose of corticosteroids were more likely to develop MTX intolerance. Glucocorticoids may have duple action on the gastric mucosa: physiological gastroprotective and pathological proulcerogenic one.[14] Several studies have indicated that corticosteroids use increases the risk of gastrointestinal adverse effects.[15,16]

Since previous studies using the MISS questionnaire have found no association between concomitant medications and MTX intolerance, further studies are needed to explain the association between corticosteroid use and MTX intolerance.

We also found that DAS28 was significantly associated with higher occurrence of MTX intolerance.

Our study suggests a trend for increasing risk of MTX intolerance with increasing disease activity score. A study in Saudi Arabia by Almalage et al find the same.

Our study was not without limitations. It was a survey with a relatively small number of participants; thus, it did not address the association between variables in detail.

Future studies are needed to investigate the relationship between RA related factors, disease-modifying antirheumatic drugs (DMARDs) and MTX intolerance using a higher sample size.

The current study demonstrates the prevalence of MTX intolerance among patients with RA in the Syrian population, while exploring its relation to several factors. To the best of our knowledge, this study is the first to evaluate the effect of corticosteroids dose on methotrexate intolerance, and the second to detect association with DAS28 while using methotrexate as monotherapy.

5. CONCLUSION

In conclusion, MTX intolerance is common among RA patients in the Syrian population and is associated with corticosteroids dose, and more active disease, based on disease activity score with 28-joint counts.

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