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Prevalence of methotrexate intolerance among patients with rheumatoid arthritis in Erbil city using methotrexate intolerance severity score

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Abstract

Background and objectives: Rheumatoid arthritis is classified as an autoimmune disease characterized by inflammation of the joints and membranes surrounding the joints.
The aim of this study was to find the frequency of methotrexate intolerance among rheumatoid arthritis patients and to detect factors contributing to intolerance.

Methods: An observational cross-sectional study was conducted in Rizgary and Hawler Teaching Hospital in Erbil/ Iraq. The study period started from the 1st of July 2021 to the 1st of July 2022. A convenient sample of hundred patients was included in the study. A validated version of the methotrexate intolerance severity score questionnaire was used for data collection. Each element in the methotrexate intolerance severity score questionnaire was given a score ranging from 0-3 depending on the absence of symptoms or the presence of mild, moderate or severe symptoms. The intolerance was diagnosed based on a cut-off score of 6 and more.

Results: Females constituted 93% of the sample, 49% were obese, and only 13% were smokers. Among the rheumatoid arthritis patients, 66% tolerated Methotrexate, and only 34% did not tolerate the treatment. The oral dose was tolerated by 71%, and the only significant relation($p=0.050$) was reported for the route of Methotrexate administration. The differences were significant for restlessness ($p<0.001$), crying ($p=0.002$), irritability($p<0.001$), and not taking medication.

Conclusions: The study concluded that Methotrexate intolerance is prevalent among Rheumatoid arthritis patients in Erbil city. The prevalence of intolerance was significant among steroid users.

Key words: Methotrexate,Methotrexate intolerance severity score (MISS),Rheumatoid arthritis.

Introduction:

Rheumatoid arthritis (RA) is chronic, systemic, inflammatory autoimmune disease characterized by inflammation of the joints and membranes that surround the joints, and causes progressive joint

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damage and disability.1 The prevalence of RA is about 1% of total population.2 The ratio of women to men ranged from 2:1 and it is incidence increases with age.3 Patients with early arthritis experience a wide range of outcomes. Meanwhile a small percentage of the affected joints will develop severe destruction.Auto antibodies such as Rheumatoid factor (RF) and Anti-cyclic citrullinated peptide (Anti-CCP) are useful for the diagnosis and prognosis of RA. For the diagnosis of RA, anti-CCP antibody showed comparable sensitivity but superior specificity than RF.4,5 Anti-CCP and RF use improves the specificity of the RA diagnosis .4 Additionally, the serum level of anti-CCP can be very accurately used to predict how soon undifferentiated inflammatory arthritis(UA) will proceed to RA.5

The European League Against Rheumatism (EULAR) advise that early treatment with a disease-modifying anti-rheumatic drug (DMARD) should be initiated as soon as a diagnosis of RA is made, later joint destruction will result without treatment.6 Studies revealed that treatment with Disease-modifying anti-rheumatic drugs (DMARDs) and short-course steroid therapy would change the disease's natural course. The biological agents include monoclonal antibodies and recombinant receptors to block cytokines that promote the inflammatory cascade responsible for RA symptoms. The non-biological DMARDs include; methotrexate (MTX), sulfasalazine, Leflonamide and hydroxychloroquine.7

Methotrexate is the most effective DMARD in the treatment of RA. it causes specific adverse effects that impair the quality of life.8 Gastrointestinal tract side effects were the most important, and folic acid was used to

reduce this side effect.9 The side effects of MTX arise after taking or could be anticipatory or associative, which influence compliance to medication during long-term. The mechanisms of the gastrointestinal side effects of methotrexate was explained by increasing the sensitivity of epithelial cells, accumulating the drug after the long-term course and the chemotactic trigger zone will be stimulated.10 Therefore, the researchers found it necessary to create a tool for monitoring patients on treatment.11 The side effects will be detected using the methotrexate intolerance severity score questionnaire (MISS).12 The aim of this study was to find the frequency of methotrexate intolerance among rheumatoid arthritis patients with factors that contributed to intolerance.

Patients and methods

An observational cross-sectional study was conducted in Rizgary and Hawler Teaching Hospital in Erbil/Iraq. The study period started from the 1st of July 2021 to the 1st of July 2022. A convenience sampling method was used, and a hundred patients were included in the study. The diagnosis of rheumatoid arthritis was confirmed using the 2010 ACR/EULAR classification criteria.13 All patients were treated with methotrexate according to the guidelines.14 Both genders were included in the study, the exclusion criteria were age below 18 or more than 80 years, Pregnant women, psychiatric illnesses, noncompliance with treatment and alcoholic. A validated version of the MISS questionnaire was used for data collection.12 The part designed by the investigator included the sociodemographic characteristics of the studied sample, duration of rheumatoid arthritis and methotrexate treatment, route of administration, and dose of the medication were all contained within the questionnaire. The use of biological and non-biological disease-modifying drugs (DMARDs) and steroids were investigated. The MISS questionnaire included four domains: behavioral, abdominal pain, nausea and vomiting. According to the

questionnaire, the symptoms were assessed for each element after taking the medication, anticipatory (before taking), and associative (on thinking about medicine). The central nervous and behavioral changes were investigated by asking about crying, restlessness, refusing to take medication and irritability.15

Each element in the MISS questionnaire was given a score ranging from 0-3 depending on the absence of symptom (0 scores) or the presence of mild (1 score), moderate (2 scores) or severe (3scores) symptoms. The total score ranged from (0-36). The intolerance was diagnosed based on a cut-off score of 6 and more.

The data was entered into the Microsoft Excel data collecting sheet 2010. The statistical package of social science (IBM SPSS statistics 26) was used for data analysis. The frequencies and percentages were measured. The mean, median, standard deviation and mode were presented for numerical variables. Patients were classified into two groups according to the MISS scoring system. Those who scored six and more were considered intolerant to MTX; the tolerant group included patients who scored less than 6. The Chi-square test was used to find associations between categorical variables, and the t-test to compare means. The risk factors of MTX intolerance were tested by multivariate analysis.

The approval of the Ethics and Scientific committees of the Kurdistan Higher Council of Medical Specialties was granted (Number 4573). Each patient was approached, and the investigator explained the purpose of the study. Written consent was taken, and confidentiality was assured.

Results:

The characteristics of the studied sample: the mean age± SD was 48.8 ± 12.2, the age range was 21-74 years, and 57% were in the age group 40-59 years. Females constituted 93% of the sample, 49% were obese, and only 13% were smokers (Table 1).

Table (1). Distribution of the studied sample by Demographic characteristics

Characteristics	No (%)
Age mean ±SD Range	48.8 ± 12.2 21-74
Age group	
20-39	19(19)
40-59	57(57)
60 and more	24(24)
Gender	
Male	7(7)
Female	93(93)
BMI	
Underweight	1(1)
Healthy	17(17)
Overweight	33(33)
Obese	49(49)
Smoking	
Yes	13(13)
No	87(87)

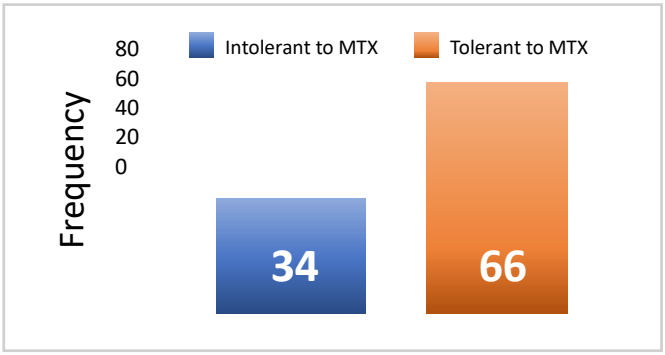

Figure (1). The rate of tolerance and intolerance to MTX in Rheumatoid arthritis patients. Among the rheumatoid patients, 66% tolerated MTX, while 34% did not tolerate the treatment.

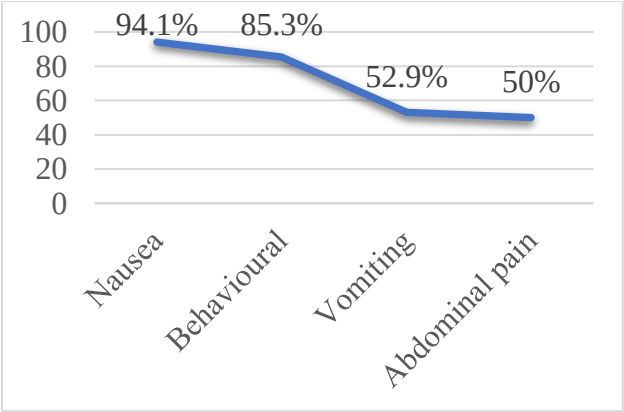

Figure (2). The frequency of intolerance for different symptoms among rheumatoid arthritis patients.

Nausea was the highest (94%); 85% had behavioral symptoms, more than half had vomiting, (52.9%) and 50% had abdominal pain.

Association between the tolerant and intolerant groups with the duration of disease(p=0.214), duration of MTX use (p=0.553), and the dose of MTX (p=0.540) were irrelevant. The oral dose was tolerated by 71%, and the only significant relation(p=0.050) was reported for the route of MTX administration (Table 2).

Table (2). Distribution of Rheumatoid arthritis patients by duration of disease, MTX dose, mode of administration, duration of treatment and MISS mean score.

Variables	Tolerance to MTX No=66	Intolerance to MTX No=34	Total No=100	p- value*
Duration of RA				
< 3years	20(74.1)	7(25.9)	27(27)	0.214

3years≥	46(63.0)	27(37)	73(73)	
Duration of MTX				
3 months<	5(62.5)	3(37.5)	8(8)	0.553
3 months ≥	61(66.3)	31(33.7)	92(92)	
Dose of MTX				
<15mg/week	7(70)	3(30)	10(10)	0.540
≥15mg/week	59(65.6)	31(34.4)	90(90)	
Mean ± Sd of MTX dose	16.69 ± 3.33	3.50±17.42	3.39±16.94	0.310
Route of MTX				
Oral	54(71.1)	22(28.9)	76(76)	0.050
Parenteral	12(50)	12(50)	24(24)	
MISS scoring	2.34± 1.57	2.82±8.76	4.53± 3.69	**<0.001
*Chi-square test. **t-test				

The prevalence of behavioral symptoms among patients who tolerated and did not tolerate MTX were significant for restlessness (36%, p<0.001), crying (15%, p=0.002), irritability (51%, p<0.001), and not taking medication (25%, p<0.001). Abdominal pain after taking MTX was (56.7%) in intolerant patients, and the result was significant (p <0.001). In 75%, the pain was associative and significant p <0.001. Nausea and vomiting were reported after taking in 42.1% and 90 % respectively. (Table 3).

Table (3). The prevalence of MTX-related symptoms in tolerant and intolerant patients.

Symptoms	Tolerance No=66	Intolerance No=34	Total No=100	p value*
Behavioral				
Restless	12(33.3)	24(66.7)	36(36)	<0.001
Crying	4(26.7)	11(73.3)	15(15)	0.002
Irritable	23(45.1)	28(54.9)	51(51)	<0.001
Refuse medication	6(24)	19(76)	25(25)	<0.001
Abdominal pain				
After taking	13(43.3)	17(56.7)	30(30)	<0.001
Anticipatory	0(0)	3(100)	3(3)	0.037
Associative	4(25)	12(75)	16(16)	<0.001

Nausea				
After taking	44(57.9)	32(42.1)	76(76)	<0.001
Anticipatory	2(18.2)	9(81.8)	11(11)	0.005
Associative	26(49.1)	27(50.9)	53(53)	<0.001
Vomiting				
After taking	2(10)	18(90)	20(20)	<0.001
Anticipatory	0(0)	6(100)	6(6)	0.002
*Chi-square test				

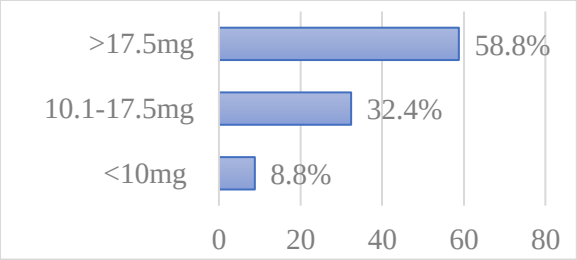

Figure (3). The consequence of weekly dose of methotrexate intolerance Patients using the highest dose reported high intolerance 58.8.

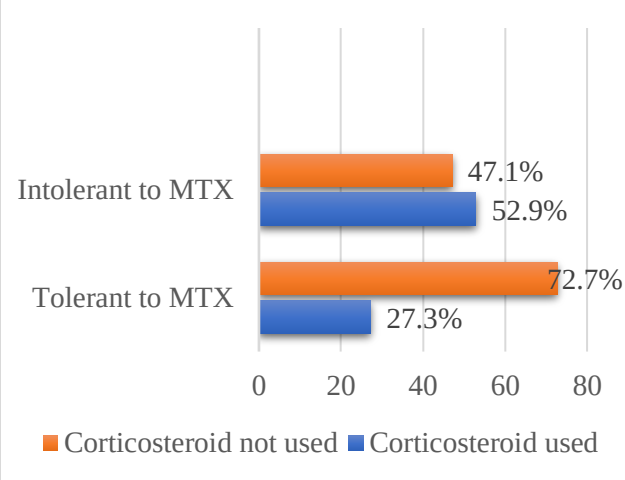

Figure (4). The frequency of steroid use among tolerant and intolerant MTX groups.

More than half of the rheumatoid patients were treated with steroids in the intolerant group and the result was tested by the Chi-square test (p=0.016). The MTX intolerance increase when combined to steroids ingestion.

Significant difference was reported between the tolerant and intolerant groups concerning disease activity. Conversely, the association with Anti-cyclic citrullinated peptide (Anti-CCP) and Rheumatoid factor (RF) was not significant statistically (Table 4).

Table (4). Disease activity score (DAS28 joints) and seropositivity among tolerant and intolerant RA patients.

DAS28 joints	Tolerant No=66	Intolerant No=34	Total No=100	p value
Remission	6 (85.7)	1 (14.3)	7 (7)	0.004*
Low	6(75)	2(25)	8 (8)	
Moderate	34 (79.1)	9 (20.9)	43 (43)	
High	20 (47.6)	22 (52.4)	42 (42)	
Mean ± Sd	4.47 ± 1.44	5.47± 1.63	4.81± 1.57	0.002**
Rheumatoid factor	38 (65.5)	20 (34.5)	58 (58)	0.539
Anti-CCP	33 (64.7)	18 (35.3)	51 (51)	0.473
Chi-square test*. t-test **				

Discussion:

Methotrexate is very commonly used as one of the conventional DMARDs due to its efficacy, availability and low cost, physicians aim to achieve remission or low disease activity. The mean MISS was higher among the intolerant group compared to the tolerant group (8.76 ± 2.82Vs2.34 ±1.57) with a significant difference ($p < 0.001$). Similar figures were reported by Almalag.[16] (10.9 ± 4.6 Vs 2.2± 1.8) with a highly significant difference ($p < 0.001$). Monitoring is required to reduce the incidence of noncompliance to medication after the appearance of side effects. In the current study, the prevalence of intolerance was 34%. The Fatimah study reported a similar intolerance rate (33%).[17] While in an Almalag study, 47% of the patients was intolerant to MTX.[16]

Patients in Ćalasan research exhibited a lower intolerance rate 11%, out of which 100% had nausea, behavioral reported in 81.3%, 62.5% had abdominal pain, and vomiting was reported in 34.4%.[18] The behavioral element was positive in 85% of this study, Nausea (94.1%), vomiting (52.9%) and abdominal pain (50%) were inconsistent with the findings in Calasan. These symptoms may affect the quality of life and make them leave the treatment. Therefore, patients should be monitor for symptoms during treatment to detect intolerance.

According to the current study findings, one-third of RA patients experience intolerance and are vulnerable to becoming non-compliant. The negative psychological impact of MTX came from its labelling. The presence of a chemotherapeutic label on the package made it worse. The behavioral symptoms could be managed by cognitive behavioral therapy through counselling.

Patients in the present study also experienced associative and anticipatory symptoms. The vomiting among intolerant patients was 100% anticipatory and 90% after taking medication. Nausea was anticipatory in 81.8% ($p=0.005$) and associative in 50% ($p < 0.001$). Abdominal pain among the intolerant group was anticipatory in 100%, and the result was significant $p=0.037$. Associative abdominal pain was 75%, with highly significant differences.

A study done by Albaqami he used the Arabic-translated version of MISS.[19] More than half (52%) of the intolerant group in this study scored high on the disease activity (DAS 28), and the result was significant ($p=0.004$). while the study of Almalag reported a higher figure (66.7%) on (DAS 28) among the intolerant group($p=0.292$).[16] The mean disease activity score was 3.2 ±1.3 and the mean MTX dose was 15.4 ± 3.0. The current study's mean disease activity 4.81± 1.57 and the mean MTX dose was 16.94± 3.39 both were higher. The gastrointestinal adverse effects can be managed by splitting the dose, using folic acid and changing the route of administration. To reduce MTX gastrointestinal side effects that were prevalent in 52.5% of an Al-malaq study performed among Saudi population, 89.2% of patients were treated with folic acid.[20]

This study showed that MTX intolerance was dose dependent, more than half of the intolerant group (58.8%) received more than 17.5mg/week. While patients on less than10mg/week the intolerance rate declined to 8.8%. However, the research done by Fatimah revealed that patients who consume 20mg/week reported ultimate intolerance (46.2%), the rate was reduced to 20% by decreasing the dose to 7.5mg/week.[17]

This study is the first to find the relationship between MTX intolerance with the route of administration, disease activity and the use of steroids in Erbil/Iraq. The limitations of this research were small sample size and the majority of patients were females. Further multicenter studies are recommended with a larger sample size to confirm our findings.

Conclusion and recommendation:

Methotrexate intolerance is prevalent among RA patients in this region and is associated with dose, route of administration, steroid use and disease activity.

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Conflicts of interest

There were no conflicts of interest.

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