Comparison of Characteristics of Methotrexate Tolerant and Intolerant Patients Having Rheumatoid Arthritis

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Abstract

Objectives: To compare the characteristics of methotrexate-tolerant and intolerant patients having rheumatoid arthritis. To determine the association of methotrexate intolerance with the patient and disease-related factors.

Method: This cross-sectional study was carried out at the rheumatology department of Combined Military Hospital Lahore from 31st April to 30th June 2022. It included 181 rheumatoid arthritis (RA) patients using methotrexate (MTX) for > 3 months. Patient demographic variables, disease duration and activity, and information regarding MTX intake were recorded. English methotrexate intolerance severity score (MISS) questionnaire was used to calculate MTX intolerance. Different variables were compared between methotrexate-tolerant and intolerant patients. Association of age, disease duration, and activity, MTX route/dose with MTX intolerance was determined.

Results: The majority of patients were females 140(77%). The median disease duration was 6(1-40) years. MTX intolerance was found in 48(26.5%) of RA patients. Intolerant patients had a higher disease activity score (DAS 28>5.1 in 20.8 vs 3.8%; P = 0.002) and longer duration of MTX intake in months (23.5 vs 12; p=0.018) compared to tolerant patients. Additionally, MTX intolerance was associated with younger age, longer disease duration and higher MTX dose>10mg/wk (P=0.007, P=0.025, P=0.050). There was no significant difference between the two groups in gender, marital status, education, and use of other DMARDs or steroids. (P >0.05).

Conclusion: There was a significant association between age, disease duration, and MTX dose with MTX intolerance. We also noted a significant association between disease activity and route of intake with MTX intolerance but this was lost when adjusted for multiple confounders.

Keywords: methotrexate, intolerance, rheumatoid arthritis, arthritis

How to cite: *Saif S, Kitchlew R, Kakalia S, Butt BA Comparison of Characteristics of Methotrexate Tolerant and Intolerant Patients Having Rheumatoid Arthritis.Esculapio - JSIMS 2023;19(01):38-42*

DOI: https://doi.org/10.51273/esc23.251918

Introduction

Rheumatoid arthritis (RA) is the most frequent deforming inflammatory arthritis, affecting 24.5 million people worldwide and imposing a huge personal and socioeconomic burden.[1] Methotrexate (MTX) is the most commonly used disease-modifying antirheumatic drug (DMARD) for the treatment of RA as it has excellent efficacy and very low toxicity.[2] MTX relieves pain, maintains normal muscle strength, and preserves joint function while preventing growth retardation and joint deformities. It has been used as the first-line treatment of inflammatory arthritis for more than two decades.[3]

However, many patients are shifted to an alternative and more expensive DMARD when they do not tolerate MTX. MTX intolerance is found in 30%-60% of patients.[4] It produces a combination of symptoms, including nausea, vomiting, abdominal pain, and irritability. It is essential to ask about these symptoms because a significant pro-

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Submission Date: 15-01-2023
1st Revision Date: 03-02-2023
Acceptance Date: 05-03-2023

portion of patients discontinue treatment and suffer from decreased quality of life while using MTX.[5] These symptoms not only occur after taking it but also before taking it, and even upon thinking about it.[6] In addition adult patients may also experience fatigue, headache, dizziness, irritation, diarrhea, and hair loss.[7]

Almost half of the patients discontinue MTX with or without informing their physician within six months to two years.[8] Different factors like age, gender, marital status, pain, and disease activity affect MTX intolerance. The behavioral component is very important as MTX-intolerant patients have more patient-reported outcomes.[9] MTX intolerance is also related to the route of intake.[10] That is the reason why managing intolerance includes patient education, counselling, and changes in dose and route of medication.[11]

MTX is the foundation of the management of RA, and it should be continued in all patients unless any contraindication arises. Intolerance of this drug is common, yet various factors affecting it are usually ignored. It is of utmost importance to be aware of the differences between MTX-tolerant and intolerant patients so that such individuals can be monitored closely for possible early intervention to ensure adherence to this vital therapy. Previously this issue has not been assessed. Therefore, the primary objective of this study was to compare the characteristics of MTX-tolerant and intolerant patients with RA and to establish the association of MTX intolerance with patients and disease-related factors.

Materials and Methods

We enrolled 181 patients with RA classified according to ACR/EULAR 2010 classification,[12] who had been on regular MTX for more than three months and were regularly followed up in the rheumatology outpatient department. We calculated the sample size by taking the frequency of MTX intolerance as 21.6%, CI as 95%, and margin of error as 6%.[13] Our RA patients were between eighteen and sixty years. Those patients who were non-compliant (who had discontinued more than two medicines in the past without a reason) or those with cognitive impairments, a history of peptic ulcer disease, or gastrointestinal (GI) complaints before going on MTX were excluded. We recruited our patients using convenience sampling after obtaining informed written consent. We interviewed these patients to assess intolerance. To avoid any bias, a single person asked the same set of questions, and patients were blinded to the results of their questionnaires. We recorded demographic details, comorbidities, and pain VAS (pain described by the patient with the help of a 100mm visual analog scale). We noted disease duration and activity, the serology status of the patients, and the dose/duration and route of MTX. We calculated intolerance to MTX using the MISS questionnaire after obtaining permission from the research team of the University Medical Center, Utrecht, Netherlands. This questionnaire comprises four areas: abdominal pain, nausea, vomiting, and behavioral issues. A patient score of six points or higher, inclusive of at least one anticipatory, associative, or behavioral symptom, is labeled as MTX intolerant.[14] MTX dose was prescribed by the rheumatologist. The treating rheumatologist reviewed and monitored the patients for any drug side effects. We entered data using IBM SPSS Version 26. Quantitative variables like age, disease duration, MTX dose and duration, and pain VAS were presented as means with standard deviation or median with interquartile range (IQR). Qualitative variables like gender and route of MTX were presented as frequency and percentages. For the normally distributed data, we used the t-test, and for abnormally distributed data we used the Mann- Whitney U test to compare the MTX-tolerant and intolerant patients. We used a chi-square test to compare the categorical variables between the two categories. After adjusting for confounding variables, we applied bivariate logistic regression to determine factors related to MTX intolerance. $P<0.05$ was regarded as statistically significant.

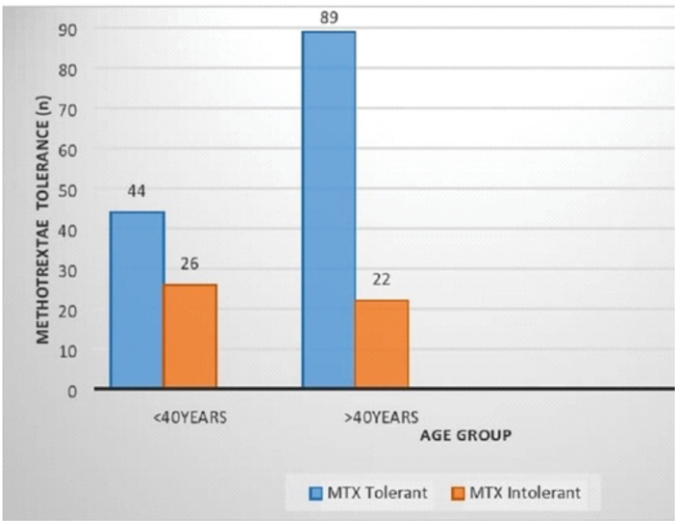
Results

We included 181 RA patients. The MTX was given by oral route in 159 (87.8%) patients and the other 22 (12.2 %) got it subcutaneously (SQ). MTX intolerant patients had a higher pain VAS (50 vs. 20; p=0.50), a higher DAS 28 value (p=0.002), and a long history of MTX intake (23.5 vs. 12 months; p=0.018) compared to tolerant patients. MTX intolerance occurred more often in patients receiving MTX by injectable route than those taking it by mouth (50% vs. 28%). (Table 1). IQR-Interquartile range; SD-Standard deviation; DAS-Disease activity score; VAS-Visual analog scale; MTX-Methotrexate; DMARD-disease-modifying anti-rheumatic drug MTX intolerance was identified in 48 (26.5%) of the patients. Nausea was the predominant symptom occurring in 45(93.8%) followed by restlessness in 38 (79%) and irritability in 37(77%) of the MTX-intolerant patients. MTX intolerance was associated with younger age (adjusted odds ratio (AOR 3.152; 95% CI 1.360, 7.307, P = 0.007), longer disease duration (AOR .341;

95% CI .133,.871, P = 0.025) and higher MTX dose> 10mg/wk (AOR .418; CI .175-.998, P= .050). We also found a significant association between SQ route, and disease activity (pain VAS, DAS 28) with MTX intolerance, but after applying logistic regression the p-value was not significant. MTX intolerance increased with disease duration, as 39/48 (81.3%) patients who were intolerant had a disease of more than three years (p= 0.025). Those who were taking more than 10mg/week of MTX showed more intolerance (p=0.05).
Comorbidities were found in 32(17.7%). There was no relation between MTX intolerance to gender, marital status, smoking history, or education level. (Table 2) MTX-Methotrexate; DAS 28-Disease activity score 28; VAS-Visual analog scale. Younger age was associated with more intolerance to MTX (p=0.007). Of the forty-eight MTX-intolerant patients, only ten (20.8%) were over fifty years (p=0.007; FIG 1). MTX intolerance was associated with disease activity as measured by DAS 28. Most of the patients having low disease activity were tolerant 77/92 (84%) while most patients having high disease activity 10/15 (67%) were intolerant.

Table 2: *Factors Associated with MTX Intolerance-Bivariate Logistic Regression*

Factors	Adjusted Odds Ratio	95% Confidence Interval	p-value
Gender	1.602	0.574-4.47	0.368
Age(years)	3.152	1.360-7.307	**0.007**
Marital status	1.055	0.290-3.832	0.935
Education	0.532	0.237-1.194	0.126
Disease duration	0.341	0.133-0.871	**0.025**
MTX duration	0.970	0.424-2.220	0.943
MTX dose	0.418	0.175-0.998	**0.050**
MTX Route	0.458	0.148-1.413	0.174
Pain VAS	0.376	0.136-1.037	0.059
DAS 28	0.622	0.242-1.602	0.326



MTX-Methotrexate

Fig-1. *Comparison of Age with Methotrexate Tolerance*

Discussion

MTX is the standard of care in RA patients in doses of less than 25-30mg/week. Low-dose (LD) MTX received FDA approval in 1988 for its use in RA as an anti-inflammatory drug with fewer adverse effects and almost no toxicity compared to high-dose (HD) MTX used in malignancies, where it acts as an anti-proliferative cyto-

Table 1: *Baseline Characteristics and Comparison of Variables Between Methotrexate-Tolerant and Intolerant Patients*

Variable	All (n=181)	MTX-Tolerant (n=133)	MTX-Intolerant (n=48)	p-value Tolerant vs Intolerant
Female n(%)	140 (77%)	99 (74%)	41 (85.4%)	0.119
Male n(%)	41 (23%)	34 (25.6%)	7 (14.6%)	0.119
Age [Mean (SD)]	43.3+11.9	45.02+11.72	38+11.43	0.861
Duration of disease (years) Median (IQR)	6 (7)	6 (9)	6 (5.5)	0.56
Dose of MTX (mg/week) Median (IQR)	15 (10)	15 (10)	10 (5)	0.879
Duration on MTX (months) Median (IQR)	12 (34)	12 (30)	23.5 (42)	0.018
Injectable MTX n(%)	22 (12%)	11 (8.3%)	11 (23%)	0.008
DAS 28 (>5.1)	15 (8.3%)	5 (3.8%)	10 (20.8%)	0.002
Pain VAS Median (IQR)	30 (30)	20 (35)	50 (40)	0.50
Use of folic acid n(%)	173 (95%)	126 (94.7%)	47 (97.9%)	0.358
Use of other DMARDS n(%)	76 (42%)	57 (42.9%)	23 (47.9%)	0.139
Using steroid n(%)	84 (46%)	60 (45%)	24 (50%)	0.561

toxic drug associated with more toxicity.[15] At low doses RA patients showed significant response compared to placebo both clinically and statistically as measured by ACR 5O response at three months and one year.[16] MTX intolerance was found in 26.5% of our patients, with nausea and behavioral symptoms being the most frequent. In a study done on 117 RA patients, 55 (47%), patients reported MTX intolerance with predominantly behavioral symptoms.[9] Haya et al. observed various side effects with MTX in 33% of patients, with GI symptoms being the most common (53%), especially in younger patients.[17] We found that MTX intolerance decreased with age, as most patients above fifty were tolerant to MTX. Braun et al. similarly reported less intolerance in patients over sixty-five.[18] The ideal route for MTX therapy in RA is not yet confirmed. The safety, efficacy, and tolerability of oral and parenteral MTX are comparable. Hence oral is always the preferred starting therapy.[18-19] In contrast, Li D found that the SQ of MTX had better bioavailability and clinical efficacy at higher doses, reducing nausea and diarrhea, but the treatment failure rates were comparable with those of the oral route.20 Another study documented higher MTX intolerance on parenteral (67.5% vs. 44.5%) compared to the oral route (p=0.001).[21] The oral route is almost always preferred by both patient and physician, and most patients in our study who were on SQ MTX were primarily started on oral and were later shifted to SQ by the treating physician due to intolerance, which persisted in 50% of them despite shifting mainly because of the behavioral component.

We found a strong association of MTX intolerance with DAS 28 but no influence of gender, marital status, or education, while Amalog found a strong association of MTX intolerance not only with pain VAS (p=0.010) and DAS 28 (p=0.036) but also with female gender (p=0.016) and marital status (p=0.042).[9] Kaya et al. studied MTX in all age groups and found different risk factors associated with MTX intolerance, including younger age, patient VAS scores, and parenteral route of administration ($p<0.05$).[22] We noticed that patients taking more than 10mg/week of MTX were more intolerant, but the use of other DMARDs did not affect tolerance. However, apart from a younger age, Mahroug et al did not find any effect of dose, duration, route of MTX administration, or other DMARDs on tolerance (p=0.048).[23-24] In our study, we noticed that MTX intolerance was more common in patients who had RA for more than three years and were taking MTX for longer. It is known that MTX-induced nausea is inversely related to age, but we still do not know which factors affect MTX's metabolism and effects. As intolerance is more common in patients using MTX for more than one year, there might be a cumulative effect of MTX on nausea.[25] Limitations of our study include a small sample size and it included only one ethnic group. Moreover, the number of patients using SQ MTX was much less than the ones using oral MTX. We recommend future studies including a larger sample size on possible ways to increase adherence to MTX therapy. The use of a smartphone for the digital monitoring of remote patients could be an option.

Conclusions

MTX intolerance is common among the Pakistani RA population and is related to younger age, higher doses of MTX, and longer disease duration. We need to educate patients about the benefits of taking MTX, which will improve the behavioral factors related to its use and address at an earlier time any untoward symptoms related to intake, thereby increasing compliance with the medication.

Conflict of Interest: *None*

Funding Source: *None*

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SS, RK: Conceptualization of Project
BA: Data Collection
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SS, SK, RK, BA: Writing of Manuscript