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Adherence to Parenteral Methotrexate Compared to Oral Route in Patients with Rheumatoid Arthritis

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Abstract

Background and objectives: Rheumatoid arthritis is a chronic autoimmune inflammatory disease, which causes discomfort, swelling, stiffness, and eventual joint destruction. Methotrexate is a Disease Modifying Anti-Rheumatic Drug with a specific role in the treatment of Rheumatoid Arthritis. Adherence to methotrexate is essential to attain low disease activity or remission. The aim of this study was to know the prevalence rate of adherence to Methotrexate in parenteral way of administration and oral route among patients with Rheumatoid Arthritis.

Methods: This observational cross-sectional study included 100 patients diagnosed as rheumatoid arthritis according to 2010 ACR/EULAR using methotrexate either in oral or parenteral route presented to Rheumatology Consultancy Department at Rizgary Teaching Hospital/Erbil City, from July 2022 to July 2023. All patients answered an interview questionnaire regarding socio-demographic, clinical and treatment information survey included the Arabic version of the eight-item Morisky Medication Adherence Scale, and blood investigations had been done to assess the determinants of adherence to methotrexate treatment.

Results: A total of 100 patients with Rheumatoid Arthritis using methotrexate either in oral or parenteral route were enrolled in this study. No significant association was detected between the drug adherence with the following variables: age, body mass index, residency, and the factors related to pattern of diseases and treatment. While higher levels of adherence (2%) were detected among those with higher levels of education as significant association was detected ($p = 0.021$).
Conclusion: More than Two-Thirds of patients with Rheumatoid Arthritis who are receiving methotrexate via parenteral or oral route were poorly adherent to methotrexate.

Keywords: Adherence, Oral Methotrexate, Parenteral Methotrexate, Rheumatoid Arthritis

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Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease, with an estimated yearly incidence of 50 per 100,000 [1] and prevalence of approximately 1%, which causes a major financial burden on society.[1] It causes discomfort, swelling, stiffness, and eventual joint destruction. Methotrexate (MTX) is A traditional synthetic Disease Modifying Anti-Rheumatic Drug (csDMARD) in the treatment of RA. MTX involves at each stage of the disease management process due to its effectiveness, safety, variety of dosages available for titration, and numerous modes of administration (parenteral or oral).[2] MTX is a drug that can be used alone or as a "anchor drug" in several DMARD combinations, whether they be conventional or biological.[3] In RA patients who are not responding adequately, switching from oral to subcutaneous (SC) MTX may enhance clinical response.[4] In fact, the restriction of active gut absorption in the case of oral route delivery does not alter the bioavailability of MTX when administered subcutaneously. Additionally, patients with RA using oral MTX who have a poor or inadequate clinical response may benefit from an increased drug exposure by changing to the SC route of administration.[4]Patients who switch to SC MTX report gastrointestinal side effects that are less severe than those who continue to take oral MTX.[5] possibly promoting higher adherence. Several international recommendations advocate optimizing MTX monotherapy with SC administration.[6] Adherence is described as the consistency between the patient's behavior and the healthcare provider's recommendations for treatment intake, dietary changes, and lifestyle alterations. Adherence to MTX is essential to its effectiveness, as it is with any long-term treatment. Patients who are non-adherent experience flares four times more frequently than those who are of good adherent.[7] Relevant patient education regarding the time it takes for MTX to reach its peak efficacy and folic acid's ability to reduce the risk of adverse events can both improve adherence to the medication.[8] A recent expert agreement on DMARDs adherence identified five broad principles and ten suggestions, they emphasize that defining treatment through patient/physician sharing processes, informing and educating patients are essential for adherence optimization.[9] Furthermore, switching from the oral to the SC route has been shown to improve adherence to MTX.[10] The aim of study is to determine the prevalence rate of adherence to Methotrexate parenteral way of administration and oral route among patients with Rheumatoid Arthritis.

Patients and methods

This study is a cross-sectional study and was conducted at the Rheumatology Outpatient Clinic at Rizgary Teaching Hospital/Erbil City during the period from 26th of march 2022 to 26th of march 2023. A total of 100 consecutive patients (male =14, female=86) diagnosed with Rheumatoid Arthritis according to 2010 ACR/EULAR with the following characteristics: age ≥18 years with disease duration > 3 months, have been on treatment with methotrexate parenterally or orally at the time of enrollment and have adequate cognitive status as determined by communicating with the patients, presented to Rheumatology outpatient clinic were studied. Exclusion criteria were: women newly diagnosed with RA wants to become pregnant or lactating, patients with cognitive impairment, patients with serious medical conditions like hepatic failure, renal failure, preexisting blood disorders, patients with active infectious disease, patients with excessive alcohol consumption and any history of GIT diseases. Ethical approval was obtained from the Ethics and Scientific Committees of Kurdistan Higher Council of Medical Specialties. The patients had been

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assured that the information obtained from them will not be used outside the research purpose and the information will not be disclosed to others. A signed consent was obtained from all patients for inclusion in the study. A questionnaire tool with verbal consent was taken from them to be included in the study. The assessed data about socio-demographic, clinical and treatment characteristics survey included the Arabic version of the eight-item Morisky Medication Adherence Scale (MMAS-8).[11] this scaling score used for assessing the self-reported medication adherence by using 8 items, scoring rate is between 0 to 8, with score of 8 reflecting high adherence, score of 7 or 6 reflecting medium adherence, and score of <6 reflecting low adherence. The following data were collected through the questionnaire: Patients age (in years), gender, and smoking status were reported. Height in centimeters and weight in kilograms were measured for all patients, body mass index (BMI) was calculated according to the equation BMI=weight/ height^2 (m^2), residence, education level (Illiterate, primary, secondary, high education level, and none) , marital status , employment status , chronic comorbidity , satisfaction with treatment , duration of RA (years) , duration of MTX intake (years) , current dose of MTX mg/week), mode of intake: oral or parenteral (Intramuscular) presence of drug side effects and DAS 28 Score involving (number no. of tender joints, no. of swollen joints, ESR, patient global assessment) all were collected through direct interview. Data were analyzed using the Statistical Package for Social Sciences (SPSS, version 26). Chi square test of association was used to compare proportions of the two study groups. Fisher's exact test was used when the expected frequency (value) was <5 of more than 20% of the cells of the table. The P-value of ≤ 0.05 was statistically significant.

Results

One hundred patients with rheumatoid arthritis were included in the study. Their mean age (SD) was 50.1 (12.4) years, the median was 51 years, and the age range was 21-75 years. The largest proportion (36%) of the sample were aged 50-59 years, and 24% aged ≥ 60 years. The majority (86%) were females, and most of the patients (90%) were married. Around two thirds (64%) were unemployed/housewives, and a considerable proportion of patients were either illiterate (2%) or of can just read and write (39%). Two thirds (66%) of the studied sample were of moderate socio-economic status, and 81% were living in urban areas as shown in Table (1). The majority (85%) of the RA patients were non-smokers, and 13% were current smokers. Regarding the comorbidities, 62% had no comorbidities, 16% had hypertension alone, 6% had diabetes alone, and 11% had both. Four patients had hypertension and ischemic heart disease, and only one patient had hypertension, IHD and diabetes. Two thirds (66%) of the patients were obese.

Table (1): Sociodemographic characteristics.

	No.	(%)
Age		
< 40	19	(19.0)
40-49	21	(21.0)
50-59	36	(36.0)
≥ 60	24	(24.0)
Gender		
Female	86	(86.0)
Male	14	(14.0)
Total	100	(100.0)

The majority (93%) of RA patients were taking the drug for years after diagnosis, half of them by oral route & the other half by parenteral route. The dose of MTX was ranging from 10-20 mg/week, around two thirds (64%) of patients were taking 15 mg/week. The majority (73%) of the patients were taking pills more than once per day in addition to weekly MTX, and 38% were

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having side effects. More than half (61%) of the patients were satisfied with treatment, and the majority (70%) were with low drug adherence, The severity of RA was assessed by DAS 28, accordingly the patients were classified as follows: remission (6%), low disease activity (11%), moderate disease activity (69%), and high disease activity (14%), as presented in Figure (1). The majority (92.1%) of patients with comorbidities had moderate or high disease activity, compared with 77.4% of patients with no comorbidities. It was close to the significance level (p = 0.058). No significant association was detected between drug adherence and the following variables: age (p = 0.134), BMI (p = 0.814), and residency (p =0.344). While higher levels of adherence were detected among those with higher levels of education compared with those with low level, except for the illiterate (only two patients, one of them with medium or high compliance) (p = 0.021) as presented in Table (2).

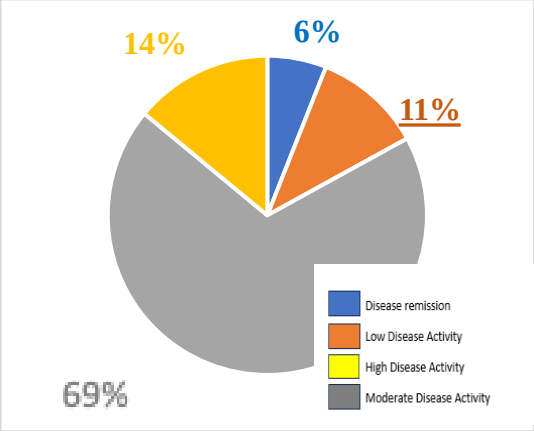

Figure (1): Severity of rheumatoid arthritis.

Table (2): Drug adherence by patients' basic characteristics.

	Low Adherence	Medium/High Adherence	Total	p value
	No. (%)	No. (%)	No. (%)	
Age (years)				
< 40	10 (52.6)	9 (47.4)	19 (100.0)	
40-49	13 (61.9)	8 (38.1)	21 (100.0)	
50-59	29 (80.6)	7 (19.4)	36 (100.0)	
≥ 60	18 (75)	6 (25)	24 (100.0)	0.134*
BMI (Kg/m^2)				
<25	7 (77.8)	2 (22.2)	9 (100.0)	
25-29	18 (72)	7 (28)	25 (100.0)	
≥30	45 (68.2)	21 (31.8)	66 (100.0)	0.814*
Education				
Illiterate	1 (50.0)	1 (50.0)	2 (100.0)	
Read and write	34 (87.2)	5 (12.8)	39 (100.0)	
Primary	13 (61.9)	8 (38.1)	21 (100.0)	
Secondary	8 (66.7)	4 (33.3)	12 (100.0)	
High education	14 (53.8)	12 (46.2)	26 (100.0)	0.021**
Residency				
Urban	55 (67.9)	26 (32.1)	81 (100.0)	
Rural	15 (78.9)	4 (21.1)	19 (100.0)	0.344*
Total	70 (70.0)	30 (30.0)	100 (100.0)	

*By Chi square test. **By Fisher's exact test.

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No significant association was detected between the drug adherence & factors related to pattern of diseases & treatment. The factors are: comorbidities (p = 0.857), duration after diagnosis (p = 0.425), DAS28 (p = 0.474), route (p = 0.081), dose (p = 0.340), daily medications (p = 0.150), side effects (p = 0.530) & satisfaction (p = 1.000). This study found that, 70% of the patients (31 patients who received parenteral MTX & 39 patients who received oral MTX) had low medication adherence rate, 28% (11 patients received parenteral MTX, 17 patients received oral MTX), had a medium rate of drug adherence, whereas 2% (two patients who received parenteral MTX) had a high drug adherence rate, as shown in Figure (2).

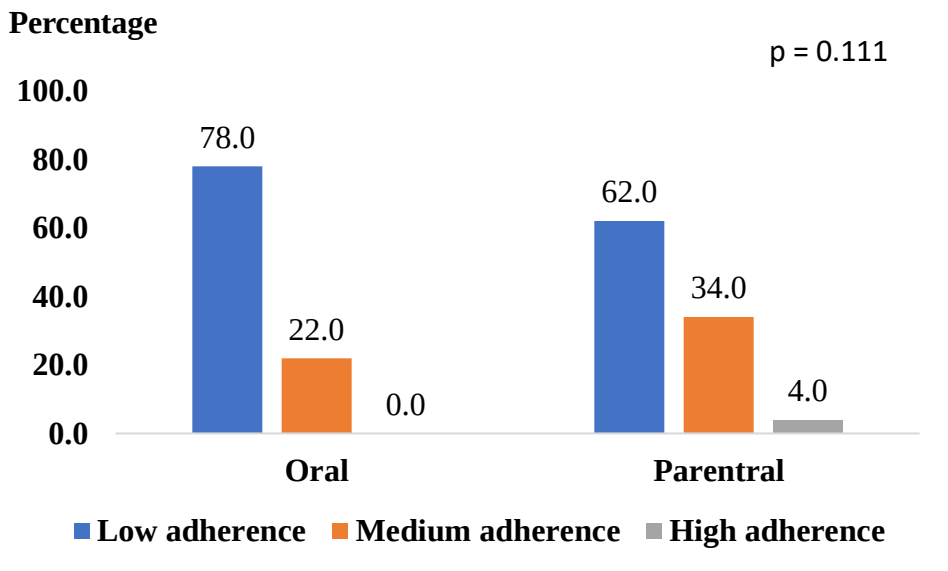

Figure (2): Drug compliance by route of methotrexate administration

Discussion

The purpose of this study was to identify the prevalence rate of adherence to the oral and parenteral routes of methotrexate treatment among patients with rheumatoid arthritis. The mean age of the patients in this study was (50.1±12.4) years, which is consistent with the results of other previous studies conducted on Iraqi patients. Al-Ani N and Faiq MK[12,13] found that the mean age of their patients was (48 years and 58 years) respectively, which confirms a high occurrence of RA in this age group among Iraqi patients. The low adherent patients in this study were older, unemployed, married females, and had a low educational level. According to a study conducted in Saudia Arabia by Almazrou S, Aljohani H [14] their findings were 52.4% of patients had low adherence. Predominantly were females with low levels of education. This study was in contrast to a study done by Al-Tuma.[15] who included 100 RA patients diagnosed according to ACR/EULAR, 2010 criteria. Their findings revealed that roughly 58% of these patients had high levels of MTX adherence. This discrepancy might be related to adherent patients had median educational level and were much younger than non-adherent patients, who were older and had lower educational levels. According to this study findings regarding the route of MTX administration, side effects, and self-dependence, the majority of patients with low adherence received MTX orally, whereas the majority of patients with medium-high adherence received MTX via parenteral route. The same conclusion was reached by

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the author Al-Tuma[15] who found that compared to the non-adherent group, the adherent group used the parenteral route more frequently than the oral route. However, our study doesn't coincides with study done over Spanish population by Pombo-Suarez.[16] whom they demonstrated that the method of administration had no effect on adherence. Although, little information is available regarding adherence and route of intake as most studies compared drug safety, efficacy, disease response, and tolerability between oral and parenteral but not adherence. According to some studies, parenteral administration of MTX has a higher bioavailability than oral administration, bypasses the liver's first pass metabolism, and has fewer and milder GI side effects. A study by De-Achaval.[17] found no significant differences between those with or without comorbidities, DAS28 score, duration after diagnosis, side effects & treatment satisfaction. As evidenced by the significantly higher drop-out rate in patients with comorbid conditions, this is different from a Danish Study by Bliddal. [18] who found adherence to MTX was associated with good general health. This may also reflect a modification of the treating physician due to comorbidities. In our study we determined that 73.7% of patients were poorly compliant to medical treatment. This was in line with research done in Poland by Brzezinska [19] which included 415 Polish patients with RA, and which discovered that 63.33% of patients have side effects, and the occurrence of side effects significantly increases the risk of discontinuation, frequently without consulting the physician. Clinical evaluation in this study revealed that low adherence patients most frequently had moderate disease activity, as opposed to low-high adherence, which is typically associated with low disease activity. This is in line with Contreras-Yanez[7] study that revealed patients with better adherence typically have lower disease activity. Limitations of the study were conducted at a single center; as a result, the adherence rate to MTX in RA patients receiving it orally or parenterally may have been over- or underestimated, the study is a cross-sectional, so only correlational analysis is possible; causality cannot be inferred. The sample size is relatively small, making it hard to generalize the results.

Conclusion and Recommendation:

More than two third of the patients with RA who are receiving MTX in parenteral or oral route were poorly adherent to MTX. We advise for patient education regarding disease's nature, chronicity, the need for long-term treatment, and prevent long term complications. Future studies that examine the impact of low adherence on patients' health outcomes are strongly advised, as are efforts to improve patient education and counseling by doctors.

Conflict of interest

The authors declare no conflict of interest related to this study.

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