

Evaluation of Adherence to Methotrexate in a Sample of Iraqi Patients with Rheumatoid Arthritis Receiving Anti - TNF Medications

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Abstract: Background: Rheumatoid arthritis is a chronic inflammatory disease. Current treatment guidelines for RA recommend early aggressive management with Disease - modifying antirheumatic drugs. Non - adherence to treatment has been associated with symptom worsening and increased disability. Aim of study: to determine the prevalence level and factors that affect adherence to Methotrexate among Rheumatoid arthritis patients receiving Anti - Tumor Necrosis Factor. Patients & Methods: This cross - sectional study included a total of 100 patients diagnosed as Rheumatoid arthritis according to ACR / EULAR, 2010 criteria. The enrolled patients answered an interview questionnaire regarding socio - demographic, clinical and treatment information survey including the Arabic version of the eight - item Morisky Medication Adherence Scale. Results: According to Morisky scale, 54% of Rheumatoid arthritis patients taking Anti - TNF medications were classified as having low adherence to Methotrexate therapy. During multivariate analysis, Older age patients >45 ($p=0.004$), illiteracy ($p=0.028$), low socioeconomic state ($p=0.050$), disease duration >10 years ($p=0.008$), Methotrexate use duration >5 years ($p=0.013$), Anti - TNF use duration >3 years ($p=0.001$), presence of side effects ($P=0.025$), non - self dependent ($P=0.020$), and moderate disease activity ($P=0.043$) were significantly independent risk factors for non - adherence to Methotrexate. Conclusions: Fifty four percent of patients who are using Anti - TNF were classified as low adherent to Methotrexate. Older age >45 years, illiteracy, low socioeconomic state, disease duration >10 years, Methotrexate duration use >5 years, Anti - TNF duration use >3 years, presence of side effects, non - self dependent, and moderate disease activity were significantly independent risk factors for non - adherence.

Keywords: Rheumatoid Arthritis, Anti - TNF Medications, Methotrexate Adherence

1. Introduction

Definition and pathophysiology of Rheumatoid Arthritis

{Rheumatoid arthritis (RA) is a chronic systemic autoimmune inflammatory disease, which primarily affects the joints and is characterized by inflammation of small and medium synovial joints in a symmetrical polyarticular pattern. Active disease is characterized by pain, swelling and stiffness of joints in combination with raised levels of inflammatory markers. It also affect periarticular structures, shows systemic manifestations, extra articular features are more frequently seen during later stages of the disease} ⁽¹⁾. The etiology of RA remains unknown, environmental and genetic influences can interact and trigger adaptive responses associated with autoimmunity before the onset of clinical symptoms ⁽²⁾.

Epidemiology

{Prevalence of RA has been estimated at 0.5% to 1% in most developed countries, with considerable regional variations}. It is more common in females (female: male ratio is 3: 1). The typical age of onset in women is late child - bearing years; in men, RA develops more often in the sixth to eighth decades ⁽³⁾. Definite RA was observed in 1% of population samples in Iraq ⁽⁴⁾

Diagnosis:

Patients are classified as having RA according to the 2010 American College of Rheumatology (ACR) / European League against Rheumatism (EULAR) classification criteria ⁽⁵⁾.

Management:

Initiating pharmacotherapy soon after the onset of rheumatoid arthritis (RA) reduces the progression of joint damage and improves long - term outcomes ⁽⁶⁾. The EULAR therefore recommends that treatment with a disease - modifying anti - rheumatic drug (DMARD) should be initiated as soon as a diagnosis of RA is made, because untreated disease do not remit spontaneously ⁽⁷⁾. {For patients with early RA and almost exclusively high disease activity, the combination of TNF, non - TNF biologics plus methotrexate (MTX) improves disease activity and (DAS) - defined remission, when compared with either biologics or methotrexate monotherapy}. ⁽⁸⁾

Methotrexate:

Methotrexate is considered the most effective DMARD for RA. Approximately 30% of patients will achieve low - disease activity on MTX monotherapy. MTX acts relatively quickly after being started, often within several weeks. In addition to its clinical efficacy, MTX retards new erosions in involved joints ⁽⁹⁾

For patients in whom doses of at least 15 mg of MTX once weekly were ineffective or poorly tolerated, there are two alternatives to switching to another disease - modifying antirheumatic drug (DMARD) or to adding a biologic agent⁽¹⁰⁾, like Tumor necrosis factor (TNF).

Adherence to medications:

Adherence to a medication regimen is "the extent to which patients take medications as prescribed by their health care providers. A patient is considered adherent if they take 80% of their prescribed medicine (s). If patients take less than 80% of their prescribed medication (s), they are considered non - adherent. "Medication adherence occurs when a patient takes their medications according to the prescribed dosage, time, frequency, and direction⁽¹¹⁾.

Aims of Study

The main purpose of this study was to determine the level of prevalence and factors that affect adherence to MTX in RA patients receiving different Anti - TNF medications.

Patients and Methods

Study Design

This cross - sectional study was conducted among RA patients at Rheumatology Unit of Baghdad Teaching Hospital/ Medical City over the period from November 2021 to May 2022.

Sample Selection

A total of 100 patients (males =26, females =74) diagnosed as RA according to ACR /EULAR, 2010 criteria were included in the study.

Inclusion Criteria

Patients with RA diagnosed according to ACR /EULAR 2010 criteria for more than one year duration are using MTX and Anti TNF for more than 3 months were enrolled in the study.

Exclusion Criteria

- 1) Presence of other autoimmune Inflammatory Disease.
- 2) Patients with cognitive impairment.
- 3) Pregnant patients.
- 4) Patients with malignancy.

Ethical Considerations

Informed consent was obtained from each participant included in the study according to the declaration of Helsinki. Ethical approval was obtained from the Ethics Committee at Medical Department / College of Medicine, Baghdad University.

Data collection and entry

A questionnaire was used to collect information from the patients and a signed consent was taken for inclusion in the study.

Studied patients attended an interview questionnaire assessing socio - demographic, clinical and treatment characteristics survey including the Arabic version of the eight - item Morisky Medication Adherence Scale (MMAS - 8)⁽¹²⁾ which ranged from 0 - 8. {A score below 6 indicates low adherence, a score of 6 & 7 indicates medium adherence and a score of 8 indicates high 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 $BMI = \text{weight} / \text{height}^2$ (m²), residence, education level (Illiterate, primary, secondary, college, and postgraduate), marital status, employment status, chronic comorbidity, satisfaction with treatment, duration of RA (years), duration of MTX intake (years), current dose of MTX mg/week) and route of intake: oral or parenteral (S. C/ I. M), Type of anti - TNF used (Etanercept, Adalimumab (or biosimilar), Infliximab or Golimumab), Duration of anti - TNF use, any medication side effects, and disease activity at the time of visit according to disease activity index {CDAI}28)⁽¹³⁾ score (mild when CDAI of 2.8 - 10, moderate from 11 - 21 and severe 22 and over).

Statistical analysis

Data were analyzed statistically by SPSS (Version 25.0). In each group, either mean±SD for quantitative variables or frequency and percentages for qualitative variables were calculated.

An independent sample student t - test was used for comparing parameters between both groups. For categorical values Chi - squared test was used. a P - value 0.05 was considered statistically significant. Factors associated with medication non - adherence were explored using logistic regression analysis and are shown as odds ratios (ORs) with 95% confidence interval (CI).

2. Results

Demographic characteristics of the patients

The study was cross sectional included 100 RA patients. The mean patients age was 51.43 ± 9.711 years, with female predominance (74%). The majority of them were married 73%. Only 15% of participants were smokers and 87% were living in urban area.

The mean BMI was 25.163 ± 2.186 kg/m², Primary and Secondary educational level were the most common (32%, 34%, respectively). More than 50% of patient had moderate socioeconomic status and 60% were unemployed, as presented in table (1).

Table 1: Patients' Characteristics and Demographic data for 100 RA Patients

Variables	Number	(Percent %)
Age, years		
Mean±SD	51.43 ± 9.711	
Gender		
Male	26	(26%)
Female	74	(74%)
Marital status		
Single	14	(14%)
Married	73	(73%)
Divorced	5	(5%)
Widow	8	(8%)
Smoking		
Yes	15	(15%)
No	85	(85%)
Residency		
Urban	87	(87%)
Rural	13	(13%)
Body mass index, kg/m²		
Mean±SD	25.163 ±2.186	
Educational level		
Illiterate	14	(14%)
Primary	32	(32%)
Secondary	34	(34%)
College	18	(18%)
Post graduate	2	(2%)
Socioeconomic status		
Low	31	(31%)
Moderate	62	(62%)
High	7	(7%)
Employment		
Yes	40	(40%)
No	60	(60%)

Clinical and therapeutic characteristics of 100 RA patients

The Clinical and therapeutic characteristics of the 100 RA patients studied are shown in table (2)

The mean duration of disease was 8.36 ± 5.126 years, while the mean duration of MTX use was 7.29 ± 3.613 years, Fifty seven percent of patients took MTX orally. The mean duration of anti - TNF use was 3.55 ± 1.641 years and high proportion were using Etanercept (47%). Majority (84%)

had no side effects. More than half of them had no comorbidities (56%), and (91%) had no systemic involvement. Majority of patients (93%) were satisfied with treatment, and (94%) were self - dependent.

On clinical assessment (44%) of patients were having moderate disease activity, (39%) had low disease activity, (13%) had high disease activity and only (4%) were in complete remission state.

Table 2: Clinical and therapeutic characteristics of patients

Variables	Values
Disease duration,years	
Mean±SD	8.36 ± 5.126
MTX duration,years	
Mean±SD	7.29 ± 3.613
Route of MTX taking	
Oral	57 (57%)
parenteral	43 (43%)
Anti-TNF duration of use,years	
Mean±SD	3.55 ± 1.641
Type of anti-TNF	
Etanercept	47 (47%)
Adalimumab or biosimilar	31 (31%)
Infliximab	15 (15%)
Golimumab	7 (7%)
Side effects experienced	
Yes	16 (16%)
No	84 (84%)
Comorbidity	
Non	56 (56%)
One comorbidity	36 (36%)
More than one	8 (8%)
Systemic involvement	
Yes	9 (9%)
No	91 (91%)
Self-dependent	
Yes	94 (94%)
No	6 (6%)
Satisfaction with treatment	
Yes	93 (93%)
No	7 (7%)
Clinical assessment	
Remission	4 (4%)
Low disease activity	39 (39%)
Moderate disease activity	44 (44%)
High disease activity	13 (13%)

Adherence Rate

According to Morisky scale, (9%) of participants had high adherence for MTX medication, (37%) of them had medium adherence, while (54%) had low adherence for MTX medication as shown in Figure (1).

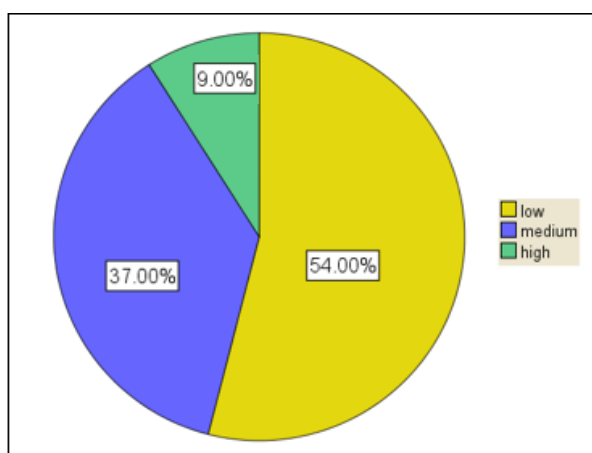


Figure 1: Adherence rate for MTX medication among 100 RA patients taking Anti - TNF according to Morisky scale.

Association of Patients Characteristics with Adherence rate:

The relation between adherence level and patient's demographic data was assessed. The mean age of the low adherent patients was (53.81 ± 9.521) years which was higher than that of medium - high adherent patients was (48.63 ± 9.267) years with highly significant differences, (P - value 0.007).

No statistical significant differences in the mean BMI between low and medium to high adherent levels, (P - value 0.47).

No statistical significant association between gender and marital status with adherence levels (P - values 0.41 & 0.14), respectively.

There is a statistical significant association between smoking and adherence level, (P - value 0.003) and 85.2% of the low adherent patients were urban residents compared to 87.0% of medium - high adherent group, but with insignificant differences (P - value 0.06). Low educational levels as well as low socio - economic state were reported significantly

more frequently among low adherent patients in comparison to medium - high adherent patients (P - values 0.005 & 0.045) respectively. Round two thirds (68.5 %) of low adherent patients were unemployed, which shows significant association (P - value 0.046) as presented in table (3).

Table 3: The association between adherence level and patient's demographic characteristics

	Variables Low (<6)	Med - high (≥6)	p - value
Age	53.81 ± 9.521	48.63 ± 9.267	0.007*
BMI	25.30 ± 2.43	24.99 ± 1.87	0.47
Gender			
Male	15 (27.8)	11 (23.9%)	0.41
Female	39 (72.2%)	35 (76.1%)	
Marital status			
Single	6 (11.1%)	8 (17.4%)	0.14
Married	39 (72.2%)	34 (73.9%)	
Divorced	3 (5.6%)	2 (4.3%)	
Widow	5 (11.1%)	3 (4.3%)	
Smoking			
Yes	8 (14.8%)	7 (15.2%)	0.003*
No	46 (85.2%)	39 (84.8%)	
Residency			
Urban	46 (85.2%)	40 (87.0%)	0.06
Rural	8 (14.8%)	6 (13.0%)	
Educational level			
Illiterate 0.005*	11 (20.4%)	3 (6.5%)	0.005*
Primary	21 (38.9%)	11 (23.9%)	
Secondary	18 (33.3%)	16 (34.8%)	
College	4 (7.4%)	14 (30.4%)	
Post - graduate	0 (0.0%)	2 (4.3%)	
Socioeconomic status			
Low	22 (40.7%)	9 (19.6%)	0.045*
Moderate	30 (55.6%)	32 (69.6%)	
High	2 (3.7%)	5 (10.9%)	
Employment			

Table 4: The relation between adherence level and disease characteristics

Yes	17 (31.5%)	23 (50.0%)	0.046*
No	37 (68.5%)	23 (50.0%)	

* The significant p - value ≤ 0.05

The non - significant > 0.05

Association of disease Characteristics with Adherence Rate:

The relation between adherence level and disease characteristics was assessed, the mean disease duration in low adherent group was 9.30 ± 5.358 years which was significantly higher than that of medium - high adherent group (7.26 ± 4.659 years). P - value 0.047

There was a significant difference between both groups regarding duration of MTX and anti - TNF use; the duration is less in med - high adherent group with a mean of MTX duration was 6.04 ± 3.596 and mean of anti - TNF duration was 2.84 ± 1.513 and p - value 0.01 and 0.001 respectively.

There is no statistical significant association between type of anti - TNF used and adherence to MTX, p - value 0.556.

Route of MTX administration, side effects and self - dependent showed that 65.1% of parenteral route patients were having med - high adherence compared to 31.6% of oral route. Side effects were reported among 51.2% of med - high adherent patients and 48.4% were self - dependent, P - values were <0.001, 0.017 and 0.02 respectively

No statistical significant differences were reported between comorbidities, systemic involvement and treatment satisfaction with adherence level, p - values were 0.064, 0.136 and 0.33 respectively.

A statistical significant difference was reported between groups of disease activities and adherence levels. P - value < 0.001, as shown in table (4).

Variables	Low (<6)	Med-high(≥6)	p-value
Disease duration (years)	9.30 ± 5.358	7.26 ± 4.659	0.047*
Duration of MTX use (years)	7.85 ± 3.253	6.04 ± 3.596	0.01*
Duration of anti TNF use (years)	4.15 ± 1.51	2.84 ± 1.513	<0.001*
Type of anti TNF			
Etanercept	26 (55.3%)	21 (44.7%)	0.556
Adalimumab(biosimilar)	14 (45.2%)	17 (54.8%)	
infliximab	9 (60.0%)	6 (40.0%)	
golimumab	5 (71.4%)	2 (28.6%)	
Comorbidity			
Non	26 (46.4%)	30 (53.6%)	0.064
One comorbidity	22 (61.1%)	14 (38.9%)	
More than one	6 (75.0%)	2 (25.0%)	
Systemic involvement			
Yes	7 (77.8%)	2 (22.2%)	0.136
No	47 (51.6%)	44 (48.4%)	
Side effects			
Yes	13 (81.3%)	3 (18.8%)	0.017*
No	41 (48.8%)	43 (51.2%)	
Self-dependent			
Yes	48 (51.1%)	46 (48.9%)	0.020*
No	6 (100.0%)	0 (0.0%)	
Route of MTX administration			
Oral	39 (68.4%)	18 (31.6%)	<0.001*
Parenteral	15 (34.9%)	28 (65.1%)	
Satisfaction with treatment			
Yes	49 (90.7%)	44 (95.7%)	0.33
No	5 (9.3%)	2 (4.3%)	
Disease Activity			
Remission+ Low disease activity	15 (34.9)	28 (65.1)	< 0.001*
Mod+ High disease activity	39 (68.4)	18 (31.6)	

* The significant p-value ≤ 0.05

The non-significant > 0.05

Multinomial logistic regression analysis

Multinomial logistic regression test was used to assess independent risk factors of low adherence to drugs. All

variables which had a significant association with adherence were entered in the model, all were independent risk factors for low adherence. The results are demonstrated in table (5).

Table 5: Multinomial logistic regression analysis

Variables	low - Adherent	Med - high Adherent	P - value	OR (95%CI)
Age, years				
≤45	15 (27.8%)	29 (63.0%)	0.004*	1
>45	39 (72.2%)	17 (37.0%)		0.225 (0.097 - 0.525)
Smoking				
No	46 (85.2%)	39 (84.8%)	0.448	1
Yes	8 (14.8%)	7 (15.2%)		0.969 (0.32 - 2.91)
Residence				
Rural	8 (14.8%)	6 (13.0%)	0.594	1
Urban	46 (85.2%)	40 (87.0%)		0.862 (0.27 - 2.69)
Education				
Yes	41 (75.9%)	42 (93.3%)	0.028*	1
No	13 (24.1%)	3 (6.7%)		4.439 (1.17 - 16.73)
Socioeconomic state				

High	2 (3.7%)	5 (10.9%)	0.273	1
Moderate	30 (55.6%)	32 (69.6%)	0.33	6.11 (0.996 - 37.49)
Low	22 (40.7%)	9 (19.6%)	0.050*	2.34 (0.422 - 13.008)
Employment				
Yes	37 (68.5%)	23 (50.0%)	0.061	1
No	17 (31.5%)	23 (50.0%)		0.459 (0.203 - 1.038)
Disease duration (years)				
≤10	31 (57.4%)	38 (82.6%)	0.008*	1
>10	23 (42.6%)	8 (17.4%)		0.284 (0.112 - 0.722)
Duration of MTX use, (years)				
≤ 5	17 (31.5%)	26 (56.5%)	0.013*	1
>5	37 (68.5%)	20 (43.5%)		0.353 (0.156 - 0.801)
Duration of anti - TNF use (years)				
≤3	20 (37.0%)	36 (78.3%)	0.001*	1
>3	34 (63.0%)	10 (21.7%)		0.163 (0.067 - 0.399)
Side effects				
Yes	13 (81.3%)	43 (51.2%)	0.025*	1
No	41 (48.8%)	46 (48.9%)		4.545 (1.206 - 17.120)
Self - dependent				
Yes	48 (51.1%)	46 (48.9%)	0.020*	1
No	6 (100.0%)	0 (0.0%)		0.489 (0.389 - 0.590)
Route of MTX administration				
Parenteral	15 (34.9%)	28 (65.1%)	0.051	1
Oral	39 (68.4%)	18 (31.6%)		4.044 (1.746 - 9.366)
Disease activity				
Remission	1 (1.9%)	3 (6.5%)	0.177	1
Low disease activity	14 (25.9%)	25 (54.3%)	0.142	0.148 (0.012 - 1.90)
Moderate disease activity	30 (55.6%)	14 (30.4%)	0.043*	0.249 (0.065 - 0.957)
High disease activity	9 (16.7%)	4 (8.7%)	0.943	0.952 (0.250 - 3.629)

* The significant p - value ≤ 0.05

3. Discussion

Patients with RA are often required to take so many medications by different routes and at varying times, which may lead to issues with medication adherence. MTX remains the initial drug of choice for most patients and is frequently used in combination with biologics. Therefore, adequate adherence to MTX remains a major therapeutic goal.

This study aimed to determine the prevalence and predictors of MTX non - adherence among Iraqi patients with RA taking anti - TNF medications. According to this study, the mean age of the patients was (51.43 ± 9.711) years, this is in accordance with previous studies performed among Iraqi RA patients. Al - Ani et al. (6) found that the mean age of their patients with RA was (48.1 ± 12.1) years, while Faiq M. K. et al. (14) found the mean age was (50.8 ± 13.1) years, this confirm a high incidence of RA in this age range among Iraqi patients.

This study showed that by using the Morisky Medication Adherence Scale, 54% of patients with RA who were taking Anti - TNF medications in combination with MTX had relatively low adherence to MTX therapy, which is less frequently compared to the results of a previous study that was carried out in Iraq in 2022 by Al tuma A. et al (15) which showed that RA patients who take MTX with Anti - TNF therapy were of lower adherence to MTX (71.42%) than those taking MTX alone (41.37%). Also another study from USA showed that among RA patients taking MTX, there were higher proportion of non - adherent patients compared to adherent patients among those treated with concomitant Tumor Necrosis Factor antagonists (p = 0.04) (16).

Similar results were obtained by Heidari et al. in 2019 (17) who suggested that non-adherence to oral RA medications was prevalent among bDMARDs users. Also, this finding is consistent with the finding of a study from USA, where the majority of bDMARDs users had <60% adherence to oral RA medications. Due to the higher effectiveness of bDMARDs. Researchers believe that patients may underestimate the effect of other medications and for that they were not taking them (18).

The low adherence patients in this study were older, mostly married females with a primary educational level, unemployed and had a low to moderate socioeconomic status. This is in accordance with a study from Saudi Arabia (19) surveyed 126 patients in 2016 using the 8 - item Morisky Medication Adherence Scale (MMAS - 8) by using a validated Arabic version and the Health Assessment Questionnaire (HAQ), were showed that 52.4% of them were of low adherence, and were mostly females of low educational and socioeconomic status. Also Arshad et al 2016 in another study (20) found that patients of low socioeconomic class were more likely to be non - adherent.

Disease duration, duration of MTX and Anti - TNF therapy, in this study we found a significant differences between the two groups in terms of the duration of RA, MTX and anti - TNF intake, with low adherent group taking them for longer period of time, this was in accordance with the study from Egypt by Gadallah et al. (21), who measured adherence rate using the 8 - item Morisky's scale (MMAS - 8), which was done among 140 RA patients and found that low adherence group is associated with longer disease duration and medication usage.

This study showed no significant differences between those with presence or absence of comorbidity, systemic involvement, or drug satisfaction with treatment. This is different from a Danish Nationwide Cohort Study in 2015⁽²²⁾ which showed the adherence to MTX was associated with good general health as demonstrated by the significantly higher drop - out rate in patients with comorbid conditions, while this development may also reflect a modulation of the treating physician due to comorbidities. Our results also opposed to another study done by De Cuyper et al.⁽²³⁾ from Belgium on 129 patients in which adherence was measured using the Medication Event Monitoring System (MEMS). This study found the positive influence of comorbidity on adherence rate. Treatment satisfaction among Egyptian studied patients showed that moderately adherent respondents had significantly higher beliefs of the importance and benefits about RA medications compared with low - adherent patients.⁽²¹⁾ These findings agreed with those reported by Trehan et al.⁽²⁴⁾ who showed that good belief about the importance of medications was associated with better medication adherence.

For route of administration of MTX, side effects, self - dependent, and type of anti - TNF therapy used, this study found that the majority of low adherence patients received MTX via oral route, whereas the majority of medium - high adherence patients received MTX via parenteral route. The same results were reported by Al tuma A.⁽¹⁵⁾ study, which concluded that the adherent group used the parenteral route more than the oral route in comparison to the non - adherent group. These findings are not consistent with a study conducted among Spanish population in 2021⁽²⁵⁾ (a total of 859 patients attended 41 centers were studied) which shows that route of administration does not have an impact on adherence rate. It was reported by some studies that parenteral intake is associated with a higher bioavailability, by passing the 1st pass hepatic metabolism, reduced frequency and intensity of some gastro - intestinal side effects than oral MTX which may improve treatment compliance and reduce MTX discontinuation rates^(26, 27). Other studies suggested that there were no differences in adherence between oral and parenteral MTX intake and an increased adherence to oral intake was reported in certain RA patients; those who had phobia from injections, elderly patients who didn't have caregivers, those with severe involvement and hand deformities who could not use their hands to inject themselves⁽²⁸⁾. Also, this was in line with what has been shown in another study,⁽²⁹⁾ which suggested that the administration of drugs via the oral route may not be a reason for poor adherence, while there are no significant differences between both groups regarding the type of anti - TNF used in accordance with the Spanish study which showed that the type of treatment did not determine the adherence rate.⁽²⁵⁾

Studying the presence of side effects the results showed about 81.3% of patients with side effects from MTX had low adherence to treatment. This is in accordance with a study from Poland including 415 polish patients with RA, which found that 63.33% of patients have side effects and the occurrence of side effects significantly increases the risk of discontinuation, often without consulting the physician.⁽³⁰⁾

Most of the participants in this study were self - dependent this is important for patients adherence to medications, previous Indian study showed that living alone has been previously associated with poor adherence. Social support seems to be an important factor contributing to proper compliance. Family support has been related to an improvement in adherence to MTX in RA⁽³¹⁾

For clinical assessment, this study showed moderate disease activity was reported most frequently in patients with low adherence compared to medium - high adherence which is mostly noted among patients with low disease activity. This is consistent with other studies^(32, 33, 34) which showed that patients with better adherence generally have less disease activity. Also an Egyptian study⁽²¹⁾ showed a significantly higher disease activity (69.3%) among low - adherent group.

In another study⁽³⁵⁾ done in the southwest of the Netherlands during 2014, on a sample of 300 patients using a medication event monitoring system' (MEMS) device to measure the adherence level suggested that non adherence was a strong predictor of higher disease activity and thus contributes to failure of remission. Another study from China⁽³⁶⁾ investigated the association of medication adherence and disease activity among RA patients, the results of this study suggest that RA patients with higher medication adherence tended to have lower disease activity.

In this study we found that the independent risk factors for low adherence according to multinomial logistic regression analysis were older age >45 years, illiteracy, low socioeconomic state, disease duration >10 years, MTX use duration >5 years, duration of anti - TNF usage of >3 years, presence of side effects, non self - dependent, and moderate disease activity

4. Conclusions

- 1) More than half (54%) of Iraqi patients with RA who are taking a combination of MTX and anti - TNF therapy were poorly adherent to MTX.
- 2) Patients aged > 45 years, illiteracy, low socioeconomic status, RA for more than 10 years duration, MTX use for more than >5 years, duration of anti - TNF use >3 years, presence of side effects, non - self dependent, and moderate disease activity were independent risk factors for low adherence. .

Conflict of interest: The authors declare no conflict of interest.

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