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RESEARCH ARTICLE

The Causes of Non-Adherence to Methotrexate in patients with Rheumatoid Arthritis

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ABSTRACT:

Background: Rheumatoid arthritis (RA) is a chronic progressive autoimmune inflammatory systemic disease; methotrexate is the first drug of choice to retard the disease progression. **Objective:** To elucidate the main factors that leading to non-adherence to methotrexate in patients with rheumatoid arthritis. **Method:** In this cross-sectional study, one hundred twenty-two (122) patients diagnosed with RA ≥ 18 years old on methotrexate (mono or combined therapy) for at least three months. Data were recorded including demographic data, socioeconomic status, education level, disease duration, duration of methotrexate therapy, current weekly methotrexate dose, concomitant drugs, and factors might contribute to non-adherence. Non-adherence was considered when three or more of weekly dose of methotrexate were omitted in the last 8 weeks. **Results:** 38 patients (31.14%) were non-adherent. Patients with longer disease duration, those with higher education level, and on concomitant steroid had higher rate of non-adherence. Among the factors contributing to non-adherence are: Methotrexate Don't treat arthritis symptoms well 25 patients (65.78%), social myths 24 patients (63.15%), Don't need it when feeling well: 22 patients (57.89%) were on the top of list. **Conclusion:** The patients with non-adherence in the current study constitute about one third of the patients. Good adherence rate can increase by good doctor-patients communication and continuous patients' education and counseling by treating rheumatologist.

KEYWORDS: Methotrexate, Rheumatoid arthritis, Non-adherence, DMARD, NSAIDs.

INTRODUCTION:

Rheumatoid Arthritis (RA) is considered as a chronic autoimmune systemic disease that characterized by progressive destructive arthritis with a symmetrical fashion that affect mainly the small joints of hands and feet with extra articular manifestations[1]. RA affects both genders with female/male ratio of about 2.5-3. RA is world –wide distribution and can affect people of any age but the peak incidence at third and fourth decades[1,2,3]. The main goal of RA treatment is to bring the disease to state of clinical remission[4].

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To avoid the structural damage of joints, reduce symptoms, normalize function and social participation and to maximize health related quality of life; disease should diagnosed and treated as early as possible[5,6,7].

The progression of the RA can be modified or even halted with long-term improvement when it is treated as early as possible by disease modifying anti rheumatic drugs (DMARDs)[8-11]. The appropriate identification of the molecular mechanism that involved in the pathogenesis of RA can lead to more powerful development of many efficient targeting therapies[12,13].

Methotrexate (MTX) can be considered by many clinicians as the first line monotherapy for early active RA as the initial disease-modifying antirheumatic drugs (DMARDs)[1,3,14-17]. To enhance the efficacy, MTX can be

used in combination with other conventional DMARDs typically sulfasalazine and/or hydroxychlorquine.

Additionally, a combination of MTX with biologics works synergistically leads to an improvement in their clinical efficacy, MTX tolerability and also suppresses the immunogenicity of these agents and increasing their serum drug levels[3,18]. The dose of MTX also showed an advantage of the adjustability in addition to the ability of administer it either orally or subcutaneously[1,3].

Despite of the usage of conventional DMARDs either as a monotherapy (methotrexate alone) or in a combination, remission doesn't achieve in all patients[19,20]. There are many factors that may affect the remission achievement negatively such as the non-adherence to the treatment prescribed. Non adherence {defined as the degree to which a patient takes medication in accordance with clinician instructions[21]. Persistence is considered as one aspect of adherence which can be define as the drug administration continuity during an overall duration of treatment[22,23]. The adherence to DMARDS can be considered as one of the crucial factor that may affect RA improvement[24].Several previous studies demonstrated that the patients adherence to medication in rheumatoid arthritis is low, ranging from 30 to 80%[25]. Improving adherence to therapy could therefore dramatically improve the efficacy of the treatment[22]. It was reported previously that there were several reasons that affect patients' compliance which can be grouped into several categories, namely, patient-centered factors, therapy-related factors, healthcare system factors, social and economic factors, and disease factors [21]. This study was aimed to elucidates the factors that may influence non adherence of patients with RA to methotrexate therapy.

METHODS:

This cross-sectional study was conducted at out-patients department of rheumatology and rehabilitation center at Merjan Teaching Hospital, Al Hillah, Babil, Iraq during the period from July to December 2018. 122 Patients diagnosed with RA were recruited in the current study who received MTX for period of more than three months and were ≥18 years of age. A verbal consent before pre-designed quaternary schedule was done. The domains of pre-designed questionnaire include the followings:

Demographic data:
Including age, gender, and occupation address of patients which recorded.

Education level:
Defined as illiteracy (no formal education), Primary school, secondary school, after secondary school.

Economic status:
Was classified as low: income 500,000 Iraqi dinar (I.D) monthly, medium: above 500.000 but below 0ne million I.D and high income when monthly income more than one million I.D

Duration of disease:
Measured in years

Duration of methotrexate therapy:
Measured in months

Dose:
Dose of current weekly methotrexate in mg/week.

Other current medications like NSAIDs, other DMARDs and corticosteroid were recorded.

Reasons might contribute for methotrexate non-adherence was recorded:

1. Forgetfulness
2. Non availability of drug at out-patients pharmacy,
3. Myths about the drug
4. Lack of governmental and familial financial support and transportation,
5. Concerns of long term safety (fearing of side effects on long term use)
6. Slow acting and initially not relieving symptoms (initially not treating arthritis well)
7. Lack of patients' awareness of drug long-term benefit
8. Because of side effects
9. Desire to form a family.
10. Don't need it when feeling well.

The adherence of patients with RA was assessed by this question: How the patients adhere to doctor's prescription of methotrexate during the last 8 weeks. non- adherence when was omission or missing of any three or more of prescribed methotrexate weekly dose.

Statistical analysis:
The results of the current study were firstly stored in a Microsoft Excel format and the numerical variables were expressed in the form of mean±SD. All the comparisons that performed were accomplished statistically by using independent t-test to compare two independent groups (patients and controls). Categorical variables were expressed as numbers and analyzed by cross tabulation to assess the frequency and percentage of each variable among studied groups. The correlation was performed by Chi square (X^2) to test the relationships between categorical variables. A p-value of ≤ 0.05 was considered as significant All statistical analyses used in this study were carried out by using the IBM SPSS Statistics for Windows, Version 20.0 (Armonk, NY: IBM Corp).

RESULTS:

Table 1 showed the association between adherence to methotrexate and sociodemographic characteristics including (age, gender, educational level and socio economic status) among study patients and revealed that the only factor that affect the adherence of patients significantly was the education level of patients whereas the other sociodemographic factors did not affect the compliance significantly.

Results postulated in table 2 revealed the association between adherence to methotrexate and study variables including duration of rheumatoid arthritis, duration of Methotrexate treatment, weekly dose of Methotrexate, Concomitant steroid therapy, use of NSAIDs and Concomitant DMARD among study patients and illustrated that there were significant association between Duration of rheumatoid arthritis, Concomitant steroid therapy and use of NSAIDs with the adherence of patients

Table 1: The association between adherence to methotrexate and sociodemographic characteristics

Socio-demographic variables	Total (N=122)	Adhere to MTX (N=84)	Not adhere to MTX(N=38)	P-value
Age	**(44.87 ± 8.73)**	**(45.97 ± 7.09)**	**(42.44 ± 11.31)**	**0.082**
Gender				0.488
Male	34 (27.9)	25 (29.8)	9 (23.7)	
Female	88 (72.1)	59 (70.2)	29 (76.3)	
Total	122 (100.0)	84 (100.0)	38 (100.0)	
Educational level				**< 0.001**
Illiterate	18 (14.8)	16 (19.0)	2 (5.2)	
Primary	39 (32.0)	36 (42.9)	3 (7.9)	
Secondary	47 (38.4)	26 (31.0)	21 (55.3)	
Higher education	18 (14.8)	6 (7.1)	12 (31.6)	
Total	122 (100.0)	84 (100.0)	38 (100.0)	
Socioeconomic status				0.125
More than 1000000	68 (55.7)	49 (58.4)	19 (50.0)	
500-1000000	34 (27.9)	19 (22.6)	15 (39.5)	
Less than 500000	20 (16.4)	16 (19.0)	4 (10.5)	
Total	122 (100.0)	84 (100.0)	38 (100.0)	

Table 2: The association between adherence to methotrexate and study variables.

Study variables	Total (N=122)	Adherent to MTX (N=84)	Not Adherent to MTX (N=38)	P-value
Duration of rheumatoid arthritis (years)	(5.47 ± 2.33)	(5.10 ± 2.18)	(6.31 ± 2.46)	0.007*
Duration of Methotrexate treatment (months)	(46.50 ± 22.58)	(48.60 ± 19.36)	(41.86 ± 28.19)	0.187
Weekly dose of Methotrexate (mg)	(14.28 ± 2.35)	(14.25 ± 2.50)	(14.34 ± 1.98)	0.852
Concomitant steroid therapy				
Yes	62 (50.8)	28 (33.3)	34 (89.5)	
No	60 (49.2)	56 (66.7)	4 (10.5)	**<0.001**
Total	122 (100.0)	84 (100.0)	38 (100.0)	*****
Use of NSAIDs				
Yes	47 (38.5)	40 (47.6)	7 (18.4)	
No	75 (61.5)	44 (52.4)	31 (81.6)	**0.002***
Total	122 (100.0)	84 (100.0)	38 (100.0)	
Concomitant DMARD				
Yes	39 (32.0)	31 (36.9)	8 (21.1)	
No	83 (68.0)	53 (63.1)	30 (78.9)	0.082
Total	122 (100.0)	84 (100.0)	38 (100.0)	

Furthermore, figure 1 showed the distribution of patients according to adherence to Methotrexate which revealed that the majority (68.9%) of patients have good adherence to Methotrexate treatment. On the other hand, results illustrated in figure 2 showed the distribution of patients that non adherent to Methotrexate according to cause of non-adherence which revealed that the Majority (44.7%) of patients non adherent to Methotrexate had multiple mentioned causes for non-adherence followed by patients did not adhere to MTX because it didn't treat arthritis symptoms (21.1%), social myths (18.4%) and patients' compliance to the treatment after feeling well (13.2%). Moreover, patients' causes for the non-adherence varied among the population selected but the most common causes for the non-adherence were their thought about the failure of MTX in the treatment of arthritis (65.79**%),** social myths (63.16%) beside their believes that there were no need for treatment when they become well (57.89%). Each of these causes can cause a non-adherence alone or in combination with other causes whereas other causes my lead to a non-adherence only in combination with others such as the concern about long-term safety, lack of patients awareness of drug long-term benefit, Availability side effects and other less common factors listed in table (3)

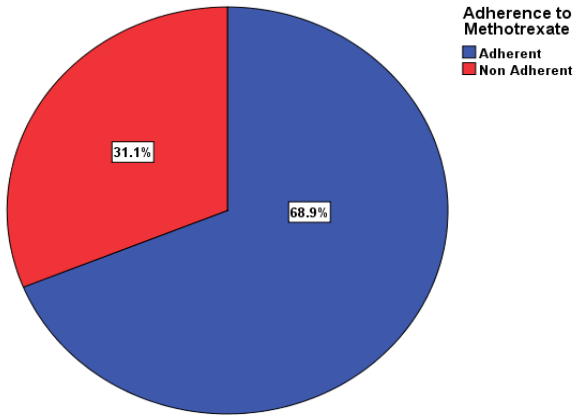

Figure 1: Distribution of patients according to adherence to Methotrexate

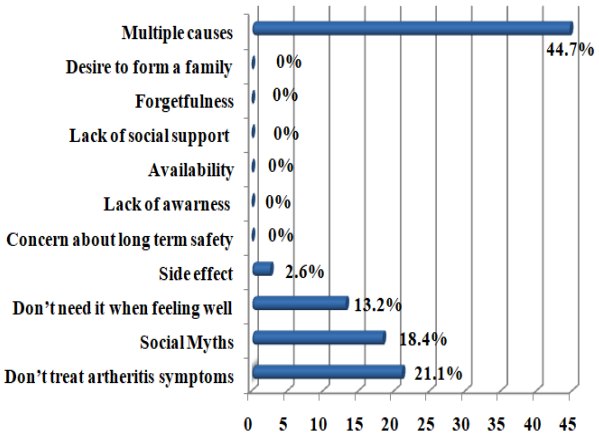

Figure 2: Distribution of patients that non adherent to Methotrexate according to cause of non-adherence

Table 3: shows number of patients according single or combined reasons for MTX non- adherence:

Reason	Single	Combined	Total (%)
Don't treat arthritis well	8	17	25 (65.78 %)
Social myths	7	17	24 (63.15%)
Don't need it when feel well	5	17	22 (57.89 %)
Concern about long-term safety	0	15	15(39.47%)
lack of patients awareness of drug long-term benefit	0	12	12 (31.58 %)
Availability	0	11	11 (28.95 %)
Because of side effects	1	8	9 (23.68 %)
Lack Of Social Support	0	6	6 (15.79%)
Forgetfulness	0	5	5 (13.16%)
Desire to form a family	0	4	4 (10.53 %)
No. of patients	21	17®	38

®Patients had multiple reasons for non-adherence

DISCUSSION:

The aim of this study was to find out the main reasons for non-adherence to methotrexate among patients with rheumatoid arthritis. The full non-compliance reasons' understanding may help in the identification and planning for the proper programs or strategies that can improve health quality through good adherence to MTX treatment. In this study 84 patients (68.85%) were adherent to MTX. This percentage of adherence is slightly lower than that of study done by Arshad et al 2016 where patients' adherence to methotrexate was 77%[26]. The expected explanation of this slight difference between the current study and the previous one is the difference in the education level, the high educational patients subjected to the present study represent about 14.8% whereas patients with high educational level represent about 26% in Arshad et al 2016 which might affect the adherence and improve patients compliance.

In the current study the most frequent reasons for MTX non adherence were the slow acting of MTX that it didn't treat arthritis immediately (65.78%), social myths regarding MTX therapy (63.16%) and the patients' thoughts that there were no needs for MTX when they feel well (59.87%) whereas the forgetfulness is at the bottom of the list (13.16%). These results were disagreed with studies of Arshad et al 2016who stated that the most common causes for MTX non-adherence are forgetfulness (74%), Affordability (69.6%), Lack of awareness regarding importance and long term need of drug (65.2%) and Lack of Social Support (56.5%)[26] and DiBenedetti et al 2015 who reported that the reasons of non-adherence included the forgetfulness (33%), not needing it when feeling well (24%), and concern about long-term safety (24%)[27]. The disagreement of our study with the previously mentioned researches may be owned to the difference in the education levels and the population subjected to the study.

As listed above, the most common reason for non-adherence to MTX in this study was the failure of MTX to treat RA symptoms which comes from the patients' observations that MTX showed no benefit regarding stiffness and joint pain in the first few weeks of starting methotrexate therapy. This finding supported by the fact that most of patients subjected to the current study were non- educationally enough to understand the slow acting nature of DMARDs therapy. Additionally, most patients in the present study had good experience with immediate relieving effects of non DMARDs agents like corticosteroid which has an immediate potent anti-inflammatory effect with no need for waiting weeks with unfamiliar slow acting drugs which affect their confidence toward MTX that result in a non-adherence pattern of drug administration. Here the bridging minimal controlling dose of corticosteroid is of importance for minimizing the symptoms while waiting the methotrexate effects which reported previously in another study[28].

The second most common cause of MTX non-adherence in this study was the myths about the drug and it is use

as one of chemotherapeutic drug for the treatment of malignancy with fearful side effects and gloomy end results, attributing in non-adherence among RA patients which require further awareness to eliminate these myths in future. Moreover, the discontinuation of the methotrexate treatment when the patients feeling well can be considered as the third most common cause of MTX non-adherence in our work. Here the patients might not be well educated about the fact that the state of clinical remission which induced by conventional DMARDs might be followed by exacerbation of disease activity after discontinuation of therapy especially those receiving MTX as a monotherapy[29]. Whereas those received MTX in combination with biologics showed more devastating withdrawal effect when they discontinued it as they will lose the potentiating effect in addition to MTX role in minimizing the immunogenicity and antibody formation to biologics as illustrated previosly[30-32].

Results postulated in this study demonstrated that the age, gender and socioeconomic were not associated with the methotrexate non adherence which are in consistent with the results obtained by Arshad et al 2016[26]. In contrast the education levels showed significant effect on that adherence given that patients with lower education showed better compliance than the higher educated groups that might be occur as a result of patients knowledge and their ability to use internet in the seeking about the long term side effects of the drug that may affect their compliance negatively. These findings are also disagreed with those concluded by previous studies who found that there was a non-significant association between the education levels and non-compliance and this disagreement may be caused by the fact that the percentage of educated patients subjected to the previous studies differs from those subjected to the current research[26,27].

Despite of the fact that the current study may add reasons for MTX non-adherence in patients with RA to the previous reports, our study faced many limitations in which the small sample size can be considered as the main limitation. Therefore, it is more important to enlarge the population subjected in an attempt to generalize the findings of the current study to more sectors of MTX population.

In conclusion this current study raised the importance of continuous doctor- patients communication skills and continuous demonstrative educational programs mainly about the nature of disease, and DMARDs in order to reduce the number of cases of non- adherance as can as possible.

CONFLICT OF INTEREST:

The authors declare no conflict of interest.

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