Available online at **www.ijmrhs.com**

ISSN No: 2319-5886

International Journal of Medical Research & Health Sciences, 2018, 7(1): 116-121

Methotrexate in Rheumatoid Arthritis Patients: Common Side Effects and Leading Cause of Discontinuation

Majed Alsubaie[1]*, Waleed Alqahtani[1], Waleed Alshardi[1], Hanan Albishi[1], Sarah Mujarri[1], Alhussain Asiri[2] and Mansour Somaily[2]

[1] *Medical Student, College of Medicine, King Khalid University, Abha, Kingdom of Saudi Arabia*

[2] *Consultant Internist and Rheumatologist, Department of Internal Medicine, Aseer Central Hospital, Abha, Saudi Arabia*

**Corresponding e-mail: majedalsubaie641@gmail.com*

ABSTRACT

Objectives: *To evaluate frequency and to identify factors which may increase the discontinuation of Methotrexate (MTX) among Rheumatoid arthritis (RA) patients in Aseer region, KSA.* ***Methods:*** *A cross-sectional study was conducted in Aseer Central Hospital, Southern region, Saudi Arabia that are currently or previously were using MTX. All the patients were included who fulfilled the 1987 revised American Rheumatism Association criteria for classification of RA. Medical records for 200 RA patients were chosen through convenience method then they reviewed and analyzed.* ***Results:*** *A total of 200 RA patients were participated, 169 (84.5%) were female and 31 (15.5%) were female. Their ages ranged from 12 to 80 years with a mean of 45.07 and standard deviation 14.37 years. About 67 (33.5%) patients told that their disease duration was 10 years and more and 147 (73.5%) patients were using MTX and 53 (26.5%) were not using the medication. Out of 147 patients, 24 (27%) of them did not take MTX regularly due to different reasons. The most common side effects were stomach ache as same as indolence and sloth. There is no statistical association between sex, education level and duration of disease and discontinuation at p=0.05.* ***Conclusion:*** *The study concluded a low rate of drug discontinuation due to adverse effects, MTX seems to be a safe drug for long-term use in RA patients. More attempts should be done to minimize side effects and discontinuation of MTX, in order to get the benefits of drug considered as the cornerstone in RA treatment.*

Keywords: Arthritis, Rheumatoid, Saudi Arabia, Methotrexate, Rheumatic diseases

Abbreviations: MTX: Methotrexate; RA: Rheumatoid Arthritis; DMARD: Disease-Modifying Anti-Rheumatic Drug

INTRODUCTION

Rheumatoid arthritis (RA) is one of the most common chronic, inflammatory condition causing systemic illness and pain, swelling and destruction of the joints [1]. It affects about 0.5-1% of the population worldwide [2]. It is characterized by the inflammation of the synovial tissue, which if untreated, leads to permanent structural damage and eventual long-term disability and impaired quality of life [3]. RA is one such condition where patients need to take daily medication to relieve their pain and reduce chances of physical disability. Use of traditional and biological disease-modifying anti-rheumatic drug (DMARD) improve outcome, induce and maintain good disease control. DMARD are the mainstay of treatment in RA. Methotrexate (MTX) is the most commonly used DMARD in RA with less toxicity and better tolerability than others [3,4]. It is pharmacologically classified as an anti-metabolite due to its antagonistic effect on folic acid metabolism. Although the mechanism by which low dose MTX modulates inflammation in RA is still unclear, the evidence for its efficacy has been well documented in several randomized controlled trials (RCT) and meta-analyses [5,6].

The safety profile of MTX has been studied over 25 years with very few clinically important adverse events in the weekly low-doses used for RA treatment. MTX courses show some of the longest continuation rates reported in clinical medicine, due to both effectiveness and safety. The safety profile of MTX indicates that it is among the safest

of any mediation used for the treatment of any arthritis [7]. It is known that 80% of all DMARDs are discontinued up to 2 years after beginning treatment owing to adverse effects or lack of efficacy, except for methotrexate (MTX), which is commonly administered for more than 5 years [8-10].

Many patients stop medications because of their physicians' order, while others discontinue medication because of experiencing unwanted adverse effects [11]. In a retrospective multicenter study of 760 RA patients that analyzed reasons for DMARD discontinuation, 47.1%, 43.2% and 9% interrupted therapy due to lack of efficacy, adverse events, or undefined reasons, respectively [12].

The study aims to evaluate frequency and to identify factors which may increase the discontinuation of MTX among our RA patients in Asir region, KSA.

METHODS

Based on Retrospective analysis reviewing the medical records of patients with Rheumatoid Arthritis (RA) who are on MTX or they were used it previously. We conducted across sectional study in a tertiary hospital (Aseer Central Hospital, southern region, Saudi Arabia) that are currently or previously were used MTX. All the patients included fulfilled the 1987 revised American Rheumatism Association criteria for classification of RA [13] and their ages more than 12 years. Medical records for 200 RA patients were chosen through convenience method then they reviewed and analyzed. Ethical considerations were considered such as not harming by used patients' information, non-malfeasance process requires which harm patients and maintain the confidentiality of patients' data.

The study included two data collection sheets; first one includes medical records number of RA patients and each file will have a specific code number and will be kept with the mentor. The other sheet will include the following information: sex, age, education level, disease duration, Use of MTX and Adherence to MTX usage. In case of lake of adherence to identify the reasons (Side-effects, what is it, lack of efficacy).

Data were analyzed using SPSS software, version 21. The data were summarized using descriptive statistics: mean ± standard deviation (SD), or frequencies (number) and percentages (%). T-test and Chi-square test were used as appropriated. A probability value $p<0.05$ was considered statistically significant.

RESULTS

This study included 200 rheumatoid arthritis patients according to the revised ACR classification criteria for RA [13]. Around 169 (84.5%) of our patients were females and 31 (15.5%) were males. Age ranged from 12 to 80 years with a mean of 45.07and standard deviation 14.37 years. Around 70 (35%) participants were illiterate, 46 (23%) of the study participants could read and write, 38 (19%) was high school and 46 (23%) had a university degree, master or above, while the majority of study participants were graduates 728 (66.9%) (Table 1). Disease duration ranged from less than 6 month to more than 10 years; 5 (2.5%) their disease duration was less than 6 months, 35 (17.5%) their duration form 6 months to two years, 42 (21%) of patients their disease duration was from 2 years to 5 years, 51 (25.5%) of patients their disease duration was from 5 years to 9 years and 67 (33.5) of patients their disease duration was 10 and more.147 (73.5%) of our patients were using methotrexate and 53 (26.5%) weren't using MTX. 107 (53.5) of patients had another source of information beside their doctors; 82.2% got the information form he internet (Figure 1).

Table 1 General characteristics of RA patients

Variables	N (%)
Gender	
Male	31 (15.5)
Female	169 (84.5)
Age (years)	
Mean ± SD	45.07 ± 14.37
Educational level	
Illiterate	70 (35)
Can read and write	46 (23)
High school	38 (19)
University graduated	45 (22.5)

Advanced studies	1 (0.5)
Duration of disease	
Less than 6 months	5 (2.5)
From 6 months - 2 years	35 (17.5)
From 2 - 5 years	42 (21)
From 5 - 9 years	51 (25.5)
Above 10 years	67 (33.5)
MTX used	
Yes	147 (73.5)
No	53 (26.5)

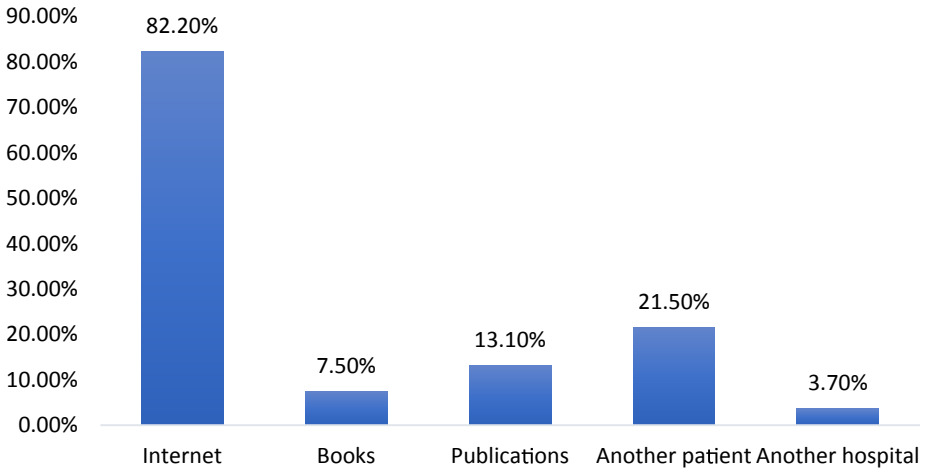

Figure 1 Sources of information about RA disease

Out of 147 patients; 24 (27%) of them didn't take MTX regularly because different causes as presented in Table 2, 19 (12.9%) patients referred to forget taking MTX, 20 (13.6%) because its side effects, also 17 (11.6%) of patients were afraid of MTX side effects, 8 (5.4%) believed that MTX not useful (poor response) as same as finished of MTX and 6 (4.1%) patients weren't regular because MTX was unavailable.

Table 2 Causes of methotrexate (MTX) Irregular used in 24 patients

Cause	N	%
Forgot	4	16.7
Side effects	9	37.5
Not useful	1	4.2
Afraid of side effects	5	20.8
Finished of MTX tablets	4	16.7
Unavailable	5	20.8
Price	1	4.2

MTX side effects were presented in Table 3. Nausea and vomiting were detected in 21 (14.3) patients; stomach ache was detected in 29 (19.7%); indolence and sloth were detected in 29 (19.7%); microbial infections were detected in 10 (6.8%) Joints pains were detected in 7 (4.8%) patients.

Table 3 MTX associated in 147 patients with RA

Side effect	N	%
Nausea and vomiting	21	14.3
Stomach ache	29	19.7
Indolence and sloth	29	19.7
Microbial infections	10	6.8
Severe headache	1	0.7

Hair loss	2	1.4
Breathing problems	2	1.4
Vision problems	2	1.4
Joints pains	7	4.8

Table 4 showed that there is no significant association between irregular cause using chi-square test for sex, educational level and duration of disease and test for age (P>0.05).

Table 4 Comparison of MTX regular and non-regular patients by demographic variables

Variables		MTX regular				P
		Yes (146)		No (54)		
		N	%	N	%	
Age (years)	Mean ± SD	46.06 ±14.13	-	39.96 ± 12.87	-	0.054
Sex	Male	20	95.2	1	4.8	0.138
	Female	103	81.7	23	18.3	
Education	Non-educated	40	81.6	9	18.4	0.58
	Can read and write	29	87.9	4	12.1	
	High school	24	80	6	20	
	University graduated	29	85.3	5	14.7	
	Advanced studies	1	100	0	0	
Duration	Less than 6 months	3	100	0	0	0.934
	From 6 months to two years	23	79.3	6	20.7	
	From 2 - 5 years	27	87.1	4	12.9	
	From 5 - 9 years	31	81.6	7	18.4	
	Above 10 years	39	84.8	7	15.2	

DISCUSSION

In the present study which included 200 RA patients with 147 (73.5%) patients were currently on MTX, while 24 (16.3%) of the patients stopped MTX due to different causes. This result is different than what was reported regarding the rate of discontinuation of MTX which was found to be 37% after about 6 years [12] about 45% after 8 years [14] and about 29.3% rate of discontinuation [14], indicating that MTX is a safe and effective medication [15] especially when comparing such rate of discontinuation to what was reported regarding other DMARDs in the first 2 years, with discontinuation of about 80% of them due to adverse effect or lack of efficacy [12].

Among causes of discontinuation of MTX in our patients is side effects was coming in the first (9; 37.5%), and also afraid of side effects (5; 20.8%) which contains nausea and vomiting and stomach ache. The side effects are a common factor of controlling regularity in using MTX or not, this result was in line with the [15-17].

Most common side effects were gastrointestinal (53.7%) in nature similar to other studies (53%) [18], and higher than an Indian study (21%) [19]. these included nausea, vomiting, stomach ache, and indolence and sloth. No side effects could be named as being definitely associated with MTX according to Narenjo scale [20]. However, no adverse effects were irreversible [18,20].

On comparing patients of Group 1 (regular using MTX) to patients of group 2 (irregular using MTX) by Chi square test significant statistical association; we found no significant statistical regarding disease duration of disease, educational level and sex. Vomiting and nausea were significant and statistically associated by two groups (P=0.004).

A main limitation of this study is that most RA patients are subjective and almost all the patients took other medications, also the retrospective pattern of our study was another restriction.

CONCLUSION

In conclusion, with respect to the relatively low rate of drug discontinuation due to adverse effects, MTX seems to be a

safe drug for long-term use in RA patients. More attempts should be done to minimize side effects and discontinuation of MTX, in order to get the benefits of drug considered as the cornerstone in RA treatment.

DECLARATIONS

Conflict of Interest

The authors and planners have disclosed no potential conflicts of interest, financial or otherwise.

REFERENCES

[1] Chen, Yen-Fu, et al. "A systematic review of the effectiveness of adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis in adults and an economic evaluation of their cost-effectiveness." *Health Technology Assessment,* Vol. 10, No. 42, 2006, pp. 1-266.

[2] Van der Heijde, D.M.F.M. "Joint erosions and patients with early rheumatoid arthritis." *Rheumatology,* Vol. 34. suppl_2, 1995, pp. 74-78.

[3] Kremer, Joel M. "The changing face of therapy for rheumatoid arthritis." *Rheumatic Diseases Clinics of North America,* Vol. 21, No. 3, 1995, pp. 845-52.

[4] Kaltsonoudis, Evripidis, Charalampos Papagoras, and Alexandros A. Drosos. "Current and future role of methotrexate in the therapeutic armamentarium for rheumatoid arthritis." *International Journal of Clinical Rheumatology,* Vol. 7, No. 2, 2012, pp. 179-89.

[5] Weinblatt, Michael E., et al. "Efficacy of low-dose methotrexate in rheumatoid arthritis." *New England Journal of Medicine,* Vol. 312, No. 13, 1985, pp. 818-22.

[6] Thompson, R.N., et al. "A controlled two-centre trial of parenteral methotrexate therapy for refractory rheumatoid arthritis." *The Journal of Rheumatology* 11.6 (1984): 760-763.

[7] Yazici, Y. "Long-term safety of methotrexate in the treatment of rheumatoid arthritis." *Clinical and Experimental Rheumatology-Incl Supplements,* Vol. 28, No. 5, 2010, p. S65.

[8] Singh, G., et al. "Toxicity profiles of disease modifying antirheumatic drugs in rheumatoid arthritis." *The Journal of Rheumatology,* Vol. 18, No. 2, 1991, pp. 188-94.

[9] Van Jaarsveld, C.H.M., et al. "Aggressive treatment in early rheumatoid arthritis: A randomized controlled trial." *Annals of the Rheumatic Diseases,* Vol. 59, No. 6, 2000, pp. 468-77.

[10] Blomqvist, Paul, et al. "Rheumatoid arthritis in Sweden. Drug prescriptions, costs, and adverse drug reactions." *The Journal of Rheumatology,* Vol. 27, No. 5, 2000, pp. 1171-77.

[11] Evsikova, M.D., and IuV Muraviev. "Unwanted reactions to modifying antirheumatic drugs." *Terapevticheskii arkhiv,* Vol. 77, No. 5, 2005, pp. 72-74.

[12] Pavelka, K., et al. "Analysis of the reasons for DMARD therapy discontinuation in patients with rheumatoid arthritis in the Czech and Slovak republics." *Clinical Rheumatology,* Vol. 21, No. 3, 2002, pp. 220-26.

[13] Banal, Frédéric, et al. "Sensitivity and specificity of the American College of Rheumatology 1987 criteria for the diagnosis of rheumatoid arthritis according to disease duration: A systematic literature review and meta-analysis." *Annals of the Rheumatic Diseases,* Vol. 68, No. 7, 2008, pp. 1184-91.

[14] Grove, M.L., et al. "Adverse reactions to disease-modifying anti-rheumatic drugs in clinical practice." *Qjm,* Vol. 94, No. 6, 2001, pp. 309-19.

[15] El-Zorkany, Bassel K., Sherif M. Gamal, and Sherine A. El-Mofty. "Frequency and causes of discontinuation of methotrexate in a cohort of Egyptian patients." *The Egyptian Rheumatologist,* Vol. 35, No. 2, 2013, pp. 53-57.

[16] Anvari, Bita. "Leading causes of methotrexate and antimalarial drugs discontinuation in Iranian patients with rheumatoid arthritis." *The Egyptian Rheumatologist,* Vol. 38, No. 3, 2016, pp. 147-52.

[17] Attar, Suzan M. "Adverse effects of low dose methotrexate in rheumatoid arthritis patients. A hospital-based study." *Saudi Medical Journal* 31.8 (2010): 909-915.

[18] Al-Malaq, Haya M., Hussein F. Al-Arfaj, and Abdurhman S. Al-Arfaj. "Adverse drug reactions caused by methotrexate in Saudi population." *Saudi Pharmaceutical Journal,* Vol. 20, No. 4, 2012, pp. 301-05.

[19] Van Jaarsveld, C.H.M., et al. "Toxicity of anti-rheumatic drugs in a randomized clinical trial of early rheumatoid arthritis." *Rheumatology,* Vol. 39, No. 12, 2000, pp. 1374-82.

[20] Naranjo, Cláudio A., et al. "A method for estimating the probability of adverse drug reactions." *Clinical Pharmacology & Therapeutics,* Vol. 30, No. 2, 1981, pp. 239-45.