

Rheumatoid Arthritis and Methotrexate Awareness

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Abstract: Background: Poor knowledge by patients concerning the adverse effects of MTX may increase the risk of serious life-threatening complications. We conducted the current study to evaluate the side effects of MTX that have affected to our patients and to determine their prior knowledge of the side effects of MTX. **METHODS:** We performed a Cross-sectional study in patients with rheumatologic diseases who are on MTX. Questionnaires with “yes” or “no” questions were conducted through clinic interview or telephone call. The main questions addressed patients’ awareness of common side effects of MTX. In addition, patients were asked if they have developed any of these effects. **RESULTS:** Knowledge of side effects associated with MTX was less than 50% overall. The most recognized side effects were teratogenicity (42.2%), followed by neutropenia (33.7%) and hair loss (31.8%). However, Hair loss was the most common side effect that patients developed (54.9%), followed by gastrointestinal upset (44.5%) and menstrual irregularity (21.4%). Patients who were aware about gastrointestinal upset and hair loss had developed these symptoms (78% for gastrointestinal upset and 81.8% for hair loss) at approximately twice the rate of those who were not aware (30.9% and 42.4%, respectively). Low education was associated with poorer knowledge. The most common factor given for non-compliance was side effect of medication (47.1%). **CONCLUSION:** MTX-related complications and side effects might be decreased by improved patient education, which can lead to less harm and better compliance. [Mohammad M. Mustafa, Yousef M. Alammari and Sami Bahlas. **Rheumatoid Arthritis and Methotrexate Awareness.** *Life Sci J* 2017;14(6):90-95]. ISSN: 1097-8135 (Print) / ISSN: 2372-613X (Online). <http://www.lifesciencesite.com>. 13. doi:[10.7537/marslsj140617.13](https://doi.org/10.7537/marslsj140617.13).

Keywords: Rheumatoid arthritis; Methotrexate; MTX; awareness; knowledge

1. Introduction

Methotrexate (MTX) is the most extensively used disease-modifying anti-rheumatic drug (DMARD) as first line treatment for rheumatoid arthritis [1]. In addition, because of its superior efficacy and tolerability compared with other DMARDs, it is commonly used for the treatment of other inflammatory arthropathies, such as psoriatic arthritis, vasculitis, and inflammatory bowel disease [2]. The cost of MTX is low and it can be used alone or in combination with other DMARDs. Although it has great efficacy, MTX is associated with side effects in more than 70% of patients [3]. Poor knowledge by patients concerning the adverse effects of MTX may increase the risk of serious life-threatening complications, such as pancytopenia or hypersensitivity pneumonitis. Furthermore, MTX is teratogenic and contraception is important for both genders.

Rheumatologists have to provide their patients with educational information concerning MTX’s common side effects and serious long-term complications. By following the medication guidelines and ensuring that patients are well informed, many side effects can be largely reduced or avoided. When questioning these patients about MTX side effects, we have noticed that most of them do not have any basic

knowledge concerning the adverse effects of MTX. Furthermore, they do not know the importance of taking folic acid as a part of treatment. Due to this, patients do not know what side effects they have to report immediately to their doctors or when to go to the emergency department in case of serious symptoms secondary to MTX. As a result, patients tend to either continue taking MTX despite a serious complication, or discontinue it without informing their doctors. A rheumatologist’s perspective study showed that all patients should know when they should call their doctor when taking MTX [4]. We conducted the current study to evaluate the side effects of MTX that have affected to our patients and to determine their prior knowledge of the side effects of MTX.

2. Material and Methods

A patient list was created in cooperation with the pharmacy of King Abdulaziz University Hospital (KAUH) by collecting every patient who receive MTX. Ethical approval was obtained from The Ethical Committee of KAUH (reference No127-17). All patients provided verbal consent to take part in our study. The study involved 173 patients with various underlying rheumatologically diseases. The majority were diagnosed with rheumatoid arthritis; other diagnoses included psoriatic arthritis, Behcet’s disease,

or undifferentiated inflammatory arthritis. Inclusion criteria were: 1) adult patient, defined as > 18 years old; 2) patient on MTX at least 6 months; 3) patient diagnosed with underlying rheumatologically disease by a rheumatologist. All patients were following at KAUH from March 2016 to March 2017.

Trained physicians interviewed all patients using a well-designed questionnaire through direct clinic interview or telephone call. Demographic data including age, sex, and nationality were recorded in the questionnaire. In our study, educated patients were defined as those with secondary education or above, and non-educated patients as those who did not obtain secondary education. The main questions addressed patients' awareness of seven common side effects of MTX (neutropenia, chronic respiratory symptoms like cough or exertional dyspnea, hepatitis, teratogenicity, gastrointestinal [GI] upset, hair loss, and menstrual irregularity) prior to development any of these side effects. In addition, patients were asked if they have developed any of these effects. Answer options were "yes" or "no". We also asked patients about their compliance with the medication and the possible causes of non-compliance. Data were collected and typed in Microsoft Office Excel 2013 and analyzed by an expert statistician.

3. Results

The study included 173 patients. Table 1 reports their baseline characteristics. The majority (91.9%) were females. Almost two-thirds (61.3%) were non-educated and Saudi (60.1%).

As demonstrated in Figure 1, the majority of patients were diagnosed with rheumatic arthritis.

Table 1: Baseline characteristics of the participants (n=173)

Baseline characteristics	Frequency	Percentage
Gender		
Male	14	8.1
Female	159	91.9
Educational level		
Non-educated	106	61.3
Educated	67	38.7
Nationality		
Saudi	104	60.1
Non-Saudi	68	39.9

As illustrated in Figure 2, in 30.6% of patients, duration of the disease exceeded 10 years, whereas duration was 2 years or less in 16.2% patients.

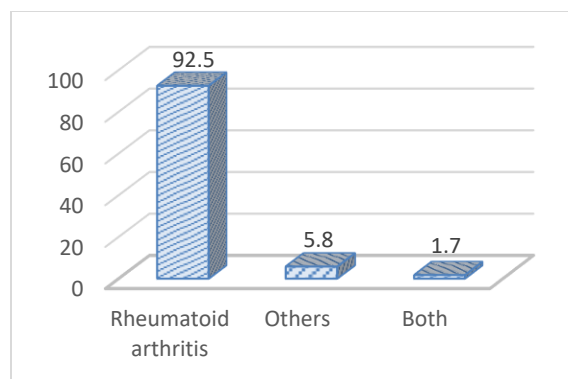


Figure 1: Distribution of the participants (percentage) according to their diagnosis.

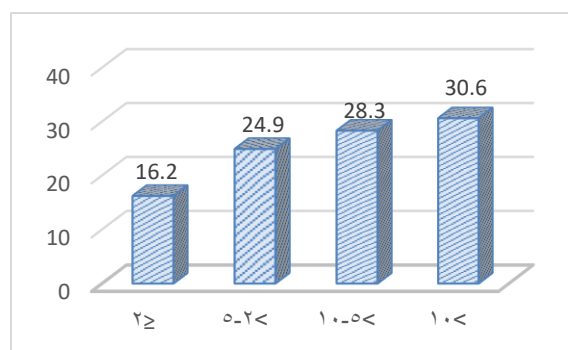


Figure 2: Distribution of the participants (percentage) according to disease duration.

Methotrexate therapy

As shown in Table 2, the dose of MTX was 15 mg or more for 37% of patients and 7.5 mg for 12.7%. All patients except one reported the oral route for MTX intake. Duration of therapy exceeded 10 years among 16.8% of patients, whereas it was 2 years or less among 30.1% of them.

Table 2: Methotrexate therapy of the participants.

	Frequency	Percentage
Dosage of MTX (mg)		
7.5	22	12.7
10.0	61	35.3
12.5	26	15.0
≥15.0	64	37.0
Route of administration		
Oral	172	99.4
Subcutaneous injection	1	0.6
Duration of therapy (years)		
≤2	52	30.1
2-5	48	27.7
5-10	44	25.4
>10	29	16.8

As seen in Figure 3, the most frequent MTX complications that patients were aware of teratogenicity (42.2%), neutropenia (34.7%), hair loss (31.8%), hepatitis (30.1%), and gastrointestinal upset (28.9%).

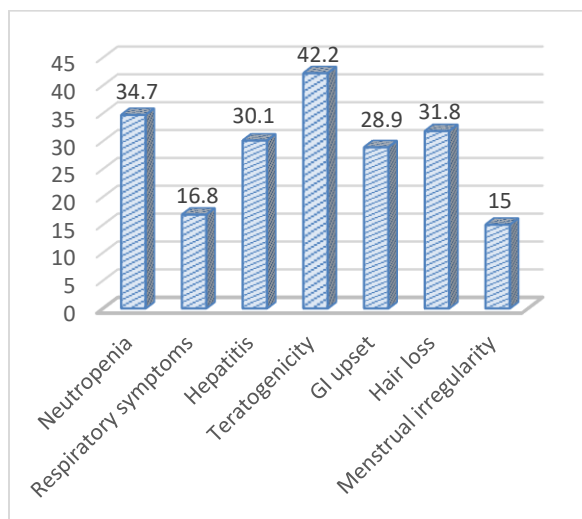


Figure 3: Awareness of patients (percentage) regarding methotrexate complications.

Regarding medications taken in combination with MTX, folic acid was taken by the majority of patients (94.2%), followed by prednisolone (32.4%) (Figure 4).

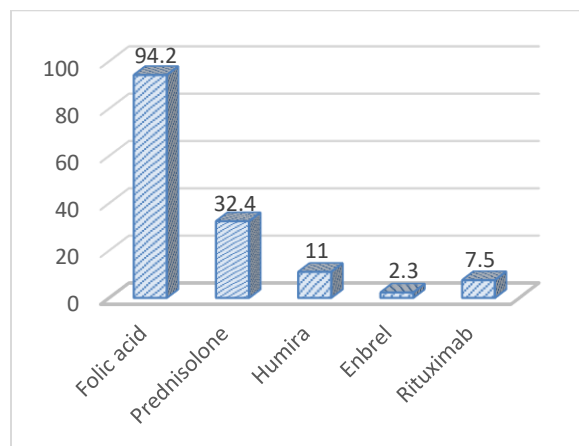


Figure 4: Distribution of combined therapy (percentage) with methotrexate among patients.

Concerning actual MTX complications reported by the participants, the most frequent were hair loss (54.9%), gastrointestinal upset (44.5%), menstrual irregularity (21.4%), and neutropenia (15%).

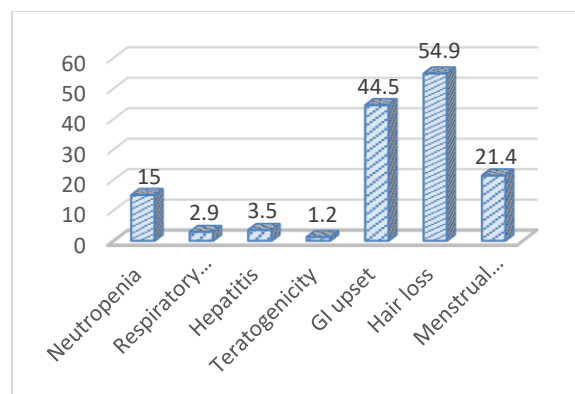


Figure 5: Actual complications of methotrexate among the participants (percentage).

The majority of patients (80.3%) were compliant with MTX therapy, as displayed in Figure 6. Among those who were not compliant, the most frequent reasons were drug side effects (47.1%), drug non-availability (44.4%), and high cost (20.6%) (Figure 7).

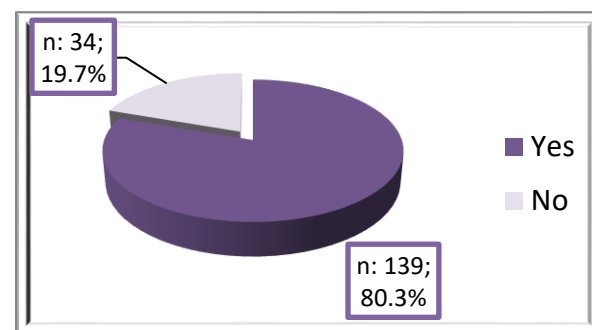


Figure 6: Compliance of patients with methotrexate therapy.

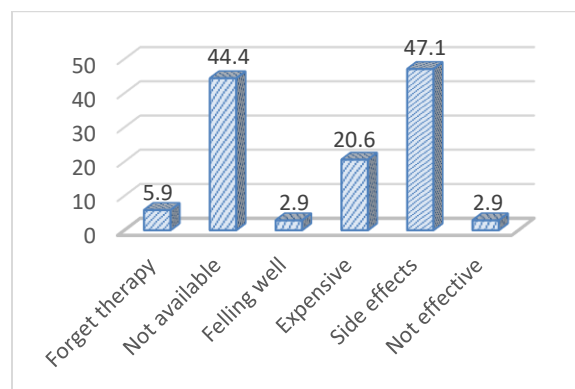


Figure 7: Reasons (percentage) for non-compliance with methotrexate.

Impact of folic acid intake on the occurrence of methotrexate complications

It is obvious from Table 3 that intake of folic acid was not significantly associated with the occurrence of any of the MTX complications except neutropenia,

where only 12.9% of patients on folic acid compared to 50% of those not taking folic acid developed neutropenia ($p=0.008$).

Table 3: Impact of folic acid intake on the occurrence of methotrexate complications

	Folic acid intake		p-value *
	Yes N=163 N (%)	No N=10 N (%)	
Neutropenia	21 (12.9)	5 (50.0)	0.008
Respiratory symptoms	4 (2.5)	1 (10.0)	0.260
Hepatitis	6 (3.7)	0 (0.0)	0.696
Teratogenicity	2 (1.2)	0 (0.0)	0.942
GI upset	72 (44.2)	5 (50.0)	0.483
Hair loss	91 (55.8)	4 (40.0)	0.257
Menstrual irregularity	35 (21.5)	2 (20.0)	0.636

* Fischer exact test

Association between educational level and compliance with therapy

Although non-educated patients were more likely to be non-compliant with MTX therapy compared to educated patients (23.6% versus 13.4%), this difference was not statistically significant ($p=0.102$, Table 4).

Table 4: Association between educational level and compliance with therapy

Educational level	Compliance with methotrexate therapy	
	Yes N=136 N (%)	No N=34 N (%)
Non-educated (n=106)	81 (76.4)	25 (23.6)
Educated (n=67)	58 (86.6)	9 (13.4)

p-value = 0.102

Factors associated with awareness of methotrexate side effects

Table 5: Awareness of methotrexate side effects according to patient's gender

	Gender		p-value*
	Male N=14 N (%)	Female N=159 N (%)	
Neutropenia	4 (28.6)	56 (35.2)	0.428
Respiratory symptoms	3 (21.4)	26 (16.4)	0.626
Hepatitis	4 (28.6)	48 (30.2)	0.899
Teratogenicity	4 (28.6)	69 (43.4)	0.282
GI upset	2 (14.3)	48 (30.2)	0.208
Hair loss	2 (14.3)	53 (33.3)	0.142
Menstrual irregularity	0 (0.0)	26 (16.4)	0.093

*Fischer exact test

Patient's gender: As shown in Table 5, awareness of some MTX side effects was higher in female patients compared to males (neutropenia, hepatitis, teratogenicity, gastrointestinal upset, hair loss, and menstrual irregularity). On the other hand, males were more aware than females regarding respiratory symptoms. However, these differences were not statistically significant ($p>0.05$).

Patient's education: As demonstrated in Table 6, awareness of all MTX side effects except menstrual irregularities was higher among educated patients compared to non-educated patients (p-values ranged from 0.007 for hepatitis to <0.001 for neutropenia, gastrointestinal upset, and hair loss).

Table 6: Awareness of methotrexate side effects according to patient's education

	Education		p-value*
	Not-educated N=106 N (%)	Educated N=67 N (%)	
Neutropenia	24 (22.6)	36 (53.7)	<0.001
Respiratory symptoms	11 (10.4)	18 (26.9)	0.005
Hepatitis	24 (22.6)	28 (41.8)	0.007
Teratogenicity	35 (33.0)	38 (56.7)	0.002
GI upset	20 (18.9)	30 (44.8)	<0.001
Hair loss	20 (18.9)	35 (52.2)	<0.001
Menstrual irregularity	13 (12.3)	13 (19.4)	0.201

*Chi-square test

Patient's nationality: As shown in Table 7, awareness of hair loss as a MTX side effect was higher among Saudi patients compared to non-Saudis (38.5% versus 21.7%, $p=0.021$). There was no statistically significant differences between Saudi and non-Saudi patients regarding awareness of other MTX side effects.

Table 7: Awareness of methotrexate side effects according to patient's nationality

	Nationality		p-value*
	Non-Saudi N=69 N (%)	Saudi N=104 N (%)	
Neutropenia	19 (27.5)	41 (39.4)	0.108
Respiratory symptoms	14 (20.3)	15 (14.4)	0.312
Hepatitis	20 (29.0)	32 (30.8)	0.807
Teratogenicity	26 (37.7)	47 (45.2)	0.327
GI upset	15 (21.7)	35 (33.7)	0.090
Hair loss	15 (21.7)	40 (38.5)	0.021
Menstrual irregularity	13 (18.8)	13 (12.5)	0.253

*Chi-square test

Table 8 shows that 30.9% of patients who were not aware of gastrointestinal upset as a side effect of MTX developed that complication, compared with 78% who were aware of this side effect ($p<0.001$). Similarly, 42.4% of patients who were not aware of

hair loss as a side effect of MTX developed this complication compared to 81.8% who were aware of this side effect ($p<0.001$). Among other side effects, there was no statistically significant association between patients' awareness and their occurrence.

Table 8: Association between awareness of methotrexate side effects and their occurrence among patients

	Known N (%)	Occurred N (%)	Unknown and occurred N (%)	Known and Occurred N (%)	p-value*
Neutropenia	60 (34.7)	26 (15.0)	13 (11.5)	13 (21.7)	0.075
Respiratory symptoms	29 (16.8)	5 (2.9)	3 (2.1)	2 (6.9)	0.196
Hepatitis	52 (30.1)	6 (3.5)	3 (2.5)	3 (5.8)	0.254
Teratogenicity	73 (42.2)	2 (1.2)	2 (2.0)	0 (0.0)	0.333
Gastrointestinal upset	50 (28.9)	77 (44.5)	38 (30.9)	39 (78.0)	<0.001
Hair loss	55 (31.8)	95 (54.9)	50 (42.4)	45 (81.8)	<0.001
Menstrual irregularity	26 (15.0)	37 (21.4)	28 (19.0)	9 (34.6)	0.074

*Chi-square/Fischer exact tests

4. Discussions

In this study, our questionnaire concentrated on patients' knowledge about the most common adverse effects of an essential medication for most rheumatologic diseases. We also aimed to determine what side effects patients had developed. All included patients were being treated with MTX, and more than 90% had rheumatoid arthritis.

Knowledge of side effects associated with MTX was less than 50% overall. However, the most recognized side effects were teratogenicity (42.2%), followed by neutropenia (33.7%), hair loss (31.8%), and gastrointestinal upset (28.9%). Only 15% of patients knew that MTX might cause menstrual irregularity. Hair loss was the most common side effect that patients developed (54.9%), followed by gastrointestinal upset (44.5%) and menstrual irregularity (21.4%). Low education was associated with poorer knowledge, compared to educated patients, regarding all side effects of MTX except menstrual irregularity ($p=0.2$). There was no significant difference in the knowledge about the side effect of MTX between genders. However, the number of males included in the study was very low compared to females.

There are few studies evaluating the knowledge of the patients taking MTX. One of these studies reported that patient knowledge varies by age, education, and English language proficiency [5]. Another study concluded that despite receiving a good education by doctors and nurses, further improved patient education is needed [6]. One study was conducted in Saudi Arabia concerning the side effects of MTX. This study showed that the most common side effect was gastrointestinal upset (52.5%); in our study,

44.5% of patients developed gastrointestinal upset, with hair loss being the most common side effect (54.9%) [7]. None of these previous studies evaluated the complications that patients already had compared to their knowledge of MTX side effects.

We found a significant difference in the side effects developing in educated versus non-educated patients. Interestingly, patients who were aware about gastrointestinal upset and hair loss had developed these symptoms (78% for gastrointestinal upset and 81.8% for hair loss) at approximately twice the rate of those who were not aware (30.9% and 42.4%, respectively).

Compliance with medication is a cornerstone for improved disease outcome and remission. In our study, 20% of patients were non-compliant with MTX for many reasons. The most common factor given for non-compliance was side effect of medication (47.1%), followed by lack of availability of MTX (44.4%). We found that there was no significant difference between educated and non-educated patients in terms of medication compliance, with educated patients showing a slightly higher rate of compliance (86.6% vs. 76.4%, $p=0.102$).

During interviewing our patients, most who developed side effects of MTX did not have any previous knowledge about them. However, educated patients received information from the internet or when they asked their doctors specifically about the possible side effects of MTX. None of the patients received education from nurses. To improve patient knowledge about MTX, some educational interventions can have a great impact. A controlled study revealed that providing a MTX information booklet to patients resulted in a favorable attitude concerning MTX understanding [8]. Another study reported that a

multimedia educational intervention for patients about prescribed medication was more effective than the usual care provided by health professionals [9].

The main limitation of our study is recall bias. We relied on patients' memory to determine their previous knowledge before or after the development of any side effect. The study was conducted in a university hospital in which patients are seen by consultant rheumatologists, specialists, and residents, which could lead to inappropriate patient education. Furthermore, this study was questionnaire based, rather than evaluating documented events. Finally, the study only evaluated oral MTX; we included only one patient receiving subcutaneous MTX, which carries a reduced risk of gastrointestinal upset [10].

In conclusion, MTX-related complications and side effects might be decreased by improved patient education, which can lead to less harm and better compliance. Initiation of multiple education sessions, supplemental books and cards, improved physician-patient communication, and establishing a nurse education program are recommended.

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References

1. National Institute for Health and Clinical Excellence. Rheumatoid arthritis: the management of rheumatoid arthritis in adults. National Institute for Health and Clinical Excellence, 2009.
2. Grove ML, Hassell AB, Hay EM, et al. Adverse reactions to disease modifying anti-rheumatic drugs in clinical practice. *QJM*. 2001;94: 309-319.
3. Salliot C, van der Heijde D. Long-term safety of methotrexate monotherapy in patients with rheumatoid arthritis: a systematic literature research. *Ann Rheum Dis*. 2009;68: 1100-1104.
4. Davis TC, Wolf MS. Health literacy: implications for family. *Fam Med*. 2004;36(8): 595-598.
5. Thompson AE1, Bashook PG. Rheumatologists' recommended patient information when prescribing methotrexate for rheumatoid arthritis. *Clin Exp Rheumatol*. 2010; 28: 539-545.
6. Barton JL, Schmajuk G, Trupin L, et al. Poor knowledge of methotrexate associated with older age and limited English-language proficiency in a diverse rheumatoid arthritis cohort. *Arthritis Res Ther*. 2013;15(5): R157.
7. Mehta P, Carlucci F, Mackworth-Young C, et al. An assessment of methotrexate-related patient knowledge. *Ann Rheum Disease*. 2015;74 Suppl 2: 1291.
8. Al-Malaq HM, Al-Arfaj HF, Al-Arfaj AS. Adverse drug reactions caused by methotrexate in Saudi population. *Saudi Pharm J*. 2012;20(4): 301-305. doi: 10.1016/j.jsps.2012.05.004.
9. Mohammad A, Kilcoyne A, Bond U, et al. Methotrexate information booklet study 2008. *Clin Exp Rheumatol*. 2009;27: 649-650.
10. Ciciriello S, Johnston RV, Osborne RH, et al. Multimedia educational interventions for consumers about prescribed and over-the-counter medications. *Cochrane Database Syst Rev*. 2013;4: CD008416.
11. Żuber Z, Turowska-Heydel D, Sobczyk M, et al. Methotrexate efficacy and tolerability after switching from oral to subcutaneous route of administration in juvenile idiopathic arthritis. *Reumatologia*. 2016;54: 19-23. doi: 10.5114/reum.2016.58757.

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