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Toxicity and Complications of Long Term Use of Methotrexate in Sohag University Hospital: A Retrospective, Record Based Epidemiological Study

Ahmed M. Said[1], Ahmed R. Alagamy[2], Meray M. Shokry[1]
Departments of [1]Forensic Medicine and Clinical Toxicology,
[2]Rheumatology, Faculty of Medicine, Sohag University, Egypt
***Corresponding author:** Ahmed M. Said, **Mobile:** (+20) 01002663856, **E-Mail:** ahmedabostate1981@gmail.com

ABSTRACT

Background: Methotrexate (MTX) is used as an anti-cancer drug in higher doses. However, lower doses of methotrexate have been used in the treatment of rheumatic diseases due to its immunosuppressant effects such as rheumatoid arthritis, psoriatic arthritis, inflammatory myopathies, asthma, and other inflammatory conditions.

Objective: The current study aimed to estimate the prevalence and severity of methotrexate toxicity among patients receiving low-dose methotrexate and followed up in the Rheumatology Department, at Sohag University.

Patients and Methods: A retrospective, record-based study. All cases with rheumatoid arthritis were treated with low-dose methotrexate for at least 3 months and were recorded in the files of the Rheumatology Department, Sohag University Hospitals, in the period from 1 Jan 2012 to 31 December 2021. The files of the selected cases were revised carefully regarding details of the demographic data, clinical history, comorbidities, and side effects and toxicities supposed to be due to methotrexate.

Results: The study included the files of 1077 rheumatoid arthritis cases. 849 cases (78.8%) were chronic MTX users, and 228 cases (21.2%) were non-chronic MTX users, taken as the control group. The comparison between MTX users and non-users as regards the clinical data revealed that MTX users had less disease duration, more morning stiffness, and less hypertension. MTX use was significantly associated with a higher incidence of gastritis, blurred vision, anemia, pneumonitis, and hepatotoxicity.

Conclusion: Although generally tolerable in low doses, MTX is sometimes associated with some toxicities including gastritis, blurred vision, anemia, pneumonitis, and hepatotoxicity.

Keywords: Methotrexate, Rheumatoid arthritis, Hepatotoxicity, Pneumonitis.

INTRODUCTION

Methotrexate (MTX) is used as an anti-cancer drug in higher doses such as acute lymphoblastic leukemia, lymphoma, carcinoma of the breast, osteogenic sarcoma, and cancer of the head and neck region [(1)]. The doses of MTX for anti-cancer purposes may reach up to 1 gram per cycle and is especially effective against child onset acute lymphoid leukemia, also malignancies as trophoblastic and hematologic types as well as cancer bladder and osteosarcomas [(2, 3)].

However, lower doses of methotrexate have been used in the treatment of rheumatic diseases due to its immunosuppressant effect [(4)], for example used for an asthmatic patient, psoriatic arthritis disease (PsA), rheumatoid arthritis disorder (RA), also inflammatory myopathies diseases, as well as used in prophylaxis in case of graft against host disorder and inflammatory conditions[(5-10)].

MTX depletes folic acid thus affecting the purine metabolism, which leads to either beneficial therapeutic or harmful toxic effects of MTX. The use of MTX is associated with deleterious effects on different organs such as the kidney, liver, testis, and bone marrow. As MTX is mainly eliminated through the kidneys nephrotoxicity is more common to occur more than other side effects, which limit its therapeutic uses in many conditions [(11)].

Even a therapeutic low dose of MTX is accepted and tolerated by the patient, but minimal side effects, mainly starting 24–48 h after a regular dose each week, but these side effects mainly do not threaten the life of the patient as described by many authors. Examples of these side effects: Skin lesions such as skin rashes and alopecia. Neurological symptoms such as headache, lack of concentration, and confusion. As well as gastrointestinal tract (GIT) symptoms like gastric inflammation, nausea, diarrhea, and difficulty in digestion [(12-14)].

On the other side low dose of methotrexate can lead to severe harmful side effects as described by many authors for example liver toxicity, lung toxicity, mucositis and bone marrow depression and these side effects lead to patients who can't tolerate treatment [(15, 16)].

About the renal system it is noticed that high dose methotrexate can cause renal toxicity in form of tubular toxicity which mainly leads to renal impairment, but in case of low dose methotrexate; it can't lead to renal impairment but renal impairment leads to more susceptibility and toxicity to low dose methotrexate for other systems [(17, 18)].

Many studies as case reports and small case series about low dose methotrexate toxicity have been done by many authors. But the largest case series up till now studied 70 cases of rheumatoid arthritis who developed side effect as pancytopenia in 17% of cases that did not recover from bone marrow suppression and unfortunately died [(19-21)].

Another case-series study described 25 cases that take low-dose methotrexate and developed

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pancytopenia and so later 2 cases died from acute myeloid leukemia and 5 cases died from generalized sepsis [22].

AIM OF THIS STUDY

The current study aimed to estimate the prevalence and severity of methotrexate toxicity among patients receiving low-dose methotrexate and followed up in the Rheumatology Department, at Sohag University, depending on the real-world data presented in the files of the patients followed in the outpatient clinic and inpatient wards of Department of Rheumatology, Sohag University in the last 10 years.

PATIENTS AND METHODS

A retrospective, record-based study. All cases with rheumatoid arthritis were treated with low-dose methotrexate for at least 3 months and were recorded in the files of the Rheumatology Department, Sohag University Hospitals, in the period from 1 Jan 2012 to 31 December 2021. The files of the selected cases were revised carefully regarding details of the demographic data, clinical history, comorbidities, and side effects and toxicities supposed to be due to methotrexate.

Inclusion criteria:

1. Cases with definite rheumatoid arthritis according to classification (ACR/EULAR) of RA disease criteria; published in 2010 [23].
2. Adult cases with age >16 years at the onset of the disease.
3. With no underlined liver, renal, or other chronic diseases.

Exclusion criteria:

4. Pediatric (Juvenile) cases, who were not classified as "Rheumatoid arthritis".
5. Patients who were not compliant with methotrexate therapy or who used it for only less than 3 months.

METHODS

The files of the selected cases were revised carefully regarding:

- Details of the demographic data of the patients.
- Clinical history and disease course.
- Comorbidities.
- Drug treatment including the dose and duration of methotrexate, other disease-modifying anti-rheumatic drugs (DMARDs), and other drugs including steroids, non-steroidal anti-inflammatory drugs (NSAIDs), tonics, and other drugs.
- Side effects and toxicities supposed to be due to methotrexate, which were recorded among the cases and their severity, management, and outcome of these toxicities.

Ethical consideration:

Before the start of the study, the protocol was approved by the Local Ethics Committee of our Faculty of Medicine at Sohag University, Sohag. Permission to review anonymous data from patients' records was obtained from the Ethics Committee. The study was conducted according to the Declaration of Helsinki.

Statistical study

Statistical analysis procedures were computed using SPSS, version 25.0 (IBM Corp., Armonk, NY, USA). Continuous variables data were represented by mean and standard deviation. On the other categorical variables were presented by percentages and frequency. Association between multiple studies parameters was evaluated by using the chi-square test. P-value less than 0.05 was considered significant.

RESULTS

The study used files of 1077 rheumatoid arthritis cases followed in the Rheumatology Department, at Sohag University. Among them, 849 cases were chronic MTX users for more than 3 months, and 228 cases were non-chronic MTX users, taken as the control group. Among the MTX users, nearly half of them receive doses less than or equal to 17.5 mg weekly, while the other half received 20 to 25 mg weekly (Table 1).

Table (1): Groups of the study according to MTX use

Group		No (%)
Methotrexate (MTX) use	**Users**	849 (78.8%)
	Non-users	228 (21.2%)
Methotrexate (MTX) weekly dose	**12.5 mg**	362 (42.6%)
	15 mg	1 (0.1%)
	17.5 mg	54 (6.4%)
	20 mg	276 (32.5%)
	25 mg	156 (18.4%)

Regarding the comparison between MTX users and non-users as regard the demographic data, we found that MTX users were significantly younger than those with no chronic MTX use, tended to be more urban, with lower socioeconomic level, and had less family history of RA compared with those with no chronic MTX use (Table 2).

Table (2): Demographic data of the study population

		MTX users	Non-MTX users	P value
Age (Years)		43.43±10.13	48.27±12.82	**<0.001**
Sex	**Male**	222(26.1%)	65(28.5%)	0.474
	Female	627(73.9%)	163(71.5%)	
Urban	**Urban**	305(35.9%)	64(28.1%)	**0.027**
	Rural	544(64.1%)	164(71.9%)	
Occupation	**Working**	399(47%)	104(45.6%)	0.710
	Not working	450(53%)	124(54.4%)	
Socioeconomic status	**Good**	180(21.2%)	95(41.7%)	**<0.001**
	Poor	669(78.8%)	133(58.3%)	
Marital status	**Married**	746(87.9%)	202(88.6%)	0.059
	Single	47(5.5%)	19(8.3%)	
	Divorced	14(1.6%)	0	
	Widow	42(4.9%)	7(3.1%)	
Smoking		242(28.5%)	64(28.1%)	0.897
Family history		149(17.6%)	64(28.1%)	**<0.001**

The comparison between MTX users and non-users as regard the clinical data of the study population revealed that MTX users had less disease duration, more morning stiffness, and less hypertension compared to the MTX non-users (table 3).

Table (3): Clinical data of the study population

		MTX users	Non-MTX users	P value
Disease duration		7.58±1.62	9.02±2.11	**0.011**
General symptoms (e.g. fever)		372(43.8%)	86(37.7%)	0.098
Morning stiffness	**None**	212(25%)	79(34.6%)	**0.012**
	<1 hour	57(6.7%)	11(4.8%)	
	>1 hour	580(68.3%)	138(60.5%)	
Deformities		174(20.5%)	49(21.5%)	0.742
Erosions		211(24.9%)	69(30.3%)	0.098
Narrowing		366(43.1%)	107(46.9%)	0.302
Comorbidities	**DM**	95(11.2%)	21(9.2%)	0.392
	Hypertension	88(10.4%)	38(16.7%)	**0.009**

The side effects and complications thought to be due to MTX use were summarized in table 4. This table shows that MTX use was significantly associated with a higher incidence of gastritis, blurred vision, anemia, pneumonitis, and hepatotoxicity.

Table (4): Comparison between MTX users and non-users regarding the side effects and complications

		MTX users	Non-MTX users	P value
GIT	**Gastritis**	152(17.90%)	8(3.51%)	**<0.001**
	Peptic ulcer	14(1.65%)	1(0.44%)	0.166
Hair	**Hair falling**	24(2.83%)	3(1.32%)	0.195
	Complete alopecia	3(0.35%)	0	0.847
Skin	**Eruption**	11(1.3%)	0	0.080
	Raynaud's	9(1.06%)	2(0.88%)	0.817
Eye	**Preorbital edema**	2(0.24%)	0	0.893
	Blurred vision	42(4.95%)	3(1.32%)	**0.015**
	Conjunctivitis	6(0.71%)	0	0.440
Mouth	**Ulcers**	4(0.47%)	1(0.44%)	0.949
Neurological	**Convulsions**	1(0.12%)	0	0.604
	CTS	92(10.84%)	23(10.09%)	0.745
Blood	**Anemia**	489(57.6%)	37(16.23%)	**<0.001**
Chest	**Pneumonitis**	49(5.77%)	3(1.32%)	**0.005**
Renal	**Renal toxicity**	7(0.82%)	0	0.362
Cardiac	**Angina**	9(1.09%)	2(0.88%)	0.817
	Arrhythmia	7(0.82%)	0	0.362
	Valve disease	4(0.47%)	0	0.671
Liver	**Hepatotoxicity**	14(1.65%)	0	0.051

DISCUSSION

Methotrexate medically used for more than seven-decade as since 1951 as it considers the most effective disease modifier in the case of rheumatoid arthritis disease [24]. Methotrexate act as an antagonist to folic acid by acting on purine metabolism so leading to the depletion of folic, so considered as chemotherapy and is mainly used in oncology cases as acute lymphoblastic leukemia and also much inflammatory disorder treatment [25].

On the other side, methotrexate can also be used in the treatment of rheumatoid arthritis disorder, generalized skin and muscle autoimmune inflammation, psoriasis disease, multiple autoimmune sclerosis, and multi other disorder causing generalized inflammation. Many side effects from methotrexate include neurological central and peripheral toxicity, lung toxicity, hepatic toxicity, hematological bone marrow depression, and GIT disorders [26].

This study aims to estimate the real-world complications and toxicities of low-dose MTX used for benign disease, namely RA, based on the file data in the Rheumatology Department, at Sohag University in the last 10 years.

The study included 849 rheumatoid arthritis cases followed in the Rheumatology Department, Sohag University, and was on chronic use of MTX for at least 3 months and another 228 cases, not on chronic MTX users as the control group. Among the MTX users, nearly half of them receive doses less than or equal to 17.5 mg weekly, while the other half received 20 to 25 mg weekly.

Regarding the comparison between MTX users and non-users as regard the demographic data, we found that MTX users were significantly younger than those with no chronic MTX use, tended to be more urban, with lower socioeconomic level, and had less family history of RA compared with those with no chronic MTX use.

The comparison between MTX users and non-users as regard the clinical data of the study population revealed that MTX users had less disease duration, more morning stiffness, and less hypertension compared to the MTX non-users.

Regarding the toxicities of MTX, we found that the most common complication was anemia (seen in 57% of the cases, compared to only 16% of the controls), followed by gastritis (17.9% among cases; 3.5% among controls) then pneumonitis (5.8% among cases; 1.3% among controls); blurred vision (4.95% among cases; 1.3% among controls) and finally hepatotoxicity (1.65% among cases and zero among controls). Other complications and possible toxicities showed non-significant differences between cases and controls and so cannot be attributed to the MTX use.

Regarding anemia and other hematological disorders, **Romao *et al.*** [27] and **Pivovarov and Zipursky** [28] stated that pancytopenia may occur due to myelosuppression in around 1% of the cases receiving low-dose steroids, and this is temporary and corrected when MTX is stopped. According to **Cansu *et al.*** [29], the occurrence of pancytopenia as a serious side effect of methotrexate is depended on the dose and duration of MTX and is nearly seen in 1.4% of reported cases of side effects, occur more common in female (62.51%), and a patient more than sixty years old (59%).

According to **Romao *et al.*** [27], the liver toxicity is variable; mild to severe and in form of steatosis, cirrhosis, and fibrosis, and patients become riskier to toxicity with a longer duration of use of MTX and if associated with alcohol consumption or obesity or diabetes mellitus (DM). Using methotrexate for a long duration leads to the elevation of aminotransferases, which is considered the most major harmful reaction against the liver [30]. As methotrexate leads to elevate aminotransferases (induced transaminitis), so many studies diagnosed transaminitis as an elevation of liver enzymes by two to three-fold more than normal. And according to that transaminitis was found in 7.5% up to 26% of all cases using methotrexate [31, 32].

According to **Saravanan and Kelly** [33] and **Kremer *et al.*** [15], about 1% up to 7% of cases taking methotrexate treatment will complain of respiratory system side effects. Also, **Romao *et al.*** [27] reported that respiratory system toxicity occurs in less than 8% of cases, and mainly happened during the first year of management.

Romao *et al.* [27] stated that GIT disorder's side effects as gastric inflammation, dyspepsia, nausea, and diarrhea are considered the most common side effects in methotrexate cases.

CONCLUSION

Although generally tolerable in low doses, MTX is sometimes associated with some toxicity including gastritis, blurred vision, anemia, pneumonitis, and hepatotoxicity.

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