National Journal of Physiology, Pharmacy and Pharmacology

RESEARCH ARTICLE

Adverse effect profile with low-dose methotrexate therapy in patients suffering with rheumatic diseases

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Received: August 26, 2023; **Accepted:** September 24, 2023

ABSTRACT

Background: Methotrexate (MTX) is the anchor drug for the management of many systemic inflammatory diseases. High-dose MTX is associated with various toxicities which may lead to drug discontinuation or interruption of therapy. Low-dose MTX is widely used for treating various systemic autoimmune diseases and is considered relatively safe. **Aims and Objectives:** In this study, we describe the clinical features and factors affecting adverse effects of low-dose MTX in a large cohort of patients with autoimmune rheumatic diseases (AIRDs) from a tertiary health center in South India. **Materials and Methods:** This was a retrospective analysis wherein we aimed to characterize the clinical features seen in and factors associated with adverse effects due to low-dose MTX. We reviewed the medical records of patients who were receiving MTX for their underlying AIRD from the Department of Clinical Immunology and Rheumatology and General Medicine. Inclusion: Patients with AIRDs being treated with MTX, who suffered from adverse events. Excluded: Patients on other csDMARDs and bDMARDs. Clinical profile, indications of therapy, dose of MTX, adverse effects, and deranged laboratory parameters were noted. **Results:** A total of 815 subjects using MTX were identified over a period of 6 months duration (n = 713 (87%) females). Underlying autoimmune conditions included rheumatoid arthritis (n = 675, 82.8%). The most common adverse event noted was hair loss (7.7%), followed by nausea (3.9%). Cytopenia and transaminitis were noted in 1.6% and 2.2%, respectively. Higher incidence of adverse events was seen in those without folic acid intake (81.2%; P = 0.0001). **Conclusion:** Low-dose MTX, although causes mild adverse effects and has the potential to cause life-threatening adverse events like cytopenia, is usually well tolerated. Identification of toxicities early improves the outcomes of patient care. Folate supplementation ameliorates side effects.

KEY WORDS: Low-dose Methotrexate; Autoimmune Rheumatic Diseases; Adverse Effects

INTRODUCTION

Although low-dose methotrexate (MTX) is generally considered safe and well tolerated, it can still have potential adverse effects. The risk and severity vary among individuals.[1] The common adverse effects associated include gastrointestinal side effects such as nausea, vomiting, diarrhea, and loss of appetite (10%)[2] hepatotoxicity leading to liver enzyme elevations (15%).[3] Bone marrow suppression leading to a decrease in erythrocytes, leukocytes, and platelets can result in anemia, increased susceptibility to infections (1–3%), and an increased risk of bleeding (3–10%).[4,5] Skin reactions such as rashes or photosensitivity while taking MTX (1–3%) also occur.[6] In rare cases, MTX can cause pneumonitis or interstitial lung disease presenting as cough,

Access this article online	
Website: www.njppp.com	Quick Response code
DOI: 10.5455/njppp.2023.13.09431202324092023	

shortness of breath, and chest pain.[7] MTX can harm a developing fetus, so it is contraindicated during pregnancy.[8] It may also affect fertility in both men and women.[9]

MTX interferes with the metabolism of cells, particularly cells involved in inflammatory processes or those that are rapidly dividing, such as cancer cells. Its frequent non-oncological anti-inflammatory uses include rheumatoid arthritis, psoriasis, and ectopic pregnancy.[10] Its dosing in rheumatoid arthritis is oral and typically low, around 7.5–10 mg per week. The dosage can be gradually increased based on the response and tolerability, up to a maximum of 25 mg per week.

Injectable MTX can be administered as a subcutaneous injection or intramuscular injection. The typical starting dose is 7.5 mg per week, with increase up to 25 mg per week. In psoriasis, oral MTX is usually prescribed in higher doses compared to rheumatoid arthritis. The starting dose is often around 10–25 mg once a week, with potential increases up to 30 mg per week. Injectable may be used, with similar dosages as the oral form. In cancer treatment, MTX dosages can vary significantly depending on the specific type and stage of cancer being treated. It is typically administered in higher doses and often in combination with other chemotherapy drugs. The dosages and schedule are determined by an oncologist and are tailored to each individual case.[11,12]

MATERIALS AND METHODS

This was a descriptive retrospective study that was conducted at Department of Rheumatology, ESIC Medical College and Hospital, Hyderabad, after approval from institutional ethics committee. Informed consent was waived as it was a retrospective study. The sample size of 815 cases was included. The objective of this study was to determine the incidence of adverse effects of low-dose MTX in patients suffering from rheumatic disease from tertiary care center, south India. The inclusion criteria was all patients above 18 years of age receiving low-dose MTX for their underlying rheumatic diseases such as systemic lupus erythematosus, rheumatoid arthritis, Sjogren's syndrome, PSA, vasculitis, dermatomyositis, sarcoidosis, juvenile idiopathic arthritis attending the department of clinical immunology and rheumatology and general medicine. Exclusion criteria were patients who are on multiple DMARDS, and those who had symptoms mimicking toxicity but are due to underlying disease activity.

The data from the medical records of patients meeting the eligibility criteria were analyzed. It included demographic data, underlying rheumatic disease, disease activity if available, dose and duration of MTX therapy, other DMARDS usage if any.

Side effects both in terms of clinical symptoms (nausea, vomiting, hair loss, glossitis, rare manifestations such as skin nodules and ulcers were noted) and from the laboratory reports evidence of cytopenia, transaminitis, bone marrow examination, and other possible side effects of the drugs and the treatment given for the toxicity and the outcomes were noted.

The adverse events were assessed using descriptive statistics such as percentages and mean ± standard deviation.

RESULTS

The observed findings are presented in Tables 1 and 2.

DISCUSSION

MTX, a folic acid antagonist, is one of the most used anti-rheumatic drugs in the treatment of various inflammatory arthritides. High-dose MTX (> 500 mg/m^2) is a major chemotherapeutic agent. Low-dose MTX is used as an anti-rheumatic drug and has a good safety profile, however, up to 30% of patients discontinuing MTX within 12 months of therapy initiation, do so due to adverse effects.

Hair loss attributed to MTX use has been observed in 7.7% of our study population. This is parallel to the 8.9% observed in a systematic review.[13] Liver toxicity associated with low-dose MTX is a major concern for clinicians and patients.[3] It has been observed at a frequency of 18.5% in prior studies.[13] Gastrointestinal adverse effects in our study were observed in 3.9% of study subjects, as compared to 30.8% described in a systematic review analyzing the adverse events due to MTX therapy in rheumatoid arthritis patients.[14]

Renal impairment and cumulative MTX dose are risk factors for MTX toxicity; however, such a correlation was not observed in our study. Cytopenia was noted in 5.2% of subjects on MTX in large studies as compared to 1.3% in our study.[15] No significant difference in rate of adverse events was observed with different dosages of MTX in our study.

	Our study	Others
Hair loss	7.7%	8.9%
Gastrointestinal effects	3.9%	30.8%
Cytopenia	1.3%	5.2%

Cellular folate stores are depleted in patients with rheumatic diseases on MTX therapy, and folate deficiency is a recognized risk factor for MTX toxicity.[16]

Prophylactic administration of folic acid can reduce the frequency of many of MTX's adverse effects, and a similar observation was made in our study, where frequency of adverse events was significantly lesser in sub-population taking concomitant folic acid along with low-dose MTX.[17] Smoking is demonstrated to influence concentration of MTX polyglutamate concentrations and thereby increase MTX-induced adverse events; however, in our study, consumption

Table 1: Demographic details of study subjects

Variables	Value (%)	Male (%)	Female (%)
Subjects	814	101 (12.4)	713 (87.6)
Age (years)	39±12	38±11	39±13
BMI	22.9±2.5 (mean±SD)	22.9±2.0	22.8±2.5
Granulomatosis with polyangiitis	2 (0.2)	0	2
Juvenile idiopathic arthritis	3 (0.3)	0	3
Psoriasis arthritis	63 (7.7)	15	48
Sjogren's disease	3 (0.3)	0	3
Scleroderma	8 (1.0)	0	8
SLE	60 (7.4)	7	53
Rheumatoid arthritis	675 (82.8)	79	596
Dose ranges	10 (2 [0.2]) 12.5 (4 [0.5]) 15 (28 [3.4]) 17.5 (9 [1.1]) 20 (654 [80.2]) 25 (118 [23])	15 (4) 17.5 (2) 20 (81) 25 (14)	10 (2) 12.5 (4) 15 (24) 17.5 (7) 20 (573) 25 (104)
Duration of treatment	2–6 months <6 m (20 [2.4]) 7–12 m (58 [7.1]) 13–24 m (287 [35.2]) 25–36 m (270 [33.1]) 37–48 m (111 [13.6]) 49–60 m (57 [6.9]) 61–72 m (12 [1.5])	7–12 (6) 13–24 (41) 25–36 (40) 37–48 (9) 49–60 (4)	<6 m (20) 7–12 m (52) 13–24 m (253) 25–36 m (287) 37–48 m (102) 49–60 m (53) 61–72 m (1)
Folic acid supplement	800	98	702
Smokers	21	21	0
Alcoholics	7	5	3

BMI: Body mass index, SLE: Systemic lupus erythematosus

Table 2: Adverse drug reactions

ADRs	n (%)	Male	Female
Nausea	32 (15)	5	17
Vomiting	6 (3)	0	6
Headache	22 (10)	2	20
Dizziness	24 (11)	1	23
Irritability	21 (10)	1	20
Hair loss	63 (29)	3	60
Mucositis	7 (3)	1	6
Mouth ulcers	7 (3)	1	6
Skin ulcers	1 (0.5)	1	1
Skin nodules	1 (0.5)	1	1
Shortness of breath	0	0	0
Cytopenia	13 (6)	2	11
Transaminitis	18 (8)	1	17
Death	0	0	0
ILD	0	0	0
CKD	0	0	0
CAD	0	0	0

of alcohol and tobacco did not cause adverse effects at a significantly increased rate.[18]

Strengths

Large cohort of patients was analyzed. Underlying varied autoimmune rheumatic diseases (AIRDs) were noted, and hence, findings could be extrapolated to different real-world situations where low-dose MTX is used. Other csDMARDs use was excluded to prevent confounding effects of the same.

Limitations

Definitions of adverse effects are not uniform among all studies in literature, and few studies do not mention the definition used. Few adverse effects could also be due to underlying rheumatic disease and might not be attributable to use of MTX alone.

CONCLUSION

Low-dose MTX with concomitant folate supplementation reduces the incidence of adverse effects, and hence, it ought to be part of standard prescription and should be educated to the patient. Factors such as body mass index, alcohol consumption, and smoking did not have any influence on rate of MTX-related adverse effects in our cohort. Dose of MTX

also did not have a significant effect on rate of adverse events in our study.

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How to cite this article: Parimi VP, Mirza MA, Bandaru RK, Surapareddy B, Bala S, Rakesh S. Adverse effect profile with low-dose methotrexate therapy in patients suffering with rheumatic diseases. Natl J Physiol Pharm Pharmacol 2024;14(05):827-830.

Source of Support: Nil, **Conflicts of Interest:** None declared.