Role of Folic Acid Supplementation in Reducing Side Effects of Oral Methotrexate in Patients of Psoriasis: A Study

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ABSTRACT

Background: Methotrexate (MTX) has been used for the treatment of severe psoriasis for more than 50 years. MTX use can be associated with many side effects, and folic acid is supplemented to reduce these side effects. MTX can be given orally or parenterally.

Materials and Methods: In this study, a total of 81 patients of severe psoriasis were given 15 mg/week of MTX orally, and side effects were noted at each visit. Results: A total of 36 patients developed side effects, of which ten patients were discontinued due to the development of serious side effects. Remaining 26 patients developing nonserious side effects were given folic acid 5mg/day on non-MTX days and continued with 15 mg/week of MTX therapy. They were further evaluated for any improvement in side effects. Folic acid supplementation was associated with improvement in gastrointestinal and mucosal side effects in 17 out of 26 patients.

Conclusion: Therapeutic effects were not compromised in all these patients after initiation of folic acid therapy. We recommend the supplementation of folic acid 5 mg/day in all patients of psoriasis who are receiving 15 mg/week of MTX therapy.

Key Words: Folic acid, methotrexate, psoriasis, side effects

INTRODUCTION

Psoriasis is one of the common skin disorders encountered in clinical practice. Methotrexate (MTX) is a time-tested, well-proven drug for all forms of severe psoriasis. Although available since 1948, MTX was only introduced as an antipsoriatic agent in 1958 and has been approved by the Food and Drug Administration for this indication since 1972.[1] Its use even with low dose, once weekly schedule in psoriasis is often associated with unpleasant side effects, particularly significant, are gastrointestinal side effects seen in up to 30% of patients.[2] MTX is also indicated for treatment of psoriatic arthritis, in the erythroderma, generalized pustular, or palmoplantar forms of psoriasis and in patients unresponsive to topical treatments and phototherapy. Selection of patients is important, taking into account the risk/benefit ratio. Compliance with the treatment is important, and the patients should be warned of the risks involved with pregnancy and abuse of alcohol. When MTX is prescribed, the patient should be submitted to regular laboratory examinations to detect side effects at early stages.

In India, MTX is usually prescribed in lower dosages, i.e., 7.5 mg/week. Supplementation of folic acid is not usually done in majority of the cases. Prompted by the study of Duhra et al. and Masuria et al.,[3,4] we decided to examine the nature and frequency of various side effects seen with 15 mg/week of MTX therapy. We also aimed to explore effects of folic acid supplementation in patients developing side effects due to this therapy.

METHODS

The present study was conducted in the Department of Dermatology and Venereology, Institute of Medical Sciences, Banaras Hindu University from March 2015 to April 2016. The study was approved by the Institutional Ethics Committee. Written informed consent was obtained from all participants. The study group comprised patients of severe psoriasis who fulfilled the following inclusion criteria: age >18 years and <65 years, psoriasis area severity index (PASI) >10, no systemic treatment for 1 month and no topical treatment for 1 week, and cumulative dose of MTX <1 g. Patients with pregnancy and lactation, chronic alcoholism (>100 g of alcohol a day), those with a history of taking
hepatic failure, tuberculosis, immunosuppression or any chronic disease, patients of peptic ulcers, and existing infections were excluded from the study.

Patients who fulfilled the inclusion criteria were enrolled for the study, and a detailed history taking and clinical examination were done. Patient’s age, sex, age of onset of disease, any other disease, and history of similar illness in family members were recorded. A thorough clinical examination was done, body surface area involved was recorded, and PASI was calculated. Baseline investigations such as complete blood count (CBC), renal function test (RFT), liver function test (LFT), and a chest X-ray were done for each patient at the first visit.

MTX was given at the dose of 15 mg weekly orally to the patient till PASI-75 was achieved or 16 weeks whichever was earlier. If PASI-50 was not achieved in 12 weeks, then patient was excluded from the study and shifted to other alternative therapy. The patients were called for follow-up every 2 weeks, and PASI was calculated at each visit. CBC and LFT were repeated every 2 weeks and RFT every 2 months. Patients were inquired about any side effects of MTX such as nausea, vomiting, history of black stools, oral ulceration, dry cough, loss of appetite, and yellowish discoloration of urine and sclera.

Onset of symptoms in relation to MTX ingestion, duration, and severity of symptoms was noted. In case of severe adverse effects, MTX was discontinued. These included rise in transaminases (>100 U/ml, leucopenia <4000 cells/cumm, thrombocytopenia (platelet count <1 lakh/cumm), rise in serum bilirubin 30% from baseline, severe nausea and vomiting, and occult blood in stools and melena. In case of patients who did not require discontinuation and who were continued in the study, folic acid 5 mg/day (on non-MTX days) was supplemented from day one of symptoms till the end of the study period. The effect of folic acid supplementation was determined by direct questioning. Patients were followed up every 2 weeks till PASI-75 was achieved or 16 weeks whichever was earlier.

**RESULTS**

The study was carried out in 81 patients of chronic plaque psoriasis attending skin outpatient department, 54 of these were males and 27 females. All necessary investigations and precautions were carried out before instituting MTX therapy. All side effects, gastrointestinal as well as nongastrointestinal were recorded. A total of 36 patients out of 81 patients (44.4%) who were started on MTX 15 mg/week therapy developed side effects. Table 1 shows the profile of side effects observed in these 36 patients. A few patients developed more than one side effect.

The patients in our study were evaluated for side effects at each visit. The most common side effect was nausea and vomiting (8/81) and feeling of weakness and tiredness (8/81). A total of five patients developed mucosal ulceration. Majority of these symptoms appeared with the first or at the second MTX pulse. Onset of symptoms was reported within 12 h of taking MTX and continued for up to 1–3 days.

Based on the withdrawal criteria, a total of ten patients who developed serious side effects were excluded from the study. In one patient, MTX was stopped due to severe nausea and vomiting which was disrupting the patient’s routine activities. Melena occurred in one patient and he was excluded from the study. One male patient developed pneumonia during the course of treatment and he was excluded from the study. The most common adverse effect for which MTX was discontinued was elevation of transaminases (twice the value of baseline). A total of four patients developed this side effect and were excluded from the study. Thrombocytopenia was the next common side effect, and total three patients developed this side effect and were excluded from the study. One patient developed mild anemia Hb-9.8 g/dl after 2 months, and MTX was continued. Two patients developed minor elevation of serum bilirubin (10% from baseline). MTX was continued. A total of ten patients were excluded due to side effects. No cutaneous side effects were noted.

In the remaining 26 patients, MTX was continued for the next visits after nonserious side effects subsided after MTX discontinuation. In all these patients, folic acid was used.

| Side-effects                              | Number of adverse effects in 36 patients |
|------------------------------------------|-----------------------------------------|
| Nausea/vomiting                          | 8                                       |
| Fatigue/weakness                         | 8                                       |
| Elevation of transaminases (>2 times the baseline) | 7                                       |
| Mucositis/ulcer                          | 5                                       |
| Thrombocytopenia                         | 4                                       |
| Headache, dizziness                      | 4                                       |
| Elevation of serum bilirubin             | 2                                       |
| Anemia                                   | 1                                       |
| Melena                                   | 1                                       |
| Dry cough/pneumonia                      | 1                                       |
| Total                                    | 41                                      |

**Table 1: Adverse effects of oral methotrexate**
In these patients, when MTX was restarted along with folic acid supplementation, the side effects reported with MTX pulse were reduced to a minimum in 17 out of 26 (65%) and patients were able to accept therapy much better. Addition of folic acid also did not interfere with therapeutic efficacy of MTX. Remaining 35% patients (nine patients) continued to take low-dose MTX based on their willingness to continue with the systemic therapy.

DISCUSSION

Majority of side effects seen in this study find mention in standard textbooks of dermatology. We chose fixed 15 mg oral MTX schedule (Weinstein regimen) to treat our patients. It is possible that incidence of side effects may be less with lower dosage or with parenteral route as reported in some studies. However, dosage lower than 15 mg/week may not achieve the desired control of psoriasis. Reduced folate is involved in normal synthesis and metabolism of neurotransmitters in central nervous system. Therefore, the centrally mediated gastrointestinal effects of MTX may be produced through intracellular folate depletion. Thus, it should be possible to abolish these adverse effects by reducing intracellular MTX: folate ratio by folic acid supplementation. In this study, it was possible to abolish or reduce severity of gastrointestinal symptoms induced by MTX by supplementation with folic acid. Similar results were experienced by Duhra et al. and Masuria et al. and others. Higher supplementation regimens have been posited to reduce the efficacy of MTX but a minimum dose of 5 mg weekly (given on any day except that of MTX dosing) is recommended.

Myelosuppression, in the form of leukopenia or thrombocytopenia, has been found in approximately 8% of rheumatoid patients on an average of 10.7 mg of MTX per week. Pancytopenia has also been recorded on low-dose MTX including in patients who have subsequently died. A much higher incidence of marrow suppression is seen in renal impairment and with high dosages. Hepatotoxicity is reported as affecting between 3% and 25% of psoriasis patients on long-term MTX therapy. It has been known for some time that predisposition to many of the adverse effects of MTX therapy such as mucositis includes factors such as folate deficiency and concomitant use of other antifolate drugs. Efforts have hence been made to prevent some of the adverse effects while preserving the therapeutic benefit of MTX using folate supplementation. There are two physiological circulating folates: folic acid and folic acid. They have different actions in the cell. MTX competes with folic acid for entry into the cell at the cell folate receptors while folic acid does not. Folinic acid, as a reduced folate coenzyme, can participate in DNA and RNA synthesis without the need for reduction by dihydrofolate reductase; folic acid, however, is dependent on reduction by this enzyme. Folinic acid (or the synthetic equivalent leucovorin) can also displace MTX from dihydrofolate reductase, thus creating a supply of fully reduced intracellular folate. Due to these mechanisms, folic acid can be used as a “rescue therapy” to counteract severe MTX-induced mucositis or myelosuppression. A recent meta-analysis of randomized controlled trials indicated a 79% reduction in mucosal and gastrointestinal side effects when folic acid supplementation was used in patients on low-dose MTX. The dose at which folic acid should be prescribed is also unclear. The British National Formulary suggests 5 mg folic acid weekly for patients with mucosal or gastrointestinal side effects of MTX. Low-dose MTX for the control of chronic disabling disease is increasingly being used.

Low-dose MTX (<15–20 mg/week) is an effective therapy for extensive and severe forms of psoriasis if patients are selected carefully and monitored regularly, particularly with respect to liver and bone marrow toxicity. This helps to reduce severe side effects even during long-term treatment. Drug interactions must be avoided. MTX therapy according to the guidelines is relatively safe and still has a place in the systemic treatment of psoriasis with 40 years of experience and an acceptable safety record. MTX still represents a treatment option with good efficacy/cost/tolerance relationship, especially in poorer countries such as India.

The final decision of the therapeutic choice for patient with psoriasis should be not only based on their needs and preferences but also on the clinical and economic consequences of the therapeutic strategy adopted, and a few studies have confirmed a longer remission time and lower cost in rotating treatments with the use of MTX. Based on our experience in a limited number of patients, we suggest adding folic acid 5 mg/day in all patients of psoriasis who are treated with MTX to reduce the side effects. In our study, we did not find a reduction in efficacy of MTX after adding folic acid.

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Conflicts of interest

There are no conflicts of interest.

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