Print ISSN: 2319-2003 | Online ISSN: 2279-0780

IJBCP International Journal of Basic & Clinical Pharmacology

DOI: http://dx.doi.org/10.18203/2319-2003.ijbcp20193178

Original Research Article

A study on the efficacy and adverse effects of methotrexate in psoriasis patients in a tertiary care centre

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Received: 17 May 2019
Revised: 07 June 2019
Accepted: 02 July 2019

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ABSTRACT

Background: Psoriasis is a common, chronic and recurrent inflammatory disease of the skin. Methotrexate has been used in patient with psoriasis, a folic acid antagonist interfering with purine pathway and the mechanism of action in psoriasis is immune modulation and anti-inflammation. So, this study aims at monitoring the efficacy and adverse effects of methotrexate in south Indian patients with psoriasis attending a tertiary care hospital.
Methods: It is a prospective, observational study conducted for a period of one year in subjects of either sex having psoriasis. Methotrexate was initiated in a single weekly oral dose of 5mg to 25mg. The efficacy was evaluated using psoriasis Area and Severity Index (PASI) score in all patients before starting methotrexate therapy and the end of first month, third month and sixth month of therapy. Adverse reaction was monitored.
Results: All 40 psoriasis patients after treatment with methotrexate therapy showed improved skin lesions by falling PASI scoring at the end of first, third and sixth month of treatment. None of the patients in our study had pulmonary toxicity, life threatening adverse effects which required hospitalization.
Conclusions: Use of methotrexate in the treatment of psoriasis in this study was found to be safe and highly efficacious and caused minimal adverse effects and it was well tolerated.

Keywords: Adverse effects, Methotrexate, Psoriasis, Psoriasis Area and Severity Index Score

INTRODUCTION

Psoriasis is an autoimmune disease in which genetic and environmental factors have a significant role. It is a common, chronic and recurrent inflammatory disease of the skin characterized by circumscribed, erythematous, dry, scaling plaques of various sizes. The lesions have a predilection for the scalp, nails, extensor surfaces of the limbs, umbilical region and sacrum.[1] Prevalence of psoriasis ranges from 0.1% to 3% in various populations.[2-4] Prevalence of psoriasis in India varies from 0.44 to 2.8%.[5]

Psoriasis can present at any age and can appear just after birth or in old age. In psoriasis the increased keratinocyte proliferation is due to increase in the proliferating cell section in the basal and suprabasal layer rather than due to shortened cell cycle time.

The transit from a basal keratinocyte to a desquamated cell takes 4-6 weeks in normal skin, but in psoriasis this occurs in only a few days.[6] The dermal capillary loops of both involved and uninvolved skin of psoriatic patients are dilated and abnormally tortuous.[7]

Methotrexate is a potent competitive antagonist of dihydrofolate reductase enzyme.[8] Mechanism of action of methotrexate in psoriasis is due to suppression of hyperproliferation of keratinocytes.[9] Methotrexate is also an immunosuppressive agent. The effect is due to inhibition of DNA production in immunologically competent cells. Primary and secondary antibody response can be suppressed by methotrexate.[10] Psoriasis Area Severity Index (PASI) is an useful tool for monitoring the response to any therapeutic regimen. It is an objective tool for the evaluation of psoriasis. Four sites of affection, head (h), upper limbs (u), trunk (t) and lower limbs (l) are separately scored. Morphologic scoring of psoriasis plaques is done by evaluation of three parameters, viz erythema, induration and desquamation, each of which is graded on a severity scale of 0-4 where 0 is nil, 1 is mild, 2 is moderate, 3 is severe and 4 signifies very severe changes. The percentage of skin affected by psoriasis in each area is given a numerical scoring (A) represent the proportion involved: 1(0-9%), 2(10-29%), 3(30-49%), 4(50-69%), 5(70-89%), 6(90-100%). Interobserver variation is a significant limitation of the PASI score, which makes evaluation by the same evaluator necessary.[11] The final PASI score ranges from 0 to 72.

$PASI = 0.1(E_h+I_h+D_h)\ Ah+0.2(E_u+I_u+D_u)\ A_u+0.3(E_t+I_t+D_t)\ A_t+0.4\ (E_l+I_l+D_l)\ A_l$[12]

METHODS

The study was carried out in the department of Dermatology, Government Rajaji Hospital, Madurai for a period of 12 months. All the newly diagnosed psoriasis patients (18-65 years) attending the outpatient department were taken for the study purpose.

Study design

Single centre, open labelled, prospective observational study was done. Sample size was 40 patients.

Inclusion criteria

- New cases of psoriasis started on methotrexate therapy
- Age group 18-65 years
- Both sexes
- Subjects who are willing to give informed consent for the study

Exclusion criteria

- Patients already on methotrexate therapy
- Patients with hepatic and renal impairment
- Immunodeficiency patients, Diabetes mellitus, Hypertension
- Pregnant and lactating women
- Chronic infective diseases like Tuberculosis, Leprosy
- Smokers
- Alcoholics

Strategy

Patients diagnosed with psoriasis were explained in detail about the study procedure, purpose and its benefits. They were assured of utmost confidentiality. Written informed consent was obtained from the patients willing to participate in the study, in the prescribed format in the regional language.

Screening and recruitment

Patients who had given the informed consent for participation in the study were screened by medical history, physical examination, systemic examination, blood samples for haematological and biochemical analysis. Finally, 40 patients who fulfilled the inclusion criteria were recruited for the study purpose.

Assessment

Efficacy:

The treatment efficacy was monitored by Psoriasis Area Severity Index (PASI) score in patients with psoriasis.

Safety:

The tolerability of drugs was monitored by assessing adherence to treatment, adverse reactions complained by the patients. Laboratory investigations like complete hemogram, erythrocyte sedimentation rate, liver and renal function tests, lipid profile, and urine routine were monitored at baseline, first, third and sixth month of therapy.

Ethical consideration

Approval of ethical committee of our institution was sought before conducting the study. Informed and written consent from all the participants was taken. Confidentiality was maintained at all times during the course of the study. There was no financial burden to the participants.

Statistical analysis

The data were analysed with SPSS statistical software package (Version 16.0 SPSS Inc., Chicago, USA) and analysed using descriptive statistics and Friedman test for skewed data. P value <0.05 was considered to be statistically significant.

RESULTS

In this study 40 patients with psoriasis were recruited for the study and analyzed for the response to drug therapy and adverse reactions. All the 40 patients were followed up to the end of the study. There was no drop out from the study.

Among the 40 psoriasis patients analyzed, patients belonging to 40-49 years of age were predominant (N=15) followed by patients in age of 30-39 years (N=13). The mean age of the subjects was 38.8±10.37 years. Among the 40 patients, 60% (24) were males and 16 were females (40%). Sex ratio in this study revealed that there was a strong preponderance of male patients (Figure1).

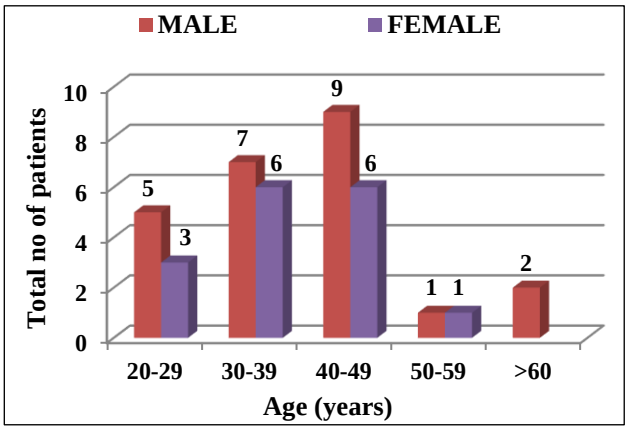

Figure 1: Age and gender distribution of Psoriasis.

Parameters for assessing the efficacy of the drug therapy:

PASI score for the evaluation of psoriasis in methotrexate therapy:

Psoriasis Area Severity Index (PASI) score is a useful tool in monitoring the response of psoriasis to methotrexate therapy. Drug therapy has improved the skin lesions as shown by the falling PASI scoring at the end of first, third and sixth months of treatment. The data is represented in the following table 1 and figure 2.

Table 1: Median PASI score of psoriasis.

Methotrexate therapy	0 Month	1 Month	3 Months	6 Months
PASI (median)	30.90	23.60*	9.50*	5.25*
Standard deviation	7.20	6.59	2.99	2.04

* = P value <0.0001

Application of Friedman's test shows that there was a statistically significant (p <0.0001) decrease in PASI score after one month (median=23.60), three months (median= 9.50), and six months (median=5.25) of treatment compared to baseline score (median=30.90) in psoriasis patients receiving methotrexate. [$\chi 2$ (3)=120.00, p <0.0001].

Adverse effects of methotrexate therapy in psoriasis

Psoriasis patients treated with methotrexate group, 34% reported nausea/vomiting, 18% of gastritis, 16% of mucosal ulcer, 14% of alopecia, 9% microcytic anaemia with minimal side effects like macrocytic anaemia (4%), and liver enzyme elevation (5%). Methotrexate induced adverse reactions reported in the study population of psoriasis was represented in the following pie diagram (Figure 3).

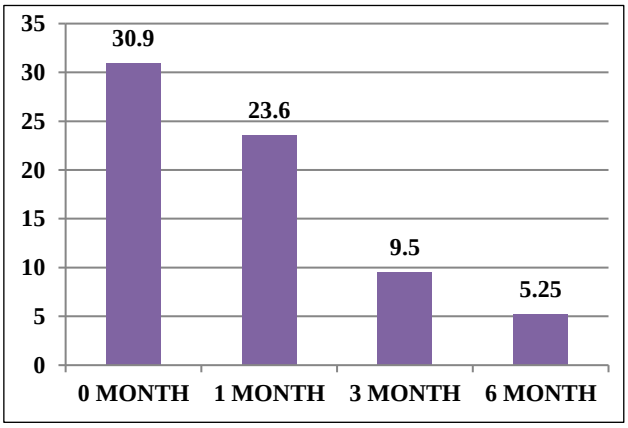

Figure 2: Median PASI score of Psoriasis.

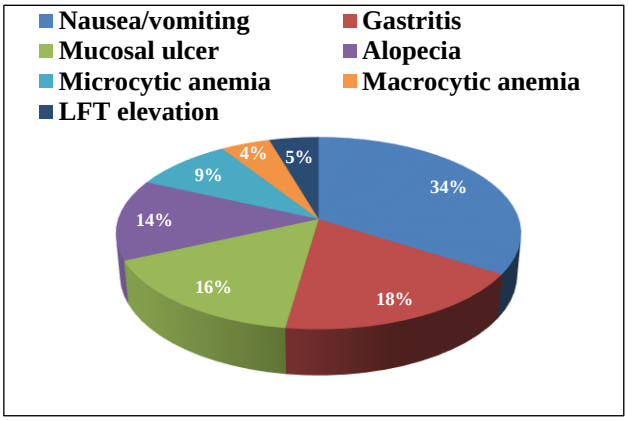

Figure 3: Adverse reactions of methotrexate.

DISCUSSION

Psoriasis is a chronic papulosquamous disorder with remission and exacerbations. The disease is believed to be multifactorial with both genetic and environmental factors playing a role in its development. Systemic therapies for psoriasis which are in common use, includes Psoralen - UVA (PUVA) therapy, retinoids and immunosuppressant's like methotrexate and cyclosporine.[13] Methotrexate was introduced as a therapy for psoriasis in 1958 and it remains one of the oldest and most widely used systemic therapy for all types of psoriasis. Oral methotrexate continues to be safe, effective, cheap and easy to use. It acts by competitive inhibition of dihydrofolate reductase, an enzyme that catalyzes the reduction of dihydrofolic acid to tetrahydro folic acid. Intra cellular polyglutamation of methotrexate and increased formation of adenosine is a key factor for clinical efficacy in psoriasis by its anti-inflammatory, anti-proliferative and immunosuppressant action.

Methotrexate is indicated as a systemic treatment in moderate to severe plaque psoriasis, psoriatic erythroderma, generalized pustular psoriasis, nail psoriasis, palmoplantar psoriasis and psoriatic arthritis. The main side effects of methotrexate are bone marrow suppression, peptic ulcer and irreversible liver cirrhosis. These adverse effects are typically seen after administration of high doses.

The weekly dose of methotrexate in psoriasis patients varies from 5 mg to 25 mg. It starts with the minimal dose, so called test dose of 5 or 7.5 mg for a week and followed by the blood samples for complete hemogram and liver function tests are taken for a possible occurrence of side effects. The most risky was myelosuppression, which could be dangerous to the patient. If the investigations are within normal levels, the dose of methotrexate could be increased. Laboratory parameters are monitored frequently (complete blood count, hepatic enzymes and renal parameters) and the patient is examined for possible side effects on skin and mucous membrane. The dose is adjusted according to the requirements.

Efficacy of the methotrexate drug therapy was assessed by Psoriasis Area Severity Index (PASI) score. Scoring was done before starting the methotrexate therapy and at the end of first month, third month and sixth month of therapy. The study shows that there is a statistically significant ($p < 0.0001$) decrease in PASI score after first month, three months and six months of treatment with methotrexate compared to baseline score.

This finding supports that Haustein et al. in a 26 year retrospective study found methotrexate to be highly efficacious in their 75% psoriasis patients while Heydendael et al. observed >75% reduction in the mean PASI score at 16 weeks in all their 43(100%) patients.[14] Similarly, van Dooren-Greebe et al. observed prolonged clearance or near total clearance in 81% of patients after long term administration of methotrexate.[15] Reduction in PASI score revealed the decrease in severity of disease and proves the effectiveness of the treatment.

In the present study methotrexate induces adverse effects like gastrointestinal upset in the form of nausea, vomiting (34%), gastritis (18%) followed by mucosal ulcer (16%), microcytic anaemia (9%) and liver enzyme elevation (5%). The mechanism of nausea/vomiting is due to direct stimulation of chemoreceptor trigger zone by the drug, as well as generation of emetic impulses from the upper gastrointestinal tract. These side effects were managed by dose reduction, addition of anti-emetics and proton pump inhibitors. Oral ulcers and stomatitis, which was resolved within a week time with folic acid therapy.

Microcytic anaemia is mainly due to depression of bone marrow function. Anaemia was treated by folic acid and iron supplementation. An elevated liver enzyme comes to normal after dosage reduction of methotrexate. The old method of daily dosing of methotrexate was more hepatotoxic than weekly dose regimen.

CONCLUSION

The study concluded that methotrexate therapy in psoriasis used in our centre was highly efficacious and caused minimal adverse effects and it was well tolerated. Significant PASI score reduction was observed during each month of methotrexate therapy. Methotrexate induces quick remission and delays relapse significantly. Methotrexate, if given with proper monitoring, will have significantly low risk of adverse effects.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Yesodha S, Sujatha G, Arunkumar J. A study on the efficacy and adverse effects of methotrexate in psoriasis patients in a tertiary care centre. Int J Basic Clin Pharmacol 2019;8:1783-7.