Methotrexate: Remission, Relapse and Safety In Psoriasis Patients

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Abstracts: Background: Methotrexate, in low dose, has been widely used therapy in psoriasis patients. It has a good safety profile if used with proper monitoring. It helps to achieve quick remission and delays relapse. This study was done to evaluate safety and efficacy of methotrexate in terms of adverse drug reaction as well as relapse and remission. This was an observational prospective study performed in dermatology department of a tertiary care government hospital. Methodology**:** : Total 43 patients with psoriasis were given methotrexate and were evaluated for remission, relapse and adverse drug reactions. Statistical analysis used: MedCalc stastical software was used to evaluate the data. Results: Out of 43 patients, 42 patients achieved remission within 2-24 weeks. (Median - 4 weeks) 28 patients out of 33 showed relapse within the span of 2-24 weeks; while five patients did not show the signs of relapse till six months after stoppage of MTX. Minor adverse reactions were seen in 21% of patients amongst which, only two cases with hepatitis needed withdrawal of methotrexate. Conclusion **:** Methotrexate is still a near to gold standard therapy for psoriasis. It induces quick remission and delays relapse significantly. Methotrexate, if given with proper monitoring, will have significantly low risk of adverse effects. [Thakkar S NJIRM 2015; 6(2):15-19]

Key Words: Methotrexate, Psoriasis, Remission, Relapse, Side effects.

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Introduction: Psoriasis, a chronic multifactorial inflammatory disease that develops in genetically predisposed individuals, affects approximately 1-3% of general population.[1,2] Methotrexate (MTX) is a time tested, well proven drug for severe form of psoriasis. The side effects and contraindications have been studied and are well known.[3] Present study was aimed to extend that knowledge of its safety and efficacy along with the assessment of the relapse rate.

Material and Methods: An observational study was performed in a tertiary care government hospital. Forty three patients attending skin outdoor department who had psoriasis and not responding to conventional therapy were enrolled during June 2009 to December 2009. Institutional ethical clearance was obtained before starting the study. Pre designed and pretested proforma was filled after taking informed consent. Privacy and confidentiality was maintained. Apart from demographic characteristics, relevant data including duration of disease, clinical type of psoriasis, body surface area involvement and response to treatment were noted. The Pre treatment evaluation included complete hematological profile, urine analysis and assessment of hepatic and renal functions. The exclusion criteria for MTX included the patients intend to become pregnant, pregnancy, lactation, abnormality in liver and renal function, severe anemia, excessive alcohol intake and patients non compliant for regular treatment. MTX was indicated in the patients who had more than 20% body surface area (BSA) involvement, disease refractory to conventional therapies and disabling psoriasis even though body surface area was less than 20%. Each patient received 7.5 mg of MTX in first dose followed by, 15 mg every week till clinical remission. Folic acid supplements were added to the patients who developed side effects with methotrexate and continued thereafter till they were followed up.

Patients were followed up weekly for first four weeks and then every two weekly. On each follow up, detailed history was elicited and physical examination was done, especially with respect to MTX toxicity. Hematological profile was repeated on each follow up visit. Liver and renal function tests were done every two months or as and when required. Special investigations like X-ray chest and USG were done depending upon the requirement. Cumulative dose of MTX was calculated by adding the dosage of MTX required controlling the current episode to the dosage of MTX consumed in the past, from the previous records available with the patients. Period of remission after MTX stoppage

was noted. The response to treatment was evaluated clinically by changes in the erythema, scaling and changes in the skin lesions. The minimum effective dose was continued for four weeks after remission and patients were followed up for six months after stoppage of the drug. The data was analysed with MedCalc stastical software.

Results: These 43 patients [M:F; 35:8] were between 24-68 years of age.[Mean age 44.9 years]. Thirteen of them were more than 50 years old. (Table 1). Duration of disease varied from 1 month to 25 years with mean of 8.53 years. BSA involvement ranged from 20%-90% (Mean 56.51 %). (Table 2)

Table 1: Age and sex distribution

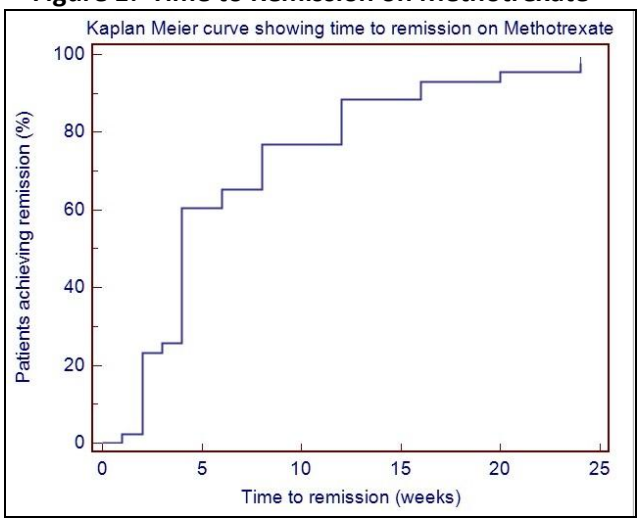
Age (Years)	Male	Female	Total
20-50	23	7	30
>50	12	1	13
Total	35	8	43

Table 2: BSA and improvement with MTX

BSA (%)	No improve-ment	Improve-ment in < 1 month	1 – 2 months	> 2 months	Total
<20	1	0	1	0	2
20-40	0	1	5	1	7
41-60	0	7	12	8	27
61-80	0	2	1	3	6
>80	0	1	0	0	1
Total	1	11	19	12	43

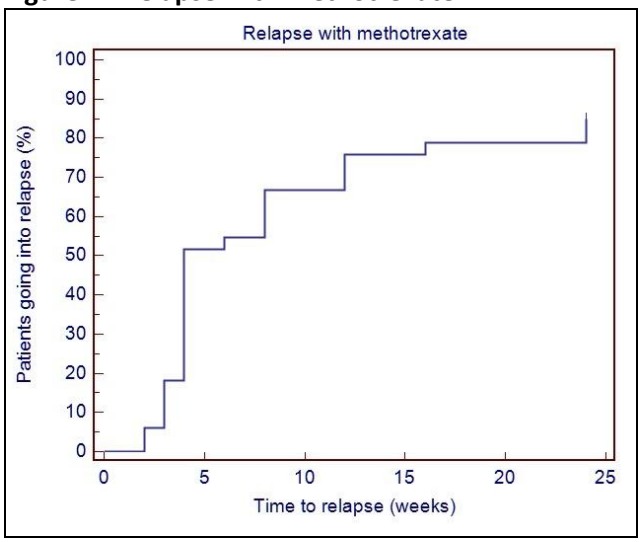
Most common indication for MTX therapy was chronic recalcitrant plaque type in 37 patients. Other indications included psoriatic erythroderma, disabling palmoplantar psoriasis and one patient with guttate psoriasis. 42 patients achieved remission with the therapy within 2-24 weeks (Median - 4 weeks) while the patient with palmoplantar psoriasis did not respond even at the end of 24 weeks. Prompt response to MTX was achieved in 30 patients within 4-8 weeks, while 9 patients responded within 16 weeks. (as shown in Figure 1)

Figure 1: Time to Remission on Methotrexate



Total cumulative dose of MTX was noted, on basis of previous record as well as current duration of therapy, to be 60-1500 mg with mean of 457 mg. Thirty three patients could be followed up for six months after achieving remission to assess relapse. Amongst which, 28 patients relapsed within the span of 2-24 weeks; (as shown in Figure 2) while five patients did not show the signs of relapse till six months after stoppage of MTX.

Figure 2: Relapse with Methotrexate



Out of 43 patients, 9 patients (21%) reported one or the other adverse effects associated with the use of MTX. (as shown in Table 3) Five patients showed more than one system involvement.

Table 3: Adverse Drug Reactions of MTX

Sr. No	Adverse Drug Reaction		No. of patients
1	Gastrointestinal side effects		5
2	Hematological effects		5
3	Hepatotoxicity		4
4	Mucocutaneous	Oral ulcers	2
		Tinea facei	3
5	Others	Burning micturition	1
		Photosensitivity	1
		Dry cough	1
Total*			21

* More than one system involved in five patients

Gastrointestinal side effects were observed in 12% of the patients in the form of nausea, vomiting and dyspepsia. Hematological side effects were found in 12% in form of mild to moderate leucopenia. Nine percent of the patients showed hepatic involvement in form of raised liver enzyme (2 patients) and hepatitis (2 patients). Two patients (5%) had oral ulcers and stomatitis. Three patients (7%) came with dermatophytic infection involving face during the course of the therapy which was well managed with topical antifungal treatment. Each of the case represented with photosensitivity and dry cough. Patient with dry cough was evaluated thoroughly and was found to have no sign of significant pulmonary involvement.

Discussion: Psoriasis is a common, chronic, disfiguring, inflammatory and proliferative condition, in which both genetic and environmental influences have critical role. The course of the disease remains as unpredictable as it was 150 years ago. It has various episodes of remissions and relapses and has a negative impact on patient's quality of life. The spectra of relapses impend upon the minds of the patient and the treating dermatologist.

A drug that cures psoriasis is yet to be discovered. In addition to conventional systemic modalities (MTX, acetretin, cyclporin and ultraviolet light), biologics (etanercept, infliximab, adalimumab and ustekimumab) have provided the dermatologists with an expanded armamentarium, thereby improving likelihood of controlling psoriasis. MTX has been used for the treatment of severe psoriasis and psoriatic arthritis sine 1950s. [4] It remains an important agent despite the advent of biological agents for psoriasis [5] MTX is an antimetabolite agent, a synthetic analogue of folate, used in the treatment of various malignancies and autoimmune diseases. MTX has anti-inflammatory, antiproliferative and immunopsuppresant action. It interferes with the metabolic pathway of folic acid, which is required for DNA synthesis. MTX also partially, and with less sensitivity, inhibits the formation of the purine ring of inosinic acid, the precursor of all DNA and RNA purine nucleotides. High concentration of MTX can even directly inhibit protein synthesis.

The effect of low dose MTX may be due to the formation of intracellular polyglutamates (poluglutamation) and the increased formation of adenosine, a potent endogenous anti-inflammatory mediator. [6,7] Some authors have suggested that the chief mechanism of action of low dose MTX in psoriasis and other inflammatory diseases may result from the induction of apoptosis in activated lymphocytes from the inhibition of these cells' activation and expression of certain adhesion molecules. [8,9,10] In regimens for psoriasis, MTX also inhibits polymorphonuclear leukocyte chemotaxis. [11] These actions may explain its clinical effects.

MTX offers distinct advantage. It may be given as a single weekly oral dose, or divided into three parts given 12 hours apart over 24 hours [12] The weekly dose schedule is very convenient and the therapeutic response is quick and assured. A small initial test dose, usually 5-7.5 mg, is advisable. [13] The dose is gradually escalated to a level (7.5-15 mg) that provides reasonable benefit without noticeable toxicity. In the present study, MTX found to be effective in 98% of patients within 2-24 weeks with an average of 6.8 weeks, which is correlated with the findings of Griffiths et al. who showed evident clinical response in 7-14 days with maximum response in 4-8 weeks. [14] In this study, 30 patients responded within 4-8 weeks, while 9 patients responded within 16 weeks. There was no association between the duration of the disease, BSA and therapeutic response as maximum patients (62%) had 41-60% BSA involvement amongst which 70% responded within 8 weeks of treatment. Similar observation was noted by

Karibasappa et al. [15] The tolerability and efficacy of MTX in psoriasis is very well known. But, relapse rate after discontinuation of therapy is an area yet to be explored. [15,16] Karibasappa et al reported relapse in all the cases after stoppage of MTX within 6-12 weeks.[15] In the present study, 33 patients could be followed up for the period of six months to assess the relapse rate while nine patients were dropped out after remission. Of these 33, five patients (15%) continued to be under remission even after six months of stoppage of MTX therapy, while the remaining 28(85%) patients relapsed in a span of 2-24 weeks, majority in 4-8 weeks. Specific correlation was not found between the duration of the diseases, age of the patient or cumulative dose of the MTX and relapse of psoriasis in this study. Hence, it is difficult to comment that for how long the therapy should be continued to prevent the relapse in such cases.

21% of the patients developed side effects during the course of therapy, which were minor and are described in the literature.[17] 55.5% had more than one system involvement. Only two cases of hepatitis compelled to discontinue the drug. They recovered completely within six weeks after withdrawal of MTX. All the patients relieved their symptoms with folic acid supplementation. Leucopenia and raised liver enzymes (with normal abdominal sonography) were transient and required temporary withdrawal of the drug for a period of two and eight weeks respectively. Addition of H_2 blockers, antacids and conventional antiemetic controlled the gastrointestinal side effects. Oral ulcers and stomatitis, which was resolved within a week time with folic acid institution. A dose of l0mg folic acid daily did not compromise therapeutic efficacy of MTX. Similar results were obtained with folic acid supplements were obtained by Masuria et al and Duhra et al. [18,19]

The most important feature of this MTX therapy is that it has best efficacy and it is well tolerated. A single gold standard for the treatment of psoriasis does not exist, but MTX can be placed closest to the gold standard amongst systemic agents. It helps to attain remission quickly and delays relapse if provided for a sufficient period after remission is achieved. In patients with socially and physically crippling psoriasis where MTX would be used, the risk of significant adverse reactions is low enough to be acceptable, provided supervision is thorough.

Conclusion: Methotrexate is still a near to gold standard therapy for psoriasis. It induces quick remission and delays relapse significantly. Methotrexate, if given with proper monitoring, will have significantly low risk of adverse effects.

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Conflict of interest: None
Funding: None
Cite this Article as: Thakkar S, Chavda P, Sharma N, Marfatia Y, Remission, Relapse and Safety In Psoriasis Patients in a Tertiary Care Center. Natl J Integr Res Med 2015; 6 (2): 15-19