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Original Article

Efficacy and safety of methotrexate in lichen planus

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Abstract

Objective To evaluate the efficacy and safety of methotrexate in lichen planus.

Methods This quasi-experimental study was carried out in the Skin outdoor, Mayo Hospital, Lahore from March 2011 to September 2011. Fifty five patients of either sex from puberty onwards were included in the study. Efficacy was determined by ≥50% clearance of number of mucocutaneous lesions after 12 weeks of oral methotrexate 15mg/week. Safety of methotrexate was analyzed by taking history of nausea, fatigue and measuring hemoglobin (Hb), white blood cell count (WBC), platelet count, serum alanine aminotransferase (ALT), aspartate aminotransferase (AST) levels at base line, 2nd, 4th, 8th and 12th week.

Results Methotrexate was efficacious in 63.6% patients. Out of these, 21.8% patients were with cutaneous involvement while 41.8% patients had both skin and mucous membrane involvement. There was a significant reduction in number of cutaneous lesions, with little or no effect on mucosal lesions of patients. Methotrexate did not prove efficacious even in a single patient with isolated mucosal involvement. The drug was safe and well tolerated in 91% cases.

Conclusion Methotrexate proved efficacious and safe in our study for most of the patients.

Keywords
Lichen planus, methotrexate, efficacy, safety**.**

Introduction

Lichen planus (LP) is an idiopathic, inflammatory and autoimmune mucocutaneous condition characterized by violaceous, polygonal, pruritic, flat-topped, scaly papules and plaques commonly seen on the flexural creases of body, lower back, oral mucosa, as well as, on scalp and nails.[1] It has a recurrent course and on healing leaves a postinflammatory hyperpigmentation and rarely scarring.[2]

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LP can be subclassified by morphology and distribution of lesions.[3] It is estimated to affect 0.5% to 2% of general population with no racial variation. It is more common in middle-aged adults with a female predominance of 2:1.[2,4,5]

Though the exact etiology of LP is unknown but its associations with the HLA DR1, hepatitis B and C and cytokine profiles suggest genetic, infective and autoimmune causes, respectively.[2,5] It is considered an autoimmune disease mediated by activated T cells directed against basal keratinocytes.[6,7] Long-standing cases of oral LP are associated with squamous cell carcinoma.[8]

LP is a therapeutic challenge to dermatologists. Currently-used topical and systemic therapies for LP include corticosteroids, tacrolimus,

retinoid, ciclosporin, photochemotherapy, azathioprine, cyclophosphamide, mycophenolate mofetil, hydroxychloroquine, thalidomide, dapsone and gold.[9,10] These therapeutic modalities are effective but serious toxicity limits their long-term use. There is always a search for new therapies aimed at good control of disease, fewer side effects and cost effectiveness.

Methotrexate (MTX) is a folic acid analog that inhibits dihydrofolate reductase (an enzyme involved in *de novo* pyrimidine synthesis) and has anti-inflammatory and immunomodulatory effects.[11] Many studies support its role in the treatment of lichen planus, as it inhibits activated T lymphocytes and downregulates the immune mediated response of skin.[12-15] The side effects of this drug are nausea, fatigue, bone marrow suppression and hepatotoxicity.[11,13]

MTX is a cheap, easily available and relatively safe drug. The unmet need for safe and effective therapies has prompted the use of MTX. Till date, there are no data available in Pakistan on use of MTX in LP patients. This study aimed to evaluate the efficacy and safety of MTX in LP.

Methods

This quasi-experimental study was carried out in the outpatient department of Dermatology unit-II, Mayo Hospital, Lahore from March 2011 to September 2011. The study was approved by the Institutional Ethical Committee. Fifty-five patients of either sex, age ≥15 years with clinical diagnosis of LP (histopathological confirmation was done in doubtful cases), with disease duration ≥3 months were enrolled in the study. All these patients had baseline Hb >10g/dl, WBC >4000/mm3, platelet count >150,000/mm3, ALT and AST <35IU/L, while patients with pregnancy, lactation, history of diabetes mellitus, renal failure, chronic liver disease, positive HBV/HCV infection, application of any topical therapy for last 2 weeks and intake of any systemic therapy for last 4 weeks were excluded from the study.

After getting informed consent and explaining the risks and benefits of the treatment to the patient, the demographic data like name, age, address and telephone number was obtained. Relevant history was taken and clinical examination was done. On clinical examination, patients were categorized into 3 groups according to the site of involvement such as:

Group A: patients with lesions of both skin and mucosa.

Group B: patients with mucosal involvement only.

Group C: patients with only skin lesions (more than 10 lesions).

Baseline investigations like Hb, WBC, platelet count, AST and ALT were done at the beginning.

All patients were given methotrexate 5mg at baseline followed by repeat of WBC count after 1 week. Patients having normal WBC count were given methotrexate 15mg/week orally in three divided doses 12 hours apart. The drug was continued till clearance of lesions or for a period of maximum twelve weeks, whichever was earlier. Folic acid 1mg was given daily to all patients. Each patient was followed up for a period of three months.

Efficacy of the drug was assessed by reduction in number of mucocutaneous lesions at 2nd, 4th, 8th and 12th week. The drug was considered efficacious when there was >50% clearance of cutaneous lesions after 12 weeks of therapy at the maximum. The side effects were assessed by

measuring WBC count after one week and Hb, WBC, platelet count, AST and ALT at 2nd, 4th, 8th and 12th week of the study. All the information was collected on a specially-designed proforma.

Data were entered and analyzed through SPSS (version 11). Data master sheet was generated for variables under study. The quantitative data (age) were presented in the form of means and standard deviations while the qualitative outcome variables (gender, efficacy and safety) were presented in the form of frequencies and percentages. Data were stratified for three sites of lesions (mucosa, skin, both skin and mucosa).

Results

A total of 55 patients were enrolled in the study. Out of these, 52 patients completed the study. There was a delayed exclusion of three patients from the study due to adverse events (rise in the levels of AST and ALT twice the upper normal limit and decreased WBC count <3500/mm3). There were 32 (58.2%) females and 23 (41.8%) males. Female to male ratio was 1.4:1. The age of patients ranged from 22 to 65 with a mean of 37±8.78 years. Most of the patients were between 31 to 40 years of age group. The age distribution is given in **Table 1**.

Fifty-five patients were divided into three main groups from group A-C, according to site of disease involvement. Group A included 31 (56.3%) patients with both cutaneous and mucosal involvement of disease while 4 (7.3%) patients with exclusive mucosal involvement were placed in group B. Group C included those 20 (36.4%) patients who had isolated cutaneous involvement of various types of LP.

Females outnumbered males in all three groups. The demographic data of patients in each group is given in **Table 2**. The age and sex distribution of LP did not vary according to site of involvement of disease.

In group A, more than 50% clearance of mucocutaneous lesions, after 12 weeks MTX therapy, was observed in 23 (74.2%) cases but there was a significant reduction in number of cutaneous lesions with little or no improvement in mucosal lesions of patients. In 12 (60%) cases of group C, more than 50% clearance of cutaneous lesions was observed.

The mean percentage reduction in number of mucosal lesions at the end of treatment in group B was 10% which did not meet the criteria for MTX to be proved efficacious. In total, the efficacy of MTX in patients of LP was seen in 35 (63.6%) cases (**Table 3** and **4**).

The drug was found safe and well tolerated as only 5 (9%) cases had side effects. Out of these 5, two patients were from group A, one from group B and two were from group C. Nausea, found in 4 cases, was controlled by anti-emetic drug (tablet gravinate 50 mg) and proton pump inhibitor (capsule omeprazole 20mg) and MTX was continued. On the whole, the safety profile of the drug was good in 50 (91%) cases (Table 5).

During the follow-up period of three months, 4 (7.3%) cases reported recurrence of the disease at the interval of 6-8 weeks. These four cases were from group C.

Table 1 Distribution of patients according to age groups (n=55).

Age (years)	*N (%)*
13-20	-
21-30	13 (23.6)
31-40	26 (47.3)
41-50	12 (21.8)
>50	4 (7.3)

Table 2 Demographic data of patients in groups (n=55).

	Group A	*Group B*	*Group C*

	(n=31)	*(n=4)*	*(n=20)*
Sex			
Female	18 (58.1%)	3 (75%)	11 (55%)
Male	13 (41.9%)	1 (25%)	9 (45%)
Age (years)			
Mean (female)	38,83 +8.49	43.0+ 19.15	31.90 + 5.43
Mean (male)	37.53+ 8.21	45	39.00+8.39
Range	22-55	30-65	23-55

Group A: both skin and mucosal lesions; group B: mucosal involvement only; group C: only skin lesions (more than 10 lesions).

Table 3 Efficacy of methotrexate in lichen planus (n=55).

	Group A (n=31)	*Group B (n=4)*	*Group C (n=20)*
Drop outs	2	1	
Effective treatment	23 (74.2%)		12 (60%)
% reduction	88.0		86.2
Ineffective treatment	6 (19.4%)	3 (75%)	8 (40%)
% reduction	33.2%	10.3%	26%

Group A: both skin and mucosal lesions; group B: mucosal involvement only; group C: only skin lesions (more than 10 lesions).

Table 4 Safety profile of patients taking methotrexate (n=55).

Side effects	*Group A (n=31)*	*Group B (n=4)*	*Group C (n=20)*
Frequency	2 (6.5%)	1 (25%)	2 (10%)
Events noted	Increased AST & ALT Leucopenia Nausea	Increased AST & ALT Nausea	Nausea

Group A: both skin and mucosal lesions; group B: mucosal involvement only; group C: only skin lesions (more than 10 lesions).

Discussion

This is the first study regarding the efficacy and safety of the MTX in LP in Pakistan. Internationally, only one pilot study by Turan *et al*.[13] from Turkey has been published till date, using oral MTX as monotherapy for LP. A few cases of LP were reported in 2008 in which MTX was used along with topical clobetasol dipropionate and tacrolimus ointments.[12]

In our study the incidence of LP was higher in females than males with a ratio of 1.4:1. The literature supports this epidemiological data. Boyd *et al.*[16] described that LP affects women preferentially. Turan *et al*.[13] from Turkey reported predominance of females among LP patients.

In present study, the maximum incidence of disease was seen in 31-40 years of age group which is comparable with other studies. Abdallat *et al.*[2] reported that majority of LP patients were between 34-59 years. In another study conducted in Bangladesh, it was observed that LP was more prevalent in the age group 30-50 years.[4]

Anber *et al.*[17] reported that up to 65% of the patients with cutaneous LP manifested oral mucosal lesions, as well. We observed 56.3% of patients having concomitant cutaneous and oral LP, an observation which is consistent with the above-mentioned study.

In our study, cutaneous LP without mucosal involvement was observed in 36.4% of patients. Almost similar result was observed in a retrospective study in 110 patients of LP by

Oliveira *et al.*[18] in which 32.72% of patients had isolated cutaneous involvement of LP.

Exclusive oral mucosal involvement was observed in 7.3% of our patients while the Brazilian data on oral LP suggests that isolated oral mucosal LP occurs in 15-35% of all LP patients.[18] This variability in results may be due to the fewer enrollments in our study as 110 patients were enrolled in the Brazilian study compared to only 4 cases in our study. Another possible reason of difference in percentage may be due to the difference in geographical conditions of Pakistan and Brazil. Further support of geographical variation is derived from the results of an Egyptian study revealing oral mucosal involvement in 8% of cases.[17] Similar finding of our study and that of study from Egypt could be due to the similar geographical distribution of environmental factors. It further supports the fact that there may be a difference in oral LP prevalence in different parts of the world.

In our study 63.6% cases had a reduction up to 100%, with a mean of 87%, in the number of lesions of LP whereas more than 90% reduction was found in 91% cases in the pilot study conducted by Turan *et al.*[13] in Turkey. Overall, the drug was found non-efficacious in 36.4% of patients in our study compared to 9% of patients in the study conducted by Turan *et al*.[13] This difference may be due to the fact that in study by Turan *et al.*[13] the patients of generalized LP only were enrolled and generalized LP is a variant which responds well to therapy. In contrast, in our study the patients with different types of LP were enrolled. The literature shows that few variants of LP like LP hypertrophicus, follicular LP and LP pigmentosus, are highly resistant to treatment. Moreover, Turan *et al.*[13] used MTX dose in the range of 15-20mg/week according to the severity of disease while we used a standard dose of 15mg/week irrespective of severity or type of the disease which may explain the reason of higher percentage of non-efficacy of the drug in our study.

In the present study, the drug was found efficacious in 60% of patients with isolated cutaneous involvement whereas Turan *et al.*[13] noticed efficacy of the drug in 82% cases. The considerable difference in percentages of patients with isolated cutaneous involvement may be due to the reason that they enrolled more patients of isolated cutaneous LP.

In our study, 29 (74.2%) patients of LP with both mucosal and cutaneous involvement achieved efficacy. Significant improvement (88% reduction) was seen in cutaneous lesions whereas no response was seen in mucosal lesions. In the Turkish study, one (9%) patient with dual involvement achieved more than 90% response. This result of efficacy goes parallel to that of our study. However, a significant difference in percentage of patients with dual involvement achieving efficacy is due to considerable difference in sample size of the two studies. Any difference in response rate between cutaneous and mucosal lesions had not been addressed in the Turkish study. The difference in response of cutaneous and oral LP with MTX has not been found in any other international study.

MTX did not prove to be efficacious in patients of isolated oral mucosal involvement in our study. According to literature, lesions of oral LP last longer than those of cutaneous LP. The reported duration of oral and cutaneous LP is 5-8 years and 1-2 years respectively. This chronicity of oral LP may be due to deficiency in mechanisms of immunosuppression mediated by transforming growth factor beta.[19] Nylander Lundqvist *et al.*[20] reported 4 cases of severe erosive LP, with both oral and genital mucosa involvement in 3 patients and isolated oral

mucosal involvement in 1 patient. All patients were given a trial of MTX supplemented with steroid ointment. The treatment continued for about 17 months and 70% lesions disappeared at the end. This is in contrast with the results of our study in which no response was achieved in the patients of oral mucosal LP. Better results of this study may be due to simultaneous use of topical corticosteroids and much longer duration of treatment (17 months compared to 3 months in our study). It is proven now that MTX has anti-inflammatory and immunomodulatory effects. Coupled with corticosteroids, MTX may have enhanced anti-inflammatory action, thus showing good results.

In our study safety and tolerability (91% patients) was found to be very good. The side effects (nausea, rise in transaminases twice the upper normal limit and decrease in the white cell count less than 3500/mm^3) were reported in five (9%) cases. The trial done in Turkey showed adverse effects of MTX, like nausea and fatigue, in 9% of the patients which is in line with our study.

Recurrence of disease was observed during follow-up period of three months in the present study, at the interval of 6-8 weeks, in 4 (7.3%) cases. Turan *et al.*[13] reported recurrence of disease in 9% cases after 10 weeks which is comparable with our study.

MTX in a short course has proved beneficial regarding its good tolerability and minimal side effects. It gave better results in patients of LP with cutaneous involvement compared to mucosal involvement. Large controlled trials are needed to determine the efficacy of MTX in oral mucosal LP. Being an effective, safe, cost effective, and readily obtainable drug, MTX can be a good option for treatment of LP in developing countries like Pakistan.

Conclusion

MTX proved efficacious in 63.6% of patients of LP as there was more than 50% reduction in number of lesions. The drug is effective in cutaneous LP where the lesions decreased significantly while no response was seen in case of mucosal LP. We can conclude that MTX is a safe-to-use drug in LP as it proved to be well tolerated in 91% cases in our study.

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