

# ORAL LICHEN PLANUS: DIFFERENT TRENDS IN TREATMENT

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## ABSTRACT

**Objective:** To find out a suitable drug for the management of OLP which could relieve the agony of the patients suffering from this incurable disease.

**Material and Methods:** In this prospective study two hundred patients were analyzed at tertiary care center. The diagnosis was made on detailed history and clinical examination and confirmed with histopathological examination. OLP was labeled as idiopathic. The patients were divided in four groups of fifty patients each without control. Every group was treated with different regimens. Responses to treatment, relapses and side effects were determined by comparing scores with baseline Scores.

**Results:** The combination of intra-lesional injection (40mg/ml) of triamcinolone acetonide (TA) with 0.1% topical flucinolone acetonide ointment was effective as compared to 0.1% topical tacrolimus and methotrexate (2.5mg/ week).

**Conclusion:** Corticosteroid remained the mainstay of treatment of OLP and intra-lesional steroids still have important place today.

**Key Words:** Oral, Lichen Planus, Intralesional, steroids, tacrolimus, methotrexate.

## INTRODUCTION

Lichen planus is a chronic inflammatory mucocutaneous disease of multifactorial origin, often idiopathic with an immunopathogenesis involving T-cell. Oral lichen planus (OLP) occurs more frequently than the cutaneous form and more resistant to treatment<sup>1</sup>. It affects 0.1-4% of the population<sup>2,3,4</sup>. The disease has most often been reported in middle-aged patients more in females than males<sup>5</sup>. The posterior buccal mucosa is most commonly involved, followed by the tongue, gingiva, and vermilion of the lower lip<sup>6</sup>. 50% patients with cutaneous lesions have oral involvement whereas only 25% of patients with oral lesions have skin involvement<sup>7</sup>.

Although there are several clinical forms such as reticular, papular, erythematous (atrophic), bullous, plaque-like, erosive. But the most common are the reticular and erosive form. The reticular is the most common, however erosive forms is typically the most symptomatic, debilitating, and difficult to treat<sup>8,9</sup>. Frequent complaints vary from burning sensation to severe pain particularly after eating foods that are either spicy or acidic.

The treatment options available for OLP are corticosteroids<sup>10</sup>, retinoids, cyclosporine, methotrexate<sup>11</sup>, azathioprine, tacrolimus<sup>12</sup>, surgery, CO2 laser, psoralen-Ultraviolet A, and photochemotherapy. Other modalities include griseofulvin, hydroxychloroquine, dapsone, and thalidomide<sup>13</sup>.

Authors were in the search of a suitable regimen for the management of OLP that was effective, having minimal or no side effects and the chances of relapse after treatment were less. The aim of this investigation was to find out such regimen, which could relieve the agony of the patients suffering from incurable OLP. Appropriate management of OLP may help to control burning sensation and pain and significantly improve the quality of life for many patients.

**MATERIAL AND METHODS**

This prospective randomized study was initially started on more than 200 patients with OLP at different sites of oral cavity from 2007 to 2012 at a tertiary care hospital. But finally only 200 patients were selected because they passed through all stages of followup. The rest of patients who could not complete their treatment and did not report back for proper follow-up were excluded from the study. Preliminary evaluation was made for each patient including age, gender, and lesion localization. The diagnosis was made on detailed history and clinical examination and confirmed with histopathological examination. There was no associated systemic disease or any other cause was found so we labeled it as idiopathic OLP. The record of previous treatments did not contain any specific drug and was not properly maintained by the patient. Therefore it could not be presented in this study. Each patient provided

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written informed consent to participate in the study. Ethical approval was obtained prior to commencing the study.

To score the symptomatic activity, the visual analogue scale (VAS) was used that was assessed by the patient. Patients were advised to determine burning sensation or pain from 0 (no symptoms) to 100 (severe symptoms) on self-assessment basis when the lesion was brushed gently or by observing the response to stimulus that was causing the discomfort that varied from individual to individual.

The patients were divided in four groups of fifty patients each without control. Every group was treated with different regimens i.e., regimen I to regimen IV. Regimen I: 0.12% chlorhexidine hydrochloride mouth wash (m/w), 0.15% benzydamine hydrochloride m/w, oral metronidazole 400mg TID. The duration of treatment was 14 days and one-month follow-up. Regimen II: 0.1% topical tacrolimus ointment 2-3 times per day for 6 months and then 12 months follow-up. Regimen III: oral Methotraxate 2.5mg/week for 6 months and then 12 months follow-up. Regimen IV: Intra-lesional triamcinolone acetonide injection (TA) 1ml (40mg/ml); one injection followed by second one after 2 weeks depending upon the response of the lesion. Second injection was repeated, if the lesion was improved less than 75%. 0.1% topical flucinolone acetonide ointment (FA) was applied 2-3 times per day for 6 months. Follow-up in this case also remained 12 months. The injection technique was as follows:

1 ml TA was mixed with 2% lignocaine with adrenaline (1:200,000) to lessen the pain at the site of injection. 25/27 G needle was used and the entry point of the needle was away from the lesion but in its close vicinity and it was approached to the lesion sub-mucosally. The solution was deposited at various areas of the lesion. Care was taken to deposit the solution just beneath the mucosa and not in the muscle or sub-periosteally depending upon the anatomical region.

In Regimen I, follow-up period was one month because patients did not get relieved with this treatment and majority came back within 15 days after the completion of the course of Regimen I. The patients were examined after every two weeks in treatment with each regimen. The instructions for maintenance of oral hygiene were advised in all regimens.

The response of the patients was measured in three categories. Complete response was defined as asymptomatic patient and complete healing of lesion or mild white striae after continuous treatment with the regimen. Partial response: decrease in symptoms or incomplete resolution lesion after continuous treatment with the regimen. No response: no change in symptoms or signs after continuous therapy with the regimen.

The collected data were analyzed by a statistical package for social sciences (SPSS) v.16. The results were reported as count and percentages. Chi-square test at 5% level of probability was applied for testing the association between different regimens and response (no response, partial response and complete response). One-way analysis of variance (ANOVA) was used for checking the significance of various regimes under study, and least significance difference (LSD) test was performed for means separation.

## RESULTS

Two hundred patients were identified from more than 200 patients with OLP at different sites of oral cavity. The symptomatic OLP had been present for a mean time of 12±5 months (4-37 months). Out of two hundred patients 32 had reticular lichen Planus; 72 Erythematous/atrophic and 96 had erosive lichen planus. There were 64 male and 136 female patients. According to the results obtained, OLP predominantly manifested between the ages 35 and 61 (47.52±7.619). 160 patients presented with OLP lesions only, while 40 had also involvement of skin. No patient with HCV was reported in this study. Patients were observed for malignant change but no such change was seen in any patient.

All 32 cases of reticular lichen Planus were presented in the posterior buccal region. And the 96 cases of erosive lichen planus were seen on the tongue, gingiva, lower lip and posterior buccal region as shown in Table 1. Erosive lichen planus was more common unilaterally in posterior buccal region as compared to reticular lichen Planus.

In regimen I, all patients were failed to respond except 2 patients who presented partial response to the treatment. In Regimen II, a complete response following 6 months of tacrolimus therapy occurred in 11 patients

**Table 1: The distribution of Lichen Planus in oral cavity**

Type of Oral Lichen Planus	Posterior buccal region		Tongue	Gingiva	Lower lip	Total
	Unilateral	Bilateral				
Reticular Lichen Planus	16	16	—	—	—	32
Erythematous (atrophic)	36	24	8	4	—	72
Erosive Lichen Planus	40	28	16	8	4	96
Total	92	68	—	—	—	—
	100		24	12	4	200

**Table 2: Scoring system for OLP**

Scoring	Clinical features
5	white striae with Erythematous (atrophic)/ erosive area > 3cm <sup>2</sup>
4	white striae with Erythematous (atrophic)/ erosive area > 2cm <sup>2</sup> but < 3cm <sup>2</sup> ;
3	white striae with Erythematous (atrophic)/ erosive area from 1cm <sup>2</sup> to 2 cm <sup>2</sup> ;
2	white striae with Erythematous (atrophic)/ erosive area < 1cm <sup>2</sup> ;
1	white striae only no matter what were the size;
0	No lesions, normal mucosa

1 was added for Erythematous lesion and 2 for erosive lesion in addition to the score mentioned above. This score was for one lesion. If lesions were located on more than one site in oral cavity then the total score was derived by summation of the scores of all lesions.

(22%); 26 (52%) showed partial response while 13 (26%) did not respond to tacrolimus ointment. Regimen III gave more or less similar results to Regimen II. 40 patients got complete response from Regimen IV and all patients said no to "no response" in this regimen. One injection of TA was sufficient in all patients with Reticular Lichen Planus but 17 out of 24 patients in Erosive Lichen Planus visited for second injection of TA after two weeks because improvement of the lesion was less than 75% in these patients. Overall Chi-square = 158.20 with P-value = 0.000. In addition, the Chi-square suggests that there is a significant (P<0.05) association between different regimes and various responses in getting relief from pain. It suggests that moving from Regimen I to Regimen IV; their effect will be changing in getting relief from pain. The details are shown in Table 3.

The baseline VAS was 56.54±14.84, which was reduced to 18.14±15.53 with response to Regimen IV. And the score of OLP was reduced from 4.38±1.95 (baseline) to 0.54±1.13 in Regimen IV. VAS and score of OLP lesion was more or less similar in response to Regimen II and III. The results of VAS and scoring of

**Table 3: The response of patients to different regimens**

Regimen	No Response	Partial Response	Complete Response	Total
Regimen I	48(96)	2(4)	0	50
Regimen II	13(26)	26(52)	11(22)	50
Regimen III	14(28)	28(56)	8(16)	50
Regimen IV	0	10(20)	40(80)	50

Overall Chi-square = 158.20 with P-value = 0.000

**Table 4: VAS and scoring of OLP lesion, with or without treatment with different regimens**

	Baseline	Regimen I	Regimen II	Regimen III	Regimen IV	F-ratio	P-value
VAS (1-100)	56.54±14.84 a (25-80)	55.60±14.29 a (25-79)	30.22± 20.19 b (0-67)	33.00± 17.15 b (0-64)	8.14±15.53 c (0-40)	74.167	0.0000
Letters a, b, c are shown with each figure. Similar letters (a & a or b & b) indicates that figures are not significantly different at 5% level of probability. And figures with different letters ( a, b,c) shows that these figures are significantly different with each other at 5% level of probability. LSD0.05 for VAS = 6.514.							
OLP lesion Scoring*	4.38 ±1.95 a (1-10)	4.03± 1.87 a (1-10)	2.25 ± 2.08 b (0-10)	2.51±2.27 b (0- 10)	0.54± 1.13 c (0-4)	32.726	0.0000

Values are given as mean + SD and the values in parenthesis are the ranges (minimum-maximum); \* OLP lesion scoring was calculated according to the scoring system mentioned in Table 2.

**Table 5: The adverse effects in each regimen**

Regimen	Number of patients (%age)	Adverse effects
Regimen I	38(78)	Metallic taste, nausea, anorexia
Regimen II	11(22)	Local irritation, burning sensation
Regimen III	50(100)	Hair fall
Regimen IV	32(64)	Oral candidosis

OLP with and without treatment (baseline) with different regimes are displayed in Table 4. It is evident, in case of VAS scoring, that minimum average score was recorded at Regimen IV which is significantly ( $P < 0.05$ ) different from the rest of other regimes. In addition, no significant ( $P > 0.05$ ) difference was observed between the average VAS scoring of base line and Regimen I, and Regimen II and Regimen III. However, the average VAS score of Regimen II and Regimen III were significantly lower as compared to Regimen I and baseline. Furthermore, exactly the same trend was found in case of OLP lesion scoring, regarding baseline and four different regimes.

The relapse occurred in all patients in Regimen I, II and III. The interval of relapse after I, II and III regimens were  $15 \pm 2$  days,  $10 \pm 2$  months and  $9 \pm 3$  months respectively. Only five patients suffering from erosive lichen planus in Regimen IV (one shows complete response and four shows partial response) showed relapse at the close of this study. The sites of relapse from Regimen IV was two each in posterior buccal and tongue and one in the gingival area.

Few adverse effects were reported. Metallic taste, nausea, anorexia were observed with Regimen I that was probably due to metronidazole. The patients complained of local irritation and burning sensation at the site of application of tacrolimus that subsided with continuous treatment. Hair fall was the only side effect with methotrexate as shown in Table 5. No significant adverse effects were observed with Regimen IV except oral candidosis, which was treated with Nystatine oral drops.

## DISCUSSION

The treatment of OLP is a great challenge to the health care workers. The various trials have been attempted to improve the refractory lesions but complete cure of OLP has not been accomplished because of its recalcitrant nature<sup>14</sup>. The treatment is aim at reducing the length and severity of symptomatic out breaks. We need to find a therapy that could improve the quality of life, if not cure the condition.

Excellent oral hygiene is believed to reduce the severity of symptoms. Therefore maintenance of oral hygiene was mandatory in all regimens in this study. 0.12% chlorhexidine mouth wash was added in Regimen I. Although results were not impressive with this regimen, but better response was seen in Regimen I through IV. It could be probably difficult for the patients to achieve high level of oral hygiene during periods of active disease. Therefore authors agree that the control of oral hygiene is the most important consideration during management of OLP and can enhance healing of lesion as described elsewhere<sup>15</sup>.

Tacrolimus is one of the members of the immunosuppressive macrolide family (cyclosporine, rapamycin, ascomycin) that suppresses T-cell activation and used to prevent transplant rejection<sup>16</sup>. The response of topi-

cal tacrolimus was encouraging in this study showing complete response in 11 patients. No serious drug-related adverse effects were observed. The local irritation and burning sensations were seen in almost 22% of patients and were transient, resolved with the passage of continuous treatment and as the OLP improved. The relapse was reported in all our patients after the interval of  $10 \pm 2$ , suggesting that tacrolimus has purely palliative and not a curative effect but the evidence indicated the effectiveness of tacrolimus in treating OLP. This study is contrary to the findings of Radfar L.<sup>17</sup> However Sonthalia S and Singal<sup>18</sup> observed that Tacrolimus 0.1% ointment is an effective alternative to topical steroid and may be considered as a first-line therapy in OLP.

The authors explored the effectiveness of methotrexate<sup>19</sup> that is not widely described for the treatment of OLP and the response was substantial. Methotrexate showed more or less similar results to topical tacrolimus. The low dose (2.5mg/week) was selected to prevent toxic effects to the bone marrow and liver. Therefore no serious side effects were observed except hair fall, which was complained by all patients. Since the dose of methotrexate was low, therefore hematological monitoring was not considered. Although relapse occurred in all patients similar to topical tacrolimus but authors were of the view that methotrexate should be considered as part of portfolio of treatment options for OLP as mentioned elsewhere. The best responses were observed in previously untreated patients. Torti DC<sup>20</sup> et al reported that most patients eventually achieved a substantial response with limited toxic effects. They observed that low-dose methotrexate as an agent with substantial activity in OLP.

Topical corticosteroids have been widely used in the treatment of vesiculo-erosive disease of oral mucosa including OLP to reduce pain and inflammation<sup>21</sup>. Many trials and formulations of steroid have been used in the treatment of OLP that showed improvement of signs and symptoms. Toxic effects were associated with systemic agents whereas side effects were mild with topical application<sup>22</sup>. Authors selected TA with topical FA. Topical FA was recommended because there would be no permanent adrenal suppression seen after 6 months treatment<sup>23,24</sup>. TA provided clinical effect with the dose of 40-80 mg at two weeks' time that was not a high dose to show any serious adverse effects. And 0.1% topical FA was applied during the remaining period of therapy in Regimen IV. This combination might definitely reduce the systemic absorption of corticosteroids and resultant adverse effects.

In the procedure of the TA injection, the entry point of the needle was selected away from the lesion but in its close vicinity because experience showed that if the lesion is approached directly then multiple pricks were required that led to leakage of the solution of injection. However it is suggested that entry point of the needle away from the lesion is not mandatory but the most

important point is to avoid multiple pricks. Secondly, the solution must be injected in the sub-mucosa and not in the muscles or sub-periosteally. Otherwise the injection will be ineffective.

The most striking feature of this study was that relapse after the use of TA and topical FA remained minimal as compared to tacrolimus and methotrexate. Only five patients with ELP showed relapse after treatment with Regimen IV and patients were more satisfied with this treatment. Corticosteroid<sup>25,26</sup> remained the mainstay of treatment of OLP and intra-lesional steroids still have important place today as it had in the past. Hydrocortisone<sup>27,28</sup>, dexamethasone<sup>29</sup>, TA<sup>30,31,32</sup> and methyl prednisolone<sup>33,34</sup>, were tried previously and were effective at inducing the lesions of OLP.

Kuo RC et al<sup>35</sup> reported prompt healing of erosive oral lichen planus lesion after combined corticosteroid treatment with locally injected triamcinolone acetonide plus oral prednisolone. Lee YC et al<sup>36</sup> done randomized controlled study on intralesional injection versus mouth rinse of triamcinolone acetonide in oral lichen planus and concluded that the efficacies of both treatments were similar. The rate of adverse effects was significantly lower for intralesional injection of TA than mouth rinse of TA.

Chuanxia Liu et al<sup>37</sup> reported that healed percentage was higher with betamethasone (93.1%) than with triamcinolone (66.7%;  $P = .02$ ), and final reduction in erosion area was greater in the experimental group ( $21.276 \pm 21.064 \text{ mm}^2$ ) than in the control group ( $11.5 \pm 12.95 \text{ mm}^2$ ;  $P = .02$ ). Reduction in pain level did not differ between groups. The proportion of participants with recurrent erosions was significantly lower in the experimental group (14.8%) than in the control group (45%;  $P = .04$ ). They concluded that Intralesional betamethasone may be used in the topical treatment of erosive oral lichen planus.

But the results were more successful with less side effects in our study than previous investigations and Chuanxia Liu et al.<sup>37</sup> The probable reason could be the addition of topical FA. However, 12-months follow-up may be observed as limitation of this study. The extended period of follow-up may provide more interesting circumstantial evidence for the combination of TA with topical FA. In the world of evidence-based medicine further investigation about the efficacy of this combination having long duration of follow-up is suggested.

## CONCLUSION

OLP is a chronic disease with no known cure. The main emphasis of its treatment was to relieve the agony of patients with the best suitable agent. Intra-lesional TA with topical FA was found to be effective in the management of OLP. However further investigation with long

term follow-up is suggested.

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