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EFFICACY OF TOPICAL TACROLIMUS IN PATIENTS WITH ORAL LICHEN PLANUS- IN A TERTIARY CARE CENTRE CHHATTISGARH

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ABSTRACT:

Background & objective - With limited resources of therapeutic options for the management of oral lichen planus (OLP), treatment is often challenging. With promising results of topical tacrolimus, we initiated our study to evaluate its efficacy in OLP on an outpatient basis in daily clinical practice.

Methods - This prospective study enrolled 42 clinically and histopathologically diagnosed OLP patients in a tertiary clinical setup and then were treated with 0.1% topical tacrolimus and evaluated between the years 2020 to 2022. Initially, topical tacrolimus 0.1% ointment was advised for twice daily application and then the dose was reduced to twice weekly to once in a week application for patients who improved after treatment. For the measurement of objective clinical response 4- point scale (complete remission (CR), major remission (MR), partial remission (PR), no response (NO), and for subjective response (pain assessment) 3- point scale (severe, mild to moderate and none) were used.

Results - Complete remission (CR) of objective clinical response was achieved in 9 (21.4%) out of 42 patients at 3 months and in 8 patients (19%) at 6 months. For patients who belonged to MR group 11(26.1%) and PR 16 (38%) at 3 months, the therapy was continued for further 6 months. Of those at 6 months, 8 patients showed CR, 11 patients MR, and 5 patients PR. After 3 months of therapy, all 6 patients with initial severe score of pain achieved a significant improvement. 11 out of 15 patients with mild to moderate score reported complete loss of pain. Overall, the pain improvement was very good. No relevant side effects other than transitory burning sensation and altered taste sensation were reported. No squamous cell carcinoma (SCC) was reported.

Conclusions- Topical tacrolimus could be a good treatment alternative for all forms of OLP where other treatment modalities have failed for initial therapy. For the maintenance therapy, the frequency

of application should be reduced guided by both signs of clinical activity and subjective impairment. Possibility of developing SCC mandates for regular follow-up.

KEY-WORDS: Topical tacrolimus, Oral lichen planus, Topical calcineurin inhibitor

Introduction: Lichen planus is an inflammatory mucocutaneous disease mostly involving the skin and the oral mucosa. It can involve other mucosae (such as genital, oesophageal conjunctival) and appendages (scalp and nails). If the lesions of lichen planus are present over oral cavity it is known as oral lichen planus (OLP).[1-3] OLP has a female dominance affecting 0.5 to 2.2% of the general population. OLP typically occurs between the 3th and 6th decade of life and the erosive form of OLP may develop into malignancy.[3-4] There are various forms of OLP seen in the oral mucosa. The most frequent form is reticular type of OLP which is mostly asymptomatic, the erosive/ ulcerative form is often associated with disabling pain, papular type, bullous and atrophic forms of OLP are also reported variably involving the oral mucosa, tongue, gingivae, floor of mouth, palate or lips.[11-12] Usually oral lichen planus tend to have a long clinical course in comparison to cutaneous lichen planus. The aetiology of lichen planus is unknown till date. Stress, hepatitis-C infection, etc. may be the probable cause of OLP. It has an autoimmune nature in pathogenesis with chronic course of exacerbation and remission.[5] There are different treatment modalities available such as drug therapy (corticosteroids, immunomodulaters, immunosuppressive and retinoid), Co2 LASER, PUVA therapy, cryotherapy, and surgical intervention. Among them drug therapy is most commonly used which can be administered by systemic or by local route[1.] Tacrolimus (FK506) is a macrolide with an immunomodulatory action, which was synthesized by Japanese soil fungus streptomyces tsukubaensis.[6] The mechanism of action of tacrolimus is to induce an inhibition of phosphatase activity of calcineurin which leads to suppression of many cytokines like interleukins, granulocyte-monocyte colony- stimulating factors, and tumour necrosis factor-α and interferon-γ. Hence the suppression of lymphocytes, monocytes and neutrophils occurs. Tacrolimus and cyclosporine both have similar action on inhibiting the activation and proliferation of T lymphocytes; but tacrolimus is preferred drug for its better efficacy. [7-8] Both topical and systemic forms of tacrolimus are available. Topical form of tacrolimus 0.1% ointment or creams has least systemic absorption and better safety profile, thereby preferred in treatment of dermatological disorders.[9] Most common adverse effects of tacrolimus are burning sensation or itching of mild to moderate intensity, systemic adverse effects like infection and flu-like symptoms has been reported with topical applications.[10] There are plenty of studies available on the topic of topical tacrolimus in treatment of OLP. However, these studies often reported adverse reaction using tacrolimus. Also, the vehicle used for delivering the drug and the concentration of the drug is highly variable in previous studies. Therefore, this study was conducted to re-evaluate the efficacy of topical tacrolimus in clinical practice in cohort of patients and the obtained results were compared with the available published data.

Subjects and Methods: This study was conducted at Chhattisgarh Institute of Medical Sciences, Bilaspur Chhattisgarh, between the year January 2020 to December 2022 and included all patients diagnosed with OLP according to clinical and histopathological criteria of WHO.[31] This study was approved by local ethics committee. A written consent was taken from all the patients who were willing to be part of this study. In all patients treatment started with topical tacrolimus 0.1% ointment for control of either symptomatic (pain or burning) or objective clinical involvement. At the start of therapy, the patients were instructed for twice daily application of the preparation on affected oral mucosa. Further the therapy was gradually tapered for patients who showed complete remission (CR) to attain a maintenance therapy consisting of one or two applications every week. Follow-up evaluations were performed at an interval of 2 weeks, for 1month, and then every month until 3 months and after 6 months of therapy.

The response to treatment was assessed using a 4-point scale: complete remission (CR) (regression of all visible lesions), major remission (MR) (regression of more than 50% of the lesions), partial (PR) (remission of at least 25% up to 50%), no response or worsening (NO) (remission of less than

25% of the lesions or clinical worsening). Pain was assessed using a 3-point severity scale (severe or food taking pain=2, mild=1, no pain or no complain=0). Baseline parameters at 3- and 6-months comparisons were performed using Pearson's chi-squared test and fishers exact test. Differences in subjective improvement between the groups from baseline to follow-up intervals were assessed using Pearson's chi-squared test and fishers' exact test taking a p-value of <0.05 as indicative of significance.

Results: The clinical features of the included OLP patients are summarized in table 1.
Forty-two (42) patients were included after an OLP diagnosis at our centre. There were 30 females and 12 males (ratio M: F=1:2.5). The median age at the baseline was 60 years of age (35-75 years), with no difference between genders. 27 of 42 (64.2%) had reticular form of OLP, although in 5 of these cases concomitant isolated erosions were also present. An erosive form of OLP was found in a total of 13 cases (30.9%). The buccal mucosa of the checks was affected in 41 cases (97.6%) and represented the most commonly affected site. 27 patients showed also an involvement of the gingival mucosa (64.2%) and 25 of the tongue (59%), 6 cases of lips (14.2%) and 12 (28.5%) patients had palate involvement. In most of the cases multiple sites were affected. 19 patients also had extra-oral (cutaneous 13 and genital 6 cases) involvement. 16 patients had received other therapies before the inclusion in the study as shown in T**able 1**.

Table no. 1: Clinical features of the enrolled patient (n=42)

Gender	Female	30 (71.4%)
	Male	12 (28.6%)
Age	Median age, Years	60 (35-75)
Ulcerative form	Yes	13 (30.9%)
	No	29 (69.04%)
Site of involvement (Multiple sites)	Buccal mucosa	41 (97.6%)
	Gingival mucosa	27 (64.2%)
	Tongue	25 (59%)
	Lips	6 (14.2%)
	Hard palate	12 (28.5%)
Previous therapy	Yes	16 (38%)
	No	26 (61.9%)
If yes then type of therapy (n=16)	Topical steroid	7 (43.75%)
	Systemic steroid	9 (56.25%)
Duration of therapy	Median, years (range)	1 year (3 months-2 years)

Clinical response after treatment

Response to treatment is summarized in **Figure 2 and 3**. After 3 months of therapy, topical tacrolimus treatment induced CR in 9(21.4%) patients especially in the ulcerative form. For the patients who showed a CR, the therapy was gradually tapered to attain a maintenance therapy consisting of once or twice weekly application of tacrolimus. 6 patients who did not response or worsened after 3 months were switched to another therapy. Patients with MR (n=11) and PR (n=22) continued the therapy for at least 3 months further, out of these 27 patients 22 were evaluated at 6 months while 5 were lost to follow-up.

Pain response after treatment- At the baseline 21 patients had no pain. 15 patients reported mild score for pain and 6 patients showed severe pain score. The pain score gradually improved during treatment.

Figure 2: Patients response to treatment at 3 and 6 months

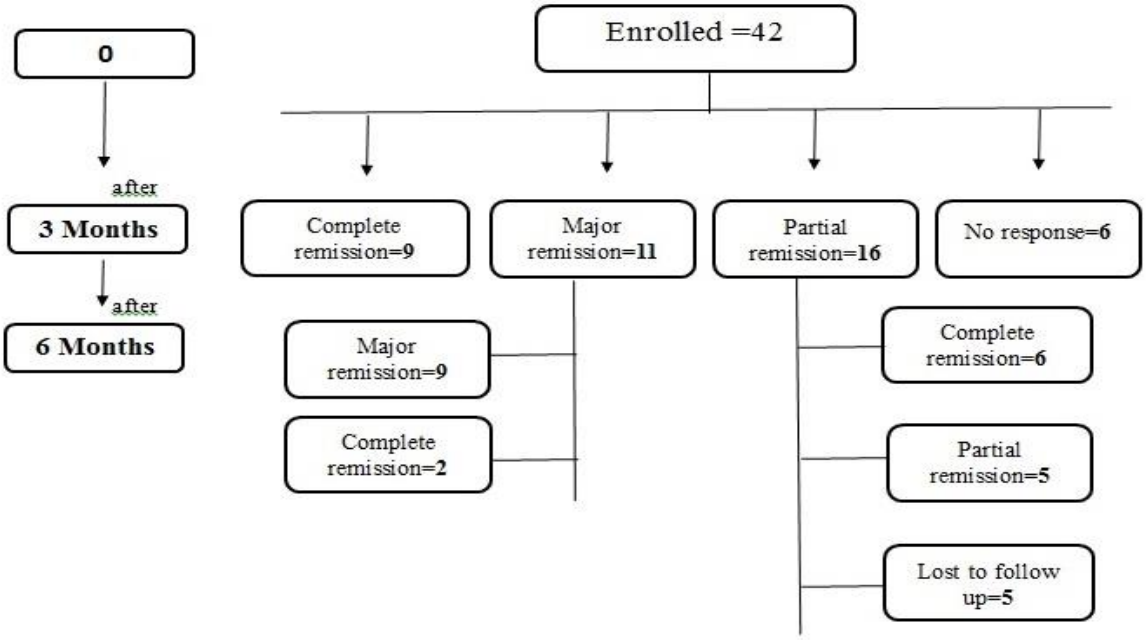
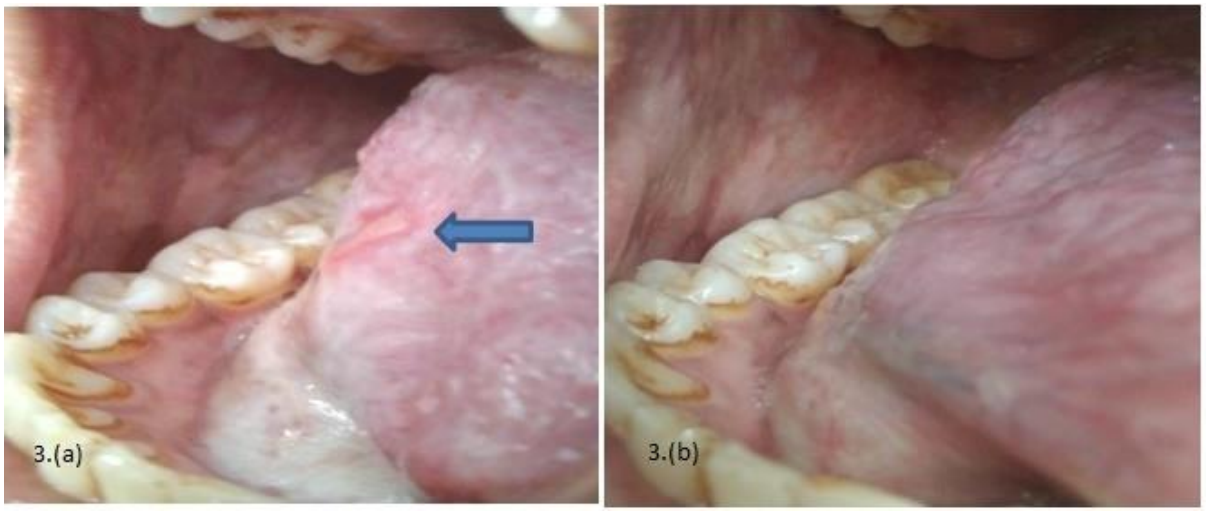


Figure 3: (a) Reticular OLP oral and buccal mucosa, erosive ulcer over tongue
(b) Complete remission of ulcer and major remission of reticular pattern after 3 months of treatment.



Side effects

Mild to moderate burning sensation was reported immediately after application of tacrolimus in the majority of cases and also unpleasant taste was reported in a few patients which never required withdrawal of the therapy. No evidence of viral infection and malignant transformation of the OLP were noted.

Discussion: The treatment of OLP may be challenging for the treating physician and patients. An effective therapy is important for pain relief, for improving the quality of life and also for the reduction of malignant transformation. The calcineurin inhibitor tacrolimus can be considered an effective treatment alternative to treat OLP.[17, 18, 19]

In meta-analysis of a multiple interventions study, tacrolimus came out to be a superior clinical responder and superior symptom reducing agent when compared with placebo and other topical modalities.[14]

However overall evidences are of low level and the most recently done Cochran review has drawn conclusion that differences in concern to objective clinical response and adverse events were uncertain and may be partially conflicting, although topical tacrolimus may be better effective in concern to subjective pain relief. On the basis of previous encouraging outcome observed in OLP, we initiated our study using topical tacrolimus for the management of all forms of OLP in off-label indication. Overall, in our study we did not observe the same high clinical response as observed in previous studies. Since our study showed CR in only 21.4% of patients and 26.1% at 3 months and at 6 months respectively, despite using similar modalities and dosage measures. Complete remission (CR) means complete absence of all visible lesions, many patients remained with persistent reticular alteration of the oral mucosa so only a smaller number of the patients achieved the state of CR. Most patients remained to the level of major remission (MR) group, and showed positive therapy response with no remaining erosions. However together with both CR and MR as clinical remission without erosive lesions, we observed clinical remission in 47% after 3 months and 42% after 6 months.

Patients in our study cohort were similar with clinical characteristics of other studies that makes possibility for comparison of the outcomes obtained (table 1). There was female gender predominance. 64.2 % of the total patients were having reticular form of OLP, while 30.9% of patients had erosive-ulcerative form, and almost similar with previous studies. Any baseline parameters such as age, sex, OLP subtype, site of lesion, previous treatment and its duration, showed no significant association with regard to both subjective and objective improvement.

Two previous prospective studies reported a complete or partial remission in 95% of 40 enrolled patients, and 80% of 15 enrolled after 2 months of treatment respectively. Whereas another study reported a significant clinical improvement in 75% of 20 enrolled patients receiving 0.1% tacrolimus ointment over 3 months.[25-27] Also Hodgson et al. in a prospective study involving 50 patients reported complete resolution, partial response and no response in 14%, in 80%, in 6% of cases respectively.[28] Four retrospective analysis of topical tacrolimus in OLP were done in previous studies; one study used either 0.03% mouthwash or 0.1%/0.3% ointment in 13 patients and reported complete remission in 23% and partial response in 62% after 8 weeks.[30] Whereas in another study using 0.1% ointment achieved 91.3% clinical improvement in 23 enrolled patients.[6, 30]. This study may be a subject of limitations regarding small number of study population and methodological parameters involved so large prospective randomized controlled trials with systematic follow-up will be valuable.

Conclusions-Topical tacrolimus could be a good treatment alternative for all forms of OLP whether it is previously failed cases treated by other modalities or for initial therapy. For the maintenance therapy frequency of application should be reduced guided by both sign of clinical activity and subjective improvement. Possibility of developing SCC mandates for regular follow-up.

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