

Clinical Evaluation of Efficacy of Triamcinolone Acetonide with Tacrolimus in the Management of Oral Lichen Planus: A Pilot Prospective Observational Study

Abstract

Introduction: Lichen planus (LP) is a relatively common chronic, mucocutaneous disease of autoimmune origin, involves oral mucosa, skin, scalp, nails, and genital mucosa. The prevalence of oral LP (OLP) varies worldwide, commonly seen in middle-aged and elderly people. It usually presents as symmetrical and bilateral or multiple lesions with burning sensation (BS) sometimes accompanied by pain. Corticosteroids and calcineurin inhibitors have shown promising results in the treatment of OLP, but its chronic course and unpredictable exacerbations/remission continues to result in a high degree of morbidity. The study aimed to evaluate the efficacy of intralesional triamcinolone acetonide (injection TA) combined with topical application of TA orabase and Tacrolimus (TAC) ointment for symptomatic cases of OLP. **Materials and Methods:** The prospective study included 52 symptomatic OLP patients to receive (0.5 ml) intralesional injection of TA once a week for the first 4 weeks followed by one injection in the 6th week along with TA mucosal paste (0.1%) and TAC ointment (0.03%) in tapering dose till 8th week. The subjective symptoms including BS and pain were assessed on a 10 cm visual analog scale (VAS) and objective signs like size and site of the lesion were scored according to criterion scale modified by Thongprasom *et al.* Differences were compared after 8 weeks treatment course and follow-up observations were performed at 20th week to record any recurrent lesion. **Results:** 41 patients (78.8%) had complete remission of disease and 11 (21%) had shown partial improvement. The VAS scores for BS and pain improved significantly. Improvement was also noted with decrease in the average size of active lesions and the number of sites with treatment. The relapse was seen in 17 patients (41%) in the 20th week. **Conclusion:** TA combined with TAC is a valuable therapeutic option for the treatment of symptomatic OLP. Our findings suggest that patients have shown statistically significant improvement.

Keywords: Intralesional injection, tacrolimus, topical therapy, triamcinolone acetonide

Introduction

Autoimmune lesions are the topic of controversy since a long time wherein some specific cells are recognized as foreign body due to antigenic alterations on their cell surface. Lichen planus is one among the common chronic inflammatory disease of stratified squamous epithelium with the prevalence rate of 0.5%–2.2% in the general population.^[1] The ambiguous nature of T lymphocytes is believed to be the trigger factor that may predispose oral mucosa to undergo apoptosis involving auto-cytotoxic T-lymphocytes. First described by Erasmus Wilson in 1869, the disease commonly involves skin, mucous membrane, nail, and hair with the predominance among women in the age

range of 30–70 years.^[2] It shows 15%–35% occurrence as mucosal/oral lesions affecting the buccal mucosa, dorsum of the tongue, gingiva, labial mucosa, and vermilion border of the lower lip.^[3] The most common reticular variety runs an asymptomatic course while erosive, atrophic, and bullous lesions are frequently associated with burning sensations (BSs) and pain affecting the quality of life. The clinical presentations of oral lichen planus (OLP) are usually significant, but biopsy is recommended to establish the diagnosis and exclude malignancy.^[4,5]

Although various empirical treatment regimens have been included to reduce the morbidity, yet definitive treatment is not established till date. However, it is now believed that drugs that directly

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target T cells at different stages of maturation may have confounding results.

Intralesional or topical corticosteroids manifest anti-inflammatory and immunosuppressive actions on the oral epithelium, wherein systemic corticosteroids are used for widespread involvement of skin, genitals, esophagus, or scalp. Topical application of TA, potent fluorinated steroids such as fluocinolone acetonide and fluocinonide, and superpotent halogenated steroids such as clobetasol have shown to reduce symptoms in OLP effectively. TA in the form of ointments, gel, mouthwash, spray, or paste is considered suitable and reasonably effective treatment of choice.^[5] Trial by Suresh *et al.* suggests evidence of the superiority of either type of corticosteroid in reducing pain and clinical signs as minimal.^[6] However, it is also important to acknowledge that though easy accessibility of the oral cavity allows direct application of the drug, achieving complete clinical cure and disease recurrence on drug withdrawal is persistent challenge among clinicians. The incomplete absorption of drugs impedes oral mucosa to attain sufficient therapeutic levels that may attribute to partial cure in some cases. The viscoelastic property of oral mucosa does not allow any foreign substances like paste or gel to adhere and clear them rapidly before being absorbed.^[7] On contrary, intralesional steroid is an effective method in achieving sufficiently high drug concentration locally for adequate anti-inflammatory action. The aqueous suspension of TA reduces its rate of absorption, hence maintains the therapeutic efficiency at site for longer time with fewer adverse effects. Transient tingling and BS at the injection site with cushioned features are few side effects noted in previous reports.^[4]

Topical calcineurin inhibitors including cyclosporin, tacrolimus (TAC) or pimecrolimus are considered as an alternative mainly to treat recalcitrant cases of OLP. Studies observed that TAC is up to 100 times more potent and effective than ciclosporin without notable adverse clinical effects.^[5,7] It suppresses T-cell activation by interfering with calcium calmodulin-dependent phosphatase calcineurin which promotes interleukin 2 and tumor necrosis factor α by targeting cytosolic FK binding protein.^[8] Zhang and Tao *et al.* suggested that TAC can decrease Treg proliferation and inhibit NF- κ B pathway, known for its potential role in the pathogenesis of OLP.^[9,10] Though the topical application of TAC has shown better therapeutic response in resistant cases yet it is often used for a short period as it may increase the risk associated with the development of oral squamous cell carcinoma.^[11]

Recently, combination therapy has evolved as a cornerstone in cancer therapeutics. Such kind of treatment controls multiple pathways by using a combination of two or more therapeutic agents. The drugs act synergistically to produce more effective treatment response in fewer cycles and reduce the incidence of drug resistance and attenuate

the rate of relapse. The side effects are relatively few as compared to monotherapy as the dose requirement of each agent is reduced. Drug repositioning has also been beneficial over traditional monotherapy treatment for cancer. The combination of drugs includes neo-protector agent that protect the normal cell and secondary agent that targets the neoplastic cells resulting in better therapeutic benefits.^[12]

In the number of studies, TA and TAC have been separately used for the management of OLP, however, a combinational approach has not been attempted yet. Thus, in the present study, we intended the use of combination drugs constituted by TA injection, TA orabase, and TC paste for assessing improvement in symptomatic OLP patients.

Materials and Methods

The study was conducted among patients attending the Department of Oral and Maxillofacial Pathology of Guru Nanak Institute of Dental Sciences and Research, Kolkata, India. A prospective randomized study was done over 1 year period by screening patients visiting the out patient department. 56 patients of either sex in the age range of 25–72 years were enrolled in the study. All the patients were diagnosed by clinical and histopathologic examinations after receiving written informed consent. Clearance certificate of this study was obtained from the institutional ethics committee.

Inclusion criteria

Patients above 18 years with clinical and diagnostic features of OLP were included. Clinical symptoms included pain, BS while eating spicy or hot food and presence of ulcerations. Patients agreed to undergo biopsy and ready to follow the prescribed drugs along with readiness to visit clinics regularly were selected.

Exclusion criteria

Patients suffering from any infectious, contagious disease, intractable medical or radiological abnormality and patients with other mucosal or skin disease, liver disease, hematological diseases were not included in the present study. Furthermore, medically compromised patients with the history of malignancy and patients who have received previous treatment, had corticosteroid allergy or biopsy of patients with histopathological features showing dysplastic features were not included. Pregnant and lactating mothers or patients with a history of drug therapy that may cause OLP like lesions were excluded from the study.

Drug treatment and clinical evaluation

All 56 patients had (0.5 ml) intralesional injection of TA (40 mg/mL; Manufactured by Abbott health care Pvt Ltd.) once a week for the first 4 weeks followed by one injection in the 6th week. The injection was placed directly into the subepithelial connective tissue underlying

the lesion adjacent to the normal mucosa. The patients were instructed to use TA mucosal paste (5 gm, trade name: Kenacort: Triamcinolone Acetonide (TA) 0.1%. Manufactured by Abbott healthcare Pvt. Ltd.) and TC 0.03% ointment (10 g, trade name: Tacroz: TAC 0.03%. Manufactured by Glenmark Pharmaceuticals Ltd.), three times daily for 4 weeks followed by twice daily application in the next 3 weeks and once-daily application in the 8th week. The patients were asked not to eat or drink following application for at least 30 min after application.

Each patient was convinced to stop deleterious oral habits like chewing or smoking tobacco and eliminate spicy food from the diet. The attention was also given to improve oral health through oral prophylaxis, rounding of sharp cuspal edges, removal of fractured tooth, and correction of any ill-fitted prosthesis 1 month before the commencement of the treatment to prevent any further mechanical injury. The patients were encouraged and motivated at psychological counseling sessions during their visit.

During the treatment, the response was assessed clinically before the start of treatment and at the end of 8 weeks. Objective and subjective parameters were used to assess clinical outcomes. The patient ranked the severity of pain and BS on a 10-cm visual analog scale (VAS). The lesion score included the number of site involved (site score) and severity of the lesion according to the criteria described by Thongprasom *et al.*^[13] In patients with multiple site involvement, the severely affected site score was considered. The patients were recalled every week for 1st month followed by alternate week in the 2nd month. Complete resolution was considered with the disappearance of atrophic/erosive/reticular lesions at all sites and appearance of normal mucosa (Score 0) along with the absence of pain and BS (VAS 0). All patients were assessed for disease recurrence for the next 3 months.

Adverse reaction

Transient BS and alteration in taste were the initial adverse effects reported by few patients which subsided within few days of application. Antifungal treatment was given by diagnosing the growth of candida in culture.

Statistical analysis

The statistical analysis of the data was expressed as mean \pm standard deviation. The observations obtained at pre-treatment were compared with post-treatment group using paired *t*-test to evaluate the significance of the results. $P \leq 0.05$ was considered statistically significant.

Results

Among 56 cases, finally, 52 patients in the age ranged from 25 to 72 years with a mean of 50.29 ± 12.64 years completed the study as 4 patients could not adhere to prescribed protocol. 34 (65.4%) were female and 18 (34.6%) were males with 1.9:1 as female: male ratio.

The primary outcome was the complete remission in 41 of 52 (79%) patients while partial response was observed in 11 of 52 (21%) patients at the end of 8 weeks. The secondary outcomes were observed in 17 of 41 (41%) patients, though the disease was less severe as compared to the primary lesion.

Objective response

The pretreatment scores of BS and pain gradually reduced over the study period. The mean score of BS at baseline was 6.80 ± 2.52 , which reduced to 0.67 ± 1.38 at the end of 8 weeks. The mean score of severity of pain at baseline was 3.19 ± 3.28 which was observed to be 0.25 ± 0.79 at the end of treatment. The mean of BS and pain scores were statistically significant when compared from the baseline score to the end of 2 months.

Subjective response

There was a reduction in mean scores of number and size of lesions with treatment. The baseline observations revealed 25% of patients had unifocal involvement, 56% of patients had involvement at 2 sites while 19% of patients had more than 2 sites of involvement with the mean site score of 1.98 ± 0.75 . Observations noted at the 8th week revealed 12% of patients had unifocal lesions and 10% of patients had bifocal site involvement with the mean score of 0.31 ± 0.64 showing statistically significant difference in the number of sites involved [Figures 1-3].

Improvement in the resolution of reticular, erosive, and atrophic varieties of OLP was markedly evident during treatment. At the beginning of the treatment, observations revealed 56% of patients had white striae with the erythematous area while 44% of patients had white striae with erosive area giving the mean score of 3.28 ± 1.10 . At the end of 8 weeks, the mean score obtained (0.29 ± 0.61) was lesser than the initial score with the statistically significance of ($P < 0.01$) [Table 1].

Discussion

The cell-mediated immune response to surface antigens is the most accepted pathogenic mechanism to initiate irregularities among histocompatibility antigens like HLA-DR complex associated with band like infiltration of lymphocytes in OLP. The CD8⁺ and few CD4⁺ T cells triggered by unknown etiological factors undergo chemokine mediated migration towards the basal keratinocytes.

Table 1: Active lesions at various intervals

Clinical parameters	Mean \pm SE			P*
	Baseline	At 8 th weeks	At 20 th week	
Burning sensation	6.80 \pm 2.52	0.67 \pm 1.38	3.64 \pm 1.08	<0.001
Pain	3.19 \pm 3.28	0.25 \pm 0.79	2.33 \pm 1.21	<0.001
Site score	1.98 \pm 0.75	0.31 \pm 0.64	1.24 \pm 0.43	<0.001
Size of lesion	3.28 \pm 1.10	0.29 \pm 0.61	1.82 \pm 0.64	<0.001

*Paired *t*-test. SE: Standard error

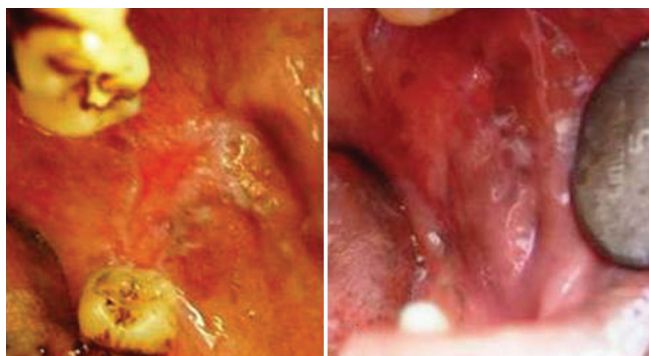


Figure 1: Intraoral (a) pretreatment photograph showing erosive lesion on left buccal mucosa surrounded by Wickham's striae and (b) post treatment photograph showing resolution of lesion

Antigen binding to CD8⁺ cells further alters major histocompatibility complex-1 on the keratinocyte to allow apoptosis of basal cells. The activated CD8⁺ T cells release cytokines that gain entry to the vicious cycle by attracting more lymphocytes in the lesion.^[14] The goal of treatment focuses to achieve complete or partial resolution of lesion secondary to palliative cure. Improvement of oral hygiene, discontinuation of detrimental oral habits, and patient counseling are important steps in the initial management strategy.^[1] Various methods, such as topical and systemic corticosteroids, griseofulvin, topical retinoids, hyaluronic acid, tetracyclin and topical cyclosporin, have been used to alleviate morbidity.^[7] Topical application to the primary site is recommended regime as it provides direct availability with ease of application, but complex oral environment with salivary secretions results in low therapeutic efficacy of topical drugs/agents. The saliva acts as a barrier to topical drugs which are washed rapidly within few seconds by the action of salivary flow without complete absorption. To attain better bioavailability, longer contact time of the drug at the application site must be attained to allow drug penetration into the deepest layers of the epithelium.^[7,15]

Topical application of midpotency corticosteroid, TA is considered effective in the management of OLP. The anti-inflammatory effects of corticosteroids application has shown dual role on the affected epithelium. It promotes the stabilization of intracellular membranes surrounding lysozymes and prevents its release from granulocytes. It also controls cell damage by inhibition of hydrolytic enzymes thereby preventing further extension of inflammatory tissue damage in the adjacent area.^[16] Al-Hashimi *et al.* observed two forms of TA 0.1% (mixed with Orabase [Colgate-Palmolive, New York, NY, USA] and as a mouthwash) categorized as Class I (treatment is useful and effective).^[1] Topical agents are economical and less likely to cause serious side effects, though cases with oral candidiasis are the most frequently observed adverse effect, treated topically with ketoconazole.^[13,17] The frequency of application of TA is variable in most studies from 2 to 4 times a day for duration ranging between 4 and 8 weeks. Arunkumar *et al.* observed reduction in

mean scores of BS in 92% using TA ointment.^[18] In contrast, Laejjendecker *et al.* and Malhotra *et al.* observed that topical TA showed improvement in 45% and 66% of patients respectively.^[19,20] In the present study, 79% of patients had complete absence of pain and BS and gradual improvement of VAS scores was noted in 21% of patients.

Injectable form of TA has been chosen to transport the medication directly in the submucosa while TA orabase facilitated to overcome the low therapeutic drug concentration in the intermediary phase. Xia *et al.* and Xiong *et al.* reported that intralesional injection of TA showed improvement in 84% and 88% of patients, respectively.^[21,22] The results obtained from the present study have shown relatively similar outcomes compared to studies using only injectable form of TA.

The immunosuppressive action of calcineurin inhibitors has been studied extensively in the literature and shown clinical benefits in the management of immunologically mediated oral mucosal diseases. Calcineurin inhibitors have been primarily used for the prevention of rejection in organ transplant recipients and graft-versus-host disease in allogeneic hematopoietic stem-cell transplant recipients. TAC is newer calcineurin inhibitors, with an improved safety profile as compared to cyclosporine. It belongs to the macrolide family, produced by *Streptomyces tsukubaensis*. Studies suggest short term use of TAC have shown improvements in mucosal diseases including OLP, pemphigus vulgaris, mucous membrane pemphigoid and oral ulceration, orofacial granulomatosis, and oral Crohn disease.^[1,23] TAC decreases the abnormal production of T-cells by binding to immunophilin (FKBPB 12) to produce calcineurin's phosphatase which controls the transcription and production of interleukins.^[3] Resende *et al.* reported observed improvement in all subjects with a complete response in 86% using TAC.^[24] In the present study, 79% of patients had shown complete healing and 21% of patients had shown reduction in the size of lesion. On the contrary, Ribero *et al.* and Malik *et al.* observed lower response rate with complete clinical cure in 20% and 55% cases with TAC.^[25,26] Mild and transient side effects are noted with the mucosal application of TAC limited to BS and alteration of taste during the initial phase as inflammatory epithelium attains increased permeability, allowing close contact of TAC to the peripheral nerve endings in the connective tissue.^[27]

Relapse was evaluated only for those patients who had complete objective response and achieved asymptomatic state. All the patients were followed up for 12 weeks after completion of treatment. The data showed resurgence of the oral lesion in 41% of patients. This is in line with the observations obtained by Lee *et al.* where in 40% of relapse occurred on drug withdrawal following intralesional injection of TA.^[4] In contrast, Malhotra *et al.* observed relapse in 22% of patients with topical TA.^[20]



Figure 2: Intraoral (a) pretreatment photograph showing erosive lesion in left buccal mucosa surrounded by wickham's striae and (b) post treatment photograph showing resolution of lesion

While the study by Laeijendecker *et al.* observed a higher rate of recurrence among 72% of patients in TAC and 78% of patients in TA groups following cessation of treatment.^[19] The size and number of sites involved were milder as compared to the primary lesion.

Both TA and TC are considered relatively safe, nontoxic, and effective alternative for many conventional drugs, due to its broad therapeutic properties and multifarious effects on various immune-mediated diseases. Statistically significant improvement in the clinical sign and symptoms were observed by the use of this regime.

Conclusion

The choice of combination therapy is beneficial and affordable drug regime which has shown its effectiveness in treating OLP. Further, monotherapy treatment is more susceptible to drug resistance because the constant treatment with a single compound induces altered cells to recruit alternative salvage pathways that may increase frequent recurrence and the malignant potential of the disease. Although among dental professionals, achieving biological cure with no future relapse of disease is still a challenge due to unprecedented multi-exacerbations. More studies with larger number of patients followed by longer follow-up period are required to reach any definitive conclusion. Moreover, we still stand deficient to identify the targeted receptor which maintains inter and intracellular homeostasis to further prevent relapse. The present study provides an insight into the role of combinational therapy in safely treating OLP, however long-term studies are recommended on a larger sample size to confirm its efficacy on oral health following treatment.

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Figure 3: Intraoral (a) pretreatment photograph showing erosive lesion on the dorsal surface of tongue surrounded by wickham's striae and (b) post treatment photograph showing resolution of lesion

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Conflicts of interest

There are no conflicts of interest.

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