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# Oral Lichen Planus - An Enigma with Limited Treatment Options

Dr. M. Deivanayagi
Senior Lecturer
Department of Oral Medicine and Radiology
Ragas Dental College & Hospital
Chennai-600 119

Dr. Mammootty I. K
Senior Lecturer
Department of Oral Medicine and Radiology
Ragas Dental College & Hospital
Chennai-600 119

**Abstract:-Oral Lichen Planus (OLP) is a chronic inflammatory, T-cell-mediated autoimmune oral mucosal disease with unclear etiology. The clinical management of OLP poses considerable difficulties to the oral physician. A proper understanding of the pathogenesis, clinical presentation, diagnosis of the disease becomes important for providing the right treatment.All therapies are palliative, and none is effective universally. Currently employed treatment modalities include corticosteroids administered topically, intralesionally, or systemically. Alternative therapies include topical and systemic retinoids, griseofulvin, Cyclosporine, and surgery. Other medical treatments and experimental modalities, including mouth PUVA, have been reported to be effective. In this review, we discuss the various current treatment modalities of OLP.**

## I. INTRODUCTION

Lichen planus was first reported in 1869 by Erasmus Wilson in Greek lichen- tree moss, planus – flat.Lichen planus (LP) is a non-infectious caused due to autoimmune disorder mediated by the T-lymphocytes acting against the skin and mucosa of the oral cavity, esophagus& genitals. Oral lichen planus (OLP) is the commonly witnessed condition wherein the overall prevalence of lichen planus is 0.1–4.0% being more common among adult femalesand tend to be difficult to treat effectively, with relapses being commonly reported among patients recovered. OLP can affect any part of oral cavity. In typical OLP the characteristic reddishpurple lesion are seen in buccal mucosa, tongue and gingival whereas palatal lesions are uncommon. The erosive, atrophic and bullous forms lesions are effected with burning sensation and pain. Understanding the exact etiology behind OLP is key for treatment as it could vary between cases. Today some of the pharmacological intervention upon immunomodulation and physical ailments plays the key role in cure of OLP which as to be probed further for better options.[1,2]

### *A. Etiology of Oral Lichen Planus*

OLP occur due to autoimmunity, most of the scientific data reveals the cytotoxic CD8+ T cells triggered apoptosis of the basal cells of the oral epithelium in hand with specific and nonspecific inflammatory mechanisms paving to homing of CD8+ T cells in subepithelial layer; there by leading to keratinocyte apoptosis resulting in characteristics lesions.

### *B. Oral Manifestations*

In the oral cavity, the lesions appear radiating white, gray, velvety, thread-like papules in a linear, annular and retiform arrangement forming typical lacy, reticular patches, rings and streaks. A tiny white elevated dot is present at the intersection of white lines known here as striae of Wickham similar to that of Wickham striae in skin.The lesions are asymptomatic, bilaterally/symmetrically present in the oral cavity, but most commonlyat the buccal mucosa, tongue, lips, gingiva, floor of mouth, palate and appear earlier than the cutaneous lesions.[3]

OLP has six classical clinical presentations: Reticular type lichen planus–on the lips and mucosa of the cheek, Bullous type lichen planus–lesion on upper buccal mucosa, Atrophic type lichen planus–sometimes representing as desquamative gingivitis, Plaque type lichen planus–lesion on tongue, Papular type lichen planus–lateral border of tongue.

- Reticular
- Erosive
- Atrophic
- Plaque-like
- Papular
- Bullous.

### *C. Treatment*

chief etiological background is predominantly immune dysfunction drugs of Corticosteroids have been the mainstay of management of OLP; calcineurin inhibitors, retinoids,

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dapsone, hydroxychloroquine, mycophenolate mofetil and enoxaparin are also reported for effective treatment.Analysis of current data on pathogenesis of the disease suggests that blocking IL-12, IFN-γ, TNF-α, RANTES, or MMP-9 activity or upregulating TGF-β1 activity in OLP may be of therapeutic value in the future.

*D. Corticosteroids*[4,5]

These are the most commonly used group of drugs for the treatment of OLP. The ability of corticosteroids to modulate inflammatory and immune response is exploited in the treatment of OLP. The mechanism involves the reduction of lymphocytic exudation and stabilization of the lysosomal membrane. Topical midpotency corticosteroids such as triamcinolone acetonide, high-potent fluorinated corticosteroids such as fluocinonide acetonide, disodium betamethasone phosphate, and more recently, super potent halogenated corticosteroids such as clobetasol are used based on the severity of the lesion. The greatest disadvantage in using topical corticosteroids is their lack of adherence to the mucosa for a sufficient length of time. Although trials were done using topical steroids along with adhesive base, no study shows their superiority when compared to steroids without the base (carboxymethyl cellulose). However, the same study also recommends the usage of adhesive paste used for dentures, which contains only inactive ingredients as a vehicle to carry the topical application. This has shown excellent bio adhesive properties, due to its high molecular weight (above 100,000) and the flexibility of the polymeric chain. Small and accessible erosive lesions located on the gingiva and palate can be treated by the use of an adherent paste in a made-to-measure tray (custom tray), which allows for accurate control over the contact time and ensures that the entire lesional surface is exposed to the drugs. Patients with widespread forms of OLP are prescribed high-potent and super potent corticosteroids mouthwashes and intraregional injections.

Malhotra et al suggested betamethasone oral therapy - moderate-to-severe OLP, and gel has to be applied to the affected area 4-6 /2-3 months. Mometasone furoate 0.1% is used in new form as microemulsion mouth wash (5 ml for 5 minutes 3 times a day). It is safe and effective in the treatment of erosive-ulcerative OLP. Carrozzo and Gandolfo et al, topical Clobetasol to be successful in 50 -65% -total reduction of symptoms. Topical steroids -do not cause adrenal suppression Clobetasol propionate (Lozada-Nur and Huang (1991) in various forms such as orobase,A recent study has shown that clobetasol is more effective than cyclosporine in inducing clinical improvement in atrophic-erosive OLP. [4]

Systemic corticosteroids are reserved for recalcitrant erosive or erythematous LP where topical approaches have failed. Systemic triamcinolone can be used as an intralesional injection of 5-10 mg/ml. (Vincent et al,1990). Systemic prednisone also proved to be very effective for severe OLP. For adults: 30-60 mg/day for 4-6 weeks followed by gradual taper. Pediatric purpose 4-5 mg/m2/day; alternatively, 0.05-2 mg/kg should be tapered over two weeks as the symptoms resolve. (Cawson et al, 1968) Acute pseudomembranous candidiasis is a side effect from Corticosteroid therapy which can be treated and prevented with antifungal drugs.

## II. IMMUNOMO DULATION THERAPY

*A. Calcineurin Inhibitors*

Calcineurin is a protein phosphatase which is involved in the activation of transcription of IL-2, which stimulates the growth and differentiation of T-cell response. In immunosuppressive therapy, calcineurin is inhibited by cyclosporine, tacrolimus and pimecrolimus. These drugs are called calcineurin inhibitors.

*B. Cyclosporine*

Cyclosporine, a calcineurin inhibitor, is an immunosuppressant used widely in post-allogenic organ transplant to reduce the activity of patient's immune system. Cyclosporine acts by virtue of its ability to suppress T-cell activity. This helps in preventing transplant rejection. Its mode of action is via binding to the cytosolic protein called cyclophilin of lymphocytes especially T-lymphocytes. This complex of cyclosporine and cyclophilin inhibits calcineurin, which under normal circumstances induces the transcription of IL-2. They also inhibit lymphokine production and IL release, leading to a reduced function of effector T-cells. Cyclosporine is used as a mouth rinse or topically with adhesive bases in OLP. Since the topical formulations are extremely expensive, they are usually recommended for highly recalcitrant cases. Its systemic absorption is limited and is infamous for its propensity to cause dose-related gingival hyperplasia which regresses on withdrawing the drug. OLP patients in the triamcinolone acetonide group showed equal cases of clinical complete and partial remission (50%). Whereas, in the cyclosporinegroup, there was partial remission in only two cases (33.5%) and no response in four cases (66.7%). However, our study showed that there were no statistical differences.

*C. Levamisole*

Developed in 1966 , Levamisole was primarily used as an antihelminthic drug though it has been shown to have immunomodulatory properties. It potentiate the activity of human interferon and interleukin -2 and inhibit aerobic tumour glycolysis. Levamisole can be administered at a dose of 50mg three times/day for threeconsecutive days per week for 4 to 6 weeks.

*D. Tacrolimus*

Tacrolimus, essentially a calcineurin inhibitor, is a topical immune-0suppressive agent which is 10- 100 times as potent

as cyclosporine. Owing to its capacity to penetrate mucosa, it has been reported to be successful in treating recalcitrant OLP cases. It inhibits the phosphatase activity of calcineurin , thereby in-turn inhibiting the first phase of T-cell activation. Side effects mainly include burning sensation and relapse after cessation. Since a recent cancer risk warning has been issued by FDA mainly from its protracted use, it is recommended mainly for short term treatment.

*E. Pimecrolimus*

Pimecrolimus derives its anti-inflammatory properties from its ability to inhibit synthesis and release of cytokines from T-cells and mast cells. Moreover, it has got low systemic immunosuppressive capability

*F. Retinoids*

Topical retinoids like tretinoin, isotretinoin and fenretinide have been reportedly found to be effective in OLP thanks to its immunomodulating properties. White striae in OLP may regress with use of topical retinoid nevertheless the effect is relatively transient. Its systemic counterpart was reported to be effective to some extent in treating severe OLP. The positive effects of retinoids should be weighed against their rather significant side effects like cheilitis, elevation of serum liver enzymes and triglyceride levels and teratogenicity.

*G. Dapsone*

Dapsone was originally developed as an anti-bacterial agent, primarily used in the treatment of leprosy owing to its ability to inhibit the synthesis of bacterial dihydrofolic acid. Its role in the management of various dermatologic diseases is probably based on its ability to inhibit the release of chemotactic factors for mast cells. The most common side effect of dapsone is haemolysis which is dose-related and is most commonly encountered in cases administered orally with dosages ranging from 200 -300mg daily. Risk of hemolytic anaemia and methemoglobinemia is greater in Glucose-6-phosphate dehydrogenase deficient patients who are receiving dapsone. This warrants screening of G6PD deficiency before initiating dapsone therapy. In patients receiving multiple drug therapy ,development of hypersensitive reactions to dapsone is more common. Symptoms like fever, rash and jaundice may occur within 6 weeks of therapy which can be managed by corticosteroids.

*H. Mycophenolate*

Originally used to treat psoriasis, mycophenolic acid (now reformulated as mycophenolate mofetil) has been reintroduced in dermatological medicine. Being a very well-tolerated immunosuppressive drug used in organ transplant, it has been successfully used to treat severe cases of OLP. Mycophenolate's are quite expensive and effective with long-term usage.

*I. Low-Dose Low Molecular Weight Heparin (Enoxaparin)*

T-lymphocyte heparanase activity is crucial in T-cell migration to target tissues. This activity of T-lymphocyte is found to be effectively inhibited by low dose low molecular weight heparin (which is devoid of any anticoagulant property). This discovery has significant prospects in the treatment of OLP.

EfalizumabIt is a recombinant monoclonal antibody used as an immunosuppressant in the treatment of psoriasis. Efalizumab, a monoclonal antibody to CD11a, binds to this adhesion molecule and causes improvement in OLP by decreased activation and trafficking of T lymphocytes. *In vitro* studies of mononuclear cells in OLP have demonstrated a decrease of 60% in migration by peripheral blood mononuclear cells after pretreatment with anti-CD11a antibodies. Recommended dosage is once a week via subcutaneous administration.

## III. NON-PHARMACOLOGICAL MODALITIES

*A. PUVA Therapy*[7]

This non-pharmacologic approach uses photochemotherapy with 8-methoxypsoralen and long wave ultraviolet light (PUVA). Psoralens are compounds found in many plants, which make the skin temporarily sensitive to UV radiation. Methoxy psoralen is given orally, followed by administration of 2 hours of UV radiation intraorally in the affected sites. Numerous cases of severe OLP has been successfully treated using PUVA therapy though its adverse effects includes nausea and dizziness secondary to psoralen and 24-hour photosensitivity when it is taken orally. Owing to the complicated geometry of oral cavity, its dosimetry can be difficult as it has been commonly used on skin over large open areas.

*B. Photodynamic Therapy*[6]

Photodynamic therapy(PDT) It works on the basis of administration of anexogenous photosensitizer to leave the tumor tissue sensitive to light of a specific wavelength. The photosensitizers are inertsubstances that have a selective affinity to tumor tissues.

When light of a specific wavelength activates the photosensitizertrapped by the tumor cells, which transfers the energy to molecular oxygen, resulting in the production of reactive oxygen species (ROS). PDT involves three main mechanismsto induce tumor destruction. First, direct killing of tumor cells via ROS; secondly, damage the vasculature causing thrombus formation and later tumorinfarction; thirdly, activation of an immune response againsttumor cells.

Moreover it has got immunomodulatory effect owing to its ability to induce apoptosis of hyperprolifrating inflammatory cells which are present in lichen planus.

*C. Laser Therapy*

Surgical management using cryosurgery and different types of laser have also been tried in patients who are suffering from symptomaticerosive OLP and are refractory to even topical super potent corticosteroids. A 980-nm Diode laser, $CO_2$ laser evaporation, bio stimulation with a pulsed diode laser using 904-nm pulsed infrared rays and low-dose excimer 308-nm laser with UV-B rays have been tried. All types of laser destroy the superficial epithelium containing the target keratinocytes by protein denaturation. A deeper penetrating beam like the diode laser destroys the underlying connective tissue with the inflammatory component along the epithelium. The few studies documented show a lot of promise, but their effectiveness is yet to be proven.[7]

No therapy for OLP is completely curative; the goal of treatment for symptomatic patients is palliation.Considerable remission can be achieved in a majority of cases through topical application of corticosteroids, with or without the combination of other immunomodulators. Very rarely does the condition necessitate systemic therapy. Laser therapy and other recent modalities are tried as the final remedy.

## IV. CONCLUSION

Patients with oral lichen planus may have a slightly increased risk of cancer, although the precise risk is unknown. Regular clinical examination and biopsy is required. It is imperative that the lesion is identified precisely and proper treatment be administered at the earliest. Re- examine patients with oral lichen planus during active treatment, and monitor lesions for reduction in mucosal erythema and ulceration and alleviation of symptoms. Follow up with patients with oral lichen planus at least every six months.

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