Review Article

Oral Lichen Planus: An Updated Review on Newer Treatment Modalities.

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Abstract

INTRODUCTION

Oral lichen planus (OLP) is a chronic autoimmune, mucocutaneous disease of unknown origin.¹ Globally, Lichen planus affects about 1-2% of population and prevalence in India ranges from 0.1% to 1.5%.² This disease has most often reported in middle-aged patients 30-60 years of age and is more common in females than in males (1.4:1). Rarely, OLP is seen in children.³ OLP constitutes 9% of all white lesions. In general OLP affects 0.5-2% of the population. The question of malignant transformation of oral lichen planus remains debatable.⁴

When lichen planus affects only the oral cavity, it is called oral lichen planus (OLP) and it does have an impact on quality of life because OLP lesions are chronic, rarely undergo spontaneous remission, potentially pre-malignant and often a source of morbidity particularly when erosive/ulcerative or erythematous lesions are present. Almost all the published reviews agree that only erosive/ulcerative or symptomatic OLP should be treated⁵. Many treatment modalities have been tried but complete cure is very difficult to achieve.¹

Topical steroids are the mainstay of palliative treatment of OLP but alternative therapeutic approaches are highly regarded given the lack of strong evidence on any available treatment modality.
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<th>S. No.</th>
<th>Category</th>
<th>Agents</th>
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CORTICOSTEROIDS

To date, corticosteroids remain the first choice of treatment for OLP, it has been found to be the most expected and successful agents in the treatment of OLP.\(^6\)

TOPOCAL STEROID THERAPY

High-potency topical corticosteroids in an adhesive medium appear to be the safest and most effective treatment of mild to moderately symptomatic lesions.\(^2\) For topical applications, they are prescribed as gels, creams, ointment with Orabase (Kenalog in Orabase), or oral rinse.\(^7\)

Various topical steroids are available, these are clobetasol propionate gel, 0.05%; betamethasone valerate gel, 0.1% or 0.05%; fluocinonide gel, 0.05%; clobetasol butyrate ointment or cream, 0.05%; and triamcinolone acetonide ointment, 0.1%.\(^3\) The patients are instructed to apply a thin layer of the prescribed topical corticosteroid up to 3-4 times a day. The patients are advised not to eat or drink for 30 min after the application. Topical aqueous triamcinolone acetonide suspension is proven to be effective in reducing mucosal erythema and ulcerations. The advantage of topical steroid application over systemic administration is that side effects are fewer.\(^2\)

Ahadian et al. in 2012 conducted a study on comparison of two corticosteroids mouthwashes, i.e., dexamethasone (0.1%) and triamcinolone (0.2%) in the treatment of 44 symptomatic OLP patients for 4 weeks and concluded that both mouthwashes were useful in reducing pain and decreasing the size of the lesion. However, in comparison of both the mouthwashes, dexamethasone mouthwash was said to be more effective.\(^8\)

Intra-lesional Steroid Therapy

Intra-lesional injection of corticosteroid for severe lesions involves the subcutaneous injection of 0.2-0.4 mL of a 10 mg/mL solution of triamcinolone acetonide (Avcort injection, Comcort injection) by means of a 1.0 ml 23- or 25-gauge tuberculin syringe.\(^9\)

Systemic Steroid Therapy

Indicated at high dose (1.5-2 mg/kg/day) for patients with recalcitrant severe erosive atrophic OLP where topical approaches have failed or for diffuse mucocutaneous involvement.\(^10\) The most common prescribed systemic steroid to manage OLP is prednisone. A single daily morning dose of 40-80 mg of prednisone is prescribed for 10 days. The ultimate dosage chosen depends on the severity and size of the lesion.\(^2\)

Another approach to reduce the amount of total prednisone is to prescribe a steroid-sparing agent such as the immunosuppressant drug azathioprine (50-100 mg/day) or levamisole (150 mg/day). The azathioprine appears to act synergistically with prednisone to reduce inflammation and combination dose also allow for a lowering the therapeutic dose of steroids. The levamisole in a dose of 150 mg/day and prednisolone 25 mg/day for 3 consecutive days each week for 4-6 weeks showed improved results in the management of erosive OLP.\(^2\)

IMMUNOSUPPRESSANT

These agents modulate the immune system. It
induces a substantial decrease of T-cells and a corresponding reduction in activated CD25-positive cells and in antigen presenting cells possibly by inhibition of interferon-gamma production.\(^\text{10}\)

**Cyclosporine**

It is a very commonly used immunosuppressive drug that belongs to a family of cyclic polypeptides derived from the fungus Tolypocladium ianflatum. It is basically used to prevent rejection of organ transplantation. The topical cyclosporine can be used either in the form of mouthwashes or in the form of adhesive base. The patients are advised to swish and spit 5 ml of mouthwash, i.e. 100 mg cyclosporine/ml 3 times daily for 4 weeks or 0.025% cyclosporine in an adhesive base to apply 4 times daily.\(^\text{7}\)

Systemic treatment has been used in severe resistant cases and in oral-cutaneous or ulcerative foot involvement. For adults, 1-2 mg/kg/day PO is the recommended starting dosage and if no response in disease pattern, the dosage can be increased to 5 mg/kg/day. The cyclosporine is available in 25, 50 mg capsule (Immusol, Immusporine), 100 mg/ml oily solution (Katzung), and 100 mg/ml oral rinse (sandimmun neoral).\(^\text{7}\)

**Tacrolimus**

It is a macrolide form of immunosuppressant derived from a type of bacterium, Streptomyces tsukubaensis. Initially, it is used to prevent organ rejection in kidney transplantation.\(^\text{11}\)

It inhibits the T-cell production of pro-inflammatory cytokines. The topical application induces a rapid improvement in OLP. It is 100 times more potent than cyclosporine, has shown to be effective without notable side effects in several uncontrollable studies.\(^\text{7}\) It has greater percutaneous absorption than cyclosporine. Its systemic use is comparable to the corticosteroids, but topical application of 0.1% tacrolimus is proved to be superior in treating symptoms of OLP. Recent studies by Corrocher et al. have shown that application of tacrolimus ointment 0.1% 4 times daily for 4-8 weeks resulted in faster resolution of symptoms as compared to the corticosteroids.\(^\text{11}\) Malik et al. in 2014, successfully treated a case of OLP with 1% of tacrolimus powder with base 3 times daily for 15 days in a patient with raised SGOT, SGPT levels along with positive tri-dot for HCV.\(^\text{12}\)

**Pimecrolimus**

It inhibits the T-cell activation by inhibiting the synthesis and release of cytokines from T-cells. It also prevents the release of inflammatory cytokines and mediators from mast cells. 1% topical cream of pimecrolimus has been successfully used as the treatment for OLP. It has a significant antiinflammatory activity and immunomodulatory capabilities with low systemic immunosuppressive potential.\(^\text{13}\)

**Levamisole**

It is an effective immune modulating agent that can restore the normal phagocytic activity of macrophages and neutrophils. It was developed in 1966 as an antihelmenthic drugs but has immune regulating properties. The levamisole is an effective drug in steroid resistant and the patients who have not responded to conventional
treatments. The levamisole is administered at a dose of 50 mg 3 times/day for 3 consecutive days per week for 4-6 weeks. It is available as 50 mg and 150 mg tablet. (Ergamisole and Vermisole). It has an adverse effect such as nausea, vomiting, headache, and agranulocytosis.

Azathioprine

It is a purine antimetabolite having anti-inflammatory properties and decrease antibody production. It is reserved for the patients who are not responding for the other treatment modalities. It can also be used in combination with corticosteroids and cyclosporines. In combination, it effectively decreases the immunosuppressive activity. So, lower doses of corticosteroids can be used. It is available in the 50 mg tablet (Imuran, Azoprin).

RETINOIDS

Retenoids have also been tried for the treatment of OLP. Previous studies revealed that side effects were common and troublesome with marginal improvement. In a study by Ferguson et al. etritinate was found to have minimal value in the management of erosive OLP when used in dose of 25-75 mg for 8 weeks, with side effects such as pruritis, cheilitis, desquamation of hands and feet and paronychia. Meirgrosky et al. in their study noted that when etritinate was used in the dose of 75 mg/day for 2 month it was effective in treating oral symptomatic lichen planus only for the duration of its use, discontinuation resulted in recurrence of signs and symptoms. Camisa and Allen treated 6 patients with systemic isotretinoin (10 to 60 mg/day for 8 weeks) and concluded that it was of minimal benefit with common side effects, such as cheilitis, dry skin, headache, rashes etc. Topical application of Fenretinide (4-HPR), a newer retinoid showed to have a positive result with minimal side-effects in the treatment of OLP.

Dapsone

In resistant cases of erosive, OLP dapsone is an effective with anti-inflammatory and immune-modulatory effects. It is available as 5% gel (acnesone) for topical application and systemically 25, 50, and 100 mg of tablets. Headache and hemolysis are significant side effects of dapsone.

Interferon

The topical application of human fibroblast interferon gel and interferon-alpha have suggested to improve erosive OLP.

PUVA Therapy

Photosensitizing psoralen drugs and ultraviolet A (UV) radiation were introduced as a new therapy by Jansen et al. in 1987 for oral mucosal lesions. The photosensitizing drugs can either be administered systemically or applied topically before irradiation. Four psoralens are used in PUVA therapy – psoralen, methoxy psoralen (Bergapten), methoxypsoralen (methoxsalen), and trimethyle psoralen (trioxsalen). UV irradiation in combination with psoralens modulate the function of cells of the immune system.

Amitriptyline

Amitriptyline (Amy), a tricyclic antidepressant, has local anesthetic properties and seems to be
more potent and safer than bupivacaine. Based on the topical anesthetic properties of Amy, a recent poor-quality randomized clinical trial compared a new mouthwash containing clobetasol, ketoconazole, and Amy with dexamethasone tablet, nystatin drop and diphenhydramine syrup. The new treatment worked better and was better accepted by the patients with OLP. Despite quoted double blind, the trial was obviously not and has other significant flaws. Furthermore, the results could simply reflect the different potency between the two corticosteroids.

**Amlexanox**

Amlexanox (C16H14N2O4) is a topical anti-inflammatory drug that has been developed as an oral paste (containing 5% amlexanox) for the treatment of patients with recurrent aphthous ulceration. Amlexanox can inhibit the formation and release of histamine, TNF-alpha, and leukotrienes from mast cells, neutrophils, and mononuclear cells, possibly through increasing intracellular cyclic adenosine monophosphate content in inflammatory cells.

**Aloe vera**

The pharmacological actions of AV include anti-inflammatory, antibacterial, antiviral and antifungal properties, and hypoglycemic effects. According to a Cochrane review, there is a weak evidence from two placebo-controlled RCTs, using different formulations, that AV may be associated with a reduction in pain in OLP.

**Bacillus Calmette–Guerin polysaccharide nucleic acid (BCG-PSN)**

A randomized comparative study employing intralesional injections of bacillus Calmette–Guerin polysaccharide nucleic acid (BCG-PSN) (0.5 ml every other day for 2 weeks) and triamcinolone acetonide (10 mg intralesional injection once a week for 2 weeks) showed similar effectiveness. However, intrallesional TA is not a common OLP treatment modality and BCG-PSN should be challenged against more effective topical corticosteroids such as fluocinolone acetonide or clobetasol propionate.

**Curcuminoids**

Curcuminoids have been well known as the major components in turmeric and used as the anti-inflammatory agents for a long time. Two RCTs on OLP have been published by the same group of researches. The first study, comparing low doses of curcuminoids (2000 mg/day for 7 weeks) and prednisolone (60 mg/day for 1 week) with prednisolone alone, was withdrawn at the first interim analysis for futility. The second one employing higher doses (6000 mg/day) showed some benefit particularly during the follow-up. However, these medications can cause adverse side effects in up to 40% of the patients, including liver dysfunction. It should be noticed that frequently patients with OLP may have liver disorders. Moreover, the above preliminary positive results need to be confirmed by other research groups.

**Hyaluronic acid**

The main function of HA appears to be in tissue healing, and a variety of mechanisms have been identified. A recent RCT evaluates the efficacy of a topical HA gel preparation (0.2%) in the management of OLP. HA (0.2%) caused just a very
transient improvement in patients with OLP.\textsuperscript{6}

**Ignatia**

Ignatia is also one of the homeopathic remedies most commonly used on patients with anxiety symptoms and depression. Because psychosocial condition might have an important role in OLP, IA could be useful for this disease treatment. A recent randomized placebo-controlled study of questionable quality suggests the potential benefit of IA in OLP management.\textsuperscript{6}

**Lycopene**

Lycopene is a red-colored, fat-soluble carotenoid, which gives tomatoes and several other fruits their deep red color. Lycopene does not have the pro-vitamin A activity and its various benefits on human health can be explained based on its properties of antioxidant activity, inhibition of cancer cell proliferation, interference with growth factor stimulation, inducing phase II enzymes, regulation of transcription and restoration of gap junctions. Lycopene exerts its antioxidant activity by physical and chemical quenching of free radicals and is the most efficient singlet oxygen quenching carotenoid.\textsuperscript{18}

The lycopene is a potent antioxidant in the management of various systemic and oral diseases including cancer and precancerous lesions and conditions. 8 mg/day of lycopene for 8 days showed significant improvement in the OLP lesions. Burning sensation was reduced up to 84% of cases.\textsuperscript{2}

**Green Tea**

It possesses both anti-inflammatory and chemopreventive properties. It inhibits the T-cell activation, migration, and proliferation and also controls other inflammatory mediators. It is known to reduce the symptoms of OLP by involving in the etiopathogenesis of the diseases.\textsuperscript{2}

**Photodynamic Therapy**

Photodynamic therapy is a technique that uses a photosensitizing compound with the specific wavelength of laser light to destroy the targeted cell via strong oxidizers, which causes cellular damage, membrane lysis, and protein inactivation. The photodynamic therapy with Parenteral Drug Association the approved drug methyle 5 aminolevulinate OLP offers a single treatment with long lasting improvement. PDA has an immunomodulatory properties, it induces apoptosis in the hyper proliferating inflammatory cells present in the disease such as psoriasis and lichen planus.\textsuperscript{7}

**Low-intensity Laser**

Several anecdotal reports suggest that low-intensity laser (LIL) might work in oral inflammatory disorders. Increased proliferation, maturation and migration, as well as transformation to myofibroblasts, a decreased production of proinflammatory prostaglandin E2, and increased production of basic growth factors have been noted in LIL.\textsuperscript{19}

**Psychiatric therapy**

Factors such as stress and psychological problems, especially depression and anxiety, have been mentioned as etiologic factors in OLP because patients with the disease report a more frequent development or exacerbation of lesions during periods of greater emotional tension However,
there is still controversy concerning the role of stress as a major or minor etiologic factor in the pathogenicity of OLP. A recent poor-quality, unclearly randomized study investigates the addiction of undetailed psychiatric drugs to topical TA in OLP. This study indicates that the combination of psychiatric drug therapy and routine treatment methods was effective in reducing the size of the lesions, but did not have any further significant effect on the symptoms.  

Purslane

Purslane is an herbaceous weed from Portulacaceae family that contains numerous biologically active compounds including omega-3 fatty acids, minerals, B-carotene, melatonin, and vitamin A, C, and E. This herbal medicine possesses anti-inflammatory, antiulcerogenic, antifungal, and antioxidant properties. A randomized, doubleblind, placebo-controlled study found that 83% of the purslane patients showed partial to complete clinical improvement. Purslane showed a significant difference in symptomatic response compared with placebo. No side effects occurred in either of the groups.

Thalidomide

Thalidomide has the anti-inflammatory and anti-immunologic properties of suppressing T-cell function. Because of its ability to decrease production of TNF-alpha, thalidomide has been used in the treatment of oral disorders likely to be TNF-alpha driven such as aphthous stomatitis. Their anti-angiogenesis, anti-inflammatory, immune-modulatory properties of thalidomide could be applied in clinical use for the treatment of erosive OLP.

Griseofulvin

Griseofulvin has been advocated for the treatment of erosive-ulcerative lesions when steroid treatment is contraindicated or when the lesions are resistant to steroids. Aufdermorte et al. administered 500 mg three times a day for 10 weeks and found it to be effective in all the 3 patients, whereas Bagan et al. did not find any improvement in 7 patients when similar dosage of griseofulvin was administered for 8 weeks.

Mycophenolate mofetil

It is an immunosuppressant used in treatment of patients with transplants. It is available as 250 and 500 mg tablets (Baxmune) and 200 mg/ml suspension (Cellcept).

Anti-malarials

Hydroxy-chloroquine sulphate showed positive results in management of OLP. 9 out of 10 patients showed excellent response to hydroxychloroquine when given in dosage of 200 to 400 mg daily as a monotherapy for 6 months. Use of anti-malarials have been discouraged in the management of OLP because of the possible lichenoid drug reactions.

Phenytoin

It is an anti-epileptic drug with immunomodulatory and wound healing properties. 2 out of 4 oral lichen planus patients treated had complete healing by phenytoin therapy. No other studies to date have been carried out to confirm significance of these findings. A recent systematic review by the Cochrane group of all published reports of randomized placebo-controlled trials of palliative treatment for patients
with symptomatic OLP concluded that there was only weak evidence that the evaluated treatment were superior to placebo.\textsuperscript{14}

**Surgical management**

Surgical treatment is more applicable to the plaque-like lesions, because the affected surface epithelium can be removed easily. It may also be recommended in management of non healing erosions because it provides excellent tissue specimens for histopathologic confirmation of diagnosis. Surgical management is not suitable for the erosive and atrophic types because the surface epithelium is eroded. Cryosurgery and carbon dioxide laser therapies have been tried in management of OLP lesions. Inspite of several trials surgical treatment is not recommended due to the recurrence of inflammation. Trauma from surgical procedures may induce new lesions via a Koebner phenomenon.\textsuperscript{14}

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<tr>
<th>Agent</th>
<th>Function</th>
<th>Outcome</th>
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<tr>
<td>Basiliximab</td>
<td>Anti-IL-2 receptor</td>
<td>Only 1 case report published with positive results</td>
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<tr>
<td>Ifliximab, Etanercept</td>
<td>Anti-TNF</td>
<td>Apparently induces lichenoid reactions. One case report with positive results (Etanercept)</td>
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<td>Efalizumab</td>
<td>Humanized antibody to CD11a chain of LFA-1</td>
<td>5 patients treated with positive results</td>
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**CONCLUSION**

Patients with OLP should be counseled as per the nature of this chronic condition and the different approaches to treatment. Even though evidence of the efficacy of these treatment approaches is not overwhelming, corticosteroid therapy remains the most common approach for managing symptomatic lesions. Because of the possibility of increased risk of malignant transformation, periodic reassessment of all patients with OLP is recommended.

**REFERENCES**


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