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REVIEW ARTICLE

Therapeutic Management of Oral Lichen Planus: A Review for the Clinicians

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ABSTRACT

Lichen planus is a chronic, noninfectious, inflammatory disease of skin and mucous membrane. Intraorally the buccal mucosa, tongue and gingiva are the sites commonly involved. It affects women more often than men in a ratio 3:2. It has well-recognized clinical signs and symptoms, the symptoms may range from none, through mild discomfort to severe burning sensation. In comparison with cutaneous form, the oral lesions are more resistant to therapy and are less likely to undergo spontaneous remission.

Treatment is administered mainly to resolve symptoms and discomfort. Choice of treatment may vary from patient to patient depending on the severity of the lesion and systemic condition of the patient. A variety of agents have been employed to treat oral lichen planus, but corticosteroid remains the mainstay of treatment. However, in the recent past, newer drugs like Tacrolimus have shown promising results. In view of fact that there is a risk of malignant transformation of atrophic and erosive forms of oral lichen planus, the patients need to be actively treated and kept on long-term follow-up. This article highlights various agents used in treatment of oral lichen planus, their mechanism of action, dosage and untoward effects.

Keywords: OLP, Tacrolimus, Corticosteroid, Management of OLP.

INTRODUCTION

Lichen planus derives its name from similar lace-like pattern produced by symbiotic algae and fungal colonies found on surface of rocks, termed lichens. Lichen planus is a common chronic mucocutaneous disorder, which was first described clinically by Wilson in 1869 and histologically by Dubdreuilh in 1906.[1] Oral lichen planus is commonly seen on buccal mucosa and vestibular areas followed by lateral borders of tongue and gingiva. The mean age at onset is in 4th to 5th decade of life, and common in females.[2] At least one-third of patients with oral lesions also demonstrate cutaneous lesions. Clinically, it can appear in six different forms—reticular, papular, plaque-like, atrophic, erosive and bullous.[3]

Oral lichen planus (OLP) appears as a hyperkeratotic plaque or striae, and is asymptomatic, except for atrophic, erosive and bullous form, wherein there could be mild discomfort to severe burning sensation. Histopathologically, oral lichen planus shows—focal hyperkeratosis, acanthosis, basal cell liquefaction degeneration and a dense band-like infiltrate of T lymphocytes.[4]

Although, the etiology of oral lichen planus is not fully elucidated, it is well-documented that oral lichen planus represents a T-cell mediated autoimmune disease in which auto cytotoxic CD8 cell triggers apoptosis of epithelium.[5]

Antigen presenting cells and basal keratinocytes are activated by antigenic stimulations. Activated antigen presenting cells and keratinocytes secrete chemokines that attract the lymphocytes into the developing oral lichen planus lesion.

MANAGEMENT OF ORAL LICHEN PLANUS

Many patients with oral lichen planus may not have any symptoms, in such cases there may be no need for active treatment except for reassurance and periodic check-ups. However, in many cases patients suffer from painful, erythematous, erosive or bullous lesions which have a slight predilection for transformation into oral squamous cell carcinoma. Thus, the principal aim of treating OLP would be to resolve the painful symptoms, the oral lesions and long-term follow-up to counter the chances of transformation into malignant lesions, especially for erosive and atrophic forms of OLP, which are more prone for transformation.[4]

Oral lichenoid reactions are lesions similar to OLP caused by unmasking of the causative gene of OLP by certain drugs and materials. The best way to treat it is to identify the drug or material causing it and replace it with another drug or material. However, in cases of cardiovascular drugs and epileptic drugs where replacements are not possible, the line of treatment is similar to that of OLP.[6]

A wide variety of therapeutic modalities have been employed to treat oral lichen planus which include corticosteroids,[2] retinoids and its derivatives,[7] immunosupressors like cyclosporine, levamisole and azithioprine,[8,9] antifungal agents like griesofulvin and PUVA therapy.[10] These agents are either prescribed alone or in combination, the choice purely depends on professional judgment.

Corticosteroids

Corticosteroids have been found to be the most predictable and successful agents in treatment of oral lichen planus. They can be used topically, intralesionally or systemically.[11]

The efficacy of corticosteroids for treatment of lichen planus is mainly attributed to its anti-inflammatory and immunosuppressive actions.[12]

Multiple mechanisms are involved in the suppression of inflammation by corticosteroids, they include reduction of the exudation of leukocytes and plasma constituents, thereby lessening edema, maintenance of cellular membrane integrity with the consequent prevention of excessive swelling of the cells, inhibition of lysozyme release from granulocytes, inhibition of phagocytosis, stabilization of the membranes of the intracellular lysozymes, which contain hydrolytic enzymes capable of cell digestion and extension of the inflammatory tissue damage. Corticosteroids also inhibit proliferation of fibroblasts with the positive effect of decreasing fibrosis.[2,12]

Topically, corticosteroid therapy is usually the treatment of choice initially, as it can be effectively delivered to the lesion surface with minimal potential for systemic side effects. Some agents used for topical application include 0.05% flucocinonide,[13] 0.05% clobetasol (Powercort®cream, Clobenol® cream),[14] 0.1 to 0.2% triamcinolone acetonide (Kenacort oral paste®, Cortrima® cream), dexamethosone and betamethasone valverate.[15]

They are prescribed as gels, creams, ointment with orabase (Kenalog in Orabase®) or oral rinses. Drugs which are available in orabase formulations are preferred because of their tenacity on the oral mucosa leading to better drug delivery. Triamcinolone acetonide is available in 0.1% buccal paste form (Tess®). These agents are either applied topically or rinsed (if in the form of solution) 3-4 times/day after meal. Patients are advised not to eat or drink for 30 minutes thereafter.[2]

Prolonged use of topical steroids over denuded areas may lead to local complications like blanching of the mucosa, hypopigmentation of the applied area, delayed wound healing with increased friability of the mucosa, and often systemic complications like, Cushing's syndrome, reversible HPA—axis suppression, hyperglycemia or glycosuria. This is especially a problem as it is absorbed rapidly in oral mucosa leading to it reaching its tolerable levels within a short span of time.

Intralesional corticosteroids are reserved for cases which do not respond to topical steroids. 10 to 20 mg of insoluble triamcinolone acetonide (Avcort® injection, Comcort® injection) is diluted with 0.5 ml saline or lidocaine 2% then injected into the lesion, which solubilize gradually and therefore have a prolonged duration of action. Main drawback of using intralesional corticosteroids being atrophy of tissue, secondary candidiasis (it can be treated with topical antifungal agent like candid mouth paint) and difficulty to deposit sufficient quantities into gingival lesions.[11]

Systemic corticosteroids are indicated for short period for recalcitrant cases that fail to respond to topical steroids. Prednisone (Wysolone®) 40 to 80 mg daily for less than 10 days without tapering is advised. The dosage regimens are determined individually based on medical status, severity of disease, and previous treatment response. If underlying medical problems are present, consultation with patient's physician is important.

If corticosteroids are used for prolonged therapy, they should not be stopped abruptly. If done so, it can flare up the underlying disease for which steroids were prescribed and cause acute adrenal insufficiency because of HPA axis suppression.

If supraphysiological doses are given for long time it can lead to electrolyte imbalance, hypertension, hyperglycemia, osteoporosis, increased susceptibility to infections and hirsutism.[12,16]

Retinoids

Systemic and topical retinoids have been employed to treat OLP. Retinoids include the natural compounds and synthetic derivatives of retinol that exhibit vitamin A activity. Retinoids were synthesized by making minor structural changes. First generation compounds include retinol and compounds derived from it metabolically—tretinoin and isotretinoin. Second generation retinoids are synthetic analogs, which include etretinate and acitretin. Third generation retinoids include arotinoids, which currently are in development.[7]

Retinoids have been noted to have antikeratinizing and immunomodulating effects. As compared to systemic retinoids, topical retinoids are preferred and generally produce good results.

Systemic retinoids can produce dryness of skin and mucosa, sloughing of skin, rashes, itching, partial hair loss, and may also increase triglyceride and cholesterol levels. In light of such adverse effects, topical preparation is preferred over systemic preparation.[13]

Tretinoin is available in the form of 0.05% cream (Retino-A®, Airol®). Isoretinoin is available as 0.05% gels (Sotret®, Acno®).

Cyclosporin

Cyclosporin is a very commonly used immunosuppressive drug which belongs to a family of cyclicpolypeptides derived from the fungus *Tolypocladium inflatum*. It is basically used to prevent rejection in organ transplantation. It inhibits chronic inflammatory reactions by inhibiting T-cell activation and proliferation, inhibits lymphokine production and release of interleukin-2.[8]

Topical cyclosporin can be used either in the form of mouthwashes or in the form of adhesive base. Patients are advised to swish and spit 5 ml of medication (l00 mg cyclosporin/ml) three times daily for 4 weeks or 0.025% cyclosporin in an adhesive base to apply four times daily, in some cases systemic cyclosporin has been suggested.[13]

Major adverse effects of cyclosporin include renal toxicity, nephrotoxicity, neurotoxicity, hirsutism and gingival

hyperplasia. The main drawback of using cyclosporin is that the drug is not readily available for topical use and secondly it is expensive.[17]

Cyclosporin is available in 25, 50 mg cap (Immusol®, Imusporin®) 100 mg/ml oily solution (Katzung®) and 100 mg/ml oral rinse (Sandimmun neoral®).

Levamisole

Levamisole was developed in 1966 as an antihelmentic drug, but has immunoregulating properties. Mechanism of action of Levamisole has been found to:

1. Restore the normal phagocytic activity of macrophages and neutrophils
2. Immunomodulate or immunopotentiate T-cell mediated immunity
3. Potentiate the activity of human interferon and interleukin-2
4. Inhibit fumarate reductase
5. Inhibit aerobic tumor glycolysis
6. Inhibit mammalian alkaline phosphatase
7. Alter the natural course of chronic recurrent inflammatory disease

Levamisole is administered at a dose of 50 mg three times/day for three consecutive days per week for 4 to 6 weeks. Levamisole (Ergamisol®, Vermisol®) is available as 50 mg, 150 mg tab.

Adverse effects include nausea, vomiting, headache and agranulocytosis.[18]

Azathioprine

Azathioprine is a purine antimetabolite. It has anti-inflammatory properties and decreases antibody production. Azathioprine is reserved for patients who do not respond to other treatment modalities. It can also be used in combination with corticosteroids and cyclosporin. When used in combination with corticosteroids, azathioprine can effectively enhance corticosteroid immunosuppressive activity. Thus, a lower dose of prednisone is required to achieve clinical efficacy and thereby diminishing adverse effects of corticosteroids.

Azathioprine (Imuran®, Azoprin®) is available as 50 mg tab.

It effects rapidly growing cells of bone marrow and GIT—resulting into leucopenia, thrombocytopenia and GI toxicity.[9]

Tacrolimus

The use of immunosuppressive agents to treat oral lichen planus is not a new concept. However, the use of tacrolimus is quite recent. Previously used to prevent organ rejection in kidney transplant cases, its topical application in cases of mucosal lesions has been highlighted only in last few years.

Tacrolimus is a macrolide form of immunosuppressant derived from a type of bacterium, *Streptomyces tsukubaensis*. It inhibits the transcription of interluekin-2 and transduction of signal to T-lymphocyte, and thus effectively causing immunosuppresion. Its main action can be contributed to its effecive inhibition to calcineurin phosphatase.

Its systemic use is comparable to corticosteroids but topical applications of 0.1% tacrolimus is proved to be far superior in treating of symptoms of oral lichen planus than 0.05% clobetasol. Recent studies by Corrocher et al[19] have shown that application of tacrolimus ointment 0.1% four times daily for 4 to 8 weeks resulted in faster resolving of symptoms in oral lichen planus as compared to topical corticosteroid application.

Tacrolimus is available as ointment for topical applications and also as tablets for systemic use. It is available in market in concentration ranging from 0.1 to 0.03% (Tacroz Forte®).

Adverse effects of topical application of tacrolimus include burning and itching sensation over the area of application for the first two days of treatment. Long-term adverse effect of tacrolimus needs to be researched.

Dapsone

Dapsone should be considered in resistant cases of erosive OLP. It has anti-inflammatory and immune-modulatory effects.

It is available as 5% gel (Acnesone®) and 25, 50 and 100 mg tablets (Dapsone).

Significant adverse effects, such as hemolysis and headache preclude its use.[20]

Interferon

Topically applied gel preparation containing human fibroblast interferon and interferon-alpha have suggested to improve erosive OLP. Development and exacerbation of OLP during and after IFN-alpha therapy for HCV infection have been reported, although systemic IFN-alpha (3-10 million IU thrice weekly) is successfully used to treat OLP in patients with and without HCV infection.[20]

It is available as vials (Roferon-A®) and syringes (Intafla-PF®).

Mycophenolate Mofetil

It is an immunosuppressant used in treatment of patients with transplants. However, its use in cases of treatment of resistant cases of OLP is also documented. It is a selective inhibitor of purine cycle in lymphocytes.[21]

It is available as 250 and 500 mg tablets (Baxmune®) and 200 mg/ml suspension (Cellcept®).

As with other immunosuppressant it reduces the patient's immunity.

Thalidomide

Use of thalidomide as a recourse to regular line of treatment is not recommended, unless all other treatment options have been exhausted. It has been documented to have anti-inflammatory action in cases of auto-immune diseases.[22]

Its role in teratogenicity has to be remembered at all times in any case it is to be recommended.

It is available as 100 mg capsules (Oncothal®).

PUVA Therapy

Photosensitizing psoralen drug and UVA radiation was introduced as a new therapy for oral mucosal lesions in 1987 by Jansen et al.

Psoralens belong to the furocoumarin class of compounds, which are derived from fusion of a furan with a coumarin. Four psoralens are used in PUVA therapy—psoralen, 5 methoxy psoralen (Bergapten®), 8-methoxypsoralen (Methoxsalen®) and 4, 5, 8-trimethyl psoralen (Trioxsalen®).

Photosensitizing drug can either be administered systemically or applied topically before irradiation. Ultraviolet irradiation in combination with psoralens modulates the function of the cells of the immune system.

Major side effects include nausea, blistering and painful erythema. Patient should be monitored for liver functions, serum creatinine and for cutaneous carcinoma (which can occur 10 times than expected frequency).[10]

NONTHERAPEUTIC OPTIONS

Photodynamic Therapy

Photodynamic therapy is a technique that uses a photosensitizing compound activated at a specific wavelength of laser light to destroy the targeted cell via strong oxidizers, which cause cellular damage, membrane lysis and protein inactivation. The exact mechanism of action of PDT is unclear. It would appear to act on hyper proliferating cells with selective uptake of photosensitizers into these cells. It has been suggested that PDT may have immunomodulatory effects and may induce apoptosis. In lichen planus, this may reverse the hyperproliferation and inflammation.

A phenothiazine dye methylene blue was described and attributed to its photodynamic properties. Methylene blue can be administered topically and orally and it may be a preferred choice for superficial lesions in skin and oral cavity. The fact that methylene blue has a strong absorption at wavelength longer than 620 nm, where light penetration into tissue is optimal, has led to the use of methylene blue as a promising candidate for PDT.[23]

Surgery and Lasers

Surgical excision, cryotherapy, CO_2 laser and ND:YAG laser have all been used in the treatment of OLP. In general, surgery is reserved to remove high-risk dysplastic areas. Excimer 308 nm laser is an effective choice for treatment of OLP cases as it is well tolerated and painless when used.[24]

CONCLUSION

Oral lichen planus is chronic mucocutaneous disease of unknown etiology. Patients with erosive or atrophic forms particularly should be observed periodically as it has malignant transformation potential varying between 0.3 to 3%. Continuous development in study of this disease along with its management protocol is required due to recent increase in incidence of squamous cell carcinoma in even non-risk population group.[4]

For the effective management of OLP, one has a wide range of drugs to choose from. When a patient with oral lichen planus presents with a burning sensation, usually as a first line of drug therapy one can prescribe a topical preparation of steroid and retinoids. As a second line of treatment in cases that do not respond to topical steroids alone, we may prescribe in conjunction with immunomodulatory drugs like Levamisole and Dapsone. It is only in resistant cases, where it is not responding to topical preparations or in severe form of OLP that tacrolimus and systemic corticosteroids in conjunction with immunosuppressive

Table 1: Management of oral lichen planus

Asymptomatic	Periodic check-up, reassurance Diazepam		
Symptomatic	Topical steroids		Good efficacy, proven track record and economical
	Topical retinoids		Of value when combined with topical steroids in conditions of OLP of gingiva
	Topical steroids with either	Levamisole	Used as an immunomodulator
		Dapsone	Has anti-inflammatory and immunomodulatory effects and very useful in cases of resistant OLP
		Cyclosporine	Has immunosuppressive properties, expensive
	Intralesional steroids with or without topical steroids		Can cause secondary candidiasis and difficult to deposit sufficient quantities in gingiva
	Tacrolimus		Good results, no long-term follow-up on adverse effects
	Systemic steroids with or without	Azathioprine	Use steroids with caution for short-term, azathioprine is used as a steroid sparring agent
	Surgery and lasers		Reserved for high-risk dysplastic areas
Lichenoid reaction	Eliminate causative agent or the drug		

like Azathioprine can be employed. So, it is essential to choose appropriate drug, mode of administration and dosage regimens individually and equal importance should be given for stress management. The treatment options have been summarized in Table 1.

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