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Review Article

Review: recent trends in management of oral lichen planus

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ABSTRACT

Oral lichen planus (OLP) is a chronic mucocutaneous inflammatory disease, associated with altered cell-mediated immunological function. It has been characterised by long-term evolution, repeated exacerbations, sometimes painful and resistant to treatment, or even all of these. OLP significantly affects quality of patient's life. There is a higher risk of malignant transformation accompanied with OLP and similar appearing oral lichenoid lesions. Current OLP therapy aims at eliminating all mucosal-related lesions reduce symptomatology and decrease the risk of oral cancer. This review summarizes recent treatment modalities used in the management of OLP which includes corticosteroids, immunomodulatory agents, retinoids, ultraviolet irradiation and/or laser therapy, herbal remedies. In addition, focus is also given upon adopting holistic approach in such patients by emphasizing on stress management.

Keywords: OLP, Management, Stress therapy, Herbal

INTRODUCTION

Lichen planus (LP) is a chronic mucocutaneous auto-immune type of disorder affecting skin, nails, scalp, oral mucosa, genitalia. It involves stratified squamous epithelium which was first described by Erasmus Wilson in 1869. It is characterised by 6Ps i.e., planar (flat-topped), purple, polygonal, pruritic, papules, and plaques. It probably represents a cell-mediated immunological response to an induced antigenic change in the skin or mucosa. The disease seems to be mediated by an antigen-specific mechanism, activating cytotoxic T cells, and non-specific mechanisms like mast cell degranulation and matrix metalloproteinase activation.[1,2]

OLP is commonly seen as symmetrical and bilateral reticular lesions with multifocal involvement in the oral mucosa. OLP is associated with Grinspan Syndrome (a triad of hypertension, diabetes and OLP). This disease most commonly affects middle aged women as compared to men mainly within 30-60 years of age. It is estimated that about 50% of the patients with oral lesions have skin lesions. About 23% of cases have only oral lesions. OLP can be seen in the posterior buccal mucosa (about 90% of cases), or on the tongue (about 30%), or alveolar ridge/gingiva (about 13%), but rarely on the palate or lip vermilion.[2,3] The reticular (92%), plaque (36%) and papule (11%) types are asymptomatic and doesn't require specific treatment. Whereas the erosive (44%) and bullous (1%) types usually cause severe burning pain and are refractory to conventional treatments. Gingival lesions frequently present as fiery red erythema affecting the entire width of the attached gingiva, a condition termed "desquamative gingivitis."[1,4] Erosive OLP is associated with a significant potential for malignant transformation. Smoking and alcohol consumption can also aggravate the chance of malignant transformation. [4,5]

Diagnosis of OLP is primarily clinical. It can be confirmed histopathologically by presence of sawtooth-shaped retepegs with increased granular layer, irregular acanthosis, liquefactive degeneration of the basal cell layer, colloid bodies (civatte, hyaline, cytoid) and variable degrees of ortho or parakeratosis and a marked layered lymphocytic infiltrate beneath the epithelium.[1,2]

The management of OLP is a challenge for clinicians. Therapeutic management of extensive disseminated and especially erosive OLP can be challenging for both the patient and the oral physician. Most clinical practice focuses on inflammation control and reduction in oral lesions. Treatment modalities include topical steroids (considered as the first line of treatment), systemic steroids, retinoids, calcineurin inhibitors, lasers, photochemotherapy, topical Interferon-α cream, antimalarials, dapsone, immunosuppressive agents like cyclosporine, cyclophosphamide, and azathioprine. natural agents such as curcumin, aloe vera, vitamin A, laser biomodulation.[4,6]

RECENT TREATMENT PROTOCOLS OF OLP

As oral LP is a chronic disease, the medical history of patient, psychological state, and treatment compliance, as well as possible drug interaction, must be considered when evaluating the cost effectiveness of any treatment modality.

The treatment algorithm according to American academy of oral medicine (AAOM) emphasizes upon the need to differentiate OLP from oral lichenoid lesion (OLL) and both should be periodically monitored for possible malignant and premalignant lesions and these suspicious areas should be biopsied. It further emphasizes the need to counsel patient in such a way that they understand that periodic examinations are necessary even if they are asymptomatic or their symptoms are well controlled.[6]

Corticosteroids have been the mainstay of management of OLP; yet other modalities like calcineurin inhibitors, retinoids, dapsone, hydroxychloroquine, mycophenolate mofetil and enoxaparin have contributed significantly toward treatment of the disease. 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.[7]

Corticosteroids

The rationale behind the usage of corticosteroids is their ability to modulate inflammation and immune response. They act by decreasing the lymphocytic exudate and stabilizing the lysosomal membrane.[7,8]

Topical steroids

For lesions that are not dysplastic and do not show malignant transformations, topical steroids should be taken into consideration. These were recommended as first-line treatment in consensus guidelines published in 2005.

Topical drugs available are: soluble prednisolone(5mg dissolved in 15 ml of water), tablets and mouthwash rinsing 3 or 4 times in 24h soluble betamethasone tablets (0.5 mg) dissolved in 10-15 ml of water, used for mouth rinse up to 4 times daily; triamcinolone acetonide 1% topical application also used; beclomethasone dipropionate (100 mcg/puff), fluticasone propionate (50 mcg/puff), metered dose inhalers, used as mouth sprays, applied on the lesions up to 3-4 times daily; Clobetasol ointment (0.05%) applied to painful affected areas 3-4 times in 24 h; Fluticasone cream (0.05%) applied to painful lesions 3-4 times daily.[8] These are the most commonly used group of drugs for the treatment of OLP. The main disadvantage in using topical corticosteroids is their lack of adherence to the mucosa for a sufficient length of time. To improve their adhesion to the oral mucosa, adhesive paste formulas like Orabase, ConvaTec, Montreal, Que-gelatin-pectin-sodium carboxymethylcellulose are used. Excellent bio-adhesive properties of denture adhesive pastes represent another option.[1,2]

Intralesional injection of corticosteroids

Patients with widespread forms of OLP are prescribed high-potent and super potent corticosteroids mouthwashes and intralesional injections. Intralesional injection of corticosteroids (triamcinolone acetonide hydrocortisone, dexamethasone, and methylprednisolone) in ulcerative OLP is also an effective treatment approach. The recommended injection is 0.2-0.4 ml of a 10 mg/ml solution of triamcinolone acetonide (kenacort A) one dose/week, 2-3 doses, in association with oral administration of prednisolone (one dose of 15-30 mg prednisolone/day for 2 weeks; the oral administration of prednisolone is progressively decreased to 5 mg per day and stopped in the third week).

Injections can be painful; to avoid mucosal atrophy, we usually administer a corticosteroid dilution of the 10 mg/ml.[5]

Long-term use of topical steroid can lead to the development of secondary candidiasis which necessitates antifungal therapy.[2] The potential tachyphylaxis and adrenal insufficiency is high when using super potent steroids like clobetasol, especially when used for a longer period.

Systemic corticosteroids

Systemic corticosteroids, methylprednisolone, or prednisone (30–80 mg/day) in short burst for 5-7 days are the most effective treatment modality for patients where topical approaches have failed; and for those with diffuse recalcitrant erosive OLP or multisite lesions of severe erosive OLP especially when cutaneous involvement is also there. Systemic administration of steroids presents more adverse effects than local application that includes adrenocortical suppression, hypertension, hyperglycemia, weight gain, mood alteration, insomnia, gastrointestinal irritation, osteoporosis.[8]

Oral mini pulse therapy

A novel approach has been suggested to give corticosteroid in a weekly pulse form (5 mg betamethasone in a single morning dose after breakfast on 2 consecutive days of a week) till the arrest of disease as well as amelioration of the signs and symptoms. This form of weekly pulse therapy helps to minimize the side effects, and ensures compliance due to less frequent dosing.[8,10]

IMMUNOSUPPRESSANTS, IMMUNOMODULATORY AND OTHER AGENTS

In cases with contraindications for systemic steroids (breast-feeding, herpetic infections, glaucoma, pregnancy, HIV, tuberculosis, diabetes mellitus or hypertension), other immunosuppressants and immunomodulatory agents are indicated.

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. Calcineurin inhibitors include cyclosporine, tacrolimus and pimecrolimus.[5,9] In OLP, these are used in topical formulations.

Cyclosporine (0.05%)

Cyclosporine calcineurin inhibitor, is immunosuppressant used widely in post-allogenic organ transplant to reduce the activity of patient's immune system. This selectively suppresses T-cell activity, main reason for transplant rejection. Cyclosporine binds to cytosolic protein cyclophilin of immunocompetent lymphocytes, especially T-lymphocytes. This complex of cyclosporine and cyclophilin inhibits calcineurin,thus inhibiting lymphokine production and IL release, leading to reduced function of effector T-cells.[5] Cyclosporine is used mouth rinse or topically with adhesive bases in OLP. However, the solution is prohibitively expensive and should be reserved for highly recalcitrant cases of OLP. Systemic absorption is very low. It is known to cause dose-related gum hyperplasia which reduces when drug is withdrawn.[10]

Tacrolimus (0.03% and 0.1%)

Tacrolimus is produced by Streptomyces tsukubaensis and belongs to the macrolide family. It is 10–100 times as potent as cyclosporine and has greater percutaneous absorption than cyclosporine. Burning sensation is the commonest side effect observed and also has a potential cancer risk.[8]

Pimecrolimus (1%)

1% topical cream of pimecrolimus has been successfully used as treatment for OLP. Pimecrolimus has low systemic immunosuppressive potential.[7]

Levamisole

Levamisole is a levisomer of tetramisole ((-)-2,3,5,6-tetrahydro-6-phenylimidazole [2,1-6] thiazole monohydrochloride), and has been used as a broad spectrum anti-helminthic drug since 1966. Levamisole reduces the levels of tumor necrosis factor-α, interleukin-6 and interleukin-8 and is found to be effective in OLP either alone or as an adjuvant to systemic corticosteroids.[11,12]

Antimalarials

Hydroxy chloroquine (HCQ), an antimalarial drug is known for its anti-inflammatory, immunomodulating, antithrombotic, and antihyperlipidemic effects. HCQ decreases inflammatory cytokine production and antigen processing. It is contraindicated in patients with liver cirrhosis. HCQ (200 mg/day) in a single dose has shown remission for the recalcitrant lesions with lesser chances of relapse. However, long-term usage causes retinal damage and visual changes.[12,13]

Retinoids

Topical retinoids such as tretinoin, isotretinoin and fenretinide, with their immunomodulating properties have shown reversal of white striae, although effects are temporary. Systemic retinoids have been used in cases of severe LP with variable degree of success. Side effects include burning sensation, cheilitis, elevation of serum liver enzymes and triglyceride levels and teratogenicity.[13]

Dapsone

Although an antibacterial agent (anti-leprotic), Dapsone acts as an anti-inflammatory agent by inhibiting the release of chemotactic factors for mast cells and is widely used for the treatment of skin diseases. It is usually administered as 100mg per day for 3 months for management of OLP. The most common untoward effect of dapsone is hemolysis of varying degree. Screening for G6PD deficiency is required before prescribing dapsone. Dapsone Reaction presents as rash, fever and jaundice within the first 6 weeks of therapy as well as can be ameliorated by the corticosteroid therapy.[10]

Mycophenolates

Originally used to treat psoriasis, mycophenolic acid (now reformulated as mycophenolate mofetil) has been reintroduced in dermatological medicine; and has been successfully used to treat severe cases of OLP (1g of MMF twice daily). Mycophenolates are quite expensive and effective with long-term usage.[11]

Low-dose, low molecular weight heparin (enoxaparin)

Low-dose heparin inhibits T lymphocyte heparinase activity which is crucial in T-cell migration to target

tissues. This promises to be a simple, effective and safe treatment for OLP when injected subcutaneously as it has no side effects.[10]

Efalizumab

It is a recombinant humanized monoclonal antibody to CD11a, which is used as an immunosuppressant in the treatment of psoriasis. It decreases activation and trafficking of T lymphocytes. It is administered once a week as a subcutaneous injection. In vitro studies of mononuclear cells in OLP have demonstrated a decrease of 60% in migration by peripheral blood mononuclear cells after the pre-treatment with anti-CD11a antibodies.[11,12]

ALTERNATIVE MANAGEMENT THERAPIES

Platelet rich plasma

Platelet rich plasma is emerging as an alternative source of growth factors contributing and leading to cell proliferation, differentiation, neoangiogenesis, withdrawal of toxins and cellular regeneration.[37] PRP is concentrated plasma of the patient's blood that predominantly contains high concentration of platelets along with increased coagulation factors. Owing to the anti-inflammatory effects, healing stimulating properties and biologically safe nature of PRP, it could be used as a novel alternative management therapy in OLP.[14]

PUVA therapy

This non-pharmacologic approach uses photochemotherapy with 8-methoxypsoralen and long wave ultraviolet light (PUVA). Methoxypsoralen is given orally, followed by administration of 2 hours of UV radiation intraorally in the affected sites. For the treatment of severe cases of OLP this therapy is proved to be beneficial.[27] Adverse effects include nausea and dizziness secondary to psoralen and 24-hour photosensitivity when this medicine is taken orally.[15,16]

Photodynamic therapy

Photodynamic therapy (PDT) is a technique that uses a photosensitizing compound like methylene blue, 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. Apart from the success achieved in the field of oncology, notably in head and neck tumors; the immunomodulatory effects of PDT have promising results to offer in psoriasis and LP.[13]

Laser therapy

In patients with painful erosive OLP and are unresponsive to even topical super potent corticosteroids, surgical management using 980-nm Diode laser, CO_2 laser evaporation, biostimulator with a pulsed diode laser using 904-nm pulsed infrared rays as well as the low-dose excimer 308-nm laser with the UV-B rays have been tried.[15]

HERBAL MODALITIES:

Turmeric

Curcuma Longa, the dried rhizome (perennial herbs) i.e., turmeric exhibit antiviral, antibacterial, anti-inflammatory properties. Growth and proliferation of head and neck tumours (e.g.: squamous cell carcinoma) has also been reduced by using turmeric. It represses tumour initiation, promotion and metastatic activities.

Turmeric is most effective in reducing burning sensation, pain and white lesions.[16]

Aloe vera

Aloe vera is successfully used in treatment of OLP because of its anti-inflammatory and antioxidant property. On application of 70% aloe mucilage in hydrophilic gel base thrice a day on erosive and ulcerative lesions of OLP for 8 weeks showed great responses.[16]

Tulsi

Ocimum tenuiflorum (*Ocimum sanctum*), holy basil or tulsi, is an aromatic plant in Indian subcontinent. Oleanolic acid, urosolic acid, rosmarinic acid, eugenol, carvacrol, linalool, beta-element are the main chemical elements found in tulsi.

Tulsi also has an ability to prevent the bad effects of metabolic stress by normalization of blood glucose, lipid levels, blood pressure and psychological stress through positive effect on memory and cognitive function. The unique combination of tulsi with pharmacological actions promote wellbeing and resilience. Hence tulsi is successfully used in treatment of OLP.[16,17]

Black pepper

Black pepper and its active principle piperine may be a potential supplementary therapy to OLP by virtue of its inhibitory effects on antigen-specific mechanisms and the overproduction of COX-2 as well as enhanced oxidative stress. Furthermore, piperine might be a possible agent for alleviating psychological disorders and preventing carcinogenesis in OLP.[18]

ANTIOXIDANTS

Vitamin A

Topical retinoids like tretinoin, isotretinoine or fenretinide have been found to induce transient reversal of white striae in OLP. [19]

Vitamin D

Studies suggest that vitamin D supplements in addition to the regular treatment improved the clinical condition of the lesion in the 1st week and disappeared completely on a period of 4 weeks.[19,20]

Vitamin E

The systemic use of vitamin E along with topical triamcinolone acetonide adhesive paste has demonstrated positive results without any adverse effects.[21]

Vitamin C

It is considered most important factors in reducing oxidative stress and thus might be protective action against OLP. [22]

Lycopene

Lycopene has been assessed in the prevention or management of OLP. Patients were given 10 mg of lycopene soft gel capsules once in a day upto two months. An important goal of Lycopene in the management of OLP is to reduce the burning sensation of the lesion.[22]

Purslane

Portulaca oleracea L. or Purslane plant is rich in compounds that have many biological activities, including omega-3 fatty acids, β-carotene, melatonin, and vitamins A, C, and E. This herb has anti-inflammatory, antiulcerogenic, antifungal, and antioxidant properties. It leads to clinical improvements of lesion type and size and can be considered as an alternative medicine for the treatment of OLP. [18]

Raspberry leaf extract

The leaf extract contains several compounds such as tannins and the two flavonoids kaempferol and quercetin. A few oral diseases, including mucosal inflammations and the treatment of OLP are treated by using raspberry leaf. The plant can reduce pain intensity and clinical features as well as the dermal symptoms. However, Raspberry leaf extract can be effective in treating OLP.[19]

Studies on recently used interventions in OLP have been summarized in Table 1.

Table 1: Stress management therapy.[19,23-25]

Stress management	Details
I Psychological interventions	
Cognitive-Behavioral Therapy such as cognitive restructuring, cognitive processing therapy	It usually spans over 8-12 sessions of 60-90 minutes. The intent is to relearn thoughts and beliefs and increase awareness of dysfunctional trauma-related thoughts and correct or replace those thoughts with more adaptive cognitions.[19] This employs principles of learning and conditioning to treat disorders, is known as Cognitive-behavioural therapy (CBT). It incorporates elements from both behavioural and cognitive therapy.
Exposure-based therapies	Therapy that involves a direct confrontation until the anxiety levels are dropped to normal. It uses frightening stimuli for the affect. Therapist tries to build a mental imagination with the help of a memory or introduces a new scene which is called as imaginal exposure.[22]
Coping skills therapy (including stress inoculation therapy);	Requires at least 8 sessions for 60–90 minute each. These all make use of techniques such as education, muscle relaxation training, breathing retraining, role playing, etc., to cope with anxiety or correct misunderstandings. [23,24]
Psychodynamic therapy	The aim is to bring unconscious memories into conscious awareness so that stress symptoms are lowered. Psychodynamic therapy would consist of weekly to bi-weekly sessions over a period of several months to an indefinite period of time.
Interpersonal therapy	It is a timed, dynamically informed psychotherapy that aims to alleviate patients' suffering and improve their interpersonal functioning so that they can better manage their current interpersonal distress. This therapy generally requires 10-20 weekly sessions in the acute phase followed by a time unlimited maintenance phase.

Continued.

Stress management	Details
Hypnosis/ hypnotherapy	It is an adjunct to psychodynamic, cognitive-behavioral, or other therapies, it is seen to enhance their efficacy for many clinical conditions.
Others: Eclectic psychotherapy; and brainwave neuro feedback.	
II. Lifestyle changes	These include regular mediation for 20-30 minutes, exercises/ brisk walking for at least 20 minutes, and eating healthy diet rich in fruits and vegetables.
III. Pharmacologic Interventions	prescription of antidepressants, antipsychotics, anticonvulsants/mood stabilizers

Table 2: Studies on recently used interventions in oral LP.[1,3-5,10,12,16,20,21,23-25]

Interventions	Study (Author, Year)
Cyclosporin	Scully et al (2000)[1], Jamei et al (2005)[4], Monshi et.al 2021[24]
Cyclosporin vs triamcinolone acetonide	Yoke et al (2006)[24], Thongprosom et al (2007)[12], Oczko.et al (2013)[5]
Clobetasol propionate	Campisi et al 2004[3], Conrotto et al 2006[3], Lodi et al 2007[23], Carbone et.al 2009[10]
Clobetasol propionate vs tracrolimus	Radfar et al 2008[12], Corrocher et al 2008[21], Sonthalia et al 2012[23]
Aloe vera	Choonhakaran et al 2008[16], Sanchez et al 2010[3], Mansourian et al 2011[16], Nair et al 2016[16], Gupta et al 2017[21], Muthusamy et al 2017[21], Sofia et al 2018[16], Pourshahidi et al 2021[22]
Aloe vera vs triamcinolone acetonide	Mansourian et al 2011[3], Reddy et al 2012[21]
Aloe vera vs low level laser therapy	Kaya et al 2011[15], Bhatt et al 2021[22], Aniyan et al 2021[22]
Pimecrolimus vs triamcinolone acetonide	Garouhi et al 2007[3], Jornet et al 2010[3], Kumar et al 2015[5], Pakfetrat et al 2015 [5]
Platelet rich Fibrin vs triamcinolone acetonide	Hausauer et al 2020[10], Bennardo et al 2021[10], Saglam et al 2021[10], Orive et al 2021[22]
Dexamethasone	Rhodus et al 2006[24], Fu et al 2021[24], Villa et al 2020[23], Lukaszewka et al 2021[24]
Curcumin vs triamcinolone acetonide	Prasad et al 2014[20], Keshari et al 2015[20], Kia et al 2015[21], Amirchaghmaghi et al 2016[20], Thomas et al 2017[21], Lv et al 2018[24], Zehi et al 2018[24], Bakshi 2020[10]
Hyaluronic acid	Nolan et al 2009[10], Shetty et al 2016[10], Hashem et al 2019[12], Hosseini et al 2021[22]

STRESS MANAGEMENT IN LP [20-24]

Stress management in LP includes three major interventions i.e., psychological interventions, lifestyle changes, and pharmacological interventions. Stress management is important as the present therapeutic approach in modern medicine focuses on holistic management of the patient and not just alleviation of symptoms of the disease (Table 1).

CONCLUSION

OLP is one of the most frequently encountered mucosal pathology by dental practitioners and Oral Medicine specialists. The importance of this is to make an adequate diagnosis of the lesions and to plan a proper treatment at the earliest. Till now no therapy is available for OLP which is completely curative. Corticosteroids still remain the primary treatment modality. LP has periods of exacerbation and remission; and therefore, tends to recur once treatment is stopped. This review is an attempt to bring forth all recent treatment modalities in LP. The current approach of modern medicine focuses on holistic management of LP and the importance of overall treatment modalities for better prognosis.

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