

A SYSTEMATIC REVIEW OF MANAGEMENT OF ORAL LICHEN PLANUS

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ABSTRACT

Oral Lichen Planus (OLP) is a relatively common chronic inflammatory disorder with a low risk of associated malignancy. A genetic predisposition linked to Th1 cytokine polymorphisms may predispose to the T-cell-mediated immunological response to an induced antigenic change that is supposed to cause OLP lesions. Topical immunomodulators such as corticosteroids and calcineurin inhibitors may control OLP lesions, but their long-term effects need to be better explored and understood. A systematic review of published data on oral lichen planus is presented with special reference to its treatment modalities. Typically, different medical and surgical modalities and newer therapeutic options are considered that contribute to symptomatic relief and palliative functional improvement to the patients. Eventually, the magnitude of the illness as a pre-malignant disease in a considerable size of patients signifies the need for promising treatment options.

KEYWORDS

Treatment Modalities, Oral Lichen Planus, Immunomodulators.

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INTRODUCTION

Lichen Planus (LP) is a chronic autoimmune, mucocutaneous disease. It can affect the oral mucosa, skin, genital mucosa, scalp and nails. In the majority of patients with Oral Lichen Planus (OLP), there is no associated cutaneous lichen planus or LP at other mucosal sites. This may be called isolated OLP.^[1] It is one of the most common oral diseases that manifest itself in the oral cavity.^[2] OLP is mainly seen in women and characteristically the lesions are symmetrical involving the buccal mucosa, tongue, gingiva, floor of the mouth, lips and palate.^[3] However, unknown if LP represents a single disease process or several closely related entities with similar clinical presentation. It can have many clinical presentations, ranging from with some lesions requiring no treatment and others needing management for decades. Numerically, OLP into 6 clinical forms: reticular, papular, plaque like, atrophic, erosive and bullous.^[4] The erosive and atrophic forms cause discomfort and painful symptoms.

Eventually, OLP has also special importance due to its malignant potential. The aetiology of LP still remains unknown. OLP is likely to be the common outcome of the influence of a limited combination of extrinsic antigens, altered self-antigens or superantigens. In some patients, precipitating factors have been identified including dental materials (Such as amalgam), drugs (Non-steroidal Anti-Inflammatory Drugs (NSAIDs) and angiotensin-converting enzyme inhibitors), stress, trauma and infectious agents (Herpes simplex virus 1, herpes virus 7, cytomegalovirus,

Human Papillomavirus (HPV), Epstein-Barr virus, Helicobacter pylori and hepatitis viruses).^[5]

LP is believed to result from an abnormal T-cell-mediated immune response in which basal epithelial cells are recognized as foreign because of changes in the antigenicity of their cell surface.^[6] whereas in the majority of instances cutaneous lesions of LPs are self-limiting and cause itching, lesions in OLP are chronic, rarely undergo spontaneous remission, are potentially premalignant and frequently a source of morbidity. OLP most commonly affects middle-aged adults of both male and female with a slight predominance in women and the condition does not appear to exhibit a racial predilection.^[7]

Management Options of OLP

Currently, treatment for OLP is focused mainly to eliminate mucosal erythema, ulcerations and alleviate symptoms during periods of activity and if possible increase the periods of disease quiescence. Excellent oral hygiene maintenance is believed to reduce the degree of severity of the symptoms and duration associated with OLP. Reticular type is often asymptomatic and seldom requires treatment. No treatment modality has been proved curative for OLP; switching on to the alternative agents used in the management of OLP suggests the inadequacy of any one agent to provide relief to the patient.^[8]

Corticosteroids have been the pillar of management of OLP and 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 up-regulating TGF- β 1 activity in OLP may be of therapeutic value in the future.^[9]

Corticosteroids

Corticosteroids to date remain the first line of treatment for OLP, because of their activity in dampening cell mediated immune activity, thereby modulating the immune function.

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These drugs can be administered topically, intralesionally or systemically.

The most widely accepted treatment for lesions of OLP involves topical or systemic corticosteroids to modulate patient's immune response.^[10] Topical corticosteroids are commonly used to treat mild to moderately symptomatic lesions, which include triamcinolone acetonide 0.1%, 0.05% fluocinonide, 0.025% clobetasol propionate, etc.^[11] Patients are instructed to apply a thin layer of the prescribed topical corticosteroid up to 3 times a day. Topical aqueous triamcinolone acetonide suspension is proven to be effective in reducing mucosal erythema and ulceration.^[12] The main problem when using topical corticosteroids is for adhering them to the mucosa for a sufficient period of time.

Adhesive pastes such as sodium carboxymethyl cellulose (Orabase), hydroxyethyl cellulose and special drug delivery systems such as lipid laden microspheres have been suggested for this purpose.^[13] Persistent localized lesions are effectively managed by local injection of up to 0.2 to 0.4 mL of triamcinolone acetonide containing 10 mg/mL. Although initially painful, this technique maximizes drug delivery to the lesion while minimizing systemic absorption; side effects like muscular atrophy are seen to be associated with this therapy.^[14] Systemic steroids are usually reserved for moderate-to-severe OLP or in cases resistant to topical therapy.

The most commonly prescribed systemic steroid to manage OLP is prednisone. The approach to therapy is to prescribe a high-dose, short-course regimen to maximize therapeutic effect while minimizing side effects. A single daily morning dose of 40 to 80 mg of prednisone is prescribed for no more than 10 days. The ultimate dosage chosen depends of the severity of the lesion and the size of the patient.^[15] Newer safer molecules like methyl-prednisolone, deflazacort can be used in place of prednisone.

Tacrolimus

Topical tacrolimus is a powerful macrolide immunosuppressant and is a non-corticosteroidal immunomodulator with a low adverse effect that presents a rapid response in the control of symptoms compared to traditional corticosteroids.^[16]

The anti-inflammatory molecular mechanism of action of tacrolimus is similar to cyclosporine, which inhibits the production of IL-2 by T lymphocytes by inhibiting calcineurin phosphatase which in turn leads to the inhibition of the nuclear gene transcription of IL-2 cytosine and several other pro-inflammatory cytosines such as IL-4 and IL-5.^[17]

As a result, activation and differentiation of inflammatory cells such as T lymphocytes, eosinophils or neutrophils are suppressed, which may explain why tacrolimus was also effective in subjects with cicatricial pemphigoid.^[18] Although the mechanism of action is similar to cyclosporine, tacrolimus is 10 to 100 times more potent and with better mucosal penetrating properties than cyclosporine. Topical tacrolimus in 0.1% strength has been reported to be safe, well tolerated and effective therapy for oral lichen planus lesions recalcitrant to traditional therapies.^[19] Pimecrolimus is also used in some studies to be as effective as tacrolimus.

Rapamycin (Sirolimus)

Topical rapamycin (Sirolimus) has been used for the treatment of some refractory cases of OLP.^[20] Rapamycin belongs to the

class of macrocyclic immunosuppressive drugs that are active only when bound to immunophilins. Intracellularly, rapamycin binds to FKBP12 (FK binding protein 12 kDa), an immunophilin and forms a complex FKBP12-rapamycin. mTOR possess a binding domain portion called FKBP12-Rapamycin Binding domain (FRB). After binding to FRB domain of mTOR protein, FKBP12-rapamycin complex potentially inhibits the activity of mTORC1 complex via autophosphorylation and dissociation of mTORC1 complex and thus blocking the binding of mTOR to its substrates.^[21,22] Inhibition of mTOR pathway blocks cytokine driven T-cell proliferation by inhibiting the progression from the G1 to the S phase of the cell cycle, thus explaining its role in immunosuppression.

Cyclosporine

Topical cyclosporine A (CSA) has been assessed by some investigators. In a study, topical CSA was used on a small sample group and results showed its benefits in the treatment of OLP.^[23] The most localized side effect of CSA is a transient burning sensation. However, several studies have not found any efficacy for CSA.^[24] A study suggested that CSA could be used as an alternative agent for the conventional treatment of acute periods of OLP, but it cannot be considered as a first choice because of its cost.^[25] Oral cyclosporine can be used as a crisis buster to control the disease in severe forms of oral lichen planus.

Azathioprine

Azathioprine is used as a corticosteroid sparing agent in the treatment of erosive and generalized OLP. It is as effective as corticosteroids. But its toxicity of bone marrow suppression needs to be monitored regularly.^[26]

Mycophenolate Mofetil

There are only a few case reports of successful use of mycophenolate mofetil in a dose of 1-1.5 grams/day in the treatment of oral lichen planus. Its comparative safety at this dose with that of cyclosporine and azathioprine holds promise for future prospects of its use in OLP.^[27]

Levamisole

Levamisole, an immunomodulator, has been used alone or as an adjuvant therapy with low-dose systemic corticosteroids. In adults it is given in oral dose of 150 mg/day for one or two consecutive days every week for a period of 6 weeks.^[28]

Retinoids

Retinoids have also been tried for the treatment of OLP. Previous studies revealed that side effects were common and troublesome with marginal improvement. Topical retinoids such as tretinoin, isotretinoin, fenretinide and tazarotene have also been used to treat OLP, but often cause adverse effects and are generally less effective than topical corticosteroids.^[29] Tazarotene is a retinoid analogue with fewer side effects than conventional retinoids and has shown promising results in treatment of OLP. Systemic retinoids have severe side effects, so nowadays they are not used for the treatment of OLP. However, there has been one controlled trial, comparing etretinate with placebo. In these patients, a prompt improvement was noted compared with the control group. Also, the relapse rate was high (About 60%) after 3 months.^[30]

Dapsone

Use of dapsone in the management of OLP has revealed some benefit, but disappointing results have been seen in gingival lesions. Generally, the use of dapsone is precluded because of significant adverse effects like haemolysis, nausea and headache.^[31]

Other drugs which are used systemically are thalidomide, metronidazole, griseofulvin, and hydroxychloroquine. The immunomodulatory activity of these drugs seems to be a possible mechanism of action beside their antimicrobial activity, but there are not much clinical trials for them.

Photochemotherapy

Mouth PUVA

Psoralens are naturally occurring compounds that are activated to triplet states by UVA to produce therapeutic effects in various cutaneous disorders. The photoactivation results in the formation of photoadducts in the DNA and photo-conjugation of psoralens to the DNA. This results in the inhibition of DNA synthesis, cell proliferation and suppression of lymphocytes and neutrophils; 8-Methoxypsoralen at doses of 0.6 – 0.8 mg/kg is administered 2 hours before localized UVA radiation every 2-3 weeks.^[32]

UVB Phototherapy

In some case reports, local UVB phototherapy using an oral phototherapy system was found to be effective option for treatment of resistant erosive OLP.^[33]

Photodynamic Therapy

Photodynamic therapy utilizes the activation of photosensitizers at specific wavelengths to produce strong oxidizers to bring about cellular damage, membrane lysis and protein inactivation. This leads to apoptosis of hyperproliferating lymphocytes and thus helps in improvement of oral lichen planus lesions. The commonly used photosensitizers are 5-aminolevulinic acid and methylene blue.^[34]

Interferons

Erosive oral lichen planus may improve with topical human fibroblast interferon (HuIFN- β) and interferon- α (IFN- α). Systemic interferon- α in a dose of 3-10 million UI thrice weekly was successfully used to treat oral lichen planus patients with or without HCV infection.^[35]

Biologicals

Several biologic agents were used in a limited number of cases of severe recalcitrant OLP unresponsive to other treatments. Satisfactory results have been reported in a limited number of patients with severe OLP that were treated with the anti T-cell agents such as alefacept and efalizumab. The dosage of efalizumab was 0.7 mg /kg - 1 mg/kg/week for 3-10 weeks and dosage of alefacept was 15 mg/week IM for 12 weeks.^[36,37] Efalizumab can cause subacute cutaneous lupus erythematosus, for which it has been withdrawn. The efficacy of these agents could be possibly attributed to their mechanism of action; efalizumab interacts with the leukocyte-function antigen-1 (LFA-1), whereas alefacept interacts with LFA-3. These antigens are detectable in the majority of cells that infiltrate skin lesions of patients with lichen planus.

In addition these agents interact with T-cell activation, which is also important in the pathogenesis of OLP.^[38] In a study of two patients with extensive oral and cutaneous lesions not responding to conventional treatments were successfully treated with the anti-TNF agent etanercept (25 mg/twice weekly) and adalimumab (40 mg every other week).^[39,40] The success of these agents is not surprising, as TNF has been proposed to be one of the major cytokines involved in the pathogenesis of OLP. There is though some scepticism concerning their use, as anti-TNF agents have been reported to be the cause of lichenoid reactions with proposed mechanism of the deregulation in the balance between TNF and interferon-alpha (INF- α).

Also, in a single case study of severe erosive OLP, the use of the anti IL-2 receptor agent basiliximab (Bolus intravenous infusion of 20 mg, 2 doses, 4 days apart) resulted in remission of oral lesions, which was only temporal as lesions reappeared soon after the agent was withdrawn.^[41] Basiliximab interferes with T-cell regulation; this cell has a central role during OLP pathogenesis, thus this agent could be considered as a prospective therapeutic option for severe OLP, but the cost and infection risk of basiliximab probably would form a barrier to planning appropriate clinical studies.

Laser

The 308 nm excimer laser has been used as a possible and additional method in the treatment of oral lichen planus. Treatments are painless and well tolerated. Clinical improvement has been achieved in most patients. Excimer 308 nm lasers could be an effective choice in treating symptomatic oral lichen planus.^[42] Other lasers such as diode laser 980 nm, carbon dioxide laser have been used to destroy the superficial epithelium and the inflammatory infiltrate to break the vicious cycle of the inflammatory mediators.

Surgical Treatment

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 histopathological 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. In spite 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.^[43]

Newer Treatment Options

Notably, topical rapamycin (Sirolimus), which has immunosuppressive and tumour inhibitor properties, inhibiting the response to IL-2 and thereby blocking activation of T and B cells has been very recently proposed in refractory erosive OLP.^[44]

The rapid development of new biologic therapeutic agents such as alefacept, basiliximab, efalizumab and etanercept, has attracted the interest of researchers on chronic intractable diseases including OLP. However, because of the general poor cost/benefit ratio in OLP, it is likely that their use will be confined to patients with severe manifestations of disease or those who have failed traditional first- and second-line therapies, such as topical corticosteroids/topical

calcineurin inhibitors. On the contrary, pharmacokinetic studies on topical medications in the mouth are clearly warranted as well as multicentre and multinational trials employing the most used topical medicaments.^[45]

CONCLUSION

The most outstanding advance in OLP has probably been the management of the disease. OLP may have a significant morbidity associated with persistent oral ulceration and the patient's quality of life can be severely affected; however, the risk of treatment should be weighed against the risks and complications of the disease itself. Therefore, topical immunomodulators may be considerably safer than systemic immunosuppressives. The availability of extremely powerful topical medication, such as halogenated corticosteroids and calcineurin inhibitors has permitted an improved and in most cases safe and satisfactory control of OLP lesions, even though current data is still insufficient to make recommendations with regard to the specific dosage, formulation or mode of delivery or length of the therapy.

Moreover, it is still unknown whether improved control of the inflammatory disease lessens the risk of malignancy. The magnitude of morbidity and premalignant potential in OLP could be addressed by combination strategies, which include the stoppage of causative ill habits, appropriate medical and surgical treatment modalities selected according to the severity of the symptoms and stage of functional impairment.

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