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REVIEW ARTICLE

Oral Lichen Planus–A Brief Review on Treatment Modalities

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ABSTRACT

Lichen planus is an autoimmune-mediated chronic inflammatory disease of unknown etiology, but studies have reported the role of cytotoxic T cells responsible for the disruption of basal keratinocytes and also causing the clinical symptoms. It is commonly seen in adults, with rare occurrence in children. It clinically manifests on the skin and oral mucosa, with skin lesions healing faster than the oral lesions. To obtain a diagnosis, a complete history and characteristic clinical features are usually sufficient for diagnosis, but there are certain other lesions like lichenoid reaction, contact sensitivity, white sponge nevus, pemphigoid and lupus erythematosus that show similar clinical characteristics, hence the need for histopathological evaluation using standard criteria given by Krutchkoff or World Health Organization (WHO). The treatment administered is always for eliminating symptoms and discomfort of the patients. A variety of pharmacological and natural alternatives have been used, along with frequent follow up visits in case of a tropic and erosive lichen planus. The purpose of this paper is to review the current trends in the management of oral lichen planus.

Keywords: Lichen planus, Management, Update.

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INTRODUCTION

Oral lichen planus (OLP) is a chronic mucocutaneous disease of multifactorial etiologies with Wilson first describing it in 1869. It was suggested by authors to an autoimmune disease triggered by antigens in the form of extrinsic or intrinsic factors that activate the lymphocytes and releases cytokines that are directed against the basilar keratinocytes leading to their apoptosis. It was seen to affect 0.5–1% of the worldwide population and 0.1–1.5% prevalence in India.[1]The condition affects the cutaneous or mucosal areas or both, where 50% of individuals with cutaneous lichen planus had oral mucosal lesions, and about 25% presented with, oral mucosal lesions alone.[2] It was seen most commonly in adults and had a female prediliction.[3]

An OLP commonly affects the buccal mucosa, gingiva, and the tongue, with an uncommon presentation on the palate.[4] It is usually seen as multiple lesions, bilaterally present in the mouth persisting for a longer duration of up to 25 years in comparison to the cutaneous counterpart.[5,6] It shows a chronic course having periods of dormancy and flare-ups with spontaneous remissions rarely seen.[7]

Andreasen[2] divided oral lichen planus into six clinical types: reticular, plaque-like, papular, erosive, bullous, and atrophic types where erosive and atrophic types caused discomfort and painful symptoms. On clinical examination, in the absence of the reticular type which is easily identifiable, the other types of oral lichen planus requires histopathological evaluation for a definite diagnosis. This is done using WHO criteria (2003) for diagnosis of OLP, that includes clinical criteria's, histopathological criteria's and final differentiation of lichen planus from lichenoid lesions.[8]

An OLP is a disease with a potential for malignant transformation. It has been noted that the rate of malignant transformation has decreased from 5.9% in 1924 to 0.5–1.1% in 2017.[9] However, this possibility may be reduced by patient counseling, consumption of a healthy diet and avoiding carcinogens.[10] The standard protocol for the management of oral lichen planus includes symptomatic relief with no complete cure. Various alternatives have been applied in the management which suggests the inadequacy of any single drug to provide relief. The present article hereby provides an overview of different treatment modalities in the management and the advancements made in obtaining control over the symptoms of OLP.

The OLP could be symptomatic (erosive, atrophic and bullous types) or asymptomatic (reticular or plaque types). The symptomatic oral lichen planus can cause a burning sensation, severe pain, inability to speak and swallow, which is seen to be the chief complaint of the patient requiring symptomatic relief[11] while the asymptomatic forms do not require pharmacological interven-

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Flow Chart 1: Treatment protocol for oral lichen planus

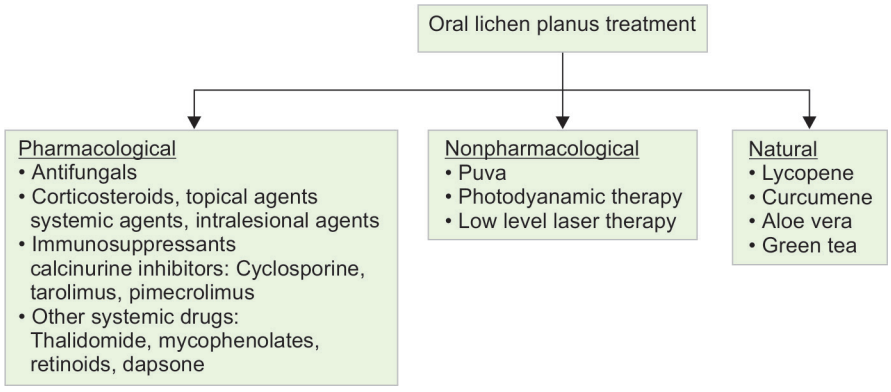

Table 1: List of antifungals used in the treatment of oral lichen planus

Drugs	*Dose*
Clobetasol	0.025%, 0.05%
Miconazole	2%
Amphoterecin B	0.1%
Tab Griseofulvin	500mg/day for 6 months

tion. The treatment plan is formulated according to the psychological state, medical history of drug interactions and drug compliance of the patient.[12] The most accepted treatment protocol for OLP is depicted in Flow Chart 1.

The treatment plan consisting of pharmacological therapy includes antifungals (Table 1), corticosteroids (Table 2), immunosuppressant's (Table 3) and other systemic drugs (Table 4), whereas, the other treatment modalities include nonpharmacological therapy (Table 5), natural alternatives (Table 6) and surgery.

Pharmacological Therapy

Antifungals

Candida albicans is seen to be present in 37% of the OLP lesions (superimposed candidal infections) which exacerbates it and produces symptoms. This could be because, in erosive lesions on the gingiva or oral mucosa, maintenance of oral hygiene is difficult leading to fungal infections. Another reason can be the prolonged use of corticosteroids, which leads to decrease in the immune mechanism of the mucosa and also reduces the salivary flow, leading to altered microflora and hence enhanced candida growth in the oral cavity.[13] Infection and inflammation caused by *Candida* was seen to show changes in the epithelium which was histopathologically misdiagnosed as dysplasia.[14] Hence an antifungal therapy is advised (Table 1) as it can change the erosive form of OLP into reticular forms.[15]

The antifungal griseofulvin was used by Sehgal in 1972 and was found to be useful in the management of oral LP, unlike others who found no improvements in the lesion.[16] Symptomatic relief was reported on using other antifungals like amphotericin B, azoles and nystatin. The use of topical miconazole was also found to be an effective antifungal against candidal superinfections during topical steroid therapy.[17] The use of clobetasol showed greater chances of oral fungal infection than any other steroid therapy; hence an accompanying antifungal (clotrimazole)could be used as it produced greater symptom relief than any other antifungal.[18]

Corticosteroids

Corticosetroids in the form of topical agents, intralesional injections and systemic drugs is considered to be the mainstay of the treatment of oral lichen planus. The details about the drugs used and its mechanism of action with adverse effects is mentioned in Table 2.

Immunosuppressans and Other Systemic Drugs

Immunosuppressant's are the agents used to suppress the immune mechanism that targets and damages the host. The details of the immunosuppressant's as well as the other systemic drugs that are used in the management of oral lichen planus along with their mechanism of action, dosage and adverse effects is mentioned in Tables 3 and 4.

Nonpharmacological Therapy

Several nonpharmacological modalities have been used for the treatment of recalcitrant oral lichen planus have been discussed in Table 5.

Natural Alternatives

The current drug treatments seem to be only palliative and have also shown to have various adverse effects, hence, valuable natural therapies have been inculcated for effective treatment of oral lichen planus. The details of the natural agents used with their mechanism of action and dosages have been discussed in Table 6.

Table 2: Corticosteroids used in the treatment of oral lichen planus

Therapy	*Drugs*	*Mechanism of action*	*Dosage*[7,19]	*Side effects*[19]
Topical (combined with adhesive base carboxy methyl cellulose, or used on custom treys, mouthwashes or sprays)	Flucinoloneacetonide	Inhibits the conversion of Phospholipids to Arachidonic acid	0.1% or 0.025%	Secondary candidiasis, thinning of oral mucosa, prolonged use casus adrenal suppression
	Disodium betamethasone phosphate		0.05%	
	Clobetasol propionate		0.05% or 0.025%	
	Fluticasone spray		0.01%	
	Topical triamcenoloneacetonide		0.1%	
	Mometasone furoate		0.1%	Does not cause any severe side effects
Intralesional	Triamcenolone acetonide		0.2–0.5 mL inj containing 40 mg/mL	Muscular atrophy
Systemic	Methyl Prednisolone	Hence, cyclo-oxygenase and Lipo-oxygenase pathways inhibited ↓ No inflammatory mediators released ↓	Morning dose of 40–80 mg, for 10 days Side effects on use for >2 weeks, hence initial higher dose of 1–1.5 mg/kg/day recommended for immediate withdrawing or tapering	Insomnia diarrhea Mood swings Nervousness Fluid retention Weakness Hypertension Muscle weakness Prone to infections
	Betamethasone		0.5 mg OD after breakfast on 2 consecutive days every 2 weeks for 10 weeks	

Mostafa and Zakaria in 2018 assessed the therapeutic advantage of the use of topical corticosteroids in combination with ozone (60% for 1 min in each session twice a week for four weeks), they found that there was considerable decrease in the discomfort in symptomatic patients and there as also decrease in the *Candida* growth due to bactericidal, fungicidal and virucidal properties of ozone[20]

Surgery

Surgical excision of the lesional tissue should not be considered as the primary treatment modality because lichen planus is an inflammatory disease which will reoccur. Its application for multicentric lesions, erosive and atopic oral lichen planus was not advisable as the surface epithelium is eroded. Laser ablation using carbon dioxide and cryosurgery is considered in erosive oral lichen planus resistant to most treatment modalities. Surgery is advisable in plaque type of lichen planus as the superficial layer of the lesion can easily be removed. Localized erosive oral lichen planus lesions also were seen showing complete eradication of symptoms following treatment with a free gingival graft after a follow-up of 3.5 years.

Table 3: Immunosuppressants used in oral lichen planus

Therapy	*Drugs*	*Mechanism of action*	*Dose*	*Adverse effects*
Calcinurin Inhibitors	Cyclosporine	Inhibits the de-phosphorylation of NFAT ↓ Inhibiting translocation of NFAT into nucleus ↓ Inhibits binding to cytokeratin promotor ↓ Leading to inhibition of mRNA transcription ↓ Prohibits the release of cytokines.	50 mg/mL or 0.025% topical application, four times daily[21] 100 mg/mL topical CsA solution	Gum hyperplasia, Burning sensation Petechial hemorrhage Hirsutism Swollen and itchy lips GI upset.[22,23]
	Tacrolimus		Adult: 0.03%–0.1% Child: 0.03% Cream or ointment twice daily for 1 week with no occlusive dressing.	Burning sensation and relapse of lesion after cessation
	Primacrolimus		1% cream	Transient burning sensation

(NFAT: Nuclear Factor of Activated T-cells, CsA: Cyclosporin A)
Systemic calcinurin inhibitors are rarely used as it causes gingival hyperplasia, HTN, DM, tremors, nephrotoxicity, nausea, seizures and dyslipidemia

Table 4: Other drugs used in oral lichen planus

Therapy	*Mechanism of action*	*Dose*	*Adverse effect*
Thalidomide	Reduces TNF-α production. Increases activity of suppressor T-cells Inhibits angiogenesis.	Initial dose of 50 mg/day progressively increased to 200 mg/day over 3 months. If adverse effects noted dose was decreased to 100 mg/day.	Dizziness Edema Rashes
Mycophenolates (used in cases resistant to topical steroids)	Suppresses dendritic cell maturation. Formation of antibodies and inhibits lymphocyte proliferation.[24]	200 mg/day in combination with calcinurine inhibitors 150 mg/day followed by tapering the dose and finally withdrawing it.	GI disturbance headache Tiredness myelosuppression embryopathy.[25]
Retinoids: Tretinoin Isotretenoin Fenretinide Etretinate	They stimulate macrophage activation and antibody dependent cell mediated cytotoxicity. They also reduce the CD4 cell infiltrate. Increases macrophage and thus heals the OLP lesions.	Systemic: 10,000 IU retinoids. Etretinate- 0.6 mg/kg/day for 2 months followed by maintenance dose of 0.3 mg/kg/day or using 0.1% Tretanoin 0.1% in adhesive base for local application twice daily. Topical: 0.1% - Adhesive gel (4 times per day for 2 months). Isotretinoin 0.1% (2 times per day for 2 months) Topical retinoid 0.05% in orabase.	Cheilitis Dry mouth and skin hair loss Itchiness Headache Elevation of serum liver enzymes conjunctivitis.
Dapsone	Inhibits the release of chemotactic factors for mast cells hence reducing inflammation.[26]	50 mg/day Hydrochloroquine 200-400 mg daily for 6 months	Hemolysis, G6PD deficiency causing hemolytic anemia or methemoglobinemia, hypersensitivity reaction.[27]
Gresiofulvin	Fungistaticaction When administered gets deposited on the keratin layer making it durable.[28]	500 mg/day for 4 weeks	Nausea, vomiting diarrhea, headaches, drowsiness, and fatigue, ukopenia and neutropenia, albuminuria, urticaria and photosensitivity.[29]
Hyaluronic acid	It enhances healing by forming a protective coat in the mucosa and thus keeping it hydrated.	0.2% gel	

Table 5: Nonpharmacological therapy used in oral lichen planus

Therapy	*Mechanism of action*[30]	*Dose*	*Adverse effects*
Puva therapy 8-methoxypsoralen (8-MOP) long wave ultraviolet light (PUVA).	Psorolen obtained from plants makes the skin temporarily sensitive to UV radiation. PUVA causes photoconjugation of psoraleanto DNA and subsequently causes suppression of mitosis, DNA synthesis, and cell proliferation. PUVA can effect specifically lymphocytes or PMNL. It causes immunologic alterations hence decreasing the levels of lymphocytes.[30]	Dose: Methoxypsoralen is given orally, followed by administration of 2 hours of UV radiation intraorally in the affected sites. Initial UVA dose was 1.5–2 J/cm^2 and was increased at the first and third sessions of each week. The maximum dose administered at the end of treatment never exceeded 7 J/cm^2 in a single session. Treated three times per week with an interval of 48 h between each session. Patient's tolerance to UVA permitted, the number of weekly sessions was progressively increased to 4 and subsequently 5.[30]	Adverse effects: nausea, dizziness, photosensitivity for 24 hours. Epidermal atrophy or pseudo-parakeratosis.[31]

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Therapy	*Mechanism of action*[30]	*Dose*	*Adverse effects*
Photodyanamic therapy contains photosensitizer along with specific harmless light.	Immunomodulating activity Photosensitizer is activated by specific wavelength, oxidizing the target cells by producing singlet oxygen and free radical, thus destroying specific cells, causing membrane lysis and protein inactivation[32]	Dose: Photosensitizers used: Methylene blue, methyl 5 aminolevulinate, Chlorine-e-6 polyvinyl pyrrolidone. Light source: Xenon arc lamp 630 ± 5 nm and 120 J/cm² Diode laser- 600–660 nm and 75 J/cm² 5% solution of photosensitizer in aquous solution used to rinse, 10 min later lesion exposed to light source.[33]	Pain and local skin reactions (LSRs), including erythema, edema, desquamation, or pustule Late changes: bullous phemphigoid, pigmentary changes and carcinogenicity.[34]
Low level laser therapy	Destroyes the keratinocytes in superficial epithelium by protein denaturation Deep penetrated lasers damage connective tissue containing inflammatory cells. Modulated mast cells, decreased prostaglandins and increased the production of basic growth factors.	The lasers used were 904 nm pulsed infrared laser (four sessions weekly) and 980 nm gallium-aluminum-arsenide diode laser.[35,36]	Erythema, soreness

Table 6: Natural alternatives used in oral lichen planus

Natural Component		*Action*	*Dose*
Lycopene	fat-soluble carotenoid obtained from red fruits and vegetables and of certain algae and fungi. Tomatoes and tomato-based products are the major sources of lycopene. Other sources of lycopene are apricot, cranberry, grapes, pink grapefruit, guava, papaya, peaches, and watermelon.[37]	Antioxidant Causes physical and chemical quenching of free radicals. Replaces the lost antioxidants in case of oral lichen planus[38]	Dose: 6–60 mg/day For 2–32 weeks
Curcumin	component of curcuma longa, i.e., turmeric	Anti-inflammatory. Immune modulatory activation of host macrophages and natural killer cells Modulation of lymphocytes hence prevents basement membrane destruction[39] Downregulates inflammatory enzymes, cytokines. Antioxidant action by inhibiting free radical and nitric oxide[40]	1 gm for 2 weeks, then tapering it to 500 mg and 250 mg every 2 weeks followed by 1 month topical application[41] No side effects at high doses
Aloe vera	Vitamins, inorganic compounds, essential and non-essential proteins	Antibacterial, Antifungal, anti-inflammatory, antioxidant, antitumor, and immune boosting properties	Gel application thrice a day for 4–8 weeks[42]
Green tea	Rich source of catechins: Epicatechin (EC), Epicatechin-3-gallate (ECG), Epigallocatechin (EGC) andEpigallocatechin-3-gallate (EGCG)	Anti-inflammatory and chemopreventive. immunomodulatory activity useful for people with abnormal T cell function[43]	10 cups (120 mL/cup) of green tea daily supplemented with green tea tablets have been recommended[43]

Contributing Etiological Factor in Oral Lichen Planus

Psychological Influence

Oral lichen planus (OLP) was considered by researchers as a psychosomatic disorder whose occurrence was influenced by the conditions of stress, anxiety or depression or was considered as etiologic factors to OLP.[44,45] A positive relation of oral lichen planus with the psychological status of an individual was noted. In 1998 studies had shown a greater incidence of OLP in people with a higher degree

of anxiety, depression, and psychic disorders.[46] On the contrary, the incidence of the lesion with their severity was also linked to the psychological condition of an individual. A long-term symptomatic lesion of lichen planus could lead to anxiety, tiredness, increased stress and cancerophobia in patients, which directly affects the everyday life of a person and also their attitude towards the disease. A prolonged disease state in an individual lead to the use of catastrophizing or strategies to cope with the intensity of pain, which in turn was seen affecting the lifestyle of the individual.[47] In such cases exacerbating factors should be minimized, stress management, breathing exercise, and yoga should be practiced.

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