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RESEARCH ARTICLE

RECENT TRENDS IN MANAGEMENT OF ORAL LICHEN PLANUS: A BRIEF REVIEW

***Dr. Tapaswini Bag**

Senior Lecturer, Department of Oral Medicine and Radiology, College of Dental Science and Hospital, F-12, Jhoomer Ghat Rau, Indore, PIN: 453331, Madhya Pradesh, India

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ABSTRACT

Oral lichen planus (OLP) is a relatively common, chronic inflammatory condition and presumably autoimmune disease, which frequently present with burning sensation. Lichen planus is a mucocutaneous disease that occurs in about 0.02 to 4% of general population affecting skin and mucosa. The lesion has a chronic clinical course with periods of exacerbation and remission with reports of lesions for up to 20 years. Although various etiological agents are proposed, the exact etiology & treatment is unknown. Only symptomatic OLP requires treatment and efforts were made in a continued searching for novel therapies for symptomatic OLP.A wide range of treatment modalities from allopathic to ayurvedic have been proposed for OLP but none have proved curative or permanent reduction of the disease. Current article reviews about the various recent trends in the management of OLP.

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INTRODUCTION

Lichen planus is a mucocutaneous disease of unknown etiology. Lichen planus is a relatively common disorder of stratified squamous epithelium that typically affects the skin and mouth. Lichen planus can also affect the non- oral mucosal surfaces such as genitals, anus, pharynx and rarely conjuctiva and oesophagus. Lichen planus (LP) is a chronic inflammatory mucocutaneous condition which most commonly affects the skin, genitelia and oral mucous membrane. The oral lesions are chronic, rarely undergo spontaneous remission are potentially malignant and often a source of morbidity. In long standing diseases espicially erosive and atrophic forms malignant transformation has been reported in 0.4 to 5.6% of cases. The disease affects approximately 1-2% of the world population. It has predilection for females and mean age of onset is in the fourth to fifth decade. Oral mucous membrane involvement may occur in addition to cutaneous lesions, or may be the only manifestation of Lichen planus. It is estimated that about 50% of the patients with oral lesions have skin lesions. About 23% of cases have only oral lesions.

****Corresponding author: Dr. Tapaswini Bag,***
Senior Lecturer, Department of Oral Medicine and Radiology, College of Dental Science and Hospital, F-12, Jhoomer Ghat Rau, Indore, PIN: 453331, Madhya Pradesh, India.

Cutaneous lesions of Lichen planus are self-limiting, whereas oral lesions are chronic, rarely undergo spontaneous remission and are potentially premalignant and are often a source of morbidity (Vente, 1999; Wilson, 1869; Bouquot *et al*., 1869; David lieberthal, 1907)

Clinical presentation of OLP

The clinical presentation of OLP varies. In some patients the onset is insidious, and patients are unaware of their oral condition. Some patients report sensitivity of the oral mucosa to hot and spicy food, painful oral mucosa, red or white patches of the oral mucosa, or oral ulcerations. OLP can occur on any mucosal surface, including the lips, but most frequently occurs on the buccal mucosa, the tongue being the next most common site. Andreasen divided Oral Lichen planus into six types: reticular, papular, plaque-like, erosive, atrophic and bullous. The reticular, papular and plaque- like forms are usually painless and appear clinically as white keratotic lesions.The erosive, atrophic and bullous forms are often associated with a burning sensation and in many cases can causes severe pain.The reticular form is the most common and asymptomatic, but the erosive, atrophic, and bullous forms are typically the most symptomatic with the complaints of severe burning sensation and pain, which can exacerbate by trauma

and foods particularly hot, spicy or acidic (Sousa, 2008; Regezi, 2012).

Review of Literature In Various Treatment Modalities For Oral Lichen Planus

There is currently no cure for OLP. Excellent oral hygiene is believed to reduce these varieties of the symptoms, but it can be difficult for patients to achieve high levels of hygiene during periods of active disease. Treatment is aimed primarily at reducing the length and severity of symptomatic outbreaks. Asymptomatic Reticular and Plaque forms of OLP do not require pharmacological intervention. Before initiating treatment, the diagnosis must be confirmed histological. It is important to rule out candidiasis. The management of OLP is primarily aimed at alleviating the symptoms, avoiding the possible contributing factors and reducing the chances of malignant transformation. Drugs/regimen used to treat OLP includes:

Stress management

Exacerbating factors should be minimized Stress counselling Breathing exercise and yoga. For stress management, psychometric evaluation has to be done by HAD scale (Vente *et al*., 1999)

Corticosteroids

Corticosteroids cannot be compared in trials with any other agent in the treatment of OLP. These are effective when applied topically or given intralesionally or systemically.

Role of Corticosteroids in Oral lichen planus: The mainstay of treatment of OLP remains corticosteroids which can be used topically, intralesionally and systemically. Corticosteroids both inhibit the membrane enzyme phospholipase A_2 and stimulate the cell membrane protein lipocortin. These factors indirectly inhibiting the prostaglandins, leukotrienes and platelet activating factor. Other proposed mechanisms include a cytostatic action, a stabilizing action on lysosomal membranes and cytokines supression. Generally corticosteroids are anti-inflammatory, immunosupressive, anti-proliferative and vasoconstrictive.The most widely accepted treatment for lesions of OLP involves topical or systemic corticosteroids to modulate the patient's immune response (Suneet Khandelwal, 2012; Raghvendra kini, 2011; Ungphaiboon, 2005)

Topical corticosteroids

In Netherlands hypromellose 20% ointment (hydropropyl methyl cellulose) is an appropriate base used for methyl cellulose. In other countries the base called as ora base is commonly used. It consists of carboxy methylcellulose, pectin and gelatin. Triamcinolone acetonide 0.1% in hypromellose 20% ointment administered at least 4 times per day useful in patients in mild symptomatic OLP. Topical corticosteroid therapy is the treatment of choice initially as it can be effectively delivered to the lesion surface with minimal potential for systemic side effects.[208] Some agents used for topical application include 0.05% flucinonide, 0.05% clobetasol (power cort® cream, clobenol® cream), 0.1- 0.2% triamcinolone acetonide (Kenacort ® oral paste, Cortrima ® cream), Dexmethasone, Betamethasone valverate. They are prescribed as gels, cream and ointment in orabase (Kenalog® in orabase) or oral rinses. Drugs which are available in orabase formulations because of their tenacity on oral mucosa leading to better drug delivery.

Triamcinolone Acetonide

KENACORT 0.1% oral paste is a synthetic corticosteroid which possesses anti-inflammatory, antipruritic & anti-allergic action. The emollient oral paste acts as an adhesive vehicle for applying the active medication to the oral tissues. The vehicle provide a protective covering which may serve to temporarily reduce the pain associated with oral irritation. It is indicated for adjunctive treatment & for the temporary relief of symptoms associated with oral inflammatory lesions such as OLP. The advantage of topical steroid application is that side effects are fewer than with systemic administration. Adverse effects include candidiasis, thinning of the oral mucosa and discomfort on application. Topical formulations of the more potent corticosteroids can cause adrenal suppression. The lowest-potency steroid that proves effective should be used.

Intralesional injection

Topical corticosteroids are of limited value for some cases of oral lichen planus. In such cases, it may be appropriate to use topical corticosteroids in combination with intralesional preparations. They are used for recalcitrant or extensive lesions involve the subcutaneous injection of 0.2-0.4 mL of an l0mg/mL solution of triamcinolone acetonide. However, intralesional corticosteroids have some contraindications, including atrophy of tissue and secondary candidiasis after frequent injections. It may not be possible to inject it in sufficient quantities into gingival lesions (Suneet Khandelwal, 2012; Raghvendra kini, 2011; Ungphaiboon, 2005).

Systemic steroid therapy

It should be reserved for patients in whom OLP lesions are recalcitrant to topical steroid management because the dosage ranges for corticosteroids are wide and patient responses variable, numerous dosing options have been proposed.Dosages should be individualized according to the severity of the lesions and the patient's weight and should be modified on the basis of the patient's response to treatment.It must be given in a dose of 1 mg/kg/day (Suneet Khandelwal, 2012; Raghvendra kini, 2011; Ungphaiboon, 2005; A Gonzalez-Garcıa, 2006)

CALCINURIN INHIBITOR

Calcineurin is a protein phosphatase which activates transcription of Inter Leukin-2 there by stimulates the growth and differentiation of T-cell response.Cyclosporine; tacrolimus and pimecrolimus are calcineurin inhibitors are generally used in treatmentof OLP

Cyclosporine A

Cyclosporine A is an immunosuppressive agent which is beneficial in cutaneous lichen planus. Cyclosporine (100 mg/mL solution, 5 mL swish and spit three times daily) can be used as a mouth rinse in OLP patients who do not respond to topical corticosteroids. Oral Cyclosporin A (5 to 6 mg/kg per day) is very effective in recalcitrant severe forms of the disease.

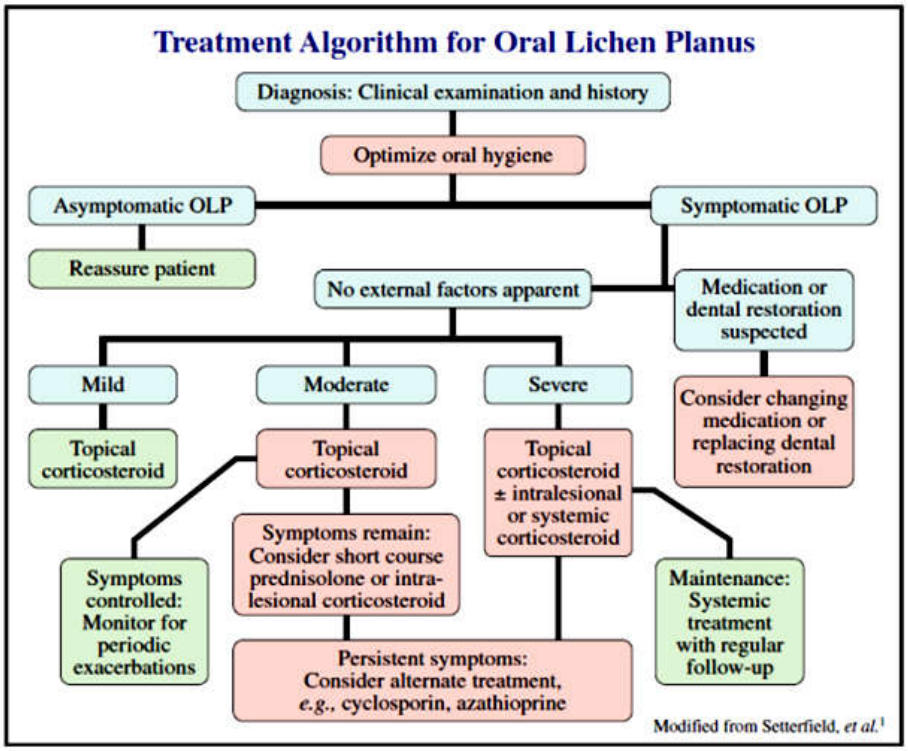

Table 1.

1. Oral lichen planus (OLP) is a mouth rash of unknown cause
2. OLP is not contagious and not inherited
3. OLP presents as white lines or spots, redness or ulceration, often in combination
4. OLP may be painless or cause mucosal sensitivity or pain
5. OLP may be more severe at times of psychological stress
6. OLP may eventually disappear, although this can take many years
7. The skin, nails and scalp may be affected
8. Lesions similar to OLP may be caused or aggravated by medicines, tooth filling materials or toothpastes
9. A biopsy is usually necessary to confirm the diagnosis
10. The aims of OLP treatment are to eliminate mucosal redness, ulceration, pain and sensitivity11. OLP is usually effectively treated with steroids, although responses vary and several treatments may need to be trialed
12. The teeth should be scaled and patients instructed in thorough oral hygiene
13. It may be necessary to have teeth, fillings and dentures smoothed and polished
14. OLP patients are at increased risk of oral cancer
15. Oral cancer develops in less than 5 per cent of OLP patients who do not use tobacco products
16. OLP patients should eliminate smoking and alcohol consumption
17. OLP patients should eat a nutritious diet including fresh fruit and vegetables
18. OLP patients are reviewed at regular intervals and lesions may occasionally require re-biopsy
19. OLP patients should attend whenever there is a change in the look or feel of lesions
20. On-line OLP patient information, including a web-based OLP chat group, is available currently at URL: 'http://www.tambcd.edu/lichen/'. Accessed January 2002.

Table 2. Oral lichen planus (OLP) patient information

Recent studies compared the efficacy of cyclosporine solution and triamcinolone acetonide 0.1% in orabase in oral lichen planus lesions, these studies concluded that cyclosporine was not effective when compared with triamcinolone acetonide 0.1% in orabase. Side-effects with cyclosporine include transient burning sensation, itching, swelling lips and petechial haemorrhages. These side effects cost of the drug and also questionable efficacy of cyclosporine limits its use in OLP **(**Yoke, 2006**)**

Tacrolimus

Tacrolimus is a potent immunosuppressive agent which can be used in topical form that can control symptoms of refractory erosive OLP. Studies showed that Tacrolimus ointment 0.1% is well tolerated and it is very effective in erosive OLP that did not respond to topical steroids. Most common adverse effect is local irritation due to burning sensation. Tacrolimus can be used as safe alternate to steroids when the lesions are resistant to the conventional treatment as there are less adverse effects with this drug. Topical tacrolimus helps to release the stress and improves the quality of life of patients suffering from OLP. Topical tacrolimus should be used for short period of about one month, as relapse of the lesions are seen within 6 to 12 mo of treatment cessation. The efficacy of usage of tacrolimus remains to be clearly established in large, well-designed clinical studies.

Dosage Administration Adult: Use Tacrolimus ointment 0.03% and 0.1% - Apply a thin layer of Tacrolimus ointment

0.03% or 0.1% to the affected skin areas twice daily and rub in gently and completely. Treatment should be continued for one week after clearing of signs and symptoms of atopic dermatitis. Tacrolimus ointment 0.03% and 0.1% should not be used with occlusive dressings.

Pediatric: Use Tacrolimus ointment 0.03% - Apply a thin layer of Tacrolimus ointment 0.03% to the affected skin areas twice daily and rub in gently and completely. Treatment should be continued for one week after clearing of signs and symptoms of atopic dermatitis.
Studies using 1% topical cream of pimecrolimus showed significant results in reducing ulceration and inflammation of lesion with better tolerance and relief from pain. Pimecrolimus has significant antiinflammatory activity with low systemic immunosuppressive Potential. Burning sensation is the common complaint experienced by the patients with the use of pimecrolimus (Gorouhi, 2007; Ruzicka Tet, 1999; Lener, 2001; Kaliakafsou, 2006; Marrision, 2007; Rozycki, 2002)

Retinoids

Various Topical retinoids such as 0.1% vitamin A, 0.05% tretinoin ointment, isotretinoin 0.1% gel, etretinate and fenretinide, with their immunomodulating properties are effective in OLP. Irritation, burning sensation are commonly observed with application of topical retinoids. Temporary reversal of white striae can be achieved with topical retinoids. Systemic Retinoids such as isotretinoin, temarotene, tretinoin have been used in cases of severe lichen planus with varied degree of success. The positive effects of retinoids should be weighed against their significant side effects (Hiren, 2015; Gangeshetty, 2012)

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.* supported its use, but Bagan *et al.* reported that they saw no improvement in the appearance of lesions from the use of griseofulvin (Hiren, 2015; Gangeshetty, 2015)

Phenytoin

It is used in refractory cases of OLP. Phenytoin is an anticonvulsant medication that has been shown to promote wound healing and modulate immunologic functions **(**Hiren, 2015; Gangeshetty, 2015)

Azathioprine

It is used in refractory cases of OLP. It is a potent immunosuppressive agent with well-known adverse effects like bone marrow suppression. Additionally long term use of mismedication may increase the risk of internal malignancies (Hiren, 2015; Gangeshetty, 2015).

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 hemolysis, nausea and headache (Hiren, 2015; Gangeshetty, 2015).

Levamisole

Levamisole is another effective immunomodulating agent that can restore the normal phagocytic activity of macrophages and neutrophills. Levamisole monotherapy is effective for treating OLP patients who are unable to use steroids and who had no response to convetional treatment. Topical rapamycin (sirolimus) impedes the response of interleukin-2 (IL-2), and thus prevents T and B cell activation. Rapamycin has both immunomodulatory and tumor inhibitory nature and hence blocks malignant transformation of OLP to some extent. In a study by Soria *et al*, 3-month application of rapamycin showed complete remission in 57% and partial remission in 30% of cases (Hiren, 2015; Gangeshetty, 2015).

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 (Hiren, 2015; Gangeshetty, 2015)

Antibiotics

2% Aureomycin mouth wash was found to be very effective to reduce severely painful erosive OLP in the study carried out by Tyldesley.32 Tetracycline (doxycycline) was also found to be useful in the treatment of gingival lesions in some reports but it has shown little benefit in others (Ronbeck, 1990; Walchner, 1999).

Other treatment modalities natural remedy

Lycopene

Lycopene is a fat‑soluble carotenoid. It has antioxidant activity, also acts by inhibition of cancer cell proliferation and interference with growth factor stimulation. It has shown to be effective in the management of oral leukoplakia and in chemoprevention of oral cancer. Supplementing with 8 mg/d of lycopene for 8 wk showed favorable results of reduced burning sensation and decreased signs and symptoms of OLP in patients, in a placebo controlled stud. Burning sensation was reduced by 84% and lowered oxidative stress in a placebo-controlled trial (Saawarn, 2011)

Curcumin

Curcuminoids are components of *Curcuma longa* (turmeric) known to have anti-inflammatory properties. Curcumin also been shown to have immune modulatory effect involving activation of host macrophages and natural killer cells and modulation of lymphocytes mediated function.Studies indicate that higher dosages of curcumin (up to 6,000 mg/ day) helped a significant number of OLP patients control their symptoms. Minimal side effects like diarrhea and gastrointestinal discomfort may occur, which are usually dose related. Whereas smaller doses of curcumin (< 2,000 mg/day) have failed to provide relief (Maryam Amirchaghmaghi, 2016; Chainani *et al*., 2012; Vibha Singh**,** 2013)

Green Tea

Green tea (epigallocatechin-3-gallate) is known to have possessing anti-inflammatory and chemopreventive properties. It is known to reduce the incidence of OLP by regulating the factors which are involved in the etiopathogenesis of the disease. Green tea is known to inhibit T-cell activation, migration, proliferation, antigen presentation and control other inflammatory mediators (Zhang, 2012).

Honey and Bee Propolis

Honey is a potential alternative therapy, due to its antioxidant and anti-inflammatory properties, as well as its ability to inhibit the release of TNF-α, IL-1β, and IL-6, free radicals and nitric oxide.Honey is also rich in polyphenols, which are strong anti-inflammatory substances. Honey is also a strong anti-bacterial substance, which promotes wound healing processes, as well as ulcerative lesions in OLP. In a study done on 18 cases of oral lichen planus using honey topical application all patients showed significant relief in pain and inflammatory changes (Sally, 2013; Buratti *et al*., 2007)

Aloe vera gel

Aloe vera (Aloe barbadensis Miller) is cactus like plant and it is a member of the Liliaceae family. Aloe vera has various biological properties as Wound-Healing Effects, Anti-Inflammatory Effects, Antibacterial Property, Antifungal Property, Immunomodulating Effects, Antioxidant Property, Antitumor Effect. There are few studies conducted using aloe vera gel or aloe vera in a aqueous suspension and it is also compared with the triamcinolone gel which showed beneficial effects in relieving symptoms of OLP. In-controlled trial of 54 patients into two groups was done by Choonhakarn *et al*.40 where pts were given aloe vera gel or placebo for 8 weeks. 22 patients treated with aloe vera had a good response after 8 weeks of treatment, 2 pts treated with aloe vera had a complete clinical remission. Burning pain completely disappeared in 9 patients treated with aloe vera **(**Arbaz Sajjad, 2014; Mansourian, 2011; Salazar-Sánchez, 2010; Choonhakarn, 2008**).** The patient's treatment involved drinking 2.0 ounces of stabilized Aloe vera juice daily for 3 months, topical application using Aloe vera lip balm and Aloe cream for itching hands. The oral lesions cleared up within 4 weeks, although the systemic lesions took longer.

MISCELLANEOUS

Ignatia

Ignatia, a homeopathic medicine, is an all-natural and gentle alternative. In a single blind randomized control clinical trial, 30 consecutive OLP patients were administered Ignatia 30º C (a measure of homeopathic potency) or placebo for 4 months. Patients treated with Ignatia showed decrease in pain and in the size of the mean lesions in comparison to placebo group (Mousavi, 2009)

Anthocyanin

Anthocyanins are polyphenolic groups which block the spread of free radicals and are considered the main antioxidants of the plant kingdom. The extracts of grape seeds and grape skins contain anthocyanins. These are also present in other fruits, vegetables, chocolate, tea. Rivarola de Gutierrez *et al* conducted a prospective, non-randomized study in 52 patients. Anthocyanins were administered in 100 mg/doses diluted in 5 mL of water, mouth rinses, during 5 min and spit, three times a day in 26 patients and control group received CP-NN cream (100 g of commercial preparation containing: 17-clobetasol propionate (micronized) 0.050g, Neomycin (as sulfate) 0.350 g; Nystatin (micronized)100.000 U/g. This was applied three times daily locally on lesions. There is improvement in the pain relief in patients with anthocyanins when compared with patients receiving CP-NN treatment (Rivarola de Gutierrez, 2014).

BCG polysaccharide nucleic acid

Bacillus Calmette-Guerin polysaccharide nucleic acid (BCG-PSN) is the third-generation BCG extract with various immunologic active materials including polysaccharide and nucleic acid. It has the ability to regulate the Th1/Th2 cytokine secretion in peripheral blood mononuclear cells (PBMC) of the OLP patients.In a study which compared the effectiveness of intralesional 0.5 mL BCG-PSN injection every alternative day with 10mg triamcinolone injection every week for about 2 wk showed equal effectiveness of both agents for erosive OLP (Hiren, 2015; Gangeshetty, 2015)

Stem cell therapy

Stem cells are master cells that have specialized capability for self‑renewal, potency and capability to differentiate to many cell types. Among oral mucosal lesions, stem cell research is presently focused on the treatment of certain lesions only like oral lichen planus. A new therapy employing T‑cell immune modulation using MSCs have been proposed to treat OLP. MSCs can be easily isolated and expanded in vitro and in vivo and can be utilized via systemic infusion or local application to the lesion site.The immunomodulatory and antiinflammatory properties of stem cells can be utilized in the treatment of this condition (Suma *et al*., 2015)

Hylauronic acid

Hyaluronic acid (HA) is a linear polymer of glucuronic acid, N-acetylglucosamine disaccharide which helps in tissue healing. HA in the form of 0.2% gel showed transient improvement in decreasing the soreness associated with OLP in a placebo controlled double blind study (Nolan *et al*., 2009)

Low dose low molecular weight heparin

Inhibits T-lymphocyte by heparinase activity which is crucial in T-cell migration to target tissues.A study done on 48pts-24pts enoxaparin 5mg/week and 24pts-0.5mg/kg prednisone orally daily for 8 weeks showed 72% improvement in enoxheparin.In prednisone group-69.6% showed complete remission Considering the less side effects low dose low molecular weight heparin can be considered as an alternative treatment for oral lichen planus (Fariba Iraji, 2013)

NON-SURGICAL MANAGEMENT OF ORAL LICHEN PLANUS

PUVA Phototherapy

One of the more common treatments for cutaneous lichen planus as well as other dermatoses involves photochemotherapy with psoralens and long wave ultraviolet-A (PUVA). Jansen *et al*. (1987) modified a unit intended for light cured dental composite fillings to administer UV-A in oral cavity. Patients ingested psoralens, a photosensitizer prior to irradiation at intervals of 2 to 3 days. All eight patients with

refractory and symptomatic atrophic and erosive oral lichen planus responded to therapy. At a 6-month follow up, five out of eight patients had complete or marked resolutions of their disease.Patients exposed to PUVA are known to have increased risk of developing squamous cell carcinomas (Forman *et al*, 1989). The efficacy of mouth PUVA and UVA in treatment of OLP supports the role of immune system in its pathogenesis, but this treatment should be considered experimental (Aghahosseini, 2006).

Photodynamic therapy (PDT)

Photodynamic therapy (PDT) uses a photosensitizing compound like methylene blue which is activated at a specific wavelength of laser light. It is known to destroy the targeted cell via strong oxidizers, leading to membrane lysis, cellular damage, and protein inactivation. PDT has shown positive results in management of head and neck tumors. PDT have immunomodulatory properties which may induce apoptosis in the hyperproliferating inflammatory cells present in diseases like psoriasis and oral lichen planus, there by reversing the hyperproliferation and inflammation of oral lichen planus (Aghahosseini Fet, 2006)

SURGERY

Conventional Surgical treatment can be used with more ease in the cases where there is a plaque like lesions, but in cases of erosive and atrophic it is not recommended. Apart from Conventional Surgical treatment carbon dioxide laser and cryosurgery also have been recommended.

Cryosurgery & Lasers

Cryosurgery and carbon dioxide laser ablation have been suggested for the surgical treatment of oral lichen planus. Lasers have been used in patients whose condition is unresponsive to topical corticosteroids. CO2 laser evaporation can cause long-term remission of symptoms, and may be the treatment of choice in patients suffering from painful OLP. Diode laser treatment is effective for plaque like-lichen planus lesions.It is an alternative to scalpel surgery where re-epithelization occurs by 4 to 6 weeks. The post-surgical period is minimal pain and healing occurs without contractions. However, excision should not be a primary method of treatment as it is anti-inflammatory condition that can recur. In addition, surgical management is not suitable for the erosive and atrophic types because the surface epithelium is eroded. This modality satisfied the patients who suffered psychologically from the long treatment by corticosteroids and the fear and suffering from their side effects (Mona Soliman, 2005)

Patient education in oral lichen planus: (Table - 2)

The importance of patient education in OLP has been reported.39 Many OLP patients are concerned about the possibilities of malignancy and contagion and patients are frustrated by the lack of available patient education. On-line OLP patient information is available currently, including a web based OLP chat group.40 Patient education may improve the outcomes of OLP therapy and further reduce the risk of oral cancer in OLP patients.

Pictorial representation of treatment of oral lichen planus shown in (Table-1)

Conclusion

Lichen planus is very common mucocutaneous autoimmune precancerous condition which is recurrent in nature with higher incidence of the oral mucosa involvement. Although steroids are believed to be the mainstay of the treatment for the OLP, many other modalities have been found to be beneficial. But the evidences for the efficacy about all these treatment modalities are weak therefore more studies and researches are mandatory.

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