Treatment Strategies of Oral Lichen Planus

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Abstract: Lichen planus is a T-lymphocyte mediated chronic inflammatory mucosal disease. It is characterized by intensely itchy polygonal papules with a violaceous hue involving the skin and, less commonly, the mucosae, hair and nails. The reticular pattern is the most frequent and consists of a network of overlapping white threads, referred to as Wickham's striae, which are rarely symptomatic. However, the ulcerative and erosive patterns cause varying degrees of symptoms ranging from a burning sensation to severe pain and difficulty in eating, significantly impairing the quality of life. The usual treatment is based on topical corticosteroids (TCSs) applied to the painful areas while systemic treatments are reserved for more severe cases. Other treatments have also been proposed, such as topical calcineurin inhibitors (TCIs), nutraceuticals, retinoids, systemic immunosuppressants, immunostimulants and biological agents like TNF-a inhibitors and BCG-PSN. In addition to these pharmacological treatments, ozone therapy, cryotherapy with nitrous oxide gas (NOG), photodynamic therapy (PDT), and low-level laser therapy (LLLT), also called photobiomodulation (PBM), have also been proposed for patients with symptomatic OLP. With respect to the effectiveness of all the above-mentioned treatments, no conclusive results have been achieved so far. This article reviews the standard operating protocol of Oral lichen planus as well as the latest treatment modalities for the same.

Keywords: oral lichen planus, burning sensation, white patch, etiology, treatment

Introduction:

Lichen planus is a T-lymphocyte mediated chronic inflammatory mucosal disease[1]. Davidson has described Lichen planus as a rash characterized by intensely itchy polygonal papules with a violaceous hue involving the skin and, less commonly, the mucosae, hair and nails. It is a condition that can affect the oral cavity, skin, nails, hair, eyes, esophagus, and other mucous membranes[2]. It was first described in 1869 by the British physician, Wilson Erasmus[3].

The term lichen refers to primitive plants composed of symbiotic algae and fungi while the term 'planus' means 'flat' in Latin. Even though the term lichen planus suggests a flat fungal condition, current evidence indicates that this is an immunologically mediated mucocutaneous disorder[4].

It is a relatively common dermatological disorder with a prevalence of 0.9% to 1.2% in the general population while that of oral lichen planus is reported to be in between 0.1% and 2.2%[5]

Etiology and Pathogenesis:

In order to understand and formulate an effective treatment plan for lichen planus, it is necessary to understand how it starts in the body and hence, its etiology has been discussed below:

1. Cell- mediated immune response: This is associated with lymphocyte-epidermal interactions resulting in degeneration of the basal cell layer. It may be caused by various mononuclear cells, like Langerhan cells, macrophages, predominantly T lymphocytes, lymphoblast cells, B lymphocytes and mast cells. In a genetically predisposed individual, haptens, drugs, dental materials or conventional antigens or super-antigens of microbial origin can induce such a cell-mediated immune response resulting in sub - epithelial T cell infiltration of the site in oral mucosa[4].

2. Autoimmunity: The activated T- lymphocytes also secrete gamma interferons, which induce keratinocytes to produce human leukocyte antigen-donor and recipient (HLA-DR) and increase their rate of differentiation with formation of a thickened surface. Lymphocytes are then attracted to HLA-DR, which can cause incorrect antigen information to be passed on the lymphocytes. These self antigens may be recognized as foreign bodies, leading to destruction of basal cells, thus leading to an autoimmune response[4].
3. Immunodeficiency: Patients with LP may show decreased serum levels of IgG, IgA or IgM. However the role of immunodeficiency is questionable as some patients have shown normal concentrations of IgA and IgM[4].
4. Genetic factors: Lichen planus has been reported in twins and families. However these reports have been accompanied with an environmental cause or they may be related to infection rather than genetics[4].
5. Infections: There are questionable reports of a bacterial etiology in lichen planus. Spirochetes and rod-like bodies resembling bacteria have also been detected[4].
6. Drugs and chemicals : Patients with lichen planus have a predisposition to lichenoid reactions that can be triggered by drugs and chemicals. If the drug is withdrawn later the antigenic stimulus is reduced and the clinical severity of the lichenoid reaction also gets reduced[4].
7. Psychogenic factors: LP is also related with stress and a neurogenic base has been suggested in its etiology. It is commonly observed in nervous and highly stressed people. Exacerbation is associated with emotional upset over work and some form of mental strain[4].
8. Habit : Chewing tobacco and Betel quid have increased prevalence of oral lichen planus. Smoking may play a role in initiating OLP of the plague type[4]

Types based on clinical features:

OLP may contain both red and white elements. This aspect, along with the different textures seen , form the basis for the clinical classification of this disorder. Thus, Lichen Planus is often found in the oral cavity with different lesion patterns, including

- Reticular
- Papular
- Plaque-like
- Bullous
- Erythematous
- Ulcerative[6]

The most involved sites are the buccal mucosa, borders, and dorsum of the tongue and gingiva. OLP shows a bilateral and symmetric distribution. The hard and soft palate, lips, and floor of the mouth are rarely affected[7].

The **reticular** pattern is the most frequent and consists of a network of overlapping white thread-like lesions, referred to as Wickham's striae, which are rarely symptomatic. The **ulcerative** (erosive) and **atrophic** patterns can affect any mucosal surface, including the buccal mucosa, tongue, and gums.They can cause varying degrees of symptoms ranging from a burning sensation to severe pain and difficulty in eating, significantly impairing the quality of life[7].

All in all, OLP is a chronic inflammatory disease that is very difficult to completely cure. Patients typically suffer from a burning sensation in the oral mucosa along with pain, and discomfort. Pain rating scales, e.g. numeric rating scale (NRS) and visual analog scale (VAS), are widely accepted and are more useful for assessing OLP symptoms[8].

Pathophysiology:

There are controversies about the exact etiology and pathogenesis of OLP. An important role in the pathogenesis of OLP is attributed to an immune dysregulation that involves cell-mediated immunity and causes damage to epithelial keratinocytes. The inflammatory infiltrate in OLP mainly consists of T cells and macrophages[9].

Peculiar findings of the histopathology of oral lichen planus are the liquefaction of the basal cells with the formation of Civatte bodies (apoptotic keratinocytes) and the presence of a band-like lymphocytic infiltrate at the interface between epithelium and lamina propria[9].

Although OLP manifestations may be clear on the oral mucosa, the clinical diagnosis, as with all the

lesions in oral pathology, needs to be confirmed by histopathological examination[9].

The biopsy can also allow excluding the presence of dysplasia, which is a fundamental parameter for the prognosis and treatment of the patient[9].

Considering the autoimmune nature of the disorder, OLP is recalcitrant, and its management is oriented toward symptom alleviation. Corticosteroids, in topical and systemic forms, are the gold standard.[10] Studies have shown the most effective treatment modality for symptomatic OLP is the use of topical corticosteroids. Typical protocols mandate application of topical corticosteroids 2–3 times per day for 1–2 months, with subsequent administration as needed. This frequency and duration aim to achieve effective symptom relief while minimizing the risk of adverse effects, such as mucosal thinning and secondary candidiasis. However, some patients can exhibit inadequate response or develop resistance to topical corticosteroids[11].

Therefore, although remarkable in symptom control, corticosteroids have substantial adverse effects curtailing their long-term use[10]

Standard Operating Protocol for Oral Lichen Planus

The following flowchart describes how a clinician can diagnose lichen planus, how to differentiate between lichenoid reactions and oral lichen planus and it provides a step-by-step guide on how to treat oral lichen planus, including recalcitrant cases.

Latest Treatment modalities in Oral Lichen Planus:

1. Laser photobiomodulation (PBM)[9] :

- A single session of laser PBM may provide some advantages in the reduction of pain for symptomatic OLP.
- Laser PBM, formerly defined as low level laser therapy (LLLT), is a medical treatment that uses a coherent beam of light that interacts with specific substances in the tissues, called chromophores, to obtain effects in terms of analgesia, anti inflammatory, and biostimulation effect.
- A 980-nm diode laser and a fat top handpiece with a 1-cm^2 spot area are employed to perform a single session of laser PBM.
- Laser energy is delivered with a spot-technique in non-contact mode, with a variable number of spots to cover all the size of the lesion and the area over the border for 5 mm.
- VAS pain scores can be assessed before and after the laser PBM, the day after, and on the 7th and 30th days after the treatment.[9]

2. Cepharanthine with topical corticosteroids[11] :

- Cepharanthine, an alkaloid preparation, is a herbal extract from Stephania cepharantha Hayata.
- CEP has been reported in Japanese case studies since the 1980s for its antioxidant and anti-inflammatory properties.
- The combination of CEP with topical corticosteroids may enhance their effects, providing more rapid and pronounced relief for symptomatic OLP.
- Dosage - 30mg/day, as per proposed treatment guidelines for OLP based on a nationwide survey in Japan.
- Studies have shown a change in pain intensity on a visual analogue scale (VAS) when drinking room temperature water, as well as reduction in target lesion size.[11]

3.Topical purslane[10]:

- Purslane, a magical herb with a plethora of rich nutrients, easy availability, and a lack of side effects, is beneficial and can be a safer alternative drug in OLP treatment.
- Fresh leaves from Portulaca oleracea are collected and washed with running water, shade dried, and powdered to granules.
- It is processed to obtain the ethanolic extract, which is formulated with the ora-base gel at 5% and 10% concentrations.
- For antimicrobial properties, a 10% concentration of purslane gel shows complete inhibition of both gram positive and gram negative bacteria.

- Te 10% formulation shows the highest radical scavenging activity of~25% - 78% and the 5% formulation showed~24% - 44%. The formulations do not show cytotoxicity against the human monocyte cell line (THP-1).
- The gel is applied three times a day on the site of the lesion for about 20 minutes. The patient is advised not to eat or drink for at least 20 minutes after the application.
- Studies have shown both 5% and 10% topical purslane gel showed significant efficacy compared to the gold standard of corticosteroid treatment, making it a reliable treatment option.[10]

4. Platelet Concentrate (PC) injection therapy[12]:

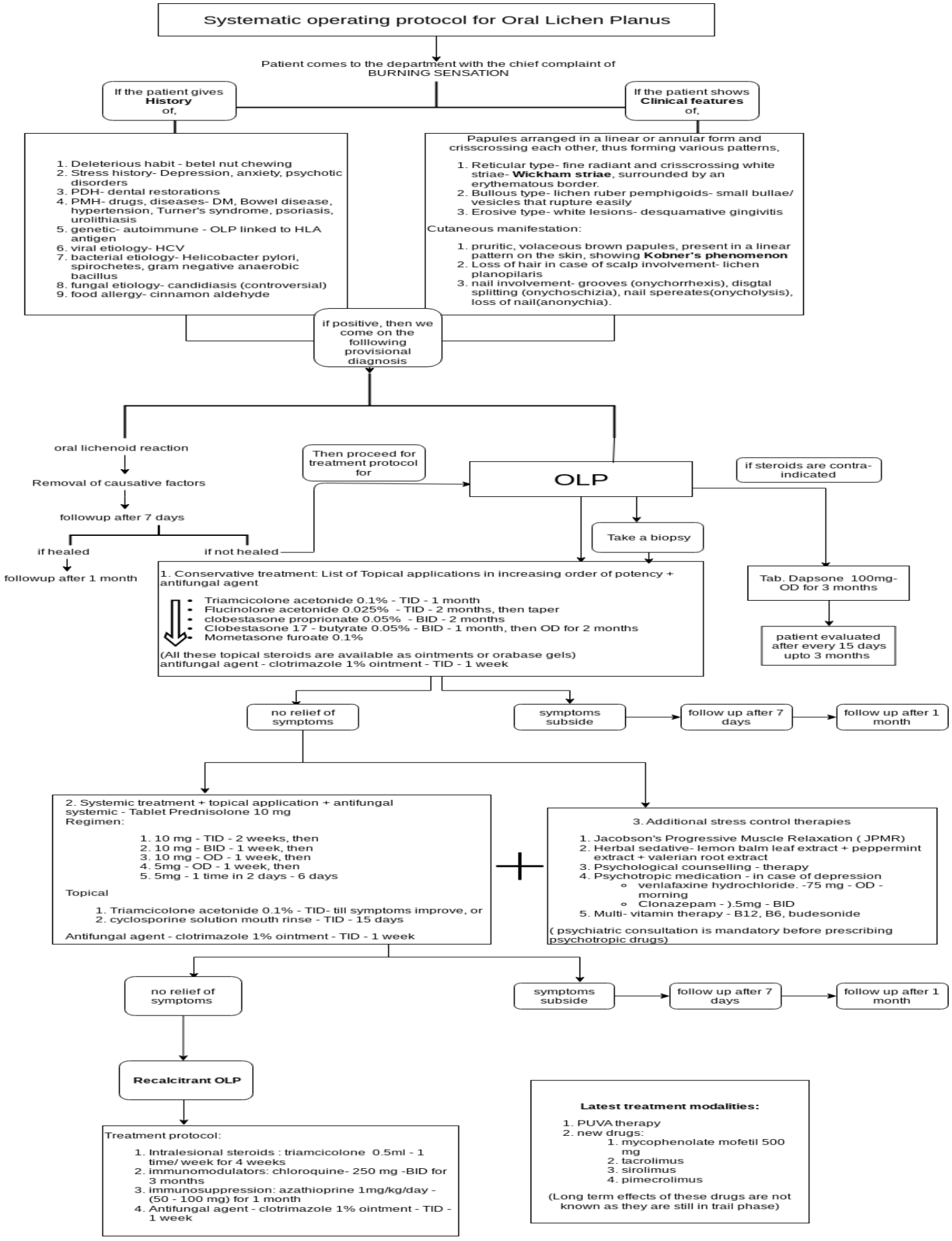
- Platelet Concentrate (PC) injection has shown potential as a local therapy for oral lichen planus.
- Platelet concentrates (PCs) are autogenous substances obtained from blood, which contain supraphysiological levels of platelets and growth factors(GFs).
- GFs can induce tissue repair and regeneration, while avoiding any potential immunological or allergic reactions.
- PCs are obtained through blood centrifugation, resulting in an optimal concentration of GFs and cytokines that exert a beneficial effect on inflammation, angiogenesis, stem cell migration and proliferation, which in turn enhances the potential for repair and regeneration.
- Thus, Locally injected antigen-presenting cells, such as platelet rich plasma or injectable platelet-rich fibrin, have demonstrated effectiveness in managing oral lichen planus. This suggests that they are a promising alternative to steroid therapy for OLP patients[12].

5. Coenzyme Q10[13]:

- Co enzyme Q10 is a lipid-soluble endogenous antioxidant compound
- It has the ability to scavenge free radicals as well as augments the function of other endogenous antioxidants. It enhances other antioxidant enzymes, and also has an anti-inflammatory role through its suppression of gene expression of NFκB1 and the overproduction of proinflammatory cytokines such as TNF-α and interleukin-6.
- Furthermore, it promotes the expression of anti-inflammatory cytokines such as IL-10, thus promoting tissue regeneration and wound healing.
- The topical use of CoQ10 mucoadhesive tablets significantly reduced both pain sensation and clinical signs with maximum clinical improvement at the fourth week and no significant differences when compared with the results of topical corticosteroid.
- The muco-adhesive nature of these tablets has many advantages including intimate contact with the target mucous membrane, sustained drug release, increased drug absorption, and bioavailability, avoidance of enzymatic degradation in the GIT, and decreased adverse drug effects[13].

6. Platelet-Rich Plasma Therapy[14]:

- platelet-rich plasma (PRP) refers to human platelet concentrates derived from a patient's blood (autologous), containing 3- to 5-times more platelets than the normal concentration found in whole blood.
- It is an autologous product, thus reducing the risk of cross-contamination, disease dissemination, or immune reactions.
- PRP contains bioactive molecules, such as growth factors, cytokines, and cell adhesion molecules.
- It acts by platelet degranulation, thus permitting the release of growth factors, amending the inflammatory reaction, and promoting cell proliferation and differentiation within the target tissue.
- PRP use has expanded considerably, encompassing many disciplines of medicine, including sports medicine, orthopedics, dermatology, cosmetic medicine, dentistry, maxillofacial surgery, and wound healing, and its therapeutic effects have also been demonstrated in various autoimmune diseases[14].


Systematic operating protocol for Oral Lichen Planus
Patient comes to the department with the chief complaint of BURNING SENSATION
If the patient gives History of,
If the patient shows Clinical features of,
1. Deleterious habit - betel nut chewing
2. Stress history- Depression, anxiety, psychotic disorders
3. PDH- dental restorations
4. PMH- drugs, diseases- DM, Bowel disease, hypertension, Turner's syndrome, psoriasis, urolithiasis
5. genetic- autoimmune - OLP linked to HLA antigen
6. viral etiology- HCV
7. bacterial etiology- Helicobacter pylori, spirochetes, gram negative anaerobic bacillus
8. fungal etiology- candidiasis (controversial)
9. food allergy- cinnamon aldehyde
Papules arranged in a linear or annular form and crisscrossing each other, thus forming various patterns,
1. Reticular type- fine radiant and crisscrossing white striae- Wickham striae, surrounded by an erythematous border.
2. Bullous type- lichen ruber pemphigoids- small bullae/ vesicles that rupture easily
3. Erosive type- white lesions- desquamative gingivitis
Cutaneous manifestation:
1. pruritic, volaceous brown papules, present in a linear pattern on the skin, showing Kobner's phenomenon
2. Loss of hair in case of scalp involvement- lichen planopilaris
3. nail involvement- grooves (onychorrhexis), disgtal splitting (onychoschizia), nail spereates(onycholysis), loss of nail(anonychia).
if positive, then we come on the folllowing provisional diagnosis
oral lichenoid reaction
Removal of causative factors
followup after 7 days
if healed
followup after 1 month
if not healed
Then proceed for treatment protocol for
OLP
if steroids are contra-indicated
Take a biopsy
1. Conservative treatment: List of Topical applications in increasing order of potency + antifungal agent
Triamcicolone acetonide 0.1% - TID - 1 month
Flucinolone acetonide 0.025% - TID - 2 months, then taper
clobestasone proprionate 0.05% - BID - 2 months
Clobestasone 17 - butyrate 0.05% - BID - 1 month, then OD for 2 months
Mometasone furoate 0.1%
(All these topical steroids are available as ointments or orabase gels)
antifungal agent - clotrimazole 1% ointment - TID - 1 week
Tab. Dapsone 100mg- OD for 3 months
patient evaluated after every 15 days upto 3 months
no relief of symptoms
symptoms subside
follow up after 7 days
follow up after 1 month
2. Systemic treatment + topical application + antifungal
systemic - Tablet Prednisolone 10 mg
Regimen:
1. 10 mg - TID - 2 weeks, then
2. 10 mg - BID - 1 week, then
3. 10 mg - OD - 1 week, then
4. 5mg - OD - 1 week, then
5. 5mg - 1 time in 2 days - 6 days
Topical
1. Triamcicolone acetonide 0.1% - TID- till symptoms improve, or
2. cyclosporine solution mouth rinse - TID - 15 days
Antifungal agent - clotrimazole 1% ointment - TID - 1 week
3. Additional stress control therapies
1. Jacobson's Progressive Muscle Relaxation (JPMR)
2. Herbal sedative- lemon balm leaf extract + peppermint extract + valerian root extract
3. Psychological counselling - therapy
4. Psychotropic medication - in case of depression
venlafaxine hydrochloride. -75 mg - OD - morning
Clonazepam -).5mg - BID
5. Multi- vitamin therapy - B12, B6, budesonide
(psychiatric consultation is mandatory before prescribing psychotropic drugs)
no relief of symptoms
symptoms subside
follow up after 7 days
follow up after 1 month
Recalcitrant OLP
Treatment protocol:
1. Intralesional steroids : triamcicolone 0.5ml - 1 time/ week for 4 weeks
2. immunomodulators: chloroquine- 250 mg -BID for 3 months
3. immunosuppression: azathioprine 1mg/kg/day - (50 - 100 mg) for 1 month
4. Antifungal agent - clotrimazole 1% ointment - TID - 1 week
Latest treatment modalities:
1. PUVA therapy
2. new drugs:
1. mycophenolate mofetil 500 mg
2. tacrolimus
3. sirolimus
4. pimecrolimus
(Long term effects of these drugs are not known as they are still in trail phase)

7. Muco-adhesive tacrolimus patch on caspase-3 induced apoptosis[16]:

- Tacrolimus is a powerful macrolide calcineurin inhibitor that has low adverse effects which lead to a rapid response in the control of signs and symptoms in comparison to that of corticosteroids in Oral Lichen Planus[15]
- Calcineurin inhibitors are immunomodulators that bind to intracytoplasmic proteins in T-lymphocytes (cyclosporine to cyclophilin; tacrolimus and pimecrolimus to FK506-binding protein). This inhibits calcineurin, leading to suppression of transcription and production of variable cytokines. Thus, this mechanism suggests a possible role of these agents in management of variable immune-mediated lesions.
- Clinical trials with calcineurin inhibitors in the treatment of symptomatic OLP have yielded promising results. Furthermore, recent systematic reviews and meta-analysis have concluded that topical tacrolimus is a safe and effective alternative to topical corticosteroids for OLP treatment[16].

Conclusion:

OLP is a debilitating auto-immune disorder that requires long-term, if not life-long treatment. Many studies have been conducted for a better treatment outcome with fewer side effects, however further studies are necessary which may lead to remission, or complete resolution of the disease. A holistic medical approach, including pharmacological, psychological and behavioral therapy; would render an effective method of healing OLP.

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