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Management of oral *Lichen planus*: a review of the current and novel pharmacological therapies on the go

Yesoda Aniyan K[a*], Krithika C L[b], Anuradha G[c], Ashwin Chandraveni[d]

a: Senior lecturer, Department of Oral Medicine and Radiology, SRM Dental College, Ramapuram, India.

b: Reader, Department of Oral Medicine and Radiology, SRM Dental College, Ramapuram, India.

c: Professor and HOD, Department of Oral Medicine and Radiology, SRM Dental College, Ramapuram, India.

d: Senior Lecturer, Department of Oral Medicine and Radiology, SRM Dental College, Ramapuram, India.

Abstract

The origin and etiology of oral lichen planus (OLP), a chronic inflammatory, T-cell-mediated, autoimmune illness of the oral mucosa, are unknown. There are many difficulties in treating OLP medically, the chief of which is the recalcitrant nature and the pain associated with the disorder. Assessing the effectiveness of pharmaceutical interventions utilized in the treatment of OLP was the goal. Cochrane Oral Health Group Trials Register, Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, and EMBASE are the databases that cover the period from January 2000 to August 2020. This systematic review took into account all Randomized Controlled Trials (RCTs) for the pharmaceutical management of OLP that compared active treatment with placebo or between active therapies. Participants who were more than 18 years old, of any gender or race, and who had histology showing OLP were included. All forms of interventions, such as topical pharmaceuticals or systemic medications with varying dosage, duration, and frequency of administration, have been taken into consideration. The review authors read the chosen studies, then using a specially created data extraction form, they combined the data from all of the trials. This review on the pharmaceutical therapy of OLP included 17 RCTs altogether. It was unable to determine whether management protocol was better. A bigger scale with numerous populations sets of different ethnicity, age, and gender are required for future studies on the management of OLP utilizing pharmaceutical compounds. Additionally, the specifications require a stricter consistency for the inspection group.

Keywords: Oral lichen planus, pharmacological therapy, steroids, calcineurin inhibitors, mycophenolate mofetil, hyaluronic acid.

Full length article **Corresponding Author,* e-mail: *yesoda.aniyan@gmail.com*

1. Introduction

The mouth can be a guard and security alarm as well as a reflection of health or disease. Due to their same embryological origin—both the oral mucosa and the ectoderm are invaginated—both are implicated in illnesses primarily affecting the skin.[1] The mucous membrane of the oral cavity is affected by the chronic inflammatory condition known as oral lichen planus. It is portrayed as a T-cell mediated autoimmune condition wherein cytotoxic CD8+ T cells cause the basal cells of the oral epithelium to undergo apoptosis. Clinically, oral lichen planus (OLP) can manifest in reticular, papular, plaque-like, atrophic, erosive, and bullous forms, the latter of which is typically symptomatic and requires treatment. There is currently no single effective treatment for this illness. Due to the recalcitrant nature of this disease entity, there is currently no one effective treatment. Additionally, the pain and burning sensation associated impedes the quality of life in patients. There is a broad range of therapeutic options to mitigate the symptoms, from topical corticosteroids to laser ablation.[2] This review compares the effectiveness of numerous therapies available for the care of this condition, ranging from the most conventional to the most cutting-edge modalities, in randomized controlled trials.[3]

2. Materials and methods

This systematic review was conducted in accordance with the PRISMA guidelines and the objectives were met with the PICOS guidelines.

2.1. Eligibility Criteria:

1. Studies with randomized controlled trials and crossover trials which employed different treatment strategies for management of OLP were included.
2. Adult patients above 18 years of age presenting with clinically and histopathological diagnosed OLP
3. Non-randomized, non-comparative, open label and retrospective trials were excluded.
4. Case reports and series were excluded.
5. Studies with patients presenting with OLP as a part of generalized lichen planus were excluded.
6. The search was limited to humans and only studies in English language were included.

Search strategy: Literature exploration was carried out from electronic database of Cochrane Oral Health Group Trials Register, Cochrane Central Register of Controlled Trials (CENTRAL) and MEDLINE for the timeline, from 1st Jan 2005 to 1st August 2020. The search strategy involved the corresponding search words: MeSH terms in all subheadings: "Oral lichen planus", "lichen planus", "pharmacological" "therapy" OR "treatment" OR "therapeutics" OR "management". Similar search strategy was employed in Cochrane Database. Manual search was performed after perusing the references of the relevant studies. Study selection was done independently in the subsequent stages:

(a) screening of titles and abstracts meeting the inclusion criteria and
(b) screening of the full article identified as relevant.
The RCTs, which compared an active treatment with placebo or active treatment with another active treatment and trials on comparison between 2 different doses or formulation of same treatment, were included.

After thorough scrutiny of the articles, descriptive summary analysis was recorded. The segregated articles were classified for the drug of choice, its mode of delivery, dose, regimen, duration of therapy, length of follow up and records of relapse. The primary outcome was assessment of pain via Visual Analog Scale (VAS) and secondary outcome included clinical resolution of erythema, ulceration, erosion and reticulation. Adverse effects and side effects were also considered as secondary outcome.

3. Results and Discussions

Study selection after the initial search and removing duplication, 321 papers were found. When the titles and abstracts were read and full text screening done, 17 papers were selected for review.[Table 1]

3.1. Steroids

Steroids with high potencies are used as the first line of treatment for OLP. In 2005, consensus recommendations were released that included them as the first-line of treatment.[4] Both topical and systemic delivery techniques are employed. Uses for the topical preparations include ora-base, ointments, creams, and mouthwashes. However, mouthwashes are thought to be more functional than other types since they have better access to the back of the mouth and have extensible surfaces. One of the main drawbacks of topical corticosteroids is that they only adhere to the mucosa for a short period of time. Systemic steroids are advised in acute exacerbated and multiple or widespread lesions. Also, in the event of non-response to topical steroids, their use is recommended. It is to be tailored to a dose of 0.5-1mg/kg weight of the patient and must be rapidly tapered once the efficacy is achieved.[6] The preferred regimen is 4 times daily, after meals and before sleep.[5]

The steroid activity has a two-pronged method of action. Steroids can considerably lower the amount of HLA DR/T6 in Langerhans cells per mm2 desquamated epidermal cells, even when applied topically. Skin and mucosal cells share the same characteristics in this regard. Corticosteroids also have the ability to lower T lymphocyte activity, which is reliant on Langerhans cells. However, steroid use promotes telangiectasia and localized atrophy. Superadded infections like candidiasis may result from it. These medications alter immune system gene transcription; therefore, their mode of action is not limited to the pathogenesis of lichen planus. [5] Intralesional betamethasone was found to be better for pain relief and resolution of lesion with minimal recurrences and intralesional therapy was found to be more effective than mouthwash due to less adverse effects (Liu et al, 2013). In a similar vein, intralesional triamcinolone acetonide (TA) was compared to a mouth rinse of TA. The efficacy in terms of VAS, OHIP-14 and objective scoring was comparable in both methods. However, in terms of adverse effects, intralesional methods had a notably positive outcome. Also, the first week assessment, ascertained an improved symptom in intralesional group. (Lee at al,2013). In another study compared, topically applied clobetasol propionate 0.05% to a placebo. The improvement in symptoms was noted in the entire experimental group post 2 months of therapy. Significantly, no adverse effects were recorded.[6]
From these studies, we alluded that topical steroid is safe, efficacious and cost- effective treatment as first line therapy for OLP. It is important to bear in mind that topical steroid should be used in a form that retains over the lesion for a sufficient amount of time in smallest possible concentration with minimal side effects. The time of contact of medication with the lesion is a priority as opposed to the concentration of formulation.

3.2. Calcineurin inhibitors

Topical calcineurin inhibitors (TCI) are an established second-line therapy, mainly for atrophic and erosive OLP. Tacrolimus (TAC) application on mucosal lesions for a period of 3 weeks has led to blood level elevation, but within the prescribed norms and without any significant adverse events. It is available in formulations of 0.1% for oral use as ointment, rinse, powder and cream. [7]
The mechanism of action of calcineurin inhibitors is based on the suppression of pro-inflammatory cytokine synthesis. Calcineurin inhibitors inhibit the transcription and production of many pro-inflammatory cytokines by bonding to cytoplasmic proteins of T cell.[8]

Table 1: Aggregate of the selected articles

Medical intervention	Author and year	Sample	Outcome	Time	Follow	Relapse	Adverse effects
Steroids	Liu et al 2013	n=29-1.4mg Intralesional betamethasone n=30-8mg intralesional triamcinolone acetonide R=Once a week for 2 weeks	1.Visual Analogue Scale (VAS) 2.Physician Global Assessment, 3.Ordinal & Nominal scales of self-assessment. 4.Oral Mucositis Assessment Scale.	2	12	E=45% C=14	Nil
	Lee et al. 2013	n=20- TA 0.4% mouth rinse R=Thrice daily n=20- intralesional injection of 0.5 mL TA (0.40mg/ml)	1.VAS 2.OHIP-14	6 weeks	52	E=20% C=40%	E=44% C=5%
	Arduino et al,2018	n=16-0.05%clobetasol propionate n=16-4% hydroxyethyl cellulose R=Twice daily	1. VAS 2. Thongprasom et al criteria scale	8	24	E=37% P=50%	
Calcineurin inhibitors	Vohra et al,2016	n=15- 1 % Pimecrolimus cream n=15-0.1% Tacrolimus Ointment R=Twice daily	VAS Thongprasom et al criteria scale	8	12	Nil	E=6% C=40%
	Passeronet al.2007	n=6-1% Pimecrolimus cream n=6-Placebo cream R=twice a day	VAS	4			
	Swift et al.2005	n=10-1%Pimecrolimus cream n=10-Placebo cream	VAS Lesion size	4	Biweekly		Nil
	Ezzat et al.2018	n=15-1% Pimecrolimus cream n=15-0.1% Betamethasone valproate cream R=4 times a day		4 weeks	4		C
Mycophenolate mofetil	Samiee et al, 2020	n=15-2% Mycophenolate mofetil in mucoadhesive patch n=8-Placebo R=twice a day	VAS Lesion size	4 weeks			
Hyaluronic acid topical ointment	Hashem et al,2018	n=0.1% Triamcinolone acetonide n= 0.2% Hyaluronic acid R=Thrice a day	VAS Lesion size and erythema	4 weks			
	Nolan et al,2009	n=62-0.2% Hyaluronic acid n=62-Placebo	1.Thongprasom scale 2.VAS	4 weeks			
BCG PSN	Xiong et al,2009	n= 31-intralesional injection with 0.5 ml BCG-PSN R=6 times over 2 weeks n=25-intralesional injection of 10 mg TA (40 mg／ml) R=Once a week	1.VAS 2. Lesion size	2 weeks			
Thalidomide	Wu Yun et al,2010	n=33- 1%thalidomide paste n=30-0.4% TA paste		4 weeks			
Curcumin	Kia et al, 2020	n=80mg nano curcumin soft gel capsule R=once daily		12 weeks			
	Nosratzehi et al, 2017	n=20-Mucoadhesive paste R=Thrice daily n=0.1% Betamethasone solution R=Thrice daily		12 weeks			
Aloe vera	Choonhakarn et al.2008	n=27-70% concentration (AV)(0.4 ml) n=27-Placebo R=Thrice daily		8 weeks			
	Salazar-Sa´nchez et al.2010						
	Mansourian et al.2011	n=70% concentration (0.4 ml) three times a day for 12 weeks					

BCG-PSN -Bacillus Calmette-Guerin polysaccharide nucleic acid
TA-Triamcinolone acetonide
AV-Aloe vera

In one of the clinical trials, topical pimecrolimus 1% was compared to topical betamethasone 0.1%, 4 times daily, for a period of 4 weeks. It was derived that the topical pimecrolimus application was superior to topical betamethasone in terms of severity of lesion, pain and recurrence rate.[5] In another RCT, topical 1% pimecrolimus was applied twice daily for 4 weeks. The follow up parameters of VAS and clinical symptoms improved at the mid-point of the study (Swift et al,2005). The final selected study evaluated a comparison between pimecrolimus 1% and tacrolimus 0.1% cream. It was applied twice daily for 8 weeks, followed by an additional follow-up of two weeks. The net clinical score used for evaluation was found to be decreased in both groups. It was inferred that, both drugs were comparably officious with no notable side effects.[3] Overall, it was discerned that, calcineurin inhibitors induced a better initial therapeutic response. It does not predispose patients to secondary candidiasis, atrophy or elevated drug levels in blood. However, relapses occurred frequently within 3–9 weeks of the cessation of treatment and the cost of treatment is 5 times higher than the conventional form.[9]

3.3. Immunomodulators

Mycophenolate mofetil (MMF) is a well-tolerated immunosuppressive drug that functions by inhibiting which the proliferation of activated T cells and is reversible in nature. Also, it is touted as an alternative therapeutic regimen in autoimmune disorders to specifically taper the dose and effects of corticosteroids.[10] It was primarily used to prevent rejection in organ transplant recipients. Also, it has been utilized to treat numerous dermatological conditions, twice a day in dose ranges of 500 and 2000 mg/day.[10] Only a single paper, could be obtained within the norms of the inclusion criteria. The authors stated that the drug concentration (2% MMF), vehicle of delivery as a mucoadhesive patch and duration of 4 weeks were all key factors in the significant finding obtained.[11] Hyaluronic acid (HA)is a linear polymer of glucuronic acid, N-acetylglucosamine disaccharide. It is an immunostimulant and functions by tissue healing wherein it stimulates angiogenesis, reduces exudation, is vaso-protective, and induces fibro genic action.[12] According to Nolan et al. there is evidence of its inherent analgesic action due to its barrier effect. [13] An additional favorable property, it is an ideal biomaterial for cosmetic, medical, and pharmaceutical applications owing to its biocompatibility, non-immunogenicity, biodegradability, and viscoelasticity. Current research by Hashem et al. only reports the topical use HA in OLP.[12] Bacillus Calmette-Guerin polysaccharide nucleic acid (BCG-PSN), the third-generation BCG extract containing immunologic active materials, polysaccharide and nucleic acid, can regulate the subsets of T cells (CD4 and CD8 cells) and subtypes of helper T cells by the principle of immunosuppression.[12] The process of extraction and removal of proteins removes the adverse effects of swelling and fever associated with the vaccine. [14] It was initially uses as a preventive measure in tuberculosis and malignancy. The short-term efficacy of topical BCG-PSN was comparable to the standard topical TA in regard to relapse and recurrence.[15]

Thalidomide is an anti-inflammatory and anti-immunologic drug with T-cell function. The mechanism of action is in essence by immunosuppression by its ability to decrease production of TNF-alpha. In addition, systemic thalidomide is a recognized alternative medication for refractory cases of erosive OLP that are insensitive to systemic glucocorticoids. The only available and researched form of this medication is the topical form. Also, the authors did not report any adverse effects and relapse. The efficacy of the drug was determined to be comparable to corticosteroid use.[16]

3.4. Nutraceuticals

Curcumin is a natural phytochemical and the active component of turmeric. Curcumin and its oily extracts have demonstrated antioxidant, anti-inflammatory, antimicrobial, and anticarcinogenic activities in multiple disease processes.[17][18]

3.5. Aloe vera

Aloe vera (AV) is widely used as a natural treatment and alternative therapy for a variety of diseases, and have proved to be healing, cosmetic, and nutritional. AV acts by inhibiting the inflammatory process by its interfering action on the arachidonic acid pathway via cyclooxygenase and by the reduction of leucocyte adhesion and TNF-a level. In a study of AV gel in the treatment of OLP, positive effects were demonstrated. The authors published that 81% of the patient's demonstrated improvement. [19][20] Another study demonstrated similar findings in improved pain, the oral lesions, and the oral quality of life. Also, no adverse effects were observed in the course of the study.[21][22][23][25]

4. Conclusions

A comparative statistical analysis was not possible owing to the multitude of variations in the drug concentration, vehicle for delivery, regimen and controls used. However, it was discernable that steroids still persist as the principal mode of therapy and that on use of nutraceuticals, an adverse effect free disease-free period could be achieved. The further trials on the management of OLP using pharmacological derivatives demand a larger scale with multiple population sets of various ethnicity, age and gender. Also, the parameters need a more acute standardization for the collective scrutiny. Also, it was derived that the management of oral lichen planus has multiple avenues and steroids need not be the only prerogative. Due diligence is also recommended to keep abreast of the various pathways of research to benefit patient treatment and compliance outcome. With the spotlight on the recalcitrant nature of the disease and the absence of an absolute cure at the moment, various palliative methods of pain and discomfort management is mandatory.

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