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REVIEW ARTICLES

Treatment of Oral Lichen Planus: A Systematic Review

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Abstract:

Objective: Oral Lichen Planus (OLP) treatment or clinical management is challenging. This systematic review aims to discuss the main therapy used in the management of OLP and the efficacy of every type of treatment to improve the quality of patient life.

Methodology: We discussed the publications on the clinical management of oral lichen planus on the PubMed database. Only randomized controlled trials (RCT) conducted in humans were considered. We included randomized controlled trials (RCT) published from 2005/1/1 to 2021/5/28 with symptomatic, clinically, or histologically diagnosed OLP. We compared different active treatments or between active treatment and placebo.

Results: Twenty randomized controlled trials involving 931 patient samples were included in the analysis. For the short time treatment (on average 2-8 weeks) of OLP, TCI, including Tacrolimus, pimecrolimus, and Ciclosporin, were similar to TCS, including Clobetasol, triamcinolone in efficacy. Tacrolimus–Triamcinolone resulted in similar outcomes. In addition, Tacrolimus and Ciclosporin showed a statistically higher incidence of local adverse events than triamcinolone and Clobetasol. A few systemic adverse events occurred in the tacrolimus and ciclosporin groups, but they were not serious.

Conclusion: Triamcinolone acetonide 0.1% should be the first drug of choice when selecting TCS, and Tacrolimus 0.1% should be the drug of choice when selecting TCI.

Key Words: Oral Lichen Planus (OLP), Randomized Controlled Trials, Steroid vs. Non-Steroid, Clobetasol, Cyclosporin, Triamcinolone Acetonide, Betamethasone, Pimecrolimus, Tacrolimus

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Introduction:

Oral lichen planus (OLP) is a chronic inflammatory immune-mediated disorder associated with altered cell-mediated immunological function. The disease is usually seen in middle-aged women in a male/female ratio of 1:2[1]. OLP has an overall prevalence of 0.2-2%[2]. Clinically, OLP may show characteristics in the form of reticular, popular, plaque-type, erythematous, erosive, or bullous lesions. It commonly occurs in the buccal mucosa, gingiva, tongue, etc. Some authors suggest that the diagnosis of OLP could be made from clinical features, especially when patients present the typical reticular form and the diagnosis is made on the modified WHO diagnostic criteria for OLP proposed by[3]. Although OLP is an idiopathic lesion, it may be associated with genetic predisposition, tumor antigens or autoantigens, microorganisms, systemic diseases, and emotional disorders[4].

Methodology:

We examined the publications on the treatment of oral lichen planus found by searching the PubMed electronic database. We searched using the titles: *oral lichen planus management, oral lichen planus treatment.*

The results were filtered with text availability: abstract to include studies published in English in the last 16 years (2005-2021.05.28). Literature reviews, case reports, and clinical trials were discarded, and only randomized controlled trials (RCT) conducted in humans were considered.

Eligibility Criteria

We used the following eligibility criteria:

- Types of studies: Randomized controlled trials (RCT).
- Publication date: From 2005/1/1 to 2021/5/28.
- Publishing Language: English
- Types of participants: patients over 18 years old with symptomatic, clinically, or histologically

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diagnosed OLP and without severe or uncontrolled systemic diseases.
- Types of intervention: comparison between different active treatments or between active treatment and placebo.
- Types of outcome measures: symptoms and/or clinical aspects of lesions.

A total of 444 citations were included in our review. Excluding the literature reviews, a total of 184 citations remained in the search. After then, we excluded clinical trials, meta-analysis, and systematic non-randomized controlled trials remaining 92 results. Then 44 studies were examined, excluding the remaining items based on titles. Finally, we included 20 studies because the remaining did not match all the eligibility criteria.

We considered a total of 931 patient samples: the number of patients in each study was relatively homogeneous, with an average of about 35-45 patients per study. The smallest sample was that examined by Lozada-Nur and Sroussi (4), using Tacrolimus Powder in Orabase 0.1%, limited to 10 patients; and the largest sample was that conducted by Yoke, Tin (5) in their randomized controlled trial to compare steroid with Cyclosporine for the topical treatment of oral lichen planus, consisting of 139 patients.

Regarding the gender and age of patients, there was a similar distribution in all the studies: the sample predominantly contained females (the average percentage of female patients was 66% or broadly 60-70%), with the average age of patients 50 years old. This confirms the typical distribution of the disease.

Among 20 trials, all of them were examined based on clinical and histological examination. This is, moreover, in accordance with the primary literature reviews, previous research articles, and consensus conferences on the subject, which establish that OLP treatment is only recommended in cases of symptomatic lesions[68].

Inclusion Criteria

The main inclusive criteria were:

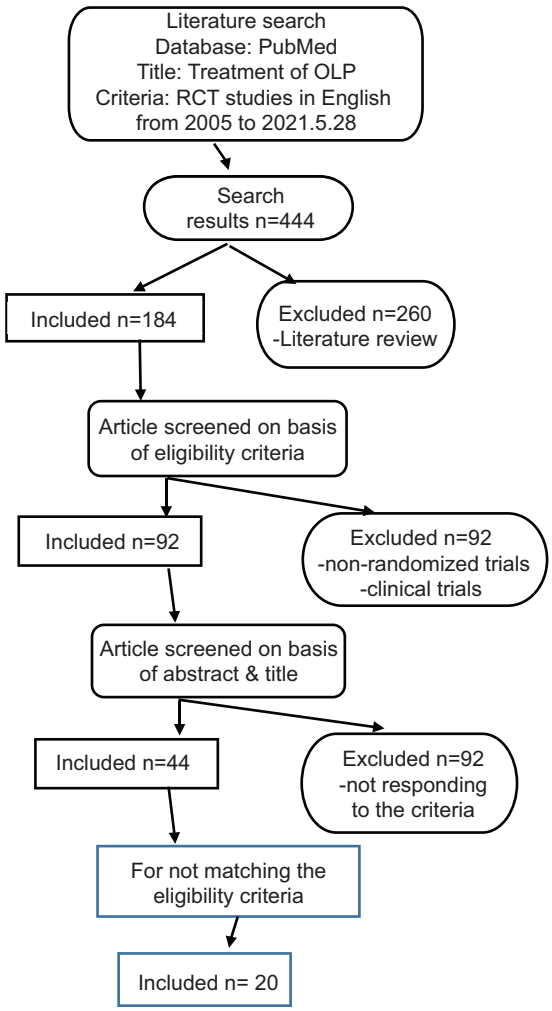
- Clinical diagnosis of OLP.
- Histological diagnosis of OLP (according to WHO criteria, the characteristic histological features include infiltration of T-cells in a band-like pattern in the basal and subepithelial layer; thickening of the epithelium with superficial hyperkeratosis and parakeratosis; and vacuolar degeneration of the basal cells with the presence of numerous Civatte bodies).
- Presence of symptomatic lesions.

Exclusion Criteria

In general, the main exclusion criteria were:
- Age < 18 years.
- Pregnancy or lactation.
- Uncontrolled systemic diseases (hepatopathies, coagulopathies, immune or hematological diseases, diabetes).
- History of allergic reactions to the active ingredient used in the clinical trial.
- Smoking
- Previous therapy for OLP in the period preceding experimentation
- Incompletion of the trial.

A flowchart has been added in Flowchart 1 showing the detailed procedure of the literature search and article screening.

Flowchart 1



Results:

Among the 20 studies we have included in this review, all were randomized controlled trials; 19 were parallel group studies, and one was a split-mouth design study[9]. Moreover, almost 12 were double-blinded studies, while the rests were single-blinded.

The main characteristics of the included studies are represented in Tables 1, 2 & Figure 1. It is to be noted that most of the criteria of both tables are the same. Some studies didn't use any scale to measure the symptomatic improvement of OLP; those are listed in Table 1, while Table 2 is prepared for those who used scales to measure the efficacy.

Study Design:

The reviewed literature consisted of different categorical research. Some studies compared active treatment with a placebo or controlled group (almost 4 of the studies)[10-13], nearly eleven of the studies compared two active treatments[5,9,13-21]. One study compared multiple non-steroids with one steroid to evaluate the therapeutic efficacy[22], while one study wholly focused on plant-based treatment[10]. In addition, one of the studies compared the use of different concentrations of the same drug[12]. Moreover, three separate studies compared different routes of administration of the same drugs for treating patients with OLP[23-25]. All the variations of studies and their characteristics are included in Tables 1 & 2. These clinical trials considered & compared different therapeutic approaches for treating OLP, starting with the more conventional treatments to the ones less used in the current days.

Outcome:

In order to evaluate the effectiveness of the treatment methods, some studies used the parameters of the remission scale defined by Carrozzo & Gandolfo[6,14,26,27]. They divided the treatment success into complete remission, partial resolution, and non-success. Some used the Grade scale, a slight modification of Carrozzo & Gandolfo's scale. These grades are Grade 1 = clearance of lesion (normal mucosa); Grade 2 = complete remission (CR; reticular with no symptoms); Grade 3 = partial remission (improvement of the lesion and/or symptom); Grade 4 = no improvement; Grade 5 = condition worsened. Some researchers considered Grade 1 & Grade 2 as complete remission and Grade 4 & Grade 5 as no remission.

Most of the recent studies used different scales to measure the efficacy of the treatment. The criteria score proposed by Thongprason Chaimusig[17] assessed the clinical aspects of Lesions improvement. The criteria score of this scale are as follows: 0 = no lesion/normal mucosa; 1 = mild white striae/no erithmetous; 2 = white striae with atrophic area < 1 cm^2; 3 = white striae with atrophic area > 1 cm^2; 4 = white striae with erosive area < 1 cm^2; 5 = white striae with erosive area > 1 cm^2 [9,17,27]. Some studies used alternative scales, which are still analogous to Thongprasom's scale but have different ranges, like Clinical Score (CS)[11,13,21] and Net Clinical Score (NCS)[19].

Most recent studies evaluated the symptomatically improvement of pain and burning sensation using the Visual Analogous Scale (VAS)[9,17,18,21,23]. The VAS is a 10-cm horizontal line marked 0 to 10. A zero VAS score means a complete resolution of symptoms or absence of any discomforts to the patients, while a 10 VAS score indicates the most severe pain ever experienced. Some studies used a Numerical Rating Scale (NRS)[25] to measure the pain and burning sensation's improvement. This scale is similar to the VAS scale, starting from 0 (= no pain) to 10 (= unbearable pain).

Some studies measured the improvement of patients' quality of life after treatment using Oral Health Impact Profile-14 (OHIP-14)[23]. It's a self-administered questionnaire conducted with the patients after treatments to measure seven dimensions: functional limitation, physical pain, physical discomfort, physical disability, psychological disability, social disability, and handicap. Additionally, some studies measured the disease relapse rates within a follow-up duration of one year.

Discussion:

Steroids:

* Ointment:

- Conrotto, Carbone[14] compared the effectiveness of Clobetasol & Ciclosporin drugs in the topical management of Oral Lichen Planus. Their study was designed as randomized, comparative & double-blinded. A total of 40 patients were selected and then divided into two groups. Among these patients, 20 received Clobetasol Propionate, whereas the rest received Ciclosporin. Both of these drugs were mixed with 4% hydroxyethyl cellulose gel. In addition to

that, Antimycotic prophylaxis treatment was also added. The duration of the treatment was two months, and a two-month follow-up was ensured for every patient. After the study, it was observed that Clobetasol is more effective in clinical improvement and also requires five times lesser daily cost than Cicsporin. However, at the end of therapy, Ciclosporin gives more stable results than Clobetasol, whereas Clobetasol also shows some side effects.

- Yoke, Tin[5] compared the efficacy of topical Cyclosporine and Steroid (Triamcinolone Acetonide 0.1% in orabase) in a randomized controlled trial over 139 patients (68 P – Cyclosporine, 71 P – Steroid). The study finds out that Cyclosporine is not much effective as Steroids. Moreover, applying these solutions to patients is less cost-effective. Although patients receiving Cyclosporine showed some side effects than those receiving steroids, the differences were not statistically significant.
- Thongprasom, Chaimusig[17] compared the effectiveness between cyclosporine solution & Triamcinolone acetonide 0.1%. In this randomized controlled study, 6P received Cyclosporine, and 7P received the other drugs. The study evaluated the pain & burning sensation using the Visual Analogue Scale (VAS) & the assessments were done by clinical scoring. The results of the study indicate that for Triamcinolone Acetonide, both complete & partial remission are equal, but for Cyclosporine, 66.7% showed no response & rest showed only partial remission. Moreover, five patients from Cyclosporine developed some side effects. While only one patient developed side effects for the triamcinolone acetonide group. Their study concluded that Cyclosporine is not as efficient as triamcinolone acetonide 0.1%.

*** Injection:**

- Liu, Xie[25] studied the efficacy and safety of using betamethasone as an intralesional treatment of erosive OLP. In this randomized controlled trial, 30 Patients (the experimental group) received 1.4 mg intralesional betamethasone & 31 Patients (the control group) received 8 mg intralesional Triamcinolone Acetonide through injection. They used a numerical rating scale (NRS) ranging from 0 (= no pain) to 10(= unbearable pain) to evaluate the pain level of OLP lesions. The study found that of patients who received betamethasone, 93.1% were healed; for the control group, it was 66.7%. Moreover, the reduction in erosion area was more significant than the control group. Additionally, the recurrent erosion for the experimental group (14.8%) was significantly lower than in the control group (45%). The study concluded that intralesional betamethasone could be used for treating patients with OLP.

*** Comparing Different Concentration**

- Carbone, Arduino[12] investigated the efficacy of increasing the concentration of Clobetasol for treating patients with OLP. In their randomized, double-blinded controlled study, a total of 35 patients were selected, most confirmed by histological diagnosis. Patients were divided into two groups: one group received 0.025% and another 0.05% Clobetasol Propionate. It was found that after two months of therapy, 93% of patients in the first group & 87% patients of in the 2nd group had symptomatic improvement. Moreover, after two months, 87% of the first group & 73% of the second group had clinical improvement. Their study concluded by mentioning that increasing the concentration of the clobetasol molecule cannot improve the therapeutic findings in a meaningful manner.

***Comparing Different Injecting Processes:**

- Lee, Shin[23] investigated the efficacy of two applying procedures of Triamcinolone acetonide (TA) in patients with OLP. One process was applying it through intralesional injection, and the other was through mouth rinse. In this randomized controlled study, 40 patients were selected based on their clinical & histopathologic examination; half received the TA through injection and the other half through mouth rinse. Their study indicated that the efficacies of both treatments were similar, especially in the Visual Analog scale & Oral Health Impact Profile. However, the rate of adverse effects for the mouth rinse group was significantly higher (44%) than in the intralesional injection group (5%).

Non-Steroid:

- Passeron, Lacour[11] evaluated the efficacy of using 1% pimecrolimus cream in treating OLP. Each of the 12P was confirmed OLP either by histological examination or by clinical. The cream was applied to six patients' ulcerated lesions twice a day and continued for four weeks. A 12-point clinical score measured the effectiveness of the treatment, and it has been observed that the score for the pimecrolimus group was much better than that of the placebo group. Some patients reported a transient burning sensation. They concluded that the 1% pimecrolimus cream seems to be an effective and well-tolerated treatment for oral erosive lichen planus but needs long-term study to maintain its clinical improvement.

*** Tacrolimus (Non-steroid) as Powder:**

- Since, Tacrolimus ointment showed some side effects and caused the recurrence of diseases due to the discontinuation of the medication, using this as ointment became challenging. Lozada-Nur and Sroussi[4] tried a different method to observe the effectiveness and safety of this medication when used as Powder. Their study shows a tremendous safety improvement and represents a likely alternative to topical steroids in treating OLP. Moreover, very minor and transient side effects from the medication were observed.

Steroidal Vs. Non-Steroidal Treatment Comparison

- Laeijendecker, Tank[15] compared the effectiveness of topical Tacrolimus (Non-steroid) & Triamcinolone Acetonide Ointment (Steroid) in treating OLP. This randomized study was conducted among 40 patients and divided into two groups with an equal number of patients. One group received 0.1% Topical Tacrolimus while the other received 0.1% Triamcinolone Acetonide in 20% Hypromellose. Both ointments were applied four times a day onto the symptomatic Oral Lesions, and the treatment continued for six weeks. The study found that Topical Tacrolimus ointment produces a better therapeutic response at the initial stage than Triamcinolone Acetonide. Both groups observed temporary burning or stinging side effects at the application site. One of the unfortunate outcomes observed while applying both of these treatments is that relapses frequently occurred within 3-9 weeks after the cessation of the treatments.
- Corrocher, Di Lorenzo[16] compared the efficacy of Tacrolimus 0.1% ointment (non-steroid) & Clobetasol 0.05% ointment (Steroid). Their randomized, double-blind, critical study was conducted among 32 patients equally divided into two groups. The duration of the treatment/study period was four weeks. The study's outcomes suggest that tacrolimus 0.1% ointment is more effective in treating OLP than

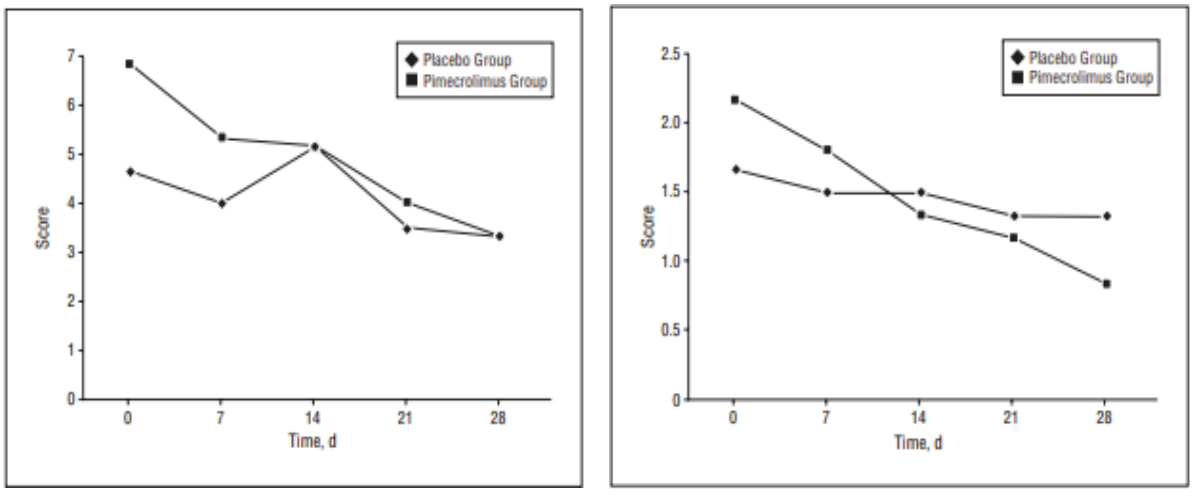


Fig.-1: *Evaluation of the (a) total score under treatment (b) erosion scale under treatment.*

Clobetasol 0.05% ointment. Some patients had a diffuse sensation of oral mucosal, which was transient. One of the significant limitations of this study is its duration. As a result, the long-term adverse effect of using tacrolimus ointment was impossible to identify.

- Radfar, Wild[18] compared the effectiveness of Clobetasol 0.05% (Steroid) & Tacrolimus 0.1% (Non-steroid) in treating patients with OLP. In this double-blind, randomized clinical study, 30 patients were recruited based on their clinical and histologically diagnosed with OLP and divided into two equal groups. Both groups showed negligible side effects. Moreover, there were no significant differences in decreasing the mean lesion size and VAS for both groups, indicating that Tacrolimus is similarly useful in treating patients with OLP as Clobetasol.
- Sonthalia and Singal[19] compared the efficacy of Tacrolimus 0.1% ointment (Non-steroid) and Clobetasol propionate 0.05% ointment (Steroid) for treating patients with OLP. Among the 40 Patients, the first half received Tacrolimus, while the rest received Clobetasol propionate. At the end of the study, both groups showed efficacious in terms of improvement. Also, both groups showed a decline in Net Clinical Score (NCS) from the baseline in each visit, which was statistically significant. 40% of patients from the Clobetasol group showed complete response, while it was 70% for the tacrolimus group. At week 8, patients reporting "good" or "very good" treatment responses were 74% in the clobetasol group and 100% in the tacrolimus group. They concluded that Tacrolimus 0.1% ointment could be effectively used as first-line therapy in OLP.
- Hettiarachchi, Hettiarachchi[9] studied the effectiveness of topically applied Tacrolimus 0.1% Cream (Non-steroid) & Clobetasol Propionate 0.05% Cream (Steroid). Their study indicates that after three weeks of treatment, both clinical parameters (pain measured on the VAS) and clinical appearance (using thongprason's scale) declined from the baseline for both groups and both sides of the mouth. For the Tacrolimus group, VAS was reduced by 1.59, while it was reduced by 0.94 for the clobetasol group. Moreover, TC was decreased by 1.18 for the tacrolimus group, while it was reduced by 0.5 for the clobetasol group. They concluded that Tacrolimus 0.1% ointment could be effectively used as first-line therapy in OLP.
- Singh, Rai[22] compared the efficacy of one steroid (0.1% triamcinolone acetonide) with three different non-steroids (oral dapsone, Topical Tacrolimus, Topical Retinoid) in a randomized open-label study for treating OLP. A total of 40 patients, who were clinically and histologically proven OLP, were divided into four groups (10P/group). It has been found that after three months of treatment, each group showed significant clinical improvement and represented equal efficacy. For the 0.1% Triamcinolone Acetonide group, 87% showed improvement in symptoms, and 72% showed improvement in signs. For the topical retinoid group, 76% showed improvements in symptoms, and 62% showed improvements in signs. For oral dapsone, 97% showed improvement in symptom score, and 84% showed improvement in signs. Regarding topical Tacrolimus, 79% showed improvement in symptom scores. However, in this study, topical Tacrolimus showed the recurrence of the disease symptoms and signs after stopping the treatment. In addition, they also noticed that, among the non-steroidal treatments, oral dapsone showed much higher efficacy than retinoid. Also, there was no significant difference between other non-steroidal pairs (oral dapsone vs. topical Tacrolimus or topical retinoid vs. topical Tacrolimus).

Plant-Based Treatment:

- Choonhakarn, Busaracome[10] studied a plant-based treatment management method and compared the efficacy between Aloe Vera (AV) & placebo for treating OLP. They conducted the study among 54 people, equally divided into two groups, and the treatment was continued for eight weeks. Among the 27 patients who received Aloe Vera, 22 showed a good response after eight weeks of their treatment, while for placebo, only one patient showed a similar response. They concluded that AV gel is more effective than a placebo for improving OLP patients' symptoms and clinical aspects. Moreover, they didn't find any severe side effects in any groups, indicating AV gel can be a safe alternative treatment for patients with OLP.

Table-I

Summary of the Included Studies for the Review of Treatment of OLP

Study (First Author, Year)	Objective /Drug & Treatment used	Method of the study	No of Patients, Diagnosis method & Interventions	Duration, Follow Up & Daily Doses	Outcomes	Side-Effects	Comments/Conclusion by the Author
Conrotto et al. (2006)	- compared between Clobetasol & Ciclosporin - which one is cost-effective - gives the most extended remission from signs & symptoms	randomized, comparative, double-blind	NP = 40; 20 P/ group; - 4% hydroxyethyl Cellulose bioadhesive gel is used to mix them - Antimycotic prophylaxis treatment was added to both group	D = 2 months - twice per day FU = 2 months	Clobetasol: 95% improved after 2 months; 95% improved in symptomatology; 33% were stable Ciclosporin: 65% had a clinical response; 85% improved in symptomatology; 77% were stable	- Clobetasol produced significantly more side-effects	- Clobetasol is more effective than Ciclosporin in inducing clinical improvement, but the two drugs have comparable effects on symptoms. - The daily cost of Ciclosporin is more than five times higher than Clobetasol.
Laeijendecker et al. (2006)	- compared topical Tacrolimus Ointment and Triamcinolone Acetonide	randomized	NP = 40; 20 P/Group; -with 20% Hypromellose ointment	D = 6 weeks - four times per day	-Topical Tacrolimus: 6P healed, 12 P improved, 2P no improvement; -Triamcinolone Acetonide: 2P healed, 7P improved, 11P no improvement; -However, relapses occurred frequently in both groups within 3–9 weeks of the cessation of treatment	- in both groups, temporary burning or stringing	- Topical tacrolimus 0.1% ointment induced a better therapeutic response than triamcinolone 0.1% ointment;
Lozada-Nur & Sroussi (2006)	- evaluated the clinical efficacy of Tacrolimus Powder	open randomized pilot clinical trial	NP = 10; 7 P = OLP 3 P = OLL	D = 2 weeks - three times per day FU = 2 weeks	Disease control was achieved in most patients by the end of 2nd week; All patients had some discomfort initially but dropped at the end of the treatment period.	Side effects were minor & transient	-Tacrolimus powder in Orabase 0.1% appears to have a relatively safe profile.

(table continued)

Table-I (cont'd)

Yoke et al. (2006)	- compared the efficacy of topical steroids (Triamcinolone acetonide 0.1%) and Topical Cyclosporine	randomized controlled trial	NP = 139; 68 P = Topical Cyclosporine; 71 P = Triamcinolone Acetonide; - Assessments were at weeks 0, 2, 4, 8	D = 8 weeks - three times per day FU = 12 weeks & then every three months for one year.	-Clinical response, pain, burning sensation, area of reticulation, erythema, and ulceration at week 4 were all worse in patients receiving Cyclosporine than in those receiving steroids.	-minor	- Cyclosporine is not much effective as Steroids. -Moreover, applying these solutions to patients is less cost-effective.
Choonhakarn et al. (2008)	- compared the efficacy of Aloe Vera and Placebo	randomized, double-blind, placebo-controlled trial	NP = 54; 27 P/Group; -Assessments were at weeks 0,2,4,6 & 8	D = 8 weeks - Twice per day	AV: 81% had a good response (22 out of 27 P); 7% complete clinical remission; 33% of burning pain disappeared; Symptomatology improved by 63%. Placebo: 4% good response, burning pain disappeared (1 out of 27 P); Symptomatology improved by 7%;	-Negligible	- AV gel is statistically significantly more effective than a placebo
Corrocher et al. (2008)	-Compared between Tacrolimus 0.1% Ointment & Clobetasol 0.05% ointment	randomized, double-blind, clinical trial	NP = 32; 16 P/Group;	D = 4 weeks - Four times daily	Tacrolimus: 68% complete remission of symptoms; Clobetasol: 6.3% complete remission of symptoms;	Tacrolimus: 9P had a diffuse sensation of oral mucosal burning but resolved rapidly within 4-5 days.	- Tacrolimus 0.1% ointment is more effective than clobetasol propionate 0.05% ointment

* NP = Number of Patients; P = Patients; D = Duration; FU = Follow-Ups; OLP = Oral Lichen Planus; OLL = Oral Lichenoid Lesions;

Table-II

Summary of the Included Studies for the Review of Treatment of OLP (Outcomes are measured by Scale)

Study (First Author, Year)	Objective /Drug & Treatment used	Method of the study	No of Patients, Diagnosis method & Interventions	Duration, Follow Up & Daily Doses	Outcomes (by percentage or by clinical score)	Side-Effects (VAS/ NRS)	Comments/Conclusion by the Author
Passeron et al. (2007)	-Evaluated the effectiveness of 1% Pimecrolimus Cream	A double-blind, randomized trial with placebo control	NP = 12 -histological examination 6 P- 1% Pimecrolimus Cream; 6 P - Placebo	D = 4 weeks -twice a day	Placebo Group: the mean score was 4.67 on day 0 vs. 3.33 on day 28. Pimecrolimus group: the mean score was 6.83 on day 0 vs. 3.33 on day 28.	some reported only transient burning sensations	- The 1% pimecrolimus cream seems to be an effective and well-tolerated treatment for oral erosive lichen planus
Thongprasom et al. (2007)	-compared the effectiveness of Cyclosporin solution with Triamcinolone Acetonide 0.1%	randomized-controlled trial	NP – 13 - proven by biopsy 6 P – Cyclosporine 7 P – Triamcinolone Acetonide 0.1%	D = 8 weeks -three times daily FU = 12 months	Triamcinolone acetonide group: similar cases of clinical complete and partial remission (50%). Cyclosporin group: partial remission in only two cases (33.5%) and no response in four cases (66.7%).	five of six cases in the cyclosporin group developed side-effects	Cyclosporine is not as efficient as triamcinolone acetonide 0.1%.
Crabone et al. (2009)	-compared the efficacy and safety of two different formulations of Clobetasol	randomized, double-blind, placebo-controlled trial	NP – 35 -histological diagnosis 15 P- Clobetasol Propionate 0.025% 15 P-Clobetasol Propionate 0.05% 4% hydroxyethyl cellulose bioadhesive gel is used. Antimycotic prophylaxis was added	D = 2 months -twice a day FU = 2 months	In all, 14 of the 15 clobetasol 0.025% patients (93%) and 13 of the 15 clobetasol 0.05% patients (87%) had symptoms of improvement after two months of therapy Also, 13 of the 15 clobetasol 0.025% patients (87%) and 11 of the 15 clobetasol 0.05% patients (73%) had clinical improvement after two months of therapy	No side effects were visible	A more significant concentration of the active molecules cannot further improve the therapeutic findings or optimize the obtained results in an effective manner

(table continued)

Table-II (cont'd)

Radfar et al. (2008)	-compared the effectiveness of topically applied Tacrolimus and Clobetasol	double-blind, randomized clinical study	NP = 30; -clinically and histologically 15 P- Clobetasol 0.05% 15 P- Tacrolimus 0.1%	D = 6 weeks -4 times/day for two weeks, followed by three times/day for two weeks, two times/day for one week, and one time/day for one week	The percentage reductions (week 0 to week 6) in mean lesion sizes were 82.6% in the Tacrolimus group and 81.6% in the Clobetasol group VAS for Clobetasol = 38% reduction; Tacrolimus = 52.3% reduction.	Negligible	Tacrolimus is as useful as Clobetasol in the treatment of OLP. The profiles of change (i.e., the treatment difference) were not statistically significant between the two groups
Lee et al. (2013)	-compared the efficacy, relapse, and adverse effects between intralesional injection and mouth rinse of triamcinolone acetonide	randomized controlled study	NP = 40; -clinical and histopathologic examination 20 P- Intralesional Injection 20 P- Mouth Rinse	D = 6 weeks - three times daily FU = 1 year	The VAS scores were significantly improved at 1, 2, 3, 4, and 6 weeks and were similar in both groups. The rate of adverse effects was significantly higher in the mouth rinse group than in the intralesional injection group (44.4% vs. 5.0%).	The adverse effects were higher for the mouth rinse group.	The efficacies of both treatments were similar except for the rate of adverse effects, which was significantly lower for intralesional injection than mouth rinse.
Sonthalia & Singal (2012)	-compared treatments with topical tacrolimus 0.1% ointment and topical clobetasol propionate 0.05% ointment	randomized double-blind trial	NP = 40; -histologically proven symptomatic OLP 20P = Tacrolimus 0.1% ointment. 20P = Clobetasol propionate 0.05% ointment	D = 8 weeks - twice per day FU = 12 weeks	NCS Score declined after 12 weeks: Clobetasol Group- from 8.00 ± 2.65 at baseline to 2.00 ± 1.49. Tacrolimus Group- from 7.78 ± 3.25 at baseline to 1.31 ± 1.06. Complete Response: Clobetasol –40%; Tacrolimus – 70% "Good" or "Very Good" Treatment Response: Clobetasol – 74% Tacrolimu-100%	-None	Tacrolimus, 0.1% ointment, can be effectively used as first-line therapy in OLP.

(table continued)

Table-II (cont'd)

Liu et al. (2013)	- Efficacy of intralesional betamethasone for erosive oral lichen planus	a randomized, controlled trial	NP = 61; -Clinically & pathologically determined 30P – 1.4 mg intralesional betamethasone 31P – 8 mg intralesional Triamcinolne Acetonide	D = 2 months - injection once a week. FU = 3 months	Healed (%) & reduction (area): Betamethosone Group- 93.1% & (21.276 ± 21.064 mm^2) Triamcinolone Group- 66.7% & (11.5 ± 12.95 mm^2) Recurrent Erosion: Betamethosone Group- 14.8% Triamcinolone Group- 45%	Betamethosone injection: 1 Injection = Irritation, candidiasis, pigmentation, Repeated injection = mucosal atrophy, hypertension, and high blood glucose	Intralesional betamethasone can be used for treating patients with OLP.
Hettiarachchi et al. (2017)	compares the effectiveness of topically-applied Clobetasol and Tacrolimus	randomized, comparative, double-blind study (Split-mouth Study)	NP = 68; -histologically-proven symptomatic OLP 34P = topical tacrolimus 0.1% cream 34P = clobetasol propionate 0.05% cream	D = 3 weeks - twice daily FU = 3 months & 6 months	VAS dropped by Tacrolimus Group- 1.59 Clobetasol Group- 0.94 Thongprason's score was reduced by Tacrolimus Group- 1.18 Clobetasol Group- 0.5	No adverse effects were identified in both groups.	Tacrolimus, 0.1% ointment, can be effectively used as first-line therapy in OLP
Singh et al. (2017)	compared the therapeutic efficacy of steroidal and non-steroidal agents	a randomized, open-label study	NP = 40; -clinical and/or histologically proven OLP 10P – Steroid (0.1% triamcinolone acetonide 10P – Oral Dapsone 10P = Topical tacrolimus 10P = Topical Retinoid	D = 3 months	%of Patient Improvement in Symptoms & Signs- 0.1% Triamcinolone Acetonide: 87% in symptoms and 72% in signs. Topical Retinoid: 76% in symptoms and 62% in signs. Oral Dapsone: 97% in symptom score and 84% in signs. Topical Tacrolimus: 79% in symptom score.	None	Non-steroidal drugs such as dapsone, Tacrolimus, and retinoid are as efficacious as steroidal drugs for treating oral lichen planus

(table continued)

Table-II (cont'd)

Siponen et al. (2017)	compared the effectiveness of topical Tacrolimus (TAC), triamcinolone acetonide (TRI), and placebo (PLA)	a double-blind, randomized controlled trial	NP = 27; -Clinically proven OLP 11P = 0.1% Topical tacrolimus Ointment 7P = Triamcinolone Acetonide 9P = Placebo	D = 3 weeks FU = 6 weeks		No severe side effects were reported	findings indicate that 0.1% TAC ointment and 0.1% TRI paste are both more effective than PLA in alleviating signs and symptoms of OLP, measured by reduction in the CS
Bakhtiar et al. (2018)	compared the effectiveness of oral methotrexate versus systemic corticosteroids	Randomised controlled trial	NP = 158 79P = Oral Methotrexate 10 mg, once/week 79P = Oral Corticosteroids 10 mg, once/day	D = 8 weeks	Methotrexate: was effective in 63 (80%) patients; Oral Corticosteroid: was effective in 57 (72%) patients.	No remarkable side effects were observed with either agent.	This study concludes methotrexate is not significantly more efficacious than systemic corticosteroids in the treatment of generalized lichen planus, but it is a good steroid-sparing alternative
Ezzatt & Helmy (2019)	Compared Topical pimecrolimus versus betamethasone	a prospective, randomized, double-blind, 8-week parallel-design clinical trial	NP = 30 P - clinically and histologically confirmed OLP 15P = topical pimecrolimus 15P = betamethasone	D = 8 weeks Four times daily	Both drugs showed a reduction in CS, VAS, and CD133 expressions after treatment termination Pimecrolimus-treated lesions showed a significantly higher 1st-week reduction in severity (33.1% (22.2)), pain score (57.53% (14.27)), less recurrence in the follow-up period, and less CD133 expression by the end of the 1st four weeks compared with betamethasone		The study proved the benefits of topical pimecrolimus in the early management of painful lesions of OLP and its ability to inhibit CSCs, suggesting a possible role in reducing the risk of malignant transformation

(table continued)

Table-II (cont'd)

Santonocito et al. (2021)	compared the therapeutic efficacy of clobetasol oral gel 0.05% versus an anti-inflammatory in oral solution (mouthwash)	randomized clinical trial	NP = 40P 20P = clobetasol oral gel 0.05% 20P = an anti-inflammatory mouthwash, which contains calcium hydroxide, hyaluronic acid, umbelliferone, and oligomeric pro-anthocyanidins	D = 3 months			The results evidenced that, compared to Clobetasol, the anti-inflammatory was less effective in determining the reduction of signs and symptoms in OLP patients.
Motta et al. (2009)	Compared placebo with clobetasol propionate	Double-blind, crossover	NP= 22 P 5P= 0.05% clobetasol propionate 17P= placebo	D=1-15 yrs	With Clobetasol: 77.2%= improvement, 22.7%= worsening With placebo: 63.6%= improvement, 36.4%= worsening	Not remarkable	No significant difference between clobetasol and placebo results

* NP = Number of Patients; P = Patients; D = Duration; FU = Follow-Ups; OLP = Oral Lichen Planus; OLL = Oral Lichenoid Lesion

Conclusion:

By analyzing our 20 RCT articles which include a total of 931 patient samples, we can come to the conclusion that TCI, including Tacrolimus (in 7 RCT), Pimecrolimus (in 2 RCT), and Ciclosporin (in 3 RCT), were similar to TCS including Clobetasol (in 4 RCT), triamcinolone (in 5 RCT) in efficacy for the treatment of OLP. Treatment duration was short time ranging from 2-8 weeks duration and only 1 RCT include 12 months duration. Although the local adverse events with TCI were higher than with TCS, they were all tolerable. The systemic adverse events with Tacrolimus and Ciclosporin were not serious with treatment. Therefore, we can suggest TCI as an alternative when OLP does not respond to TCS. Due to a few systemic adverse events with and high cost of Ciclosporin, Tacrolimus 0.1% should be the first drug of choice in TCI and Triamcinolone acetonide 0.1% when selecting TCS for the treatment of OLP.

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