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Research Article

Comparison of Steroids and Calcineurin Inhibitors in the Management of Oral Lichen Planus– A Meta-Analysis

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Abstract

Context: Lichen planus is the one of the most common muco-cutaneous disorder in India with a wide variety of therapeutic modalities such as Steroids and immuno-modulators.

Aim and Objective: The present study was done to compare the efficacy of corticosteroids with immune-suppressants like Calcineurin inhibitors in treating Oral lichen planus (OLP).

Materials and Methods: PubMed, Scopus and Google scholar database were searched using keywords Oral lichen planus, Corticosteroids, Triamcinolone, Clobetasol, Immuno-modulators, Tacrolimus, Pimecrolimus, local application. From each article, information regarding the type of drug used, duration, response to the drug, side effects and recurrences were recorded. The data was entered in a spreadsheet and subjected meta-analysis of relative risk and mean difference.

Results: A total of 56 studies were obtained through the search. Out of them 40 articles were excluded as they contained only one drug in the treatment of OLP (either corticosteroid or Calcineurin inhibitor). Out of 16 articles, 3 articles have study methodologies below standard, and the statistical data was not complete or clear. Hence a total of 13 articles were included in the study, which were subjected to meta-analysis. Calcineurin inhibitors are 1.31 times more potent than corticosteroids in curing OLP. Steroid cases have 1.69 times more recurrences when compared to Calcineurin inhibitors. Calcineurin inhibitors produced higher side effects when compared with Steroids. Steroids showed significant reduction in Visual analog scale (VAS) score when compared to Calcineurin inhibitors.

Conclusion: Our study proved that Steroids are best in giving symptomatic relief (such as reducing burning sensation) to the patient with minimal side effects. On the other hand, Calcineurin inhibitors are profound in suppressing the disease with minimal recurrence rate.

Keywords: *Oral Lichen Planus; Corticosteroids; Triamcinolone; Clobetasol; Immuno-Modulators; Tacrolimus; Pimecrolimus*

Introduction

Lichen planus is the one of the most common muco-cutaneous disorder in India. It is a chronic noninfectious, inflammatory disease of skin and mucous membrane. It was first described by Wilson clinically in 1869 and histologically by Debdreuilh in 1906 [1]. Although, the etiology of Oral lichen planus (OLP) is not fully elucidated, it is well-documented that oral lichen planus represents a T-cell mediated autoimmune disease in which auto cytotoxic CD8 cell triggers apoptosis of epithelium. OLP presents as white striations, white papules, white plaques, erythema, erosions, or blisters affecting predominantly the buccal mucosa, tongue and gingiva. Oral lichen planus (OLP) appears as a hyperkeratotic plaque or striae, and is asymptomatic, except for atrophic, erosive and bullous form, wherein there could be mild discomfort to severe burning sensation [2,3]. In such cases patient's food habits get hampered disturbing their day to day life. The

erosive and bullous/atrophic cases are considered to have some malignant transformation in long term conditions [2]. Hence the aim in treating OLP should be concentrated on resolving the painful symptoms with minimal side effects.

Till now a wide variety of therapeutic modalities have been employed in treating oral lichen planus which include Corticosteroids, Retinoids and its derivatives, Immunosupressors like Calcinueurin inhibitors, Levamisole and Azathioprine, antifungal agents like Griesofulvin and PUVA therapy [4]. In earlier days corticosteroids were most commonly used for management of oral liche planus. Steroid drugs like Triamcinolone and Clobetasol are being widely used in treatment of lichen planus. With the advent of potent immunomodulators in the recent years, the management of oral lichen planus has become an easy task. Among them Calcineurin inhibitors are well known for immunosuppression. They inhibit T-cell activation by inhibiting Calcineurin and blocks dephosphorylation events critical for lymphokine gene expression [4].

Potent corticosteroids have been used in the treatment of severe lichen planus. But their application has been limited due to profound side effects. On the other hand, many contemporary immunomodulators like Calcineurin inhibitors are now available with local drug delivery systems which increased their usage for treating OLP [5]. Hence the present meta-analysis was done to compare the efficacy of corticosteroids with immunosuppressants like Calcineurin inhibitors in treating OLP.

Materials and Method

The study was carried out to assess the efficacy of corticosteroids and Calcineurin inhibitors in treatment of OLP. PubMed, Scopus and Google scholar database was searched using keywords Oral lichen planus, Corticosteroids, Triamcinolone, Clobetasol, Immunomodulators, Tacrolimus, Pimecrolimus, local application. Only general keywords with exact phrases were selected in order to narrow the search and make it simpler. Studies only with local application of these drugs (published between years 2000 to 2017) were included in the study. Irrelevant articles which are out of the scope of our study were excluded.

The full texts of the obtained articles were evaluated by an author and necessary information was derived. The methodology in each article was clearly evaluated and articles with low quality study statistics were deliberately excluded. Each article was reevaluated by a second author and both the data were compared. In case of any discrepancy between the two authors necessary advice was taken from our statistician in obtaining the correct data. From each article, information regarding the type of steroid used, duration of application, response to the drug in the form of Visual analog scale (VAS) score, side effects and recurrences were recorded. The data was entered in a spreadsheet and subjected to statistical analysis. Meta-analysis of these studies was carried out. Relative risk was evaluated to compare the probability of drug responses in disease cure rate, recurrence rate and in producing side effects. Mean differences were evaluating to know the difference in drug responses in reducing burning sensation. All the results were plotted in forest plots. Heterogeneity in the studies were evaluated at each level to know the reliability of the results.

Results

A total of 56 studies were obtained through the search. Out of them 40 articles were excluded as they contained only one drug in the treatment of OLP (either corticosteroid or Calcineurin inhibitor). Out of 16 articles, 3 articles have study methodologies below standard, and the statistical data was not complete or clear. Hence a total of 13 articles were included in the study, which were subjected to meta-analysis.

Rate of complete remission of disease was calculated in both steroid group and Calcineurin group. Out of 179 cases in steroid group 74 cases were completely cured. Out of 172 cases in Calcineurin group 112 cases were completely cured. Meta - analysis results showed risk ratio of 0.758, which indicated that Calcineurin inhibitors are 1.31 (100/75.8) times more potent than corticosteroids in curing OLP (Figure 1). But the results were found to be non-significant. The heterogeneity of the study was calculated to be 76.24%, which was statistically significant (Table 1).

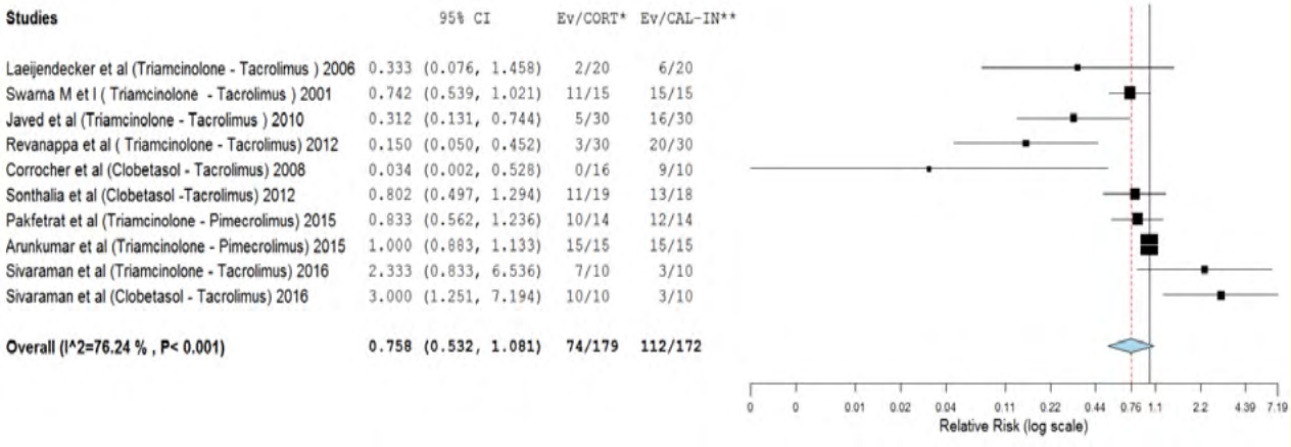

Figure 1: *Forest Plot for Total Cure Rate of the Study. (* Corticosteroids, ** Calcineurin Inhibitors).*

Heterogeneity	tau^2	Q (df = 7)	Het. p-Value	I^2
	0.178	37.885	< 0.001*	76.3%
Relative Risk	Estimate	Lower bound	Upper bound	p-Value
	0.758	0.532	1.081	0.126

Table 1*: Total Study Cure Rate.*

**Statistically Significant*

Rate of recurrence was calculated in both the groups. Out of 85 cases in steroid group, 22 cases showed recurrence. Interestingly out of 94 cases only 16 cases showed recurrence in Calcineurin group. Risk ratio of 1.690 was calculated, which indicates that steroid cases have 1.69 times more recurrences when compared to Calcineurin inhibitors, which was found to be statistically insignificant (Figure 2). The heterogeneity of the study was only 25% which was found to be statistically insignificant (Table 2).

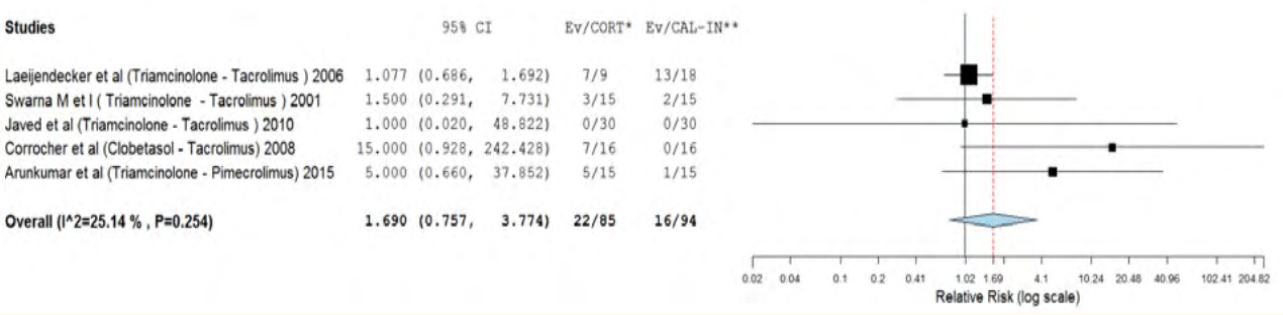

Figure 2: *Forest Plot for Recurrence Rate in the Study. (* Corticosteroids, ** Calcineurin Inhibitors).*

Heterogeneity	tau^2	Q (df = 4)	Het. p-Value	I^2
	0.238	5.343	0.254	25%
Relative Risk	Estimate	Lower bound	Upper bound	p-Value
	1.690	0.757	3.774	0.201

Table 2: *Total Recurrence Rate.*

Calcineurin inhibitors produced higher side effects when compared with Steroids. The relative risk was observed to be 0.543 in the study, which indicated 1.84 times higher side effects in Calcineurin group (Figure 3).

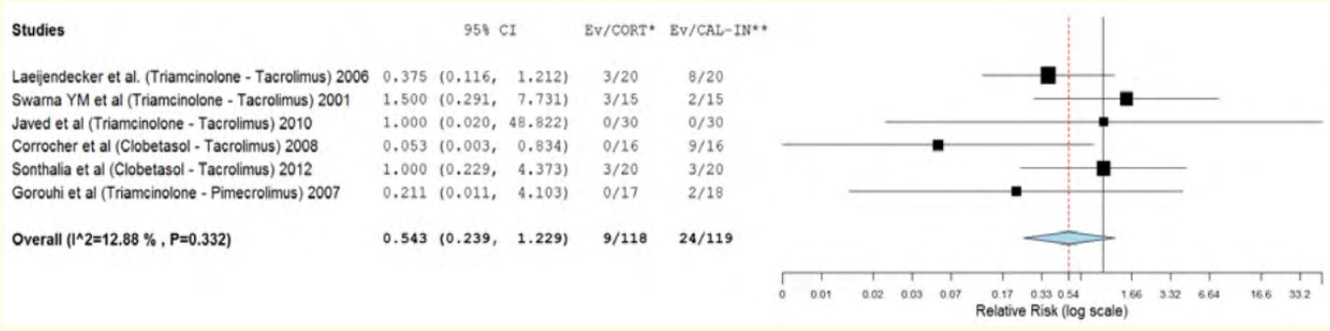

Figure 3: *Forest Plot for Side Effects in the Study. (* Corticosteroids, ** Calcineurin Inhibitors).*

The heterogeneity in the studies was comparatively low (12%), which was statistically insignificant (Table 3).

Heterogeneity	tau^2	Q (df = 4)	Het. p-Value	I^2
	0.139	5.739	0.332	13%
Relative Risk	Estimate	Lower bound	Upper bound	p-Value
	0.543	0.239	1.229	0.143

Table 3: *Side Effects.*

Evaluation of VAS score in both the groups showed interesting results. Steroids showed significant reduction in VAS score when compared to Calcineurin inhibitors (Figure 4). The mean difference in VAS score values between the groups was observed to be 0.773 (Table 4).

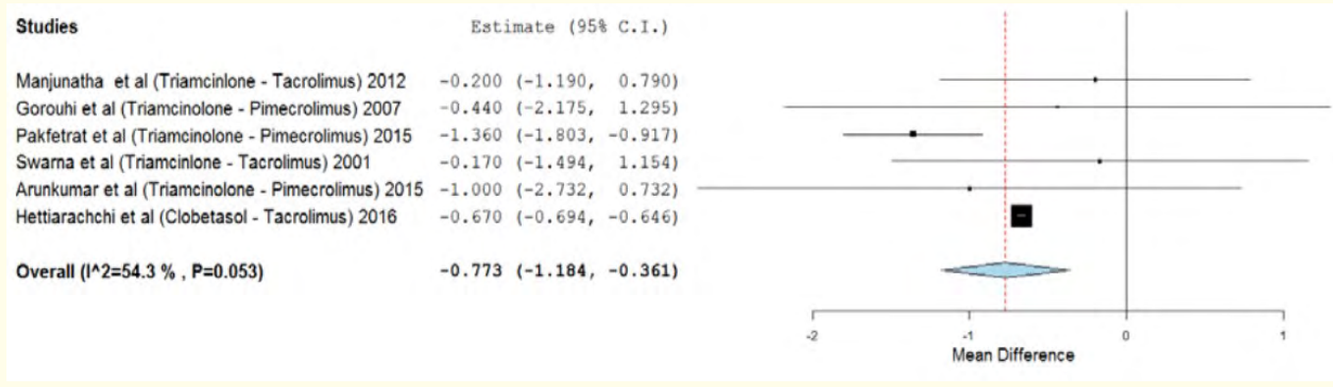

Figure 4: *Forest Plot for VAS Score in the Study. (* Corticosteroids, ** Calcineurin Inhibitors).*

Heterogeneity	tau^2	Q (df = 4)	Het. P-Value		I^2
	0.105	10.941	0.053		54%
Mean Difference	Estimate	Lower bound	Upper bound	Std. error	P-Value
	-0.773	-1.184	-0.361	0.210	0.001*

Table 4: *Vas Score.*

**Statistically Significant*

Discussion

Immunity is mainly meant to protect the body from various foreign objects which have entered into the body. So, it has capability to distinguish the self from non-self. T cells are one of the important constitutes of the immune system [6]. When such immune system fails to differentiate from own body cells and recognize it as foreign body then it tries to kill, leading to development of autoimmune diseases. Lichen planus is one such immunologically mediated disease in which T cell mediated inflammation is seen along sub mucosa [7]. Various treatment modalities have been presented to treat oral lichen planus. Among them corticosteroid's are first line drugs.

Immuno-modulators may be defined as biological or synthetic substances which can stimulate, suppress, or modulate any of the components of immune system. They are immune-adjuvants, immune-stimulants, and immune-suppressants. Among them Calcineurin inhibitors have significant impact in treatment of many immunological disease because of their role in T-cell activation. These drugs produced significant results in treatment of OLP. In this context a meta-analysis was done to compare the efficacy of immune-modulators and corticosteroids in the treatment of OLP.

Our results showed that 65% of cases were cured completely using Calcineurin inhibitors, but only 41.3% cases were successfully treated using topical Steroids. Similar results were obtained in the studies conducted by laeijendecker., *et al.* [8], Swarna., *et al.* [9], Javed., *et al*. [10], Revanappa., *et al.* [11], Corrocher., *et al.* [12], Sonthalia., *et al.* [13] and Pakfetrat., *et al.* [14]. The possible explanation for this is attributed to the truth that Calcineurin inhibitors are more target sensitive when compared to Steroids. They are smaller molecules and can be easily penetrated into mucosa [15]. They directly inhibit T-lymphocyte activation by inhibiting Calcineurin. This leads to inhibition of lymphokines, interleukin-2 and gamma interferons resulting in decreased number of T-lymphocytes in the lesion area [16]. As a result, there will be decreased production of RANTES (regulated on activation, normal T-cell expressed and secreted), resulting in prevention of mast cell activation, which is a major step in triggering OLP [17].

On the other hand, Steroids have a gross anti-inflammatory action, which helps in successful treatment of symptomatic features of OLP, such as burning sensation [18]. This was supported by our study, where we found increased reduction of burning sensation in patients using Steroids when compared to Calcineurin inhibitors. Similar results were observed in the studies conducted by Swarna., *et al.* [9], Pakfetrat., *et al.* [14], Carbone., *et al.* [19], Gorouhi., *et al.* [20], Arun Kumar., *et al.* [21], Hettiarachchi., *et al* [22].

The most common side effect in patients using Steroids is candidial infection. Ellepola., *et al.* preferred usage of chlorhexidine mouthwash during the treatment to reduce the incidence of candidiasis in these patients [23]. Interestingly greater extent of side effects were documented in patients using Calcineurin inhibitors when compared to Steroids. The most common side effect among them is transient burning sensation [10]. Sontalia et al advocated that usage of Tacrolimus with orabase reduces transient burning sensation after application on to mucosa [13]. Valerie., *et al.* reported tingling sensation and irrtitation in his study on topical Tacrolimus [24]. Lozada., *et al.* reported intermittent head aches and pigmentation in his study on Tacrolimus [25]. Volz., *et al.* reported ulceration with blisters in his study on Pimecrolimus cream for treatment of erosive lichen planus [26].

High recurrence rate in OLP is another annoying feature which hinders successful treatment using topical drugs. Our study observed high recurrence rate in steroid cases when compared to Calcineurin inhibitors. Sonthalia., *et al*. proposed, continuation of immunomodu-

lators for a period of 1 to 2 months after remission of disease to decrease the recurrence rate. Even though increased cancer risk is an evident feature in usage of these immune modulators, hence he insisted upon a pre-treatment biopsy to rule out any dysplasia in the lesion [13].

Conclusion

The overall study has given a wide input in the treatment aspects of OLP. Our study proved that Steroids are best in giving symptomatic relief (such as reducing burning sensation) to the patient with minimal side effects. On the other hand Calcineurin inhibitors are profound in suppressing the disease with minimal recurrence rate. These results strongly suggest that Corticosteroids or Calcineurin inhibitors alone cannot produce complete relief from the disease. Hence a combination of these two treatment modalities is advocated for the best outcome of the disease.

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