Efficacy of topical Tacrolimus in the treatment of oral lichen planus

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ABSTRACT

Introduction: Oral lichen planus (OLP) is a common benign inflammatory disease affecting mainly middle-aged and elderly people. Various studies have found topical Tacrolimus to be effective in the treatment of OLP and some have also reported a better initial therapeutic response than Triamcinolone. The present study evaluated the efficacy of topical Tacrolimus (0.1%w/v) prescribed for 6 months in the treatment of OLP in Indian population, and also evaluated the relapses after cessation of therapy.

Methods: 35 patients of symptomatic OLP were identified from retrospective review of medical records. All these patients were prescribed Tacrolimus Ointment (0.1%w/v) to be applied 3 times a day for 6 months period. A survey was mailed to all patients to assess the response of therapy to Tacrolimus, continuous use of ointment, adverse effects (if any), and relapse after cessation of therapy. Surveys were completed a mean 9.2 months after initiating the treatment. 81% patients had significant symptomatic improvement with use of topical Tacrolimus Ointment, whereas 84% patients reported lesion clearance/significant reduction. 43% patients reported relapse after cessation of therapy and relapse rate could have been greater with longer follow-up period.

Conclusion: Within limitations of this study, it can be concluded that topical Tacrolimus (0.1%w/v) is safe and effective for the treatment of Oral Lichen Planus, but high relapse rate after cessation of therapy makes its treatment difficult.

Keywords: Tacrolimus, Oral lichen planus, Survey, Inflammatory disease.

INTRODUCTION

Oral lichen planus (OLP) is a common benign inflammatory disease affecting mainly middle-aged and elderly people.[1] Oral Lichen Planus most commonly produces symptoms of burning sensation while eating and interferes with patients oral hygiene regimen. Sometimes such patients are not able to tolerate slightest amount of spices in their food. The prevalence of OLP varies from 0.1% to about 4% depending on the population sampled.[2-3] The clinical diagnosis of OLP can be done on basis of characteristic clinical findings and history and can be confirmed by histopathological examination.

Six different clinical forms of OLP have been described by Andreason - reticular, papular, plaque, atrophic, erosive, and bullous.[4] The most form of OLP is reticular with the characteristic Wickham's striae, but patients with reticular lesions are commonly asymptomatic. Patients with atrophic (erythematous) or erosive (ulcerative) OLP are often associated with symptoms like burning sensation and pain. Although the etiology and pathogenesis of OLP are not fully understood, oral lichen planus has been associa ted with multiple disease processes and agents, such as viral and bacterial infections, autoimmune diseases, medications, vaccinations and dental restorative materials.[5] In various studies in has been established that OLP represents a cell-mediated immune response with the infiltrating cell population composed of both T4 and T8 lymphocytes.[6]

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Various treatments have been used for OLP but use of topical corticosteroids like Triamcinolone is still most commonly used first line therapy. Although topical corticosteroids are effective in relieving the symptoms, some cases are resistant to the treatment with such drugs. Moreover, relapses are common on cessation of therapy[7] which makes treatment of OLP challenging.

Tacrolimus is an immunosuppressive drug used mainly after allogeneic organ transplant to reduce the activity of the patient's immune system. It is also used in a topical preparation in the treatment of atopic dermatitis and other dermatologic lesions. Various studies have found topical Tacrolimus to be effective in the treatment of OLP and some have also reported a better initial therapeutic response than Triamcinolone.[7-8] But studies evaluating the efficacy of topical Tacrolimus in Indian population especially over long periods, are scarce.

The present study evaluated the efficacy of topical Tacrolimus (0.1%w/v) prescribed for 6 months in the treatment of OLP in Indian population, and also evaluated the relapses after cessation of therapy.

MATERIALS AND METHODS

35 patients of histopathologically confirmed, symptomatic erosive type of OLP were identified from records of Dental Department, VMMC & Safdarjang Hospital. All these patients were prescribed Tacrolimus Ointment (0.1%w/v) to be applied 3 times a day for 6 months period. Patient related data and treatment given was obtained from retrospective review of medical records. Patients who had any established medical

condition or received any previous treatment for OLP, were not included in this study. A survey was mailed to all patients to assess the response of therapy to Tacrolimus, continuous use of ointment, adverse effects (if any), and relapse after cessation of therapy. (Table 1)

Table 1 – A sample of Survey mailed to patients

CHARACTERISTIC	RESPONSE(Tick the appropriate circle)
Whether used ointment 3 times a day regularly	Yes ◯ No ◯
Symptoms	Totally alleviated ◯ Much better ◯ Slightly better ◯ Same ◯
Lesion appearance	Not visible ◯ Much reduced ◯ Somewhat reduced ◯ No Change ◯
Time taken for improvement	_____
Adverse effects	_____
Whether symptoms/lesion reappeared after stopping the treatment	Yes ◯ No ◯

RESULTS

35 patients who were prescribed topical Tacrolimus Ointment (0.1%w/v) were mailed the surveys. Out of 35 patients, 2 did not mail back the surveys, and 4 patients responded that they did not use the ointment regularly. The results of this study are from remaining 29 patients who used the medicine regularly and mailed back the surveys.

The patient data are summarized in Table 2. The mean age of 29 patients included in the study was 47.2 years. 31% patients were male and 69% were female. Most common symptoms reported by patients were burning sensation/irritation at the site of lesion (69%), followed by difficulty in eating various foods (28%), difficulty in performing and maintaining oral hygiene (24%), and pain (17%). Most common location of OLP was Buccal mucosa (27%).

Table 2 – Patient data (n = 29)

CHARACTERISTIC	Number	Percentage
Sex		
Male	9	31
Female	20	69
Symptoms		
Burning	20	69
sensation/irritation	5	17
Pain	7	24
Difficulty in brushing	8	28
Difficulty in eating		
foods		
Location		
Buccal mucosa	19	66
Labial mucosa	2	7
Gingiva	8	27

Patients' responses to survey are summarized in Table 3. Surveys were completed a mean 9.2 months after initiating the treatment (range 45 days to 347 days), whereas Tacrolimus Ointment (0.1%w/v) was prescribed for 6 months period. 9% patients reported that their symptoms were totally alleviated whereas 72% patients said that symptoms were much better. Therefore 81% patients had significant symptomatic improvement with use of topical Tacrolimus Ointment (0.1%w/v). 11% patients reported that symptoms were somewhat reduced, whereas 5% had no change in symptoms. Mean time taken for improvement was 1.2 months.

Table 3 – Patient response (n = 29)

CHARACTERISTIC	RESPONSE	Percentage
Whether used ointment 3 times a day regularly	Yes	100
	No	0
Symptoms	Totally alleviated	9
	Much better	72
	Slightly better	12
	Same	7
Lesion appearance	Not visible	8
	Much reduced	76
	Somewhat reduced	11
	No Change	5
Time taken for improvement	Mean – 1.2 months	
Adverse effects	Burning/irritation	18
	Tingling	3
	None	79
Whether symptoms/lesion reappeared after stopping the treatment	Yes	43
	No	57

Majority of patients wrote that lesions were much reduced (76%), whereas 8% said that lesions were not visible at all. 11% patients had lesions somewhat reduced and 5% patients had no change in appearance of lesion. Most common adverse effect was transient burning sensation at the site of application (18%). The recurrence of symptoms/lesions after cessation of treatment was reported by 43% patients. Clinical findings during follow-up visits were available for 11 out of 29 patients (38%), and these findings co-related to the responses filled by patients in the surveys.

DISCUSSION

Tacrolimus is an immunosuppressive macrolide drug produced by Streptomyces tsukubaensis and used to prevent transplant rejection.[9] Topical Tacrolimus (0.1%w/v) has been reported to be effective and safe for the treatment of OLP by various investigators.[7-9] It has been found to be an effective means of controlling the symptoms and signs of erosive or ulcerative oral lichen planus and had no notable adverse effects over a mean duration of application of 19.8 months.[10]

Cell-mediated immunity seems to play a critical role in the pathogenesis of lichen planus.[8] Although the specific antigens responsible for the activation of T-cell has not been identified, studies have demonstrated the interaction of T-cells and mast cells in a cyclical nature via the production of cytokines, such as RANTES (regulated on activation, normal T-cell expressed, and secreted) and TNF-α, which may explain the chronic nature of this disease.[11] Although its exact mechanism of action in OLP remains unknown, topical tacrolimus was shown to inhibit T-lymphocyte activation by inhibiting the phosphatase activity of calcineurin. Without calcineurin to dephosphorylate the nuclear factor of activated T cells, gene transcription for lymphokines, IL-2, and interferon-γ is inhibited leading to a decrease in the number of lymphocytes.[12]

In results of our study, OLP was more common in females (69%) and the most common location was buccal mucosa (66%). Topical Tacrolimus Ointment (0.1%w/v) was effective and safe in most of the patients, 81% patients experienced significant symptomatic relief and 84% patients reported lesion clearance/significant reduction. Mean time for response was 1.2 months. Only 5 % patients reported no change in their lesion.

Most common adverse effect reported in our study by the patients was burning/irritation at site of application, which is consistent with the findings from other studies.[9-10] 43% patients reported relapse after cessation of therapy, which is in line with previous studies and shows that although Topical Tacrolimus is effective in

controlling the disease, it rarely results in complete remission of OLP.[9, 12-16] Surveys were completed a mean 9.2 months after initiating the 6 month treatment, and relapse rate could have been greater with the longer follow-up period.

Though many studies have evaluated the efficacy of topical Tacrolimus in treatment of OLP, the studies in Indian population are very scarce. Our study evaluated the efficacy of topical Tacrolimus in Indian population through retrospective review of patient records and is therefore subject to recall bias. Many patients live far from hospital and find it difficult to turn-up for regular clinical follow-up visits. In our study we were able to find clinical records of follow-up visits for only 38% of patients, and thus the drop-out rates in long term clinical studies are very high. Clinical findings during follow-up visits were available for of 38% patients, and these co-related with the responses filled in the surveys. Mailed survey has been used previously in some studies and was found to be standard and objective method to follow-up with patients of chronic diseases requiring long term therapies.[17]

Within limitations of this study, it can be concluded that topical Tacrolimus (0.1%w/v) is safe and effective for the treatment of Oral Lichen Planus.

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