Title:

EFFICACY OF 0.1% TACROLIMUS IN LONG-TERM MANAGEMENT OF EROSIVE LICHEN PLANUS

ABSTRACT

INTRODUCTION:

Erosive oral lichen planus is a painful, chronic inflammatory disorder that often becomes a management challenge. This study documented aimed to document the response of patients with erosive OLP to 0.1% topical tacrolimus over a 12-month period or until the patient became unresponsive to therapy.

MATERIALS AND METHODS:

It is a retrospective cohort study. Retrospective data of 12 patients with recalcitrant OLP that were prescribed 0.1% tacrolimus was reviewed. Patients with a biopsy proven diagnosis of OLP who were prescribed 0.1% tacrolimus after they failed to respond to conventional corticosteroid therapy were included. Information about their response to medication initially and on flare ups were included in this study.

RESULTS:

The sample consisted of 9 women and 3 men. All patients were given 0.1% tacrolimus to be applied 3 times a day. Two patients did not respond to the treatment at all, 4 patients showed partial response to tacrolimus treatment. Six patients showed complete initial response to treatment. Four patients failed to show response to the medication following first and second flare ups.

CONCLUSION:

50% of our patients showed a suboptimal response to 0.1% tacrolimus use for erosive OLP, thus suggesting that 0.1% tacrolimus may be an ineffective option for managing erosive OLP, in some cases.

KEYWORDS: effectiveness, oral lichen planus, side effects, corticosteroids, tacrolimus

INTRODUCTION

Oral lichen planus (OLP) is a chronic inflammatory immune-mediated mucocutaenous disorder which primarily affects skin, oral mucosa and genitalia of middle aged or elderly females. It is characterized by reticular striations of the buccal mucosa and other sites. Its prevalence is 0.1-2.2%.[1] Several clinical forms are associated with the disease, among which reticular striation, white plaques and papules generally in a bilateral distribution. While reticular type and the hyperplastic or plaque-like forms of OLP are asymptomatic and do not require management, erosive type is associated with erythema, erosions, intense and disabling pain, difficulty in food consumption, and malignant transformation rates of 0.5 to 2.5% over 5 years.[2]

The etiology of this disease process is unknown. OLP is a T cell mediated disease in which CD8+ T cells trigger apoptosis of the basal cells of the oral epithelium. Different cytokines like interleukin 2, interleukin 12, interferon gamma and tumor necrosis factor alpha take part in the disease process. There is an increase in HLA types B15, Bw57, B5, B7, BX, DR2 in OLP patients. In OLP topical and systemic corticosteroids are the attractive choices for alleviating symptoms.[3] Recalcitrant cases are managed with topical agents like calcineurin inhibitors like tacrolimus, pimecrolimus, cyclosporine A, rapamycin, sirolimus, TNF-a inhibitors like etanercept, tetracycline, systemic agents like thalidomide, mycophenolate mofetil, retinoids, curcumin, glycyrrhizin. Advanced treatment modalities include phototherapy, laser therapy, photodynamic therapy and ultraviolet therapy.[4, 5]

Tacrolimus is an immunomodulator that is primarily used in transplant patients to lower the risk of organ rejection. It inhibits calcineurin phosphatase that prevents release of interleukin-2 and other pro-inflammatory cytokines responsible for activation of T-lymphocytes, eosinophils and neutrophils.[6] The chronic nature of the disease is very incapacitating for the patient. As a matter of fact there is a need to improve the therapeutics to facilitate and ameliorate the quality of patient care. In literature there is a lack of proper randomized controlled trials to document the accurate efficacy of various drugs available for management of OLP. Studies have documented efficacy of 0.1% tacrolimus in treatment of recalcitrant OLP but there is deficient information about long-term use of this medication. Here we aim to present retrospective data on 12 patients with recalcitrant OLP that were offered 0.1% tacrolimus in ointment formulation evaluating drug effectiveness.

MATERIALS AND METHODS

This study was approved by the ethical review committee of Riphah International University (Ref No. IIDC/IRC/2019/05/001). It is a retrospective cohort study. Retrospective data on 12 patients that were treated with 0.1% tacrolimus during the past 3-year period at Islamic International Dental Hospital, Islamabad, Pakistan, was collected. It was ensured that the selected patients met with clinico-pathological parameters of erosive OLP like erythema, erosions, intense and disabling pain, difficulty in food consumption, had a biopsy proven diagnosis, were non-responsive to conventional treatment with topical corticosteroids, and had at least a 12-month follow-up available. The patients with other forms of OLP and those who were not biopsy proven were excluded from the study.

The patients fitting the inclusion criteria were cultured for candida albicans before initiation of treatment. If the culture was positive, the patients were treated with Fluconazole, Clotrimazole, or Nystatin. The extent of eroded or ulcerated areas was recorded before and after the treatment by using

a white-erosive-atrophic-modified (WEA-MOD) scoring system, modified from Thongaprassom K et al. scoring system, based on the following criteria:

Score 5 = white striae with erosive area more than 1 cm^2

Score 4 = white striae with erosive area less than 1 cm^2

Score 3 = white striae with atrophic area more than 1 cm^2

Score 2 = white striae with atrophic area less than 1 cm^2

Score I =mild white striae, no erythematous area

Score 0 = no lesion, normal mucosa.

The patients were asked to apply the 0.1% tacrolimus ointment on the lesions after mealtimes thrice a day. They were requested not to consume any food or drink following application to ensure extended contact with mucosa. The use of tacrolimus application was to continue until complete resolution of symptoms as the clinician performed periodical follow-up visits leading to objective clinical evidence, such as absence of erythema, erosions or ulcers. Reapplication was advised if the symptoms returned.

The data collected from the patient's medical records included information on the sites of involvement, number of years of disease, previous treatments, initial response and recurrence. Response of gauged on resolution of lesions and alleviation of symptoms. Reported side effects to the treatment were also documented. The data was entered in SPSS version 22.0 for descriptive analysis of ages and duration of OLP and Wilcoxon signed rank test was applied for clinical scoring of OLP. A p-value equal or less than 0.05 was considered significant at 95% confidence interval.

RESULTS

Out of 12 patients there were 3 men and 9 women. The age range was from 33 to 92 years with mean age of 59.08±16.21 years. The onset of symptoms before reporting to our clinics was between 3 months to 20 years with the mean of 4.05±5.37 years.

All patients showed bilateral buccal mucosa involvement. Desquamative gingivitis was seen in 6, labial mucosal involvement in 1 and tongue lesions were seen in 3 patients. Involved areas showed erythema and ulceration with white striations at their periphery. At least one site was biopsied to confirm the diagnosis of lichen planus histologically. All cases were diagnosed as true OLP with only a T-cell lymphocytic infiltrate. Six patients also had positive direct immunofluorescence results for fibrinogen deposition at the basement membrane zone as it is mandatory for diagnosis of OLP but few people can afford it because of its expensiveness. Chronic ulcerative stomatitis or other lichenoid variants which typically do not respond to topical corticosteroid treatment were ruled out.

The most common complaints were pain at sites of involvement, and intolerance to spicy food. Associated diseases included diabetes, arthritis, hypertension and unspecified heart disease. This information is summarized in Table I.

All patients had used topical corticosteroids, and 11 had intralesional corticosteroids. Six patients had taken systemic corticosteroids during the course of their disease. Hydroxychloroquine had been prescribed to 7 patients and azathioprine was to 4. The possible combination therapy used was

hydroxychloroquine along with topical corticosteroids in the respective 7 patients but it also resulted in therapeutic failure. Prior treatments produced little to no improvement in symptoms.

The WEA-MOD scoring system demonstrated a mean of 4±0.74 pre-treatment scores and post-treatment score mean was 2.42±1.56 showing some improvement in the clinical features of OLP as shown in Table II. Statistical analysis shows a significant statistical difference between the pre-treatment and post-treatment scores with p= 0.017.

Over a 12-month period, 2 patients did not respond to tacrolimus treatment at all, while 4 patients had a partial response to tacrolimus as the signs and symptoms did not completely resolved.

Six patients showed complete response as the erythema, erosions and pain resolved at least during the first phase of treatment. Initial response to topical application was noted at least 2 weeks of continuous use of tacrolimus. 4 patients had no flare ups and 1 had a flare up after 2 and half months and the other had after 6 months but responded to tacrolimus again.

Patients were periodically followed up over the course of the treatment to ensure patient compliance and reassure them regarding their health condition. Overall in 3 patients flare up of symptoms was seen within 10 weeks, while the other 3 had flare up at least 6 months after initial use. Four patients failed to respond to tacrolimus following flare ups. One of these patients responded to treatment following the first flare up, but became recalcitrant to the medication following the second flare up 8 weeks later. These patients were switched to systemic Cyclosporin A and the signs and symptoms alleviated with 8 weeks of treatment. This information is summarized in Table III. Only 2 patients in our sample complained of mucosal irritation.

DISCUSSION

Erosive OLP can significantly affect a patient's quality of life by making food consumption painful. It is also associated with a risk of transformation emphasizing the need of timely management of this condition.[7]

Recent literature has introduced tacrolimus, calcineurin inhibitor as a potential treatment option for recalcitrant OLP.[8] Three randomized control trials (RCT) compared the performance of 0.1% tacrolimus with 0.05% clobetasol on erosive OLP in 102 patients. In one study complete response rate with tacrolimus was 70%, while that for clobetasol was 40% at 8 weeks and at 12 weeks complete to partial response rate was 90% with clobetasol and 95% with tacrolimus. Other two also demonstrated positive and superior response of tacrolimus thus documenting the efficacy of this medication for management of erosive OLP.[8-10] Another randomized control trial compared 0.1% tacrolimus and 0.1% triamcinolone acetonide documenting a better response of tacrolimus.[11]

Excluding these randomized control trials, there were 223 patients discussed in studies summarized in table IV. One hundred and ninety two of these patients showed either partial or complete response to different concentrations of tacrolimus use, but most commonly 0.1%.[12-24] Our data corroborates the initial general positive response to tacrolimus use.

From 192 patients, at least 91 recurrences were documented in these studies.[12, 14, 17, 20, 22, 24] Our recurrence rate was higher in comparison to previously documented studies. We saw flare ups in 50% of

our sample. We believe that this may be because the patients were followed up for a longer period than previously reported cases.

Comparing the response rate of our long term follow up of tacrolimus use with the response patients showed after a mean time documented in the literature, mixed results were found. A study conducted by Hodgson et al. followed up 50 patients for 19.8 months. It is the only study with a long term follow up. They reported 14% complete resolution and 80% partial resolution of OLP while our study showed 50% patients with a suboptimal response. Another study by Resende JPM et al. evaluated 15 patients with 5 months follow up. 12 patients showed total or partial response to 0.1% tacrolimus while in our study 4 patients showed partial response and 6 showed initial complete response.

A study conducted by Malik U et al. used the WEA-MOD scoring system. The pre-treatment mean scores were 2.75±0.64 and the post-treatment scores were 0.48±0.81 with the changes in value being 2.27±0.92. These results were different from our study as our pre-treatment score was high with patients having significantly large lesions and being more symptomatic and the changes in value in our study was 1.58±0.82 showing less improvement.[17]

The side effects documented by previous studies include dry mouth, palatal changes, sore throat, tingling sensation, altered taste and burning mouth. These were reported by at least 63 patients from a pool of 223 cases.[14, 16, 18-21] Our patients tolerated the drug well. Two patients in our sample complained of mucosal irritation. No other adverse effect was documented.

While these studies document patients' initial response with this medication, very few of them followed all the patients longitudinally over a period of time. Long-term follow-up of our sample reveals that 0.1% tacrolimus may only benefit some patients. It was interesting to note that some of our patients failed to respond to tacrolimus following flare ups. This may be attributed to development of drug tolerance. Our data is small for any definitive conclusions and consists of uncontrolled reporting. Larger RCTs may help in developing a better understanding about the efficacy of this drug.

CONCLUSION

50% of our patients showed a suboptimal response to 0.1% tacrolimus use for erosive OLP. While we will continue using it as a treatment option for patients that do not respond to conventional therapy, we did not find tacrolimus an effective option for managing erosive OLP.

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Table I: Clinical Data of Patients

Patient No	*Age (years)*	*Gender*	*Duration (years)*	*Site*	*Morphologic type*	*Associated disease*
1	62		2.5	Bilaterally buccal mucosa, desquamative gingivitis	Erosive	Diabetes Mellitus, arthritis
2	65		2.5	Bilaterally buccal mucosa, alveolar ridge	Erosive	Hypertension, heart disease
3	60		3	Bilaterally buccal mucosa, desquamative gingivitis	Erosive	Diabetes Mellitus
4	37		0.5	Bilaterally buccal mucosa, desquamative gingivitis	Erosive	-
5	70		20	Bilaterally buccal mucosa, labial mucosa, lateral tongue	Erosive	Hypertension
6	33		2	Palate	Erosive	-
7	67		5	Bilaterally buccal mucosa	Erosive	-
8	92		6	Bilaterally buccal mucosa and tongue	Erosive	Heart disease, hypertension
9	62		5	Bilaterally buccal mucosa, desquamative gingivitis	Erosive	Hypertension, diabetes mellitus
10	67		1.5	Bilaterally buccal mucosa and tongue	Erosive	Hypertension
11	42		0.3	Bilaterally buccal mucosa	Erosive	-
12	52		0.3	Bilaterally buccal mucosa and desquamative gingivitis	Erosive	-

Table II: WEA-MOD Scoring Before and After the Treatment

Patient No.	*Pre-treatment Clinical Scoring*	*Post-treatment Clinical Scoring*
1	5	5
2	4	4
3	4	4
4	4	4
5	3	3
6	5	1
7	4	3
8	4	1
9	3	1
10	4	1
11	5	1
12	3	1

Table III: Treatment History of Patients

Patient No	*Treatment before Tacrolimus*	*Reason for initiating Tacrolimus*	*Starting Dose*	*Concomitant Treatment*	*Response to treatment*	*Side Effects*	*Recurrence*
1	Topical, intralesional and systemic steroids, Hydrochloroquine	Minimal response to prior treatment	0.1%	Fluconazole	2 and half weeks to 2 and half months	-	Flare up after 2 and half months then no control
2	Topical, intralesional and systemic steroids, Hydrochloroquine, azathioprine	No response	0.1%	Fluconazole	No response	-	-
3	Topical, intralesional and systemic steroids, Hydrochloroquine, azathioprine	No response	0.1%	Fluconazole	2 and half weeks to 2 and half months → flare up → tacrolimus → 2 weeks to 3 months → flare up→ tacrolimus → no response	-	2 flare ups then did not respond to tacrolimus
4	Topical and intralesional steroids	Partial response	0.1%	-	2 weeks to 6 months	-	Flare up after 6 months then no control
5	Topical, intralesional and systemic steroids	No response	0.1%	Fluconazole/ clotrimazole	No response	Mucosal irritation	-
6	Topical, intralesional and systemic steroids, Hydrochloroquine, azathioprine	Partial response	0.1%	-	2 weeks to 12 months	-	No flare up
7	Topical, intralesional and systemic steroids, Hydrochloroquine	No response	0.1%	-	2 weeks to 2 and half months	Mucosal irritation	Flare up after 2 and half months then no control
8	Topical, intralesional and systemic steroids, Hydrochloroquine, azathioprine	Partial response	0.1%	Fluconazole	2 weeks to 6 months → flare up → tacrolimus → 3 weeks → responded	-	Flare up after 6 months but then control with tacrolimus
9	Topical and intralesional steroids	No response	0.1%	-	2 weeks to 6 months→ flare up→tacrolimus→ 1 week→ responded	-	Flare up after 6 months that responded to tacrolimus
10	Topical, intralesional and systemic steroids	No response	0.1%	-	3 weeks to 18 months	-	No flare up
11	Topical and intralesional steroids	No response	0.1%	-	1 week to 12 months	-	No flare up
12	Topical steroids	No response	0.1%	-	2 weeks to 12 months	-	No flare up

Table IV: Literature review regarding tacrolimus treatment of OLP

Author	*Study Type*	*Number of Patients*	*Type OLP*	*Tacrolimus Treatment*	*Treatment Duration/ Follow up*	*Results*
Vente et al.	Retrospective	6	Erosive	0.1%	4-12 weeks/ 3 weeks-6 months	3 patients showed complete response and other 3 partial response
Rozycki et al.	Retrospective	13	9 Erosive , 3 plaque, 2 bullous, 1 papular	0.03% in 6 patients, 0.1% in 4 patients and 0.3% in 3 patients	1 week-1 month/ 1-12 months (6.5 months)	11 patients had symptomatic relief, 8 showed partial response, 3 complete response with respect to lesion clearance
Resende JPM et al.	Prospective	15	Symptomatic OLP	0.1%	8 weeks/ 5 months	12 patients showed total or partial response
Malik U et al.	Prospective	20	Symptomatic OLP	0.1% tacrolimus powder in Oraguard-B	1 month to 6.5 months/ 3 months	13 patients had complete lesion clearance and 16 had complete symptomatic relief
Byrid JA et al.	Retrospective	37	22 reticular, 14 Erosive	0.03% and 0.1%	5 days -2.7 years (1.1 year)/ 2 months-12 months	Symptomatic relief in 33 patients, partial to complete lesion clearance in 31
Kaliakatsou et al.	Open clinical phase II trial	17	Erosive/Ulcerative	0.1%	8 weeks/ 22 weeks	All patients responded positively
Olivier et al.	Prospective	8	Erosive	0.1mg tacrolimus in 100ml water (Mouthwash)	6 months/6 months	All responded well initially for a year
Morrison et al.	Open Clinical Trial	6	Erosive	0.1%	10 weeks / 3 months	All patients responded positively
Hodgson et al.	Prospective	50	Erosive/Ulcerative	0.1%	8 weeks/ 19.8 months	14% complete resolution and 80% partial resolution of OLP
Eckardt et al.	Prospective	18	Erosive/Ulcerative	0.1%	8 weeks/22 weeks	55% complete clearance of lesion, 94% symptomatic relief
Thomson et al.	Retrospective	23	Erosive	0.1%	6 weeks/ 4-29 months	Clinical improvement in 21 patients
Lozada-Nur et al.	Prospective	10	7 Symptomatic OLP and 3 oral lichenoid lesions	0.1%	2weeks/ 4 weeks	All patients responded well
Laeijendecker et al.	Prospective randomized study	40	Erosive/ Ulcerative	0.1% tacrolimus in 20 patients and 0.1% triamcinolone acetonide in 20 patients	6 weeks/3 months	Better response to tacrolimus
Corrocher et al.	Randomized control trial	32	Symptomatic OLP	0.1% tacrolimus in 16 and 0.05% clobetasol in 16 patients	4 weeks/ 6 weeks	43.7% of patients maintained complete pain remission
Radfar et al.	Randomized double blind study	30	Erosive/ Ulcerative	0.1% tacrolimus in 15 and 0.05% clobetasol in 15 patients	6 weeks/ 9 months	Reduction in mean lesion sizes were 82.6% in the tacrolimus group and 81.6% in the clobetasol group
Sonthalia S, Singal A	Randomized Controlled Trial	40	Symptomatic OLP	0.1% tacrolimus in 20 patients, 0.05% clobetsol in 20 patients	8 weeks/ 12 weeks	Complete or partial response at 12 weeks: 90% with clobetasol, 95% with tacrolimus