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Case Series

# Evaluation of Muco-adhesive Tacrolimus Patch in Oral Lichen Planus

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## Abstract

**Background and Aim:** Tacrolimus (TAC) is an immunomodulator drug. This study aimed to evaluate the clinical effectiveness of topical TAC patches for symptomatic treatment of erosive/atrophic oral lichen planus (OLP).

**Materials and Methods:** Twenty patients complaining of symptomatic erosive/atrophic OLP were treated by applying topical TAC 0.1% patch twice daily for 8 weeks. Each patient was assessed for painful symptoms using visual analog scale (VAS) at baseline, 2, 4, and 8 weeks of treatment, and were followed for 4 weeks of treatment free period. The clinical improvement grading (CIG) was also calculated for the study intervals.

**Results:** TAC patch resulted in significant reduction in VAS [-70.21% (15.82)] within the first two weeks, and this was observed throughout the treatment period, all patients were symptoms free and showed dramatic clinical improvement with most of the lesions disappeared by the end of the study.

**Conclusion:** Tacrolimus 0.1% patch was well tolerated and significantly reduced painful symptoms and induced rapid and sustained clinical improvement in management of symptomatic OLP with minimal and transient side effects.

**Keywords:** Oral Lichen Planus; Tacrolimus; Patch; Visual Analog Scale; Clinical Improvement Grading

## Abbreviations

OLP: Oral Lichen; VAS: Visual Analogue Scale; TAC: Tacrolimus; HPMC: Hydroxypropyl Methyl Cellulose; CIG: Clinical Improvement Grading; PIP2: Phosphatidylinositol 4,5-Bisphosphate

## Introduction

Oral lichen planus (OLP) is a T-cell-mediated disorder affecting the oral mucosa [1]. There are of OLP lesions are presented as reticular, papular, plaque-like-white, atrophic (erythematous), erosive (ulcerated), or bullous-red forms, which may occur alone or in various combinations [2].

Many reviews on OLP therapy recommend topical steroids as the first-line treatment for symptomatic OLP. However, other therapies represented effective alternatives for its management but required further research [3].

Calcineurin inhibitors (cyclosporine; tacrolimus and pimecrolimus) are immunomodulators that bind to intracytoplasmic proteins in T-lymphocytes, which inhibit calcineurin, thus suppress transcription and production of variable cytokines and could have a role in management of immune-mediated lesions [4].

Calcineurin inhibitors in the treatment of symptomatic OLP have yielded promising results in various clinical trials [5-7]. Furthermore, topical tacrolimus was a safe and effective alternative to topical corticosteroids for OLP treatment according to recent systematic reviews and meta-analysis [8,9].

The muco-adhesive buccal film provides the advantage of advanced retention time, increased patient compliance, prolonged release of the drug and better bioavailability at the site of action [10]. A published in vitro and in vivo study had investigated the use of muco-adhesive tacrolimus patch for oral mucosal delivery as a drug model conducted on goat mucosa and showed promising results [11]. We hypothesized in the current study that tacrolimus delivered via a mucoadhesive patch could improve clinical outcomes and patient compliance. Thus, this study aimed to evaluate the clinical efficacy of tacrolimus 0.1% in mucoadhesive patches.

## Materials and Methods

### Sample size calculation

We postulated that if the visual analog scale (VAS) dropped a minimum of 20% with tacrolimus patch, it would mean clinically significant improvement based on the outcome of previous clinical trial [12]. Assuming decrease of this size with one tailed p-value of 0.05 and power of 0.80, we calculated that 20 patients will be recruited for this study using G-power analysis program (G*Power version 3.1.9.7).

### Patients' recruitment criteria

This study was a prospective, 12-week pilot study that included 20 patients diagnosed with erosive or atrophic OLP lesions. Patients were recruited from the out-patient clinic in the Department of Oral Medicine, Oral Diagnosis and Periodontology, Faculty of Dentistry, Ain Shams University, and Faculty of Oral and Dental Medicine, Future University.

This study included both genders, systemically free with age ranged from 25 to 60 years old, having clinically symptomatic painful erosive or atrophic OLP and histologically confirmed according to the American Academy of oral and maxillofacial pathology [12] as shown in (Figure 1). The exclusion criteria were pregnancy, breast-feeding, smoking, history of drug-induced lichenoid lesions, loss of pliability or flexibility in the tissues involved by the oral lesions of lichen planus, potential treatment of OLP for less than 2 weeks by topical and 4 weeks' systemic therapy before study, and known hypersensitivity or severe adverse effects to the treatment drugs or to any ingredient of their preparation [13].

### Patients' grouping, treatment protocol, and interventions

At baseline, all patients had full mouth rehabilitation including self-performed plaque control measures, full mouth scaling and removal of any local irritating factors if needed. Patients were instructed to apply the tacrolimus buccal mucoadhesive patch (TAC patch) on the most painful lesion as shown in (Figure 2). twice daily for 8 weeks. The patches were fabricated in (Nano-Gate Company, Mokattam, Cairo, Egypt) as following [10% Tacrolimus (0.1% weight/weight [w/w]), Chitosan 2% (weight/volume [w/v]), 3% w/v hydroxypropyl methyl cellulose (HPMC) in addition to propylene glycol, acetic acid and citric acid in 100ml distilled water [11]. Patients were instructed to apply slight pressure on the entire surface of the patch at the time of application, to avoid chewing or excessive jaw movements, and to avoid eating or drinking for at least 1 hour following application of the patches [14].

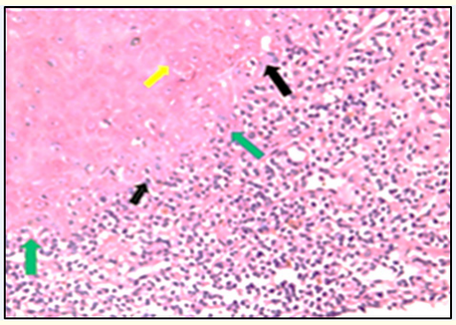

**Figure 1:** Photomicrograph of OLP specimen at baseline showing dead keratinocytes (civatte bodies) (yellow arrow), vacuoles in the basal cell layer (black arrow) lymphocytic infiltrate obscuring the epithelial-connective tissue junction (green arrow) (H and E. 40X).

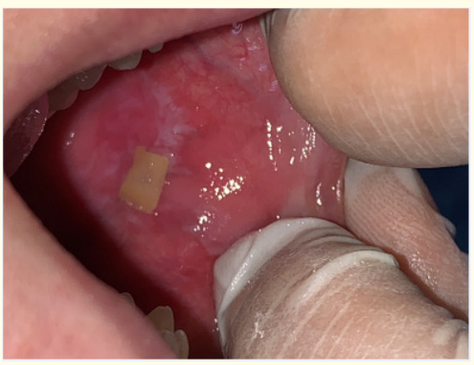

**Figure 2:** Tacrolimus mucoadhesive patch applied to the OLP lesion on the buccal mucosa.

### Clinical assessment

Patients were evaluated in 4 visits over the course of the 12-week study: at baseline, at the end of the 2nd, 4th, and 8th weeks of treatment, and after 4 weeks of treatment cessation (12$^{th}$ week).

Patients ranked the severity of pain and burning sensation on a 100-mm visual analog scale (VAS) [15]. Any unwanted side effects were reported, and patients were examined generally for any abnormal vital signs or any alteration in the appearance of mucosa at each visit.

The clinical improvement Grading (CIG) was assessed as following; Grade 0 (No improvement), Grade I (Minimal improvement indicating mild subjective relief and small reduction in the lesion size), Grade II (Moderate improvement with obvious subjective relief and moderate resolution in the lesion size). Grade III (Dramatic improvement with remarkable subjective relief and most of the lesion disappeared) and Grade IV (The patient gets pain free and complete disappearance of the lesion) [16].

### Statistical analysis

Data was expressed in terms of mean and standard deviation [mean (SD)] or frequencies and percentages [n (%)] when appropriate. The data was explored for normality by checking the data distribution and using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Comparisons between different intervals with respect to normally distributed numeric variables were compared by the repeated measure ANOVA test, followed by a Tukey's post hoc test when ANOVA revealed a significant difference. Qualitative variables were expressed as numbers and percentages and were compared using the chi square test. A *P*-value of less than 0.05 was considered statistically significant for all variables. Statistical analysis was performed using SPSS Version 18 (SPSS Inc., Chicago, IL, USA).

## Results and Discussion

### Results

A total of thirty-four patients were examined for eligibility for this study between January 2019 and November 2020. Twenty patients of them [17 females (70%) and 3 males (30%)] were diagnosed clinically and histopathologically with oral lichen planus. Patients' mean age (SD) was 55.8 (11.88) years, the average disease duration was 5.7 (3.02) months, 7 were erosive form (35%) and 13 (65%) were atrophic form. All patients were committed to the treatment protocol throughout the twelve weeks of the study period with no dropouts. The only reported adverse effect was mild burning sensations in 4 patients (20%) in the 1st week and the symptoms disappeared without any medication at the beginning of the 2nd week, there were no complaints of gag reflex or incompliance from any patient.

The Tacrolimus patch resulted in a high reduction in VAS [-70.21% (15.82)] within the first two weeks and this was observed throughout the treatment period, all patients were symptoms free as shown in (Figure 3). As for clinical improvement grading, by the end of the second week, 70% of the patients showed moderate improvement, by the end of the 4th week, 70% of the patients showed dramatic improvement, by the end of the 8th week, 90% of the patients showed dramatic improvement while by the 12th week, 90% of the patients were free of lesions and symptoms (Figure 4). Clinical changes in OLP lesions with TAC patch were observed in photographs in (Figure 5).

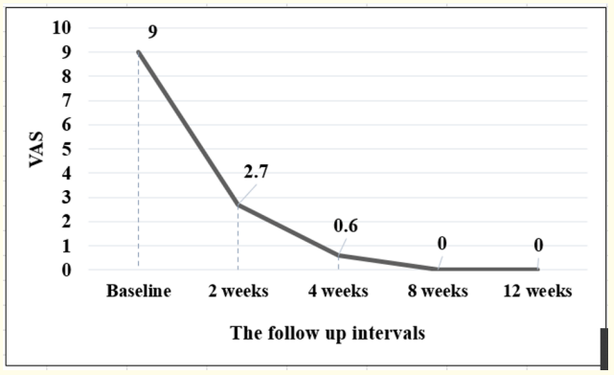


**Figure 3:** Line graph showing reduction of visual analog scale VAS through study intervals.

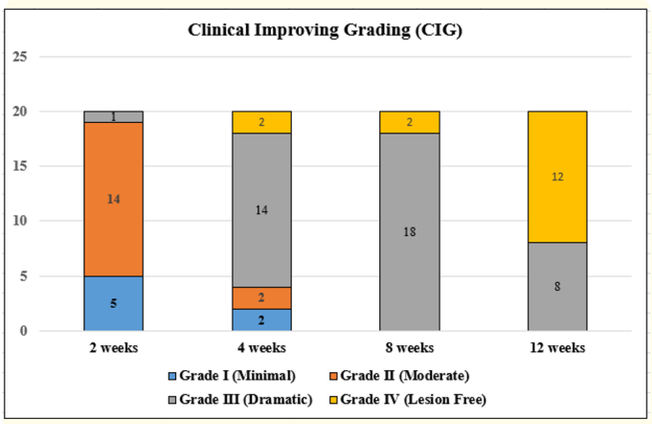


**Figure 4:** Bar graph showing changes in percentage of clinical improvement grading (CIG) through study intervals.

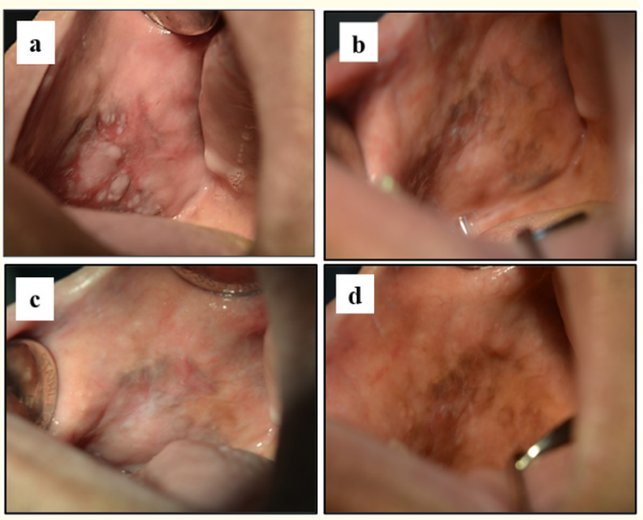


**Figure 5:** (a) Photograph of erosive oral lichen planus lesion in the buccal mucosa at baseline. (b) Reduction in lesion size and severity by topical Tacrolimus patch after 2 weeks' treatment. (c) Dramatic clinical improvement of the lesion after 4 weeks' treatment. (d) Complete healing of oral lesions treated with Tacrolimus patch after 4 weeks' treatment free period (12th week of the study).

## Discussion

Tacrolimus in an oral patch carrier system was used for the management of OLP. The patch was applied only 2 times/day because its release profile ranged from 10- 12 hours and the patch disintegration time was 30- 45 minutes with minimal salivary washout [11].

The study demonstrated that tacrolimus patch showed significant reductions in VAS after treatment termination. These results were consistent with other studies which used calcineurin inhibitors [6,9,17].

Topical application of tacrolimus could initially stimulate sensory neurons through substance P release. This would explain the transient burning or painful sensations documented in tacrolimus groups. However, the calcium influx provoked by the neuron activation probably led to a depletion of phosphatidylinositol 4,5-bisphosphate (PIP2) and subsequent inactivation of the calcium channels [18]. This would explain the analgesic effect which was maintained by close contact and deep penetration associated with the patch, which was consistent with Ahmed., *et al*. 2018 who reported that at the end of 12$^{th}$ week follow-up periods, complete relief of pain and burning sensation with 0.1% tacrolimus gel was 100% [19].

## Conclusion

Generally, this study showed that topical tacrolimus patch had initial rapid clinical effect with high patient compliance. The study was limited by the short follow-up, precluding the opportunity to evaluate the relapse rate and highlighted the need to assess treatment efficacy and durability with further randomized controlled clinical trials.

## Conflict of Interest

The authors declare that they have no conflict of interest.

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