Evaluation of Serum Desmoglein 1 and Desmoglein 3 in Oral Erosive Lichen Planus before and after Topical Application of Tacrolimus

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ABSTRACT

Aim: The current study will attempt to throw light on the role of desmoglein 1 and desmoglein 3 in the pathogenesis of erosive lichen planus and their response to topical application of tacrolimus.

Materials and methods: Twenty patients with erosive oral lichen planus received tacrolimus ointment three times daily for eight weeks. Assessments using the clinical score and a visual analog scale were recorded at each visit. Serum concentrations of circulating autoantibodies to desmoglein 1 and desmoglein 3 will be determined by enzyme-linked immunosorbent assay (ELISA) at baseline, four weeks and eight weeks after treatment. Statistical software SPSS v.17.0 was used for statistical analysis.

Results: All patients showed significant improvement in all outcomes within the follow-up periods when compared with the baseline (p < 0.05). The mean value of the visual analog scale were 8.30 ± 1.49, 4.15 ± 1.14, 2.10 ± 0.91, 0.90 ± 0.79, and 0.0 ± 0.0 starting from baseline to the end of follow up period. The mean value of the clinical score were 4.7 ± 0.48, 2.9 ± 1.29, 1.8 ± 1.32, 1.31 ± 0.69, and 0.69 ± 0.09 starting from baseline to the end of follow-up period. There was a significant decrease in the levels of anti-Dsg1 and anti-Dsg3, during the follow-up period (p ≤ 0.05).

Conclusion: The concluded data suggest that antibodies against desmoglein 1 and desmoglein 3 seem to play a key role in the pathogenesis of oral lichen planus. Also, there is a significant decrease in the level of anti-Dsg1 and anti-Dsg3 autoantibodies with topical tacrolimus 0.1% ointment.

Clinical significance: Monitoring the serum level of antibodies against keratinocyte cadherins Dsg 1 and Dsg 3 can be used to evaluate the effect of topical application of tacrolimus on Erosive Oral lichen planus.

Keywords: anti-Dsg1, anti-Dsg3, Oral erosive lichen planus; Topical tacrolimus.

INTRODUCTION

Oral lichen planus (OLP) is a long-lasting immunologic, inflammatory mucocutaneous disorder of obscure etiology that is characterized by several episodes of relapse and remissions.1,2 It is a relatively common disease assessed to influence 0.5 to 2% of the general population.3,4 Clinically, six types of OLP have been depicted: reticular, papular, plaque, atrophic, erosive or ulcerative and bullous, but the lesions are frequently observed as white, erythematous and/or ulcers.5

It is believed that OLP represent an abnormal immune reaction in which keratinocytes are recognized as an antigen, secondary to changes in the antigenicity of the cell surface, eliciting an immune response characterized by invasion of inflammatory cells into the subepithelial layer of connective tissue with degeneration of the epithelium of the basal membrane,6 however, the antigen or antigens triggering factors have not been identified.7

Humoral immunity had been reported to play a role in the pathogenesis of OLP in addition to the presence of immunoglobulins, fibrinogen, and C3 complement in the basement membrane at the lesional and perilesional...
tissue, and concentrations of salivary IgG and IgA sub-classes may also be changed. Although, Ingafou et al. revealed that OLP was not related to IgG circulating antibodies to epithelial antigens, there are other studies suggest the chance of the presence of circulating antibodies to Desmoglein 1 (Dsg1) and Desmoglein 3 (Dsg3) in patients suffering from OLP.

Desmoglein was described as a calcium-binding transmembrane glycoprotein component of desmosomes in epithelial cells and identified as the autoantigen of the autoimmune diseases like pemphigus and erosive lichen planus. Autoantibodies against Dsg1 and Dsg3 desmosomal cadherins usually presented in stratified squamous epithelia and involved in cell-to-cell adhesion, play an important role in the pathogenesis of autoimmune blistering diseases, destroying desmosomes followed by acantholysis. At present, commercial ELISA tests for antibodies against Dsg1 and Dsg3 are available and have been used as a routine indicative method for diagnosis of autoimmune blistering diseases.

Till now, there is no definitive cure for OLP, although that there is a variety of medications they are palliative as opposed to therapeutic. The primary role of the treatment is to reduce the duration and severity of symptomatic exacerbation episodes. Excellent oral hygiene is suggested to play a role in reducing the severity of the symptoms especially those with gingival involvement, yet it can be troublesome for patients to accomplish high levels of hygiene during periods of active disease.

Since the etiology of OLP stays obscure, most treatments were aimed to relieve symptoms only. Atrophic and erosive subtypes exhibit resistant to systemic and topical therapy and have a low-resolution rate. Topical corticosteroids were considered first-line treatment; short-acting systemic corticosteroids were also frequently used. Other agents, such as topical or systemic retinoids, griseofulvins, psoralen and ultraviolet A (PUVA) therapy, and nonsteroidal anti-inflammatory drugs, have been utilized as an alternative treatment for OLP particularly for patients respond poorly to or who developed adverse effects from prolonged administration of corticosteroids.

Another immunosuppressive drug that had been introduced in the management of autoimmune blistering lesions was tacrolimus which is also called FK 506, it was derived from Streptomyces tsukubaensis, where its immunosuppression activity was observed to be like cyclosporine despite the fact that it can infiltrate profoundly in the mucosa and is 10 to 100 times more potent in comparison to cyclosporin.

Tacrolimus was first manufactured as a systemic drug to prevent allograft rejection in kidney, liver, and heart transplantation. Furthermore, it has been utilized as a part of the treatment of other immunologic diseases such as psoriasis, Behçet disease, pyoderma gangrenosum and nephrotic syndrome. Its topical use has been utilized in the management of atopic dermatitis, contact allergy, and corticosteroid-induced rosacea. It inhibits inflammation as steroids without causing skin thinning (atrophy), or other steroid-related side-effects. Topical tacrolimus has additionally been used in the management of oral mucosal lesions of MMP, PV of the lip and the oral ulceration of oral Crohn’s disease.

In March 2005, a public health advisory report for the healthcare professionals and patients about a potential cancer risk may result from the use of tacrolimus has been published by the United States Food and Drug Administration (FDA), this report was supported on the findings of animal studies and case reports in a small number of patients. On the other hand, the Academy of Dermatology Association Task Force has found no evidence that the use of topical immunomodulators plays a role in lymphoma or non-melanoma skin cancer, and the systemic immunosuppression after short-term or intermittent long-term topical application seems to be an infrequent side effect. It has been stated that studies involving periods of 10 or more years would be needed to determine whether or not treated with these drugs is associated with an increased risk of cancer.

To date, there is no report in English literature on the therapeutic effects of topical tacrolimus on the serum autoantibodies to Dsg1 and Dsg3 in patients with erosive oral lichen planus (EOLP). To the best of our knowledge, the role of Dsg1 and Dsg3 in the pathogenesis of EOLP has not been verified in response to topical tacrolimus ointment and the current study will attempt to throw light on their possible role if present.

MATERIALS AND METHODS

Subjects

Twenty adult patients (14 females and 6 males) who were previously diagnosed with OLP were included in this study. There were selected from the outpatient clinic of Oral Medicine, Periodontology, Oral Diagnosis and Radiology Department, Faculty of Dentistry, Alexandria University. An informed consents were obtained from all patients after providing detailed information and description of the study to all patients.

The selected patients were suffering from a painful histologically proven erosive OLP of no less than 10 mm in the longest dimension of the lesion. Confirmation of diagnosis after obtaining an oral mucosal incisional biopsy of approximately 5 mm from the most clinical representative part of the lesion before application of the treatment (baseline).
The diagnosis was based on the clinical and histopathological examination according to WHO criteria.\textsuperscript{38,39} The clinical criteria included the presence of unilateral or bilateral, painful lesions with presence of a lacylike network of slightly raised grey white lines. Erosive form of OLP lesions was only accepted in our study. The histopathological criteria include the presence of a well-defined band-like zone of infiltration mainly lymphocytes confined to the superficial part of the connective tissue, liquefaction degeneration in the basal cell layer and absence of epithelial dysplasia.\textsuperscript{40}

**Study Inclusion/Exclusion Criteria**

All patients included in this study were selected according to the following criteria:

**Inclusion Criteria**

Age ranged from thirty to sixty years with a mean of 47.8 years, clinically and histologically proven EOLP based on the modified WHO diagnostic criteria for OLP.

**Exclusion Criteria**

Presence of dermatologic and/or genital lesions with histopathologic signs of epithelial dysplasia based on WHO criteria of oral epithelial dysplasia,\textsuperscript{41} Drug-induced lichenoid reactions, previous treatment with topical or systemic corticosteroids and/or immunosuppressant drugs within the last eight weeks, chronic liver disease, hematologic disorders and pregnant or nurserywomen.

**Pretreatment Evaluation**

*History:* Full detailed patient history was obtained from the selected patients including name, age, sex, onset, smoking habit, symptoms, medical history, drug history, any extra-oral lesions and any previous treatments

*Clinical Examination:* Examination of all clinical signs of erosive OLP, distribution of the lesion, the extension of the lesions was recorded photographically, and baseline data were collected.

*Histological Examination:* Incisional biopsy was obtained from the area of the lesion under local anesthesia before treatment using disposable blade number 15, fix it in 10% neutral buffered formalin (PH 7.4) for 24 hours at least then send to lab of Oral Pathology Department, Faculty of Dentistry, Alexandria University, where it was processed for histopathological evaluation.

**Treatment Protocol**

The selected patients of were instructed to apply a thin layer of tacrolimus ointment 0.1% (Protopic\textsuperscript{®} Astellas Pharma Manufacturing, Grand Island, USA) on the oral lesions, three times daily, for 8 weeks.

**Treatment Schedule**

Before starting the treatment (baseline) and during each visit, subjective and objective assessments were recorded for each patient. All patients were instructed to apply the medications on dried lesions after meals without eating, drinking, smoking or speaking for at least thirty minutes afterward and the last time before sleeping. The reasons for this administration schedule were to achieve patient compliance and to achieve effective numbers of application of the treatment because topical agents do not easily adhere to the moist mucous membranes.

Chlorhexidine mouthwash was also recommended every night; also, Nystatin (Bristol-Myers Squibb Corporate, USA) oral suspension, the most common preventive measure for oral candidiasis, was prescribed once daily during the follow-period.

**Posttreatment Evaluation**

**Clinical Evaluation**

All patients were evaluated regularly at two weeks interval before and after treatment for eight weeks.

**Subjective Evaluation**

Visual analog scale (VAS) had been used for subjective evaluation, which consisted of a 10 cm horizontal line marked 0–10 (0 no pain 10 most severe pain experienced).\textsuperscript{42} In the present study the score of 9 or 10 was arbitrarily defined as very severe, 7 or 8 as severe, 5 or 6 as moderate, 3 or 4 as mild, and 1 or 2 as asymptomatic. Patients were requested to point the scale each follow-up visits. In this way, it was possible to obtain the patient’s own evaluation without any interference and/or interpretation by the clinical investigators. Based on the score, it was possible to distinguish the treatment outcomes as no effect (same score of symptoms at the two subsequent visits) partial response (reduction in score of symptoms), complete response (complete absence of symptoms) and worsening. All patients were assessed at baseline (before the treatment) and regularly after treatment every other week at the 2nd (visit 1), 4th (visit 2), 6th (visit 3) and 8th (visit 4) weeks.

**Objective Evaluation**

The most severe and extensive lesion was identified and digitally photographed to be used as a reference point. All photos were evaluated for areas of erosion, and ulceration before and after application of the topical therapy by visual examination using clinical scoring (CS) set by Thongprasom et al.\textsuperscript{43,44} (Table 1).
Influence of Topical Tacrolimus on Dsg1 and Dsg3 in OELP

Table 1: Clinical scoring

<table>
<thead>
<tr>
<th>Score</th>
<th>Clinical lesion</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>Represented no lesion/normal mucosa.</td>
</tr>
<tr>
<td>1</td>
<td>Mild white striae/no erythematous area.</td>
</tr>
<tr>
<td>2</td>
<td>White striae with atrophic area less than 1 cm².</td>
</tr>
<tr>
<td>3</td>
<td>White striae with atrophic area more than 1 cm².</td>
</tr>
<tr>
<td>4</td>
<td>Whitestriae with erosive area less than 1 cm².</td>
</tr>
<tr>
<td>5</td>
<td>Whitestriae with erosive area more than 1 cm².</td>
</tr>
</tbody>
</table>

The score of each visit was statistically compared to the baseline. The differences between baseline and scores of each visit numerically express the clinical and symptomatic improvement.

Serum Immunological Study

Sera were collected from all patients and stored at -20°C. Serum levels of circulating autoantibodies to Dsg1 and Dsg3 were detected by ELISA at baseline, 4th week and 8th week after treatment.

Detection of Autoantibodies to Dsg1 and Dsg3

MESACUP Desmoglein test was performed to detect autoantibodies to both Dsg1 and Dsg3 by using Commercial enzyme-linked immunosorbent assay (ELISA) kits (Medical and Biological Laboratories Co. Ltd, Nagoya, Japan). According to the manufacturer’s instructions, patients sera were diluted X100 and tested in duplicate. Autoantibodies to Dsg1 and Dsg3 were detected by horseradish peroxidase-conjugated anti-human IgG with tetra-methyl-benzidine as a substrate. The optical densities were read by the Dynatech MRX Microplate Reader at 450 nm, with 650 nm reference filter. The results were presented in units per milliliter of sera (U/mL).45

Statistical Analysis

The results were statistically analyzed using the Statistical Package for Social Sciences (SPSS for Windows, release 17 Chicago, IL.). The statistical test used as follows:

- Number and percent of each category.
- Mean and standard deviation (SD) for numerical data.
- Yates corrected chi-square test used for analysis of categorical data.
- Wilcoxon matched pairs signed ranks test: A non-parametric significant test used to compare paired ordinal data.
- Mann Whitney test used for comparison between unpaired signed ranks test.

RESULTS

Clinical Data

Out of 20 subjects, 6 were males, and 14 were females with age range from 36 to 57 years with a mean of 46.30 ± 6.95 years. The duration of the lesion before diagnosis ranged from 3 to 48 months with a mean of 19.10 ± 6.95 months (Table 2).

The sites of the lesions were on buccal mucosa (100%), tongue (50%), lip (25%), alveolar mucosa (15%), and finally retromolar area (5%) (Table 3).

Therapeutic Data

Tables 4 and 5 demonstrate the results of a clinical status score (CS) and VAS score at baseline, 2nd, 4th, 6th and 8th weeks. In this study, tacrolimus resulted in a suppression of painful symptoms, the lesion dimension and improved patient’s quality of life during the period of 8 weeks. The improvement
started to appear after 2 weeks of drug application. There were significant differences from baseline of till the end of the follow-up period in terms of VAS and CS scores, \((p > 0.05)\).

**Clinical Presentation before and after Treatment with Topical Tacrolimus**

**Base Line Appointment**

Clinical examination of patient before application of Tacrolimus revealed mixed red and white lesions with areas of ulceration and Wickham striation (Figs 1A and B).

**Visit 1 (after 2 weeks)**

Clinical examination of the patient after 2 weeks of treatment with Tacrolimus revealed a partial improvement of the lesion. (Figs 2A and B).

**Visit 2 (after 4 weeks)**

More regression and improvement of the lesion were observed after 4 weeks of treatment with Tacrolimus. The erythema was further reduced, and ulceration was disappeared (Figs 3A and B).

**Visit 3 (after 6 weeks)**

More regression and improvement of the lesion were observed after 6 weeks of treatment with Tacrolimus. The erythema was further reduced, and ulceration was disappeared (Figs 4A and B).

**Visit 4 (after 8 weeks)**

Complete regression and improvement of the lesion were observed in the last visit after 8 weeks of treatment with Tacrolimus. The complete absence of erythema in the OLP lesions (Figs 5A and B).

**Table 4:** Mean and standard deviation of CS in studied groups at baseline and after treatment

<table>
<thead>
<tr>
<th>Studied groups</th>
<th>Baseline</th>
<th>2 weeks</th>
<th>4 weeks</th>
<th>6 weeks</th>
<th>8 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Group 4</td>
<td>4.7 ± 0.48</td>
<td>2.9 ± 1.29</td>
<td>1.8 ± 1.32</td>
<td>1.31 ± 0.69</td>
<td>0.69 ± 0.09</td>
</tr>
<tr>
<td>p-value</td>
<td>---</td>
<td>(p &lt; 0.001)**</td>
<td>(p &lt; 0.000***)</td>
<td>(p &lt; 0.000***)</td>
<td>(p &lt; 0.000***)</td>
</tr>
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</table>

*Significant \(p < 0.05\); **\(p < 0.001\) moderate significance; ***\(p < 0.000\) highly significance

**Table 5:** Mean and standard deviation of VAS in the studied groups at baseline and after treatment

<table>
<thead>
<tr>
<th>Studied groups</th>
<th>Baseline</th>
<th>2 weeks</th>
<th>4 weeks</th>
<th>6 weeks</th>
<th>8 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Group 4</td>
<td>8.30 ± 1.49</td>
<td>4.15 ± 1.14</td>
<td>2.10 ± 0.91</td>
<td>0.90 ± 0.79</td>
<td>0.0 ± 0.0</td>
</tr>
<tr>
<td>p-value</td>
<td>---</td>
<td>(p &lt; 0.001***)</td>
<td>(p &lt; 0.001***)</td>
<td>(p &lt; 0.001***)</td>
<td>(p &lt; 0.000***)</td>
</tr>
</tbody>
</table>

* \(p < 0.05\) significant; **\(p < 0.001\) moderate significance; ***\(p < 0.000\) highly significance

Serum concentrations of circulating autoantibodies to Dsg1 and Dsg3 were determined by ELISA at baseline, 4th week and 8th week after treatment.

For anti-Dsg1 ELISA, 16 of 20 sera from patients (80%) showed positive scores at baseline and for anti-Dsg3 ELISA, 19 of 20 sera from patients (95%) showed positive scores at baseline.

The level of anti-Dsg1 in EOLP patients was ranged from 8.40 to 130.30 with a mean of 48.88 ± 37.87 and

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**Figs 1A and B:** Clinical photographs of a patient with bilateral atrophic-erosive OLP on posterior buccal mucosa and before tacrolimus application
median of 38.85 before treatment (baseline). After 4 and 8 weeks of using topical tacrolimus ointment 0.1% in the same patient, the level of anti-Dsg1 were ranged from 1.65 to 54.45 with a mean of 17.15 ± 15.61 and median of 12.05, and 0.49 to 10.35 with a mean of 4.31 ± 3.65 and median of 3.80 respectively (Table 6).

Upon comparing between the different periods regarding the level of anti-Dsg1, it was found that there...
was a significant decrease in the level from baseline after 4 and 8 weeks (p ≤ 0.05).

On the other hand, the level of anti-Dsg3 in EOLP patients was ranged from 6.65 to 43.55 with a mean of 21.59 ± 11.81 and median of 17.95 before treatment (baseline). After 4 and 8 weeks of using topical Tacrolimus ointment 0.1% in the same patient, level of anti-Dsg3 were ranged from 0.43–15.13 with a mean of 6.36 ± 4.69 and median of 6.13, and 0.18–3.38 with a mean of 1.15 ± 1.03 and median of 0.88 respectively (Table 7).

Upon comparing between the different periods regarding the level of anti-Dsg3, it was found that there was a significant decrease in the level from baseline and after 4 weeks and after 8 weeks (p ≤ 0.05).

DISCUSSION

EOLP is a chronic, inflammatory, and often mucosal disease manifested by persistent, painful and burning erythema and erosions. It is one of the potentially malignant disorders as it predisposes to squamous cell carcinoma development which often recalcitrant to treatment; hence its optimal treatment continues to be a considerable issue for the clinicians.

Several topical and systemic modalities have been implicated in the management of symptomatic EOLP including immunosuppressants such as a corticosteroid, cyclosporine, tacrolimus, antifungal agents, retinoid, diode laser, PUVA etc.48

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**Table 6:** Comparison between the different periods according to anti-Dsg1.

<table>
<thead>
<tr>
<th>Anti-Desmoglein 1</th>
<th>Base line</th>
<th>4 weeks</th>
<th>8 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Range</td>
<td>8.40–130.30</td>
<td>1.65–54.45</td>
<td>0.49–10.35</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>48.88 ± 37.87</td>
<td>17.15 ± 15.61</td>
<td>4.31 ± 3.65</td>
</tr>
<tr>
<td>Median</td>
<td>38.85</td>
<td>12.05</td>
<td>3.80</td>
</tr>
<tr>
<td>P₁</td>
<td>&lt;0.001*</td>
<td>&lt;0.001*</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>P₂</td>
<td>*: Statistically significant at p ≤ 0.05</td>
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</tbody>
</table>

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**Table 7:** Comparison between the different periods according to anti-Dsg3.

<table>
<thead>
<tr>
<th>Desmoglein 3</th>
<th>Base line</th>
<th>4 weeks</th>
<th>8 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Range</td>
<td>6.65–43.55</td>
<td>0.43–15.13</td>
<td>0.18–3.38</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>21.59 ± 11.81</td>
<td>6.36 ± 4.69</td>
<td>1.15 ± 1.03</td>
</tr>
<tr>
<td>Median</td>
<td>17.95</td>
<td>6.13</td>
<td>0.88</td>
</tr>
<tr>
<td>P₁</td>
<td>&lt;0.001*</td>
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</tr>
<tr>
<td>P₂</td>
<td>*: Statistically significant at p ≤ 0.05</td>
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Figs 5A and B: Clinical photographs of the same OLP patient after 8 weeks of treatment with tacrolimus showing nearly a complete regression of the lesion.
As for intractable EOLP lesions and topical corticosteroids side effects (drug tolerance and insensitivity, pseudomembranous candidiasis, and mucosal atrophy), second-line topicals such as calcineurin inhibitors seem to be a promising and effective treatment.46

The patients participated in the present study aged from 36 to 57 years. This age range was chosen because it is the typical age of OLP presentation.47 Lesions were localized to the buccal mucosa since the buccal mucosa is the most commonly involved site and for the ease of patients comparison.46

Patients with skin lesions were excluded as they need both topical and systemic treatment; also epithelial dysplasia was also excluded because the condition is more likely to progress to cancer.49 Previous treatment with topical or systemic corticosteroids and/or immunosuppressants drugs within the last eight weeks was excluded to avoid interference with the study results. Patients with chronic liver disease and HCV did not participate in the current study because of the mysterious relationship between OLP and liver disease. The fear of teratogenic effects led to exclusion of the pregnancy; also excretion of both medications into the breast milk led to the exclusion of the nursing mothers.50,51

The methods employed for evaluation included clinical CS for lesions appraisal and VAS for pain assessment.44 These methods are used in the present study because they are easy to use and widely accepted to record and monitor OLP activity.52

In the present study, tacrolimus has been found useful in the treatment of EOLP. This is manifested by the significant improvement of CS and VAS. There were significant differences between in the regression of the lesion from baseline to week 8 from the application of topical tacrolimus ointment 0.1%. The effectiveness of tacrolimus in EOLP may be attributed to local inhibition of T-lymphocyte activation.

These results have been found to be in agreement with several clinical studies that have suggested effective treatment of OLP by tacrolimus.53-55 Lozada-Nur and Sroussi.56 reported in an open clinical trial study that disease control was achieved in most of ten patients participated in the study by the end of two weeks after treatment with tacrolimus powder in orabase 0.1% three times a day. Likewise, Læijendecker et al.,57 reported that tacrolimus induced a better therapeutic response than the steroid in a prospective study of 40 patients where 18 out of 20 patients healed or improved in the tacrolimus group, while nine out of twenty patients healed or improved in the triamcinolone group.

On the other hand, Radfar et al.,58 in a comparative study of 30 patients, found no difference between tacrolimus and clobetasol in the treatment of OLP. They suggested that the cause of their result could be because clobetasol is a stronger topical steroid than triamcinolone.

Adverse-effects such as burning sensation, transient taste disturbance, and nausea after application of treatments have occurred. The most frequent adverse-effect was a temporary burning sensation at the site of application lasting for about 10 to 30 minutes; however, it did not lead to suspension of the treatment in any patient. Furthermore, the local irritation after treatment was essentially decreased when the lesions turned out to be less erosive. These findings are in consistency with Rozycki et al.,53 where it was reported, in a retrospective review of 13 patients with symptomatic OLP, that burning sensation was experienced in two patients.

Also Kaliakatsou et al.,54 reported, in an open trial study of nineteen patients, that burning sensation was experienced by seven patients, but was decreased within 72 hours after the cessation of topical tacrolimus therapy. On the other hand, Lozada-Nur and Sroussi55 reported the absence of burning sensation at the site of application of the tacrolimus powder in Orabase. They conjectured that the vehicle in the tacrolimus ointment might in part contribute to the burning sensation. Furthermore, tacrolimus powder in orabase may have a different degree of mucosal penetration.

The production of recombinant Dsg1 and Dsg3 molecules has provided the opportunity to determine levels of antibodies to them (anti-Dsg1 IgG and anti-Dsg3 IgG respectively) and see if they correlate with disease severity. ELISA is a simple and effective tool for the quantitative analysis of antibody levels.59

In 1997, Ingafou et al.,45 revealed that OLP was not associated with circulating antibodies (IgG) to keratinocytes. However, they used indirect immunofluorescence to detect the presence of autoantibodies to the epithelial components of monkey esophagus instead of desmoglein autoantibodies, where Lukac et al.,45 likewise performed indirect immunofluorescence used the same substrate and found 21 positive among 37 tested patients with oral lichen planus. This distinction might result from different serum dilutions used for indirect immunofluorescence (1:100 dilution in Ingafou’s study vs. 1:20 used in Lukac’s study). However, the present study found significantly increased levels of both desmoglein autoantibodies in patients with the EOLP, which is in accordance with results of Lukac’s study.45

The results of the present study showed increased levels of both anti-Dsg1 and anti-Dsg3 autoantibodies, which were detected in the sera of patients with erosive form of oral lichen planus at baseline and with the use of topical Tacrolimus 0.1% results revealed a statistically significant decrease in the level of both anti-Dsg1 and anti-Dsg3 autoantibodies during the follow up period. In all of the EOLP patients, anti-Dsg1 and anti-Dsg3 ELISA values showed parallel fluctuation with disease activity, which is in accordance with the result of Lukac’s et al.45
CONCLUSION

Topical tacrolimus ointment 0.1% was found to be effective in relieving the symptoms and the resolution of the lesions of EOLP. The conclusions data suggests that humoral immunity against keratinocyte cadherins Dsg1 and Dsg3 seems to play a role in the diagnosis of oral lichen planus. Significant differences in their serum levels may be indicative of different immunopathogenic mechanisms involved in EOLP. Results revealed a statistically significant decrease in the level of both anti-Dsg1 and anti-Dsg3 autoantibodies with treatment with topical tacrolimus ointment 0.1%.

Further studies are suggested to evaluate its effect in a larger number of patients to establish its effectiveness, safety, and superiority over the other existing therapeutic modalities. The precise molecular mechanisms by which tacrolimus produces its effects on OLP also needs further elucidation.

CONSENT

All authors declare that written informed consent was obtained from the patient before conducting this research.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee (EA/5035/2018) and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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