Randomized trial of tacrolimus 0.1% ointment versus triamcinolone acetonide 0.1% paste in the treatment of oral pemphigus vulgaris

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Background: Pemphigus vulgaris is a rare autoimmune disorder characterized by cutaneous and mucosal blistering. Surprisingly, the management of oral lesions has been detailed only infrequently. As current topical therapies for oral lesions are of limited efficacy, application of calcineurin inhibitors is considered to be a potential option. The aim of this essay was to investigate the efficacy of tacrolimus 0.1% ointment (Protopic®) versus triamcinolone acetonide 0.1% paste (Volon-A®) in the treatment of oral pemphigus vulgaris.

Method: Fifteen patients were involved in a prospective randomized trial with a split- mouth design. After two weeks of administering study drugs, oral lesions were monitored and quantified pain and mucosal surface involvement scores were obtained.

Result: Within 14 days, the degree of involvement and pain scores significantly reduced in both tacrolimus-treated and triamcinolone-treated sites, but there was no significant difference between them. No severe adverse events were observed.

Conclusion: This study showed that tacrolimus could be as effective as triamcinolone acetonide in the topical treatment of oral pemphigus vulgaris**.**

Keywords: oral pemphigus vulgaris, tacrolimus, triamcinolone acetonide, treatment

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INTRODUCTION

Pemphigus vulgaris is a rare mucocutaneous disease, occurring at an approximate incidence of 0.5-3.2 per 100000 persons annually [1]. It affects mainly adults and only occasionally children and adolescents [2]. Pemphigus vulgaris ultimately produces oral lesions in nearly all patients and the oral cavity is the site of primary presentation in about 50-70% of the cases [3]. It has been suggested that this is due to the high amount of pemphigus antigen expression in the buccal mucosa [4]. Lesions are rarely composed of intact bullae, because most of them rupture and leave superficial painful erosions. Current treatments, largely based on systemic immunosuppression using systemic corticosteroids with azathioprine, dapsone, cellcept, methotrexate, cyclophosphamide, gold, cyclosporine and IVIG as adjuvants or alternatives, have significantly reduced its mortality [5,6]. Despite the high frequency of oral involvement in pemphigus vulgaris, there are surprisingly few recent studies on their management and possible topical therapies in combination with systemic drugs. Moreover, most topical therapies are empirical and randomized clinical trials (RCTs) are rare in this regard.

Corticosteroids are beneficial in the management of oral pemphigus vulgaris because of their anti-immunologic properties of suppressing T-cell function [7], but their prolonged use should be

avoided because of the associated adverse effects (skin atrophy, hypothalamic-pituitary-adrenal axis suppression, candidiasis overinfection, fragility and telangiectasia) [8,9].

Tacrolimus is a topical calcineurin inhibitor that binds to macrophillin-12 and subsequently inhibits dephosphorylation of the nuclear factor of activated T cells by calcineurin. This markedly reduces T-cell cytokine production [10,11]. Given the T-cell-mediated pathogenesis of pemphigus vulgaris, application of calcineurin inhibitors seems to be a promising therapeutic option.

The aim of this study was to compare the clinical efficacy and safety of topical tacrolimus 0.1% with the more commonly used triamcinolone acetonide 0.1% paste in treating oral pemphigus vulgaris.

PATIENTS AND METHODS

Participants

Fifteen adult patients (9 men and 6 women, mean age: 46 years) with pemphigus vulgaris of the oral cavity were included in this study. All participants had bilateral buccal lesions and histopathological and immunostaining confirmation of pemphigus on oral or cutaneous biopsies.

Inclusion criteria were confirmed pemphigus vulgaris: diagnosis was based on typical clinical manifestations, the histologic pattern of the lesions and direct immunofluorescence (DIF) study; presence of bilateral buccal erosions; and no topical immunosuppressive therapy (including corticosteroids or calcineurin inhibitors) in the last 2 weeks before the study.

Exclusion criteria were pregnancy or breast feeding; immunodeficiency or human immunodeficiency virus infection; current malignancy or malignancy in the history; known renal or hepatic insufficiency; known allergy to either immunomodulators or corticosteroids; and any viral infection affecting their mouths.

An informed written consent was obtained from each patient prior to inclusion in the study. This study was approved by the Ethics Review Board of Tehran University of Medical Sciences.

Study design and treatment protocol

This trial was performed as a pilot investigator-blind, randomized, single-centre clinical trial and had a split-mouth design. Randomization was performed according to a list made by simple randomization block (size of 4) design. This study was a single-blind trial in which the investigators (and not the patients) were unaware of drug allocation to each patient.

Fifteen individuals who met the eligibility criteria of the trial were subjected to a detailed review of their clinical history (age, sex, duration of disease, sites of involvement), drug intake and physical examination. After this initial visit, topical treatment with the study medications (tacrolimus ointment 0.1% (Protopic®) and triamcinolone acetonide paste 0.1% (Volon-A®)) was administered twice daily (in the morning and in the evening) for two weeks. Patients were carefully instructed to apply a thin layer of triamcinolone acetonide on one side and a thin layer of tacrolimus on the other side of buccal mucosa according to the randomization list. The patients were asked not to eat, drink or smoke for 30 minutes after each application. Moreover, all patients received systemic drugs (prednisolone with or without azathioprine) as their main treatment.

All patients were examined prior to study start and after 2 weeks (end of blinded treatment period). Both initial and final visits were performed by one blind investigator.

On each visit, quantified spontaneous and food-triggered pain scores as well as total erosive surface involvement and buccal erosive surface area on each side (left and right) were determined and the patients were asked about any undesired side effect, such as burning sensation and sense malfunction, and examined for any abnormal alteration in the appearance of mucosa (atrophy, dermatitis, telangiectasia or fungal/viral infection).

Continuous and food-triggered pain was quantified using a visual analogue scale (VAS) from 0 to 10. To quantify the erosive surface area of the oral mucosa (total severity index), the following estimation scheme was applied similar to previous studies [12]: buccal mucosa (10% each side), dorsum, lateral border and ventral surface of the tongue (10% each), floor of the mouth (10%), hard palate (15%), soft palate (5%), gums supero-external and infero-external (10% each). An erosive area of <5% was scored as 1, 5-15% as 2, 15- 25% as 3, and >25% as 4. The buccal erosive surface area on each side was measured by a gauged abaisse langue.

Statistical Analysis

The data were processed with software SPSS 16.0 for windows. Only P values less than 0.05 were considered significant. Because of the few patients in this study, data were analyzed with non-parametrical statistical tests. The difference of buccal erosive surface areas, spontaneous pain scores and food-triggered pain scores of both sides, before and after treatment were assessed by Wilcoxon test. The chi-square gamma test was used for the analysis of total severity index before and after topical treatment.

RESULTS

From 15 patients who were enrolled in this study, 1 was lost because of developing oral herpes infection one day after applying the study medications and 14 patients completed the course of trial, 8 (57%) men and 6 (43%) women with an age range of 22 to 64 years (mean age: 46 years) a disease duration of 1-24 months (mean duration: 12.5 months).

No statistically significant baseline differences were found regarding the erosive surface area and degree of spontaneous and food-triggered pain between both sides of buccal mucosa (P value 0.53, 0.713 and 0.713, respectively). After 14 days of treatment on both tacrolimus side and triamcinilone acetonide side, buccal erosive surface area was reduced significantly compared with baseline data. (P value 0.011 and 0.012, respectively).

A significant decline in the spontaneous pain and meal-triggered pain, both detected by VAS, was seen on the tacrolimus (P values: 0.011 and 0.005, respectively) and triamcinolone acetonide sides (P values: 0.12 and 0.003, respectively).

There were no significant differences between the tacrolimus side and the triamcinolone side in terms of buccal erosive surface area and spontaneous and meal-triggered pain scores (P value 0.221, 1 and 0.401, respectively) and the total severity index did not change significantly before and after treatment with study medications (P value: 0.153).

No clinically detectable atrophy, telangiectasia or infection was observed on either side. Patients only reported a prominent but transient burning sensation on the tacrolimus side.

DISCUSSION

Pemphigus vulgaris is a severe autoimmune blistering disease of the skin and mucous membranes. Before the corticosteroid era, pemphigus vulgaris was associated with a high mortality rate. Nevertheless, corticosteroids have their own side effects and morbidity. Later, combination therapy was recommended to reduce corticosteroid requirements but surprisingly, there have been few studies describing topical medications as an adjunctive treatment for either cutaneous or oral lesions of pemphigus vulgaris. In one study on 32 patients with oral pemphigus vulgaris treated with topical steroids, treatment resulted only in 4 patients (12%) being controlled with topical corticosteroids such as betamethasone alone [13], but there have been several case reports describing the successful use of topical corticosteroid alone in cases where pemphigus vulgaris is not extensive and lesions are limited to the oral cavity [14-16].

One preliminary clinical trial study of clobetasol propionate therapy showed that clobetasol propionate ointment in adhesive paste (orabase) was an effective topical steroid alternative to other less potent topical and systemic drugs for recalcitrant oral vesiculoerosive diseases including pemphigus vulgaris [17].

Although pemphigus vulgaris autoantibodies are pathogenic, autoreactive T-cell responses to desmogelin 3 (the main antigen of oral epithelium) may be critical to the pathogenesis since antibody production generally requires T-cell help [18]. Thus, the use of immunomodulators such as calcineurin inhibitors to control the disease would appear reasonable.

Tacrolimus, like pimecrolimus, belongs to the ascomycin class of macrolactam immunosuppressives, acting through the inhibition of T-cell activation by the calcineurin pathway and inhibition of the release of numerous inflammatory cytokines [19].

In contrast with topical steroids, tacrolimus does not produce epithelial atrophy [20]. In addition, tacrolimus has been shown to be effective and well tolerated in the treatment of patients with erosive oral lichen planus [21-24], one case of recalcitrant mucous membrane pemphigoid and one patient with paraneoplastic pemphigus secondary to non-Hodgkin lymphoma [25,26]. Regarding the beneficial effects of topical tacrolimus on oral erosions of

pemphigus vulgaris, to our knowledge, only one case report has been published in the literature, in which a case of recalcitrant labial ulceration due to pemphigus vulgaris was managed successfully with topical tacrolimus [27].

To the best of our knowledge, this is the first investigator-blind randomized clinical trial to compare the efficacy of tacrolimus and triamcinolone in the treatment of oral pemphigus vulgaris. In this study, both drugs resulted in the reduction of painful symptoms and the lesion size, demonstrating the effectiveness of both study medications in treating oral pemphigus vulgaris, but the difference of these scores between the groups was not statistically significant at the end of the treatment period. However, because of the small number of the patients in this study and its special design (split-mouth) chosen to remove the confounding effect of systemic therapy, caution must be exercised when considering clinical significance of the results.

Triamcinolone acetonide paste has been shown to be effective for oral pemphigus vulgaris [13-17] and was used as the comparator in this study. Regarding the safety profile of triamcinolone acetonide paste, we found no adverse events. This was similar to a recent study on this agent that found no side effects, and was more promising than a previous report of 25% (4 of 16) occurrence of candidiasis infection [28]. This may be explained with routine use of chlorhexidine mouthwash for our patients, which proved to reduce the risk of overinfection [29].

On the tacrolimus side, the only experienced side effect was a prominent but transient burning sensation which was in accordance with previous reports [9,30].

It could be stated that the effectiveness of tacrolimus and triamcinolone acetonide seen in this study is simply due to systemic therapy, not the study medications per se, but according to our results, the total severity index did not change significantly which might be due to the relative resistance of oral lesions of pemphigus vulgaris to systemic therapies and the fact that these therapies may require more time to exert their effect on oral lesions of pemphigus vulgaris. Thus, the significant decrease in the buccal erosive surface area and pain scores in tacrolimus-treated and triamcinolone-treated lesions are more likely to be the result of administering study medications, not systemic therapies.

In conclusion, topical tacrolimus appears to be a promising alternative as an adjunctive treatment of oral pemphigus vulgaris and can be used as effective as triamcinolone acetonide in these patients. It is not associated with skin atrophy as seen in the prolonged use of topical corticosteroids and is well-tolerated. However, further studies on a larger population with long-term follow-ups and monitoring of the blood level of tacrolimus are required to better evaluate its usefulness and safety in the treatment of oral pemphigus vulgaris.

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