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The Effectiveness of Topical Pimecrolimus in the Treatment of Oral Lichen Planus

Oral Liken Planusun Tedavisinde Pimecrolimusun Etkinliği

Abstract

Objectives: Oral lichen planus (OLP) is a chronic inflammatory disorder of unknown etiology that affects the skin and the mucosa, especially the oral mucosa. Several therapeutic agents have been investigated for the treatment of OLP. All agents used in the OLP therapy are palliative. Potent topical steroids are used as the conventional therapy for OLP. Since side-effects or steroid resistance may be encountered, alternative treatments may be necessary. This study aimed to evaluate the efficacy and safety of the topical pimecrolimus in the treatment of OLP.

Methods: Seventeen patients with OLP were recruited into this study. Topical pimecrolimus 1% cream was applied twice a day to the affected areas. Patients were followed up for 3-6 months. Photographs of the lesions were taken and analyzed for areas of ulceration, erythema, and reticulation in every clinical examination.

Results: We found that topical pimecrolimus 1% cream was an effective treatment for OLP. Two patients could not complete the treatment protocol because of the side effects such as local irritation and nausea.

Conclusion: Topical pimecrolimus may be a valuable second treatment choice for patients with steroid-related side-effects or steroid-resistant OLP. However further randomized controlled studies have to be conducted to compare conventional treatment of topical corticosteroid with topical pimecrolimus.

Keywords: Oral lichen planus, pimecrolimus, calcineurin inhibitor, treatment, efficacy, safety

Öz

Amaç: Oral liken planus (OLP) deri ve mukozaları özellikle de oral mukozayı tutan, etiyolojisi bilinmeyen kronik enflamatuvar bir hastalıktır. OLP tedavisi için birkaç terapötik ajan araştırılmıştır. OLP'nin tedavisinde kullanılan bütün ajanlar palyatif etkilidir. OLP'nin geleneksel tedavisinde potent topikal steroidler kullanılır. Steroidlerin yan etkileri veya steroide direnç ile karşılaşılabileceğinden alternatif tedaviler gerekli olabilir. Bu çalışmada topikal pimecrolimusun OLP'nin tedavisindeki etkinliğini ve güvenilirliğini değerlendirmek amaçlandı.

Yöntemler: OLP'li 17 hasta çalışmaya alındı. Topikal pimecrolimus %1 krem etkilenmiş bölgelere günde 2 kez uygulandı. Hastalar 3-6 ay süreyle aylık olarak takip edildi. Her kontrolde lezyonların fotoğrafı çekilerek ülserasyon, eritem ve ağ yapısı gibi özellikleri değerlendirildi.

Bulgular: Biz OLP'nin tedavisinde topikal %1 pimecrolimusu etkili bulduk. Çalışmaya alınan iki hasta bulantı hissi ve lokal irritasyon gibi yan etkiler nedeni ile tedavi protokolünü tamamlayamadı.

Sonuç: Topikal pimecrolimus, steroid ile ilişkili yan etkileri olan hastalarda veya steroide dirençli OLP'nin tedavisinde ikinci seçenek olarak düşünülebilir. Ancak etkinliği tam olarak değerlendirebilmek için OLP'nin geleneksel tedavisi olan topikal steroid ile topikal pimecrolimusun karşılaştırmalı, randomize, kontrollü çalışmaları yapılmalıdır.

Anahtar kelimeler: Oral liken planus, pimecrolimus, kalsinörin inhibitörü, tedavi, etkinlik, güvenlik

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Introduction

Lichen planus (LP) is a common mucocutaneous disease. It was first defined by Wilson in 1869. The disease can affect either the skin or mucosa or both. About half of the patients with skin lesions have oral lesions, whereas about 25% present with oral lesions alone (1). Oral LP (OLP) may exist whithersoever in the oral cavity. The buccal mucosa, tongue and gingival are the most common sites, whereas palatal lesions are uncommon (2,3). It is seen worldwide, mostly in the fifth to sixth decades of life, and is twice as common in women than in men (1,3,4). OLP is a T cell-mediated autoimmune disease however its cause is unknown in most cases (5).

OLP can present in a number of forms: reticular, plaque-like, papular, atrophic, erosive, and bullous (1,4,6). Reticular, papular, and plaque-like OLP are generally without symptoms. Erosive, bullous, and atrophic lesions are generally a source of pain and discomfort (4,6).

Unlike cutaneous lesions, especially erosive OLP is extremely resistant to topical treatment and tends to pursue a chronic process with little tendency to spontaneous resolution (1,7). OLP is a persistent problem, such that most often the best one can achieve is an amelioration of symptoms until resolution occurs. Most of the therapeutic recommendations are empirical, rather than evidence-based. Treatment is centered primarily on reducing symptoms through immune response modulation, primarily using corticosteroids with widely known side-effects (8,9).

A potent topical steroid is the traditional therapy for OLP. Side-effects or steroid resistance can be encountered and second line therapy such as topical pimecrolimus may be required (10). An adverse effect of higher potency corticosteroids is skin atrophy and initiation of striae distensae. In contradistinction to topical corticosteroids, skin atrophy by topical calcineurin inhibitors is almost no risk, particularly in sensitive regions, such as the face, the neck, and the genital area (6,11).

Pimecrolimus is a derivative of the macrolide ascomycin, which is a compound isolated from *Streptomyces hygroscopicus*. Pimecrolimus binds to macrophilin-12 and thereby limits the calcium linked phosphatase calcineurin. By blocking the transcription of early cytokines and in this way downregulating synthesis of both T-helper 1- and 2-type cytokines, pimecrolimus inhibits T-cell activation in vitro (6,7,11-13). The purpose of this study was to evaluate the efficacy, relative safety, and tolerability of 1% pimecrolimus cream in the treatment of OLP.

Materials and Methods

A total of 17 patients with OLP were accepted in this study after giving their informed consent. The diagnosis of OLP was determined after conducting a comprehensive clinical history together with dermatologic examinations. The diagnosis of OLP was approved by mucous membrane biopsies for routine histology and direct immunofluorescence protocol. There was no family history of patients for OLP. Laboratory investigations were done in all patients for serology of both hepatitis B and hepatitis C. The exclusion criteria were: to have any malignant involvement or viral

infection in mouth; to have been received topical therapy for OLP in the last two weeks or systemic therapy in the last four weeks such as azathioprine, cyclosporine, phototherapy; or to have a history of allergy to either immunomodulators or corticosteroids.

All the patients were treated with pimecrolimus 1% cream. It was used twice daily to affected areas after meals for three months. The patients were instructed to apply a small pea-sized amount of topical therapy at each application. The patients were asked not to eat, drink, or smoke for 30 minutes after each application.

All patients were identified monthly throughout the treatment period and followed up with six months of treatment-free observation. The symptoms of the subjects and clinical view of the lesions in every patient were registered before and after treatment. Photographs of the lesions were taken every visit and analyzed for areas of reticulation, erythema, and ulceration. The clinical evaluation of each patient was carried out by the same physician.

In all visits, the patients were asked about any unwanted side effect such as burning sensation, taste sense malfunction, and other discomforts. They were investigated for any abnormal vital signs and particularly for any abnormal change in the appearance of mucosa (atrophy, dysplasia, dermatitis, telangiectasia, and viral/fungal infection). They were also observed for any allergic reaction to the drug.

Changes in the clinical signs and symptoms of the disease were perused as follows: complete response was appointed when oral erythema, erosion, ulceration, and reticulation were all fully gone and without symptom; partial (incomplete) response was appointed when only one or two of the signs and symptoms disappeared; no response was registered when the disease stayed serious (no change or worsening).

Results

The average age of the 17 patients (5 male + 12 female) was 48 years (range 18-66 years). The most frequent symptom before treatment was burning sensation and pain. Buccal mucosa were affected in 16 of the 17 patients, lingua in 5, lips in 2, palate in 2, gingival in 2. The most frequent form of lesions was reticular form. Hepatitis C antigen was positive only in one patient.

Fifteen patients finished the treatment protocol. These patients showed either complete or partial response or no response at 8-12 weeks. Two patients could not finish the treatment protocol because of side effects such as local irritation and nausea. Most of the patients displayed an important development in their symptoms and the clinical view in their disease. After three months of treatment, complete remission (Figure 1a, 1b) was seen in seven patients (41%), partial remission (Figure 2a, 2b) in six patients (35%) however two patient (12%) indicated no response at all.

The most common reaction noticed at the application area was a burning sensation (six patients, 35%). Application site reactions, which were mild to moderate and transient, occurred within the first week of treatment.

No clinically definable atrophy, telangiectasia, mucosal dysplasia, taste sense malfunction, any kind of allergic reaction, adverse systemic effects were registered. There were no oral infections, including viral, bacterial, or fungal infections. OLP recrudesced in third months in one patient and fifth months in another patient (total of two patients) during the follow-up period after treatment. These patients were retreated with the same protocol and they replied partially or completely.

Discussion

LP is a chronic inflammatory mucocutaneous disease. The involvement of mucous membranes is generally seen. In spite of generally without symptom, the disease is sometimes complicated by wide painful erosions, causing a significant loss of quality of life (7). Whether OLP has a premalignant potential is a matter of discussion. The reported transformation incidence to oral cancer changes from 0-9% (14). For this reason, a clinical follow-up of patients with OLP, including repeated biopsies of recurrent or recalcitrant lesions is recommendable for any treatment (12,15).

Different topical and systemic drug have been used in the treatment of this disorder with various results, occasionally with significant side effects (13,16). Well-known side effects related to longtime topical corticosteroid use to oral cavity include dermal atrophy, contact sensitivity, and fungal infections (13,16,17). Because of the chronic course of OLP and the potential side effects mentioned above related to potent topical steroids, there is a need for choice well tolerated treatments, which is why we investigated the efficacy and safety of topical pimecrolimus in OLP.

Pimecrolimus 1% cream has been certified by the Food and Drug Administration for the treatment of atopic dermatitis. It has been tried to be effective in different inflammatory skin diseases, eg, seborrheic dermatitis, psoriasis, vitiligo, and cutaneous lupus erythematosus. In addition, some case reports have shown its safety and successful use in the treatment of children with anogenital lichen sclerosus and children with lichen aureus (8,13,16,18,19).

There are some case reports and studies about use of pimecrolimus in OLP with successful results (7,8). A small series of three patients with OLP that is unresponsive to



Figure 1a. Before of treatment (erosion and reticular lesions on the right buccal mucosa)



Figure 2a. Before of treatment (reticular lesions on the left buccal mucosa)



Figure 1b. Complete response was seen after 3 months of treatment



Figure 2b. Partial response was seen after 3 months of treatment

standard treatment has been reported. Involvement of the lips improved within two weeks and intraoral lesions healed within 3-8 weeks (8).

In addition, pimecrolimus has been demonstrated to be effective and well tolerated in treatment of patients with erosive OLP in one open-label trial. In this trial, Swift et al. (6) administered a placebo-controlled trial on 20 patients with erosive OLP (10 pimecrolimus, 10 placebo) and displayed that pimecrolimus was superior to placebo in point of areas of erythema, ulceration, and reticulation and in point of discomfort scores.

Recently, Passeron et al. (17) reported a randomized placebo-controlled trial for pimecrolimus in the treatment of erosive OLP cases with a sample size of 12 (6 pimecrolimus, 6 placebo). They showed that pimecrolimus significantly improved the clinical score of patients from baseline and it was better than placebo.

Gorouhi et al. (16) showed that in an investigator-blinded parallel-group randomized clinical trial, 40 patient were randomly assigned in two equal groups to receive either pimecrolimus 1% cream or triamcinolone acetonide 0.1% paste four times daily for a total two months and followed up for another two months. Both pimecrolimus and triamcinolone groups showed significant improvement in all measured efficacy and points throughout the visits. There was no significant difference between changes from baseline median values of pimecrolimus and triamcinolone groups after treatment termination in terms of visual analog scale score, clinical score, and Oral Health Impact Profile score. Two patients in pimecrolimus group observed important but temporary burning sensation whereas none of the patients in triamcinolone group had any significant adverse result. However, in our study minimum burning was monitored in six patients. In addition, there were fewer relapses and no rebounds, such as frequently seen with corticosteroids.

In an open prospective study, including 11 women with genital LP were treated twice daily with pimecrolimus cream. Two patients dropped out because of intolerable local adverse effects (12). In our study, two patients could not complete the treatment protocol because of side effects such as local irritation and nausea.

A randomized vehicle-controlled small study (20) showed that topical pimecrolimus was effective in controlling pain caused by OLP erosions/ulceration during and up to 30 days after cessation of therapy.

An another study, McCaughey et al. (21) conducted a randomized, double-blind study involving 21 patients with OLP and found that pimecrolimus 1% cream was superior to vehicle cream in reducing mean investigator's global assessment, pain, and erosion size after 6 weeks of treatment. Pimecrolimus levels were detected in 9 out of the 10 treated patients, with a maximum level of 0.814 ng/mL.

A recent randomized controlled study (22) showed that important healing in symptom scores; on the other hand, the entire treatment response was higher in the pimecrolimus group compared with the triamcinolone acetonide group. On intergroup comparison, there was no statistically important distinction between the groups

in the reduction in burning sensation and erythematous area, but there was a statistically extremely important improvement in reduction of clinical scoring.

A recent randomized controlled study (23) suggested that pimecrolimus 1% cream is equally effective as tacrolimus 0.1% ointment in OLP. No severe adverse effects necessitating stopping treatment were observed in the two groups.

Zożycki et al. (24) reported retrospectively 13 patients with OLP who had received topical tacrolimus for a mean duration of 6.5 months. Eleven patients had either complete resolution or partial improvement of painful oral mucosal lesions within four weeks from the start of the treatment although two patients showed no response.

A retrospective analysis of 50 patients with OLP and erosive/ulcerative OLP recalcitrant to topical corticosteroids demonstrated the long-term (mean: 19.8 months) efficacy and safety of 0.1% topical tacrolimus, 94% of patients having either complete or partial resolution of mucosal erosions (25).

Two recent randomized trials reported that tacrolimus was more effective than topical corticosteroids (triamcinolone and clobetasol) in controlling painful symptoms of erosive OLP (26,27). However, another randomized, double-blind study found no significant differences between tacrolimus and clobetasol in the management of symptomatic OLP (28).

Conclusion

Topical pimecrolimus may be a valuable second-line treatment for patients with steroid-related side effects or steroid-resistant OLP. Further blinded, randomized, placebo-controlled studies involving larger groups of patients are required to determine the effectiveness of therapy with pimecrolimus for OLP.

Ethics

Ethics Committee Approval: This study was approved by Çukurova University Faculty of Medicine.

Informed Consent: All participants gave written and verbal informed consent.

Peer-review: Internal peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Mehmet Kamil Mülayim, Concept: Mehmet Kamil Mülayim, Soner Uzun, Design: Mehmet Kamil Mülayim, Perihan Öztürk, Soner Uzun, Data Collection or Processing: Mehmet Kamil Mülayim, Soner Uzun, Analysis or Interpretation: Mehmet Kamil Mülayim, Perihan Öztürk, Soner Uzun, Literature Search: Mehmet Kamil Mülayim, Perihan Öztürk, Soner Uzun, Writing: Mehmet Kamil Mülayim.

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