



SUCCESSFUL TREATMENT OF ORAL LICHEN PLANUS WITH TOPICAL TACROLIMUS

ORAL LİKEN PLANUSUN TOPİKAL TAKROLİMUS UYGULAMASI İLE BAŞARILI TEDAVİSİ

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ABSTRACT

Tacrolimus is a new, non-steroidal immunosuppressive macrolide which modulate the immunological mechanism by blocking T-cell activation. The topical form of tacrolimus constitutes a promising new treatment for recalcitrant inflammatory skin and mucosal disorders. In this report we present the successful treatment of two specific oral lichen planus cases with tacrolimus. Case I is a 68-year-old female patient suffering perpetually from lichen planus lesions involving gingiva for 10 years. She had painful, erythematous lichen planus lesions especially on the gum of maxillary incisors region. She wore full- mouth fixtures on both jaws. The patient was allergic to dental materials which caused the lichen planus lesions to be more recalcitrant. Case II is a 34-year-old female who had recalcitrant lichen planus lesions on oral and vaginal mucosa. The oral lesions on the buccal mucosa and gingivae were in reticular form. In both cases the lesions were unresponsive to different types of topical steroid agents which are applied for one month. After the steroid therapy, although there was a relative relief of the pain complaint, the appearance of lesions disclosed no change. Following these therapies, the patients were administered % 0.1 tacrolimus ointment per twice a day. On the third week of the therapy we achieved to control the symptoms and to clear the lesions.

In conclusion, topical tacrolimus forms a new option for the treatment of oral lichen planus.

Keywords: Oral Lichen Planus, Tacrolimus, Management, Local Application

ÖZET

Steroid içermeyen, makrolid grubundan immunsupresif etkili bir ajan olan tacrolimus, T hücre aktivasyonunu inhibe ederek immün sistemi düzenlemektedir. Topikal formu inatçı, inflamatuvar, deri ve mukozaları tutan hastalıklar için umut verici bir tedavi seçeneği oluşturmaktadır. Makalemizde iki spesifik oral liken planus vakasının tacrolimus ile sağlanan başarılı tedavisi anlatılmaktadır. 68 yaşında kadın hasta olan birinci vakamızın 10 yıldan beri dişetlerinde oral liken planus lezyonları mevcuttu. Özellikle üst çenesinde, kesici dişler bölgesinde ağrılı ve eritematöz lezyonları vardı. Hem alt hem de üst çenesinde full-mouth köprü protezleri kullanan hastanın çeşitli dişhekimliği malzemelerine karşı alerjisi vardı. Bu durumun var olan liken lezyonlarının daha da inatçı olmasına sebep olduğu düşünülmüyordu. 34 yaşında kadın hasta olan ikinci vakamızın ise oral ve vajinal mukozasında inatçı liken planus lezyonları mevcuttu. Bukkal mukoza ve dişetlerini tutan lezyonlar retiküler formdaydı. Her iki vakada da çeşitli tiplerdeki steroid tedavisi yaklaşık olarak bir ay süreyle uygulanmasına rağmen tam bir cevap alınmadı. Hastaların ağrı şikayeti göreceli olarak iyileşmesine rağmen lezyonların görünümünde hiçbir değişiklik olmadı. Bu tedavileri takiben hastalara tacrolimusun %1'lik merhem formunun günde iki defa lezyonların üzerine sürülmesini içeren bir tedavi uygulandı. Tedavinin üçüncü haftasında semptomlar kontrol altına alındı ve lezyonlar tamamen iyileşti. Sonuç olarak, tacrolimusun topikal uygulaması oral liken planus tedavisinde yeni bir seçenek oluşturmaktadır.

Anahtar kelimeler: Oral Liken Planus, Tacrolimus, Tedavi, Lokal Uygulama

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INTRODUCTION

Oral lichen planus (OLP) is considered to be an autoimmune disease of unknown aetiology in which epithelial cells are recognized as foreign due to changes in cell surface antigenicity.¹ It affects 0.2–1.9% of the population^{1,2}. The clinical management of OLP is symptomatic and is determined by the severity of the disease. Treatment should be directed at achieving specific goals after considering the degree of clinical involvement, the predominant clinical type of lesions, and the patient symptoms and age.³ A range of treatments have been proposed for OLP: topical and systemic corticosteroids, topical cyclosporine, topical and systemic retinoids, antimicrobials, azathioprine, photochemotherapy and surgery.²⁻⁴ The investigation of new topical antiinflammatory agents without the adverse effects of topical corticosteroids has resulted in the development of new topical modulators, including tacrolimus.²⁻⁵

Tacrolimus is a macrolide compound isolated from *Streptomyces tsukubaensis*, a soil fungus found in Japan. Since it was discovered in 1984, in vitro and animal experiments helped to characterize its mechanism of activation and its potent immunosuppressive properties.^{6,7} It has established a significant role in the field of transplantation. It is being prescribed to the majority of new liver kidney transplant recipients in Europe, North America and Asia. It provides immunosuppression by suppression of interleukin-2 production, associated with T-cell activation; and inhibits differentiation and proliferation of cytotoxic T cells.⁶ In recent years, the topical form of tacrolimus was used for the treatment of recalcitrant inflammatory skin and mucosal disorders (such as lichen planus, atopic dermatitis, psoriasis, allergic reactions etc.) which are T-cell mediated diseases⁷⁻⁹. According to literature, a 70-75% clearance or marked improvement was observed within 1-4 weeks based on the type of disease.^{7,9}

In this report, we present the successful treatment of two specific cases with 0.1% tacrolimus ointment.

CASE I

Case I is a 68-year-old female patient suffering from painful, erythematous lesions on attached gingiva for over ten years. Particularly the lesion on the gum of maxillary incisors region was more erythematous, fragile and painful (Figure 1). The onset of the lesions was 10 years prior to admission, just after the fabrication of full- mouth fixtures on both jaws. She was suspected to have three potential conditions including allergy to dental materials, fungal infection and dermatologic disease such as lichen planus or pemphigoid. To exclude the possibility of an allergic reaction to dental materials, the patient was instructed not to wear prosthesis; and a patch test, including different types of dental materials was carried out. The result of patch test revealed allergic reaction to goldsodiumthiosulphate and nickel sulphate. Microbiologically, *Candida albicans* colonization was not isolated from swab culture and saliva sample. An incisional biopsy from the affected and intact gingiva was performed. The direct immunofluorescent and light microscopy investigations of tissue specimen revealed the diagnosis of oral lichen planus, and the pathologists suggested that the lesions may be the result of a reactive response associated with hypersensitivity to dental materials. A topical steroid cream including 0.05% clobetasol 17-propionate was prescribed with a twice daily application. This ineffective therapy caused the lesions get worse and the lesion was flared. A 0.05% dexamethasone mouthwash which was prescribed with a twice daily application provided a decrease in pain complaint. Also a benzydamine HCl mouthwash was prescribed as an adjacent therapy. After a ten weeks therapy, it was experienced that the treatment was inefficient. She was administered 0.1% tacrolimus ointment with twice application on the lesions per day. On the third week of topical tacrolimus therapy the erythematous appearance of the lesions disappeared and the healthy gingiva took the place of fragile bleeding tissues (Figure 2). But on the buccal mucosa where no lesions were detected initially white striae with an accompanying burning sensation occurred. We believe that white striae occurred as a result of the effect of tacrolimus leading immunosuppression on healthy mucosa. Because of in microbiological examination of swab cultures and saliva samples which are applied

before and after the treatment, *Candida albicans* colonization was not isolated. Tacrolimus therapy was ceased and white striaes on buccal mucosa started resolve gradually.



Figure1. Intraoral view of Case I prior to treatment



Figure 2. Healthy appearance of gingiva after topical tacrolimus treatment (Case I)

CASE II

Case II is a 34-year-old female patient presenting with clinically diagnosed oral and vaginal lichen planus. On the buccal mucosa and gingiva, the lesions were in reticular form with a white lace-like appearance, slightly raised pattern and with slight inflammatory changes (Figure 3). 0.01% triamcinolone acetonide orabase pomade was prescribed with twice daily application. The patient was referred to Istanbul University, Istanbul Medical Faculty, and Department of Dermatology for the examination of vaginal lesions. The management of vaginal lesions was evaluated by the dermatologists. The oral lesions were unresponsive to this two week therapy; hence two types of mouthwashes, one of them including 0.05% dexamethasone and the other including benzydamine HCl

were prescribed with a twice daily application. No improvement was disclosed. Following these therapies which can not provide an expected outcome for four weeks, the patient was administered 0.1% tacrolimus ointment twice a day application on the lesions. On the third week of the topical tacrolimus therapy, a complete resolution of lesions was detected, and there was no evidence of inflammatory change (Figure 4). No adverse effect was observed.



Figure 3. Lesion on the buccal mucosa prior to treatment (Case II)



Figure 4. Appearance of buccal mucosa following tacrolimus treatment (Case II)

DISCUSSION

Tacrolimus is thought to inhibit T- lymphocyte activation by binding FKBP-12, calcium, calmodulin and calcineurin is then formed, subsequently inhibiting the phosphates activity of calcineurin. This activation prevents the dephosphorilation and translocation of nuclear component thought to initiate gene transcription for the formulation of lymphokine such as

IL-2, γ -IFN. The net result is the inhibition of T-lymphocyte activation, so the immunosuppression¹. The pathogenesis of oral lichen planus is known as being a T-cell mediated process which there is an imbalance between T-lymphocyte helper and suppressor activity^{10,11}. Hence the researchers hypothesized that providing the suppression of suppressors, T lymphocytes may be efficient in the management of oral lichen planus^{8,12-14}.

The first study of topical application of tacrolimus in OLP published by Vente et al.¹⁵ in 1999, involving the treatment of six patients (five females and one male). Three cases resolved after 4 weeks and three showed improvement. There were no adverse effects other than slight burning sensation immediately after application (twice a day for 4 weeks). Five patients suffered relapse between 3 and 8 weeks after the end of treatment.

Other studies on the management of OLP with tacrolimus ointment showed that therapy period for controlling the symptoms and clearing lesions is variable. Hodgson et al.⁸ reported the treatment duration as eight weeks; whereas Morrison et al.¹² defend this period as four weeks. Similar results have been reported by other researchers, suggesting that twice daily applications of 0.1% tacrolimus ointment can provide control of the symptoms at the second week, clearance of the lesions at third week of the treatment regimen^{13,14}. So we can conclude that our results are in accordance with the previous researches on therapy duration.

The increase in the occurrence of secondary infection with fungal and viral origin over the lesions, particularly in prolonged treatment regimens is the side effect associated with topical tacrolimus application⁷. As a result of the effect of tacrolimus leading immunosuppression on healthy mucosa, white striaes with an accompanying burning sensation occurred on the buccal mucosa where no lesions were detected initially; but as a result of microbiological examination we did not observe any infectious side effect. The common adverse effects associated with systemic administration of tacrolimus are a result of long-term exposure⁸. Researches show that there is an increased risk of malignancy, especially squamous cell carcinoma and lymphoid tumor by the systemic usage of tacrolimus¹. Also, it is known that OLP has an inherent potential risk to undergo malignant

transformation¹⁶. The low blood levels of tacrolimus associated with topical administration can provide the sufficient immunosuppression. But sometimes topical administration of tacrolimus required long term application; and the blood level of topical application can arise up to that of systemic administration and this case composes a risk for malign transformation of oral lichen planus lesions. Hence the patients with topical administration should be closely monitored.

In conclusion, as a promising new treatment method we suggest application of topical tacrolimus which forms a well-tolerated and effective therapy for patients with OLP. However, the reliability of this approach needs further evaluation with a larger study group.

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