Successful Treatment of Erosive Lichen Planus With Topical Tacrolimus

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The Cutting Edge: Challenges in Medical and Surgical Therapeutics

REPORT OF A CASE

A 69-year-old woman with a history of colon carcinoma, cirrhosis of the liver secondary to hepatitis C, and erosive oral lichen planus presented to the dermatology clinic for therapeutic options regarding a growing ulceration on her lower lip. In the past year, the ulceration had enlarged and she had begun to develop new, painful, shallow ulcerations in the oral mucosa. In addition, she complained of intermittently pruritic papules involving the distal volar surfaces of her forearms. Biopsies and direct immunofluorescence were performed to evaluate histopathological features. The patient was diagnosed with erosive oral and cutaneous lichen planus. The cutaneous lesions resolved on treatment with fluocinonide cream. However, the lip and oral ulcerations persisted despite topical application of fluocinonide and clobetasol propionate gel once or twice daily for 1 year.

Physical examination showed a 2.0 × 1.0-cm shallow ulceration involving the central lower lip (Figure 1). The oral mucosa revealed extensive superficial ulcerations involving the buccal, gingival, and lingual mucosal surfaces. In addition, there were ulcerations on the dorsum of the tongue and a superficial ulceration on the hard palate, with a fine, reticulated grayish-white plaque surrounding the area (Figure 2). The volar aspect of the forearms revealed violaceous, lichenoid papules. There were no nail changes detected.

Histopathological examination revealed an interface dermatitis with a dense bandlike infiltrate along the dermoepidermal junction. An occasional civette body was noted. Direct immunofluorescence showed a continuous, strong, shaggy deposition of fibrinogen along the basement membrane, with many scattered and clumped cystoids that tested positive for IgM and C3.

THERAPEUTIC CHALLENGE

Treatment options for erosive lichen planus are numerous, including both topical and systemic agents; however, therapeutic results are often disappointing. Systemic immunosuppressive, immunomodulatory, and retinoid compounds were contraindicated because of the patient’s recently diagnosed colon carcinoma and her history of liver cirrhosis. Our challenge was to find a safe and effective therapeutic modality with long-term benefits.
Therapy was initiated with 0.1% topical tacrolimus ointment (compounded by the Dermatology Pharmacy, Northwestern Medical Faculty Foundation, Chicago, Ill) to the lip ulceration twice daily. Follow-up at 1 month revealed complete resolution of the lower-lip ulceration (Figure 3). This proprietary formulation base (white petrolatum [US Pharmacopoeia (USP)], mineral oil [USP], propylene carbonate [National Formulary (NF)], white wax [NF], and paraffin [NF]) is designed to quickly deliver the drug to mucocutaneous tissue while minimizing systemic absorption. A solution or gel formulation would not have been optimal because it might have contained irritating solvents; in addition, it would not have targeted the drug to the lesions as well as an ointment. A paste base was not used to minimize the risk of inadequate diffusion of the drug from the vehicle into the target tissue.

With the resolution of the lip ulceration, the patient was instructed to apply the tacrolimus ointment to the persistent oral mucosal ulcerations. The challenge was the application of the medication to the oral mucosa. The patient found it easy to apply the ointment as long as she dried the area with a gauze pad prior to application. She reported no difficulty with the dosage form. The intraoral ulcerations resolved after 3 months of daily application. The intraoral and lip ulcerations remained in remission after 1 year without maintenance therapy.

At the time of this report, the patient continued to have recurrences of the tongue ulceration 1 or 2 times per month. However, after a single application of tacrolimus, the tongue lesions resolve, and she returns to her normal eating habits.

Lichen planus, a relatively common mucocutaneous disease, is estimated to occur in 0.5% to 1% of the adult population.1-3 Fifty percent of patients with cutaneous lesions have oral involvement, whereas only 25% of patients with oral lesions have skin involvement.3 It is proposed that both endogenous and exogenous factors play a role in the development of the disease.

Clinical presentations of oral lichen planus are variously reported as reticulated, plaque-like, erosive, papular, atrophic, and bullous.4 The reticular form is the most common; however, the erosive, atrophic, and bullous forms are typically the most symptomatic, debilitating, and difficult to treat.3 Frequent complaints include severe burning and pain, particularly after eating foods that are either spicy or acidic. Most commonly, lesions are found on the posterior buccal mucosa and, in order of decreasing frequency, the gingiva, tongue, palate, lip, and floor of the mouth.5

Cell-mediated immunity seems to play a critical role in the development of lichen planus. Presently, the specific antigen(s) responsible for the activation of T cells has not been identified.3 HLA-Bw356 and HLA-B87; contact sensitizers such as dental amalgam7 and other metals8; medications; and infectious causes such as hepatitis C, herpes simplex virus, human immunodeficiency virus, syphilis, and amebiasis have all been reported to be associated with oral lichen planus eruptions.7

Treatment options exist for oral lichen planus, but all are less than optimal. These include topical and intralesional high-potency corticosteroids, retinoids, cyclosporine, psoralen–U-VA, and extracorporeal photochemotherapy. Other, anecdotal modalities include griseofulvin, hydroxychloroquine, dapsone, and thalidomide.

In a recent evidence-based review, topical corticosteroids were found to be the most helpful treatment for oral lichen planus.8 The efficacy of fluocinonide and fluocinolone has been assessed in small trials, with some improvement noted compared with placebo.9 In a comparison trial, 0.1% triamcinolone acetonide was shown to be less effective than 0.1% fluocinolone acetonide.10 In one study, 23 (96%) of 24 patients improved with the use of topical corticosteroids under occlusion.11 Systemic corticosteroids are often used based on clinical experience, despite a lack of rigorous controlled studies to evaluate efficacy.

There have been controlled studies to evaluate the use of topical and systemic retinoids in the treatment of oral lichen planus. Topically, both 0.1% tretinoin and 0.1% isotretinoin seem to be effective in reducing the number of lesions and providing symptomatic relief. A comparison between 0.05% tretinoin and fluocinonide showed better results in the fluocinonide-treated groups.12 It is hypothesized that this poor response to tretinoin may be due to the low concentration of tretinoin studied.13 Systemic treatment with etretinate was shown to reduce the number of lesions. However, systemic retinoids may produce significant adverse effects that patients may not tolerate.14

Topical cyclosporine has been evaluated for the treatment of erosive lichen planus in controlled trials.15-17 Although topical cyclosporine was shown to be effective, there does not seem to be any benefit compared with using topical corticosteroids alone.

Psoralen–UV-A has been shown to be of some benefit in controlled trials.18-19 Adverse effects include nausea and the potential for carcinogenicity. In addition, directing the light source to the target tissue may pose a significant obstacle to effective therapy.

Figure 3. Complete resolution of the lip ulceration after 1 month of 0.1% topical tacrolimus ointment applied twice daily.
Tacrolimus is one of the members of the immuno-suppressive macrolide family, which includes cyclosporine, rapamycin, and ascomycin. It suppresses T-cell activation by initially binding to cytosolic FK-binding proteins, which, in turn, interferes with the Ca\(^{2+}\)/calmodulin–dependent phosphatase calcineurin.\(^{20}\) This ultimately results in the inhibition of cytokine (mainly inter-leukin 2 [IL-2], IL-4, and IL-5) gene transcription.\(^{21}\)

Tacrolimus was introduced for the prevention of allograft rejection, with successful use in kidney, liver, and heart transplantation. Recently, topical tacrolimus was shown to be efficacious in atopic and contact dermatitis.\(^{20,22-24}\) Systemic administration has been beneficial in psoriasis, Behçet disease, pyoderma gangrenosum, and Crohn disease.\(^{25-28}\) It is presumed that some of the most promising targets for topical tacrolimus therapy are cyclosporine-responsive dermatoses, including lichen planus.\(^{20}\)

In a recent case report of 6 patients with recalcitrant erosive oral lichen planus, complete resolution was noted in 3 patients and substantial improvement in the other 3 patients after 4 weeks of therapy. Prolonged treatment resulted in continued improvement to complete resolution.\(^{30}\)

Percutaneous penetration of topical tacrolimus in various ointment concentrations (0.03%-3%) has been evaluated. In vitro studies have shown relatively low percutaneous absorption through intact skin.\(^{20}\) Percutaneous absorption through damaged skin was approximately 7-fold higher than through intact skin. Occlusion did not significantly alter percutaneous penetration in one study.\(^{20}\) Transmucosal penetration studies have not been reported.

Based on the safety demonstrated in atopic dermatitis trials that included children as young as age 2 years,\(^{31}\) topical tacrolimus ointment is apparently a safe, effective, and well-tolerated therapeutic modality. In order to fully evaluate its efficacy, randomized, controlled, double-blinded trials using topical tacrolimus are needed. In addition, comparison trials with high-potency topical corticosteroids are necessary to demonstrate any differences in treatment outcomes.


Editor’s Comment

Tacrolimus is the first T-cell selective immunosuppressive agent with demonstrated topical applications. The Food and Drug Administration recently approved topical tacrolimus ointment with an indication for treating atopic dermatitis in patients as young as age 2 years. In clinical trials, significant absorption did not occur through intact skin and rarely occurred through dermatitic skin. Detectable blood levels diminished as the skin improved. In phase 3 atopic dermatitis trials lasting more than 3 years, reported adverse effects have been minor. Recipes have long been available for compounded formulations similar to the proprietary agent. This case report is another example of compounded tacrolimus ointment used with success for a difficult-to-treat inflammatory cutaneous problem. Other reported uses include pyoderma gangrenosum, cutaneous Crohn disease, and ichthyosis linearis circumflexa. However, uncontrolled enthusiasm for this drug must be tempered with the caution reserved for any medication that has a wide range of systemic adverse effects, especially when prescribed for infants, young children, and patients with a widespread skin disease that features very poor skin barrier function.

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