Systemic tacrolimus in the treatment of recalcitrant mucosal lichen planus

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INTRODUCTION

Lichen planus is a chronic, inflammatory, autoimmune skin condition that can affect the skin, mucosal surfaces, and nails. Mucosal lichen planus might occur in conjunction with or without cutaneous involvement. Current treatment options include both topical and systemic medications. ¹

Tacrolimus (FK-506 or fujimycin) is a macrolide immunosuppressant that inhibits calcineurin. Topical tacrolimus has been shown to be effective in treating oral lichen planus, ² but systemic tacrolimus is not commonly used for lichen planus. Herein, we report 2 cases of patients with oral lichen planus and 1 case of a patient with oral and vaginal lichen planus (mean age 52.3 years) who responded to systemic tacrolimus after failing multiple medication regimens. The diagnosis was confirmed by a biopsy in all 3 patients. They also denied starting any new medications and tested negative for hepatitis B and C.

CASES

Case 1

A woman in her 40s with a 2-year history of oral lichen planus sought help from the clinic for the management of her condition. At the time of her visit, the patient had significant oral involvement of the buccal mucosa, gingiva, and palate. She was initially treated with systemic steroids. Subsequent systemic therapies were discontinued because of a lack of efficacy or serious side effects (such as leukopenia), not allowing her to decrease the prednisone dosage below 15 mg/d (Table I).

The patient was subsequently given tacrolimus 1 mg/d while on prednisone. The patient reported a good response after 4 weeks, having improved oral intake with no complaints of oral pain. She had mild erythema of the upper and lower gums along with complete healing of previous lesions on physical exam. She was slowly tapered off of the prednisone over the next year. An attempt to taper the tacrolimus by 0.5-1.5 mg/d resulted in an exacerbation of her oral disease. At 1.5 years after starting tacrolimus, the patient had no gingival erythema or active lesions in her oral cavity and continues to remain stable on a maintenance dosage of tacrolimus 1 mg twice daily as monotherapy without any reported notable side effects.

Case 2

A woman in her 40s with a >20-year history of biopsy-confirmed oral and vulvovaginal lichen planus sought help from the clinic for the management of a worsening disease. She had responded to high-dose systemic steroids (prednisone 60 mg/d). However, systemic dapsone did not provide a steroid-sparing effect. Strong topical steroid (class 1) and cyclosporin were used as adjuvant treatments with minimal relief. She noted that her lichen planus had been worsening over the past year and had noticed progressive introital narrowing, increasing erosions involving the vagina, and painful intercourse. On physical exam, the patient had gingival erythema with erosions on buccal mucosa and white patches on the dorsal tongue. She also had erythema surrounding the vaginal introitus and erosions in the vaginal canal. She failed 4-5-month treatments of azathioprine, methotrexate, and mycophenolate mofetil (Table I).
The patient was given oral tacrolimus 1 mg/d, which was increased to 1 mg twice daily after 2 weeks. At her 1-month follow-up, the patient reported improvement with decreased number of oral lesions and gingival bleeding. She stated her vaginal area had also improved. Physical examination revealed minimal gingival erythema along with healing of previous erosions in the oral cavity. The patient was able to taper the prednisone to 5 mg/d over the next 3 months. She did not report any adverse reactions from the tacrolimus except fatigue, which was tolerable. The patient self-discontinued the tacrolimus after 5 months because of a burning sensation in her oral cavity. She developed an exacerbation in both the oral and genital area after discontinuing the tacrolimus, requiring her to increase prednisone to 40 mg/d.

**Case 3**
A woman in her 70s presented with a 1.5-year history of generalized oral pain with difficulty swallowing. She was initially seen by her primary care physician for an oral ulcer and had tried chlorhexidine and steroid rinses, both resulting in no improvement. On physical exam, the patient had erythema of the anterior gingival and erosions on the
buccal mucosa but no cutaneous involvement. She had difficulty tapering below 20 mg/d of systemic prednisone as monotherapy without experiencing an exacerbation. Over the next 3 years, the patient failed or had difficulty tolerating multiple topical and systemic agents (Table I).

The patient was subsequently given oral tacrolimus 0.5 mg twice a day and reported decreased gingival bleeding along with improved oral intake because of decreased pain. Physical examination at her 1-month follow-up showed a significant decrease in the gingival erythema along with complete healing of previous erosions and no new oral lesions. Tacrolimus was discontinued after 4 months by her primary admitting team to minimize the risk of infection during an unrelated prolonged hospitalization. The condition of the patient was under good control at the time, and she did not notice any adverse reaction to the tacrolimus besides fatigue.

**DISCUSSION**

Lichen planus is an autoinflammatory condition, thought to be T-cell mediated, which can affect the skin, hair, nails, and mucosal tissues. No standardized treatment algorithm has been established for lichen planus. Most patients are treated with topical therapy as monotherapy or adjuvant to a systemic agent.

Topical tacrolimus has been shown to be an effective treatment for oral lichen planus. Tacrolimus is a calcineurin inhibitor that decreases interleukin 2 production and T-cell activation. Byrd et al reported that application of topical tacrolimus twice daily for reticulated erythematous or erosive lichen planus resulted in improvements within about a month and concluded that topical tacrolimus was a safe and effective treatment in alleviating symptoms and improving lesions.

Systemic therapy is usually considered for recalcitrant disease after failure of other treatment modalities, including topical therapy and ultraviolet therapy for skin. Systemic cyclosporine is a calcineurin inhibitor that has been used in severe and refractory cases of lichen planus. However, systemic cyclosporine has a number of potential adverse reactions and drug–drug interactions, which might limit its usage, especially in chronic long-term autoimmune diseases.

Systemic tacrolimus has been described in the literature for the treatment of autoimmune conditions, including rheumatoid arthritis and dermatomyositis. Since topical tacrolimus has reported efficacy and because the patients failed multiple systemic agents (Table I), systemic tacrolimus was chosen for our 3 recalcitrant patients. In the literature, only 1 report by Yeo et al describe erosive lichen planus (2 cases) treated with systemic tacrolimus. Our report is unique in that we used less than half the dose described in the literature to achieve remission of recalcitrant mucosal lichen planus. Moreover, we document more extensive follow-up over 1.5 years demonstrating that tacrolimus is safe to take over a long duration. Our experience suggests that a lower dosage of systemic tacrolimus (1-2 mg/d) might be adequate to provide effective control as compared with doses that are needed in dermatomyositis and rheumatoid arthritis. Improvements might be seen within a few weeks after initiating therapy, but maintenance therapy might be required to prevent flares. The lower dosage might allow for a decreased risk of reported adverse effects of tacrolimus.

Side effects reported from tacrolimus use include nephrotoxicity, electrolyte imbalances, and hyperlipidemia. Tacrolimus has been reported to exhibit less nephrotoxicity as well as less hirsutism, hyperlipidemia, and gingival hyperplasia when compared with the effects of cyclosporine. All 3 patients were monitored with scheduled laboratory testing while on tacrolimus, including complete blood counts, metabolic panels, and lipid panels, and all results were stable throughout the duration of treatment. While 2 of our 3 patients experienced fatigue, the tacrolimus was not discontinued because of lack of tolerability or side effects.

We realize there are multiple limitations to this study and a larger, randomized-controlled study would be useful to determine the efficacy of systemic tacrolimus in the treatment of mucosal lichen planus. However, our observations might offer another treatment option for the treatment of recalcitrant lichen planus.

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