The Effect of Tacrolimus on Lower Extremity Ulcers: A Case Study and Review of the Literature

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Tacrolimus, a calcineurin inhibitor, has become an increasingly valuable tool in the treatment of dermatological disorders during the last few years. However, its effect on wound healing is still under investigation and remains the subject of safety concerns. A 75-year-old woman with lichen planus, diabetes mellitus, and a foot ulcer was prescribed tacrolimus for the treatment of her lichen planus. After starting the treatment, her ulcer healed and the medication was discontinued. Shortly thereafter, re-ulceration occurred, treatment was re-introduced, and the wound continued to heal until treatment was discontinued. When the third course of tacrolimus was prescribed, the ulcer started healing again but a diagnosis of osteomyelitis necessitated surgical intervention. A review of the literature suggests that tacrolimus does not adversely affect healing in vivo or in vitro and may facilitate healing lower extremity skin ulcers, especially those of inflammatory origin. Studies are needed to clarify which lower extremity wounds would improve with tacrolimus.

KEYWORDS: tacrolimus, lichen planus, foot ulcer, diabetes

Cyclosporine is an immunosuppressive agent produced as a metabolite by the fungus species _Beauveria nivea_; it has been available in the US since 1983. A year later, tacrolimus was isolated from a Japanese soil sample that contained _Streptomyces tsukubaensis_. Tacrolimus was initially introduced as a systemic immunosuppressant for the prevention of rejection in solid organ transplant and approved for sale in the US in 1994. Both cyclosporine and tacrolimus are immunosuppressants that competitively inhibit calcineurin, an essential component in T-lymphocyte activation. By blocking the transcription of...
cytokines, these medications facilitate an anti-inflammatory effect.14–7

Because both systemic cyclosporine and tacrolimus can cause hepatotoxicity and nephrotoxicity, they should not be used concomitantly. As with other systemic immunosuppressants, patients receiving systemic cyclosporine or tacrolimus are at an increased risk for developing lymphomas and other malignancies, particularly those of the skin. In animal models, the increased risk appears related to the intensity and duration of immunosuppression. To reduce these risks, topical alternatives have been examined.

In 2000, the US Food and Drug Administration (FDA) approved tacrolimus ointment for the treatment of moderate to severe atopic dermatitis (eczema).3,4 Unlike cyclosporin, which lacks activity upon topical application, topical tacrolimus is efficacious. The reasons for this may be that tacrolimus has a greater ability to permeate human skin and has been shown to be 10 to 100 times more potent than cyclosporine.1,4,7

Pimecrolimus, another immunosuppressant, has a mechanism of action and indication similar to tacrolimus. Pimecrolimus is derived from Streptomyces hygroscopicus and has been approved for use in the US since 2001 for the treatment of mild to moderate atopic dermatitis. Unlike cyclosporin and tacrolimus which are available for systemic use, pimecrolimus is only available in a cream base. A common side effect of topical tacrolimus and pimecrolimus is burning or itching during the first few days of application.8,9

In 2006, the FDA required labeling changes for topical tacrolimus and pimecrolimus, including the placement of a boxed warning about the potential cancer risk.10 The agency recommended that healthcare providers, patients, and caregivers consider the following:

• Use these medications only as second-line agents for short-term and intermittent treatment of atopic dermatitis in patients unresponsive to, or intolerant of, other treatments
• Only use these medications for short periods of time, not continuously
• Use the minimum amount needed to control the patient’s symptoms
• Avoid use in children younger than 2 years of age and in anyone with a weakened or compromised immune system.

The American College of Allergy, Asthma, and Immunology and the American Academy of Allergy, Asthma, and Immunology formed a joint task force to review the data that led to the “black box” warning. They concluded that, “current data do not support the use of the black box warning on topical pimecrolimus and tacrolimus.”11,12 Similarly, a task force from the American Academy of Dermatology reported, “there is no causal proof that topical calcineurin inhibitors cause lymphoma or nonmelanoma skin cancer.”13 The European Dermatology Forum determined that “available data suggest that long-term application of topical calcineurin inhibitors is safe.”14

Robert S. Stern, MD, served as chairman of the FDA committee that initially recommended approval of tacrolimus ointment; he also was a member and consultant to subsequent meetings that assessed benefit versus risks. He wrote a comment in defense of the decision to require labeling changes.15 After recalling the history that led to the boxed warning, he concluded:

Removal from the market did not seem warranted. In our view, bringing more balanced information about the potential benefits and unknown but real potential risks of long-term use of these medications to prescribers through relabeling and to consumers through the FDA Web site and objective patient materials was justified.

KEY POINTS

• Patients presenting with chronic wounds and a variety of medical conditions, such as inflammatory skin disease, may challenge standard diagnostic and treatment paradigms.
• The author describes how a treatment, initially prescribed to manage the patient’s lichen planus, appeared to facilitate healing of her chronic foot wound.
• When the tacrolimus treatment was discontinued, her foot wound either recurred or stopped healing.
• A review of the literature suggests that studies to examine the effects of this treatment on patients with lower extremity wounds of inflammatory origin are needed.
Effect on Skin and Wound Healing: Literature Review

The physiological process of acute wound healing has been described as a cascade of overlapping events that occur in a reasonably predictable fashion in phases: hemostasis, inflammation, proliferation of new tissue, and remodeling of scar. Chronic wounds are those that have failed to proceed through this series of events in an orderly and timely process.16

Reports are conflicting on whether cyclosporine reduces wound healing rates. Ahonen et al17,18 demonstrated that cyclosporin does not impair wound repair in vivo. They implanted viscose cellulose sponges subcutaneously in Sprague-Dawley rats under anesthesia. The rats were given cyclosporine 40, 10, or 2.5 mg/kg intraperitoneally once a day for 10 days. Cyclosporine did not reduce the accumulation of hydroxyproline in the granulation tissue. On the other hand, Fishel et al19 implanted polyvinyl alcohol sponges subcutaneously in Sprague-Dawley rats under anesthesia. Cyclosporine 25 mg/kg was given on days 1, 2, 3, 4, and 7. After 10 days, rats that received cyclosporine had wound strips that weighed less and had diminished breaking strength as compared to controls. The authors also commented that they have conducted studies that demonstrated the effect of cyclosporine on wound healing depended on the total dose given rather than on the timing of administration.

The effect of systemic tacrolimus on dermal wound healing in Sprague-Dawley rats also has been investigated. At 2 mg/kg/day (10 times the recommended human dose), dermal wound mechanical strength and collagen deposition were reduced. No increase in wound infections was noted. At 1 mg/kg/day (five times the recommended human dose), wound healing also was not affected. In both dosage groups, tacrolimus levels in dermal wound fluid were found to be approximately 10-fold higher than blood levels.20,21

Duncan22 studied the effects of cyclosporin and tacrolimus on human keratinocytes in vitro. Cyclosporin inhibited keratinocyte growth and remnants of dead cells were evident after 2 weeks. No inhibitory effect was observed with tacrolimus.

A randomized, double-blind, placebo-controlled trial by Reitamo et al23 demonstrated that tacrolimus ointment does not affect collagen synthesis. In a combined group of 14 atopic dermatitis patients and 12 healthy volunteers, tacrolimus, betamethasone valerate, and a vehicle control were applied in a randomized order to nonsymptomatic regions of abdominal skin. After 7 days under occlusion, the concentration of terminal propeptides of procollagen in betamethasone-treated areas was reduced. Additionally, betamethasone reduced skin thickness as measured by ultrasound. These effects were not seen after application of tacrolimus.

Case Report

A 75-year-old Caucasian woman presented to the author’s office on May 21, 2004, with an ulceration of her right hallux. She had been under the care of another physician for 1 year without improvement. Her arterial perfusion was intact, radiographs and MRI could not detect osteomyelitis, and biopsy demonstrated granulation tissue without neoplastic change. Her past medical history included diabetes mellitus, hypertension, arthritis, and lichen planus.

Attempts to keep the patient non-weightbearing were futile. She could tolerate only an unpadded surgical shoe despite collapse of her arch from a prior Charcot deformity. The patient was evaluated at least once weekly, at which time the ulcer was debrided. At home, she was instructed to irrigate the ulcer with saline, apply a collagen wound dressing, and secure the dressing with gauze. During the course of her treatment, she developed multiple infections that were treated with oral antibiotics.

Shortly after her initial consultation, she developed another ulcer along the medial edge of her right foot (see Figure 1). On August 5, 2004, the patient’s dermatologist prescribed tacrolimus for her lichen planus. The starting dose was 1 mg orally, twice daily, and adjusted based on serum tacrolimus levels, in increments of 1 mg. When the ulcers closed on November 30 (see Figure 2), she was prescribed a custom diabetic shoe.

The patient discontinued tacrolimus on January 3, 2005 because she could no longer afford the medication. After bumping her right hallux on February 7, her hallux re-ulcerated. This was followed by re-ulceration along her medial foot. Tacrolimus was reintroduced on May 2 (see Figure 3), starting at 1 mg orally.
daily with dose adjustments as previously described. The ulcers were slowly decreasing in size until the tacrolimus was discontinued in January 2006 (see Figure 4). The ulcers then began to worsen and tacrolimus was reintroduced a third time at the end of April 2006 (see Figure 5).

In July 2006, significant improvement was seen and only a portion of the hallux remained ulcerated (see Figure 6). However, resorption of the distal phalanx tuft was identified on x-ray. Ceretec bone scan confirmed the presence of osteomyelitis. The hallux was amputated in August, methicillin-resistant Staphylococcus aureus grew from the bone culture, intravenous vancomycin was prescribed postoperatively, and tacrolimus was discontinued. One month later, the patient developed a Pseudomonas aeruginosa infection at the surgical site, which was treated with oral ciprofloxacin.

As of January 2007, the surgical site remains closed but the patient has ulcerations along the medial side of her foot. She also has very dry, scaly skin around her toes and on the medial side of her heel. Furthermore, there are an increased number of plaques on other areas of her body.

**Discussion**

Lichen planus is an inflammatory mucocutaneous condition. Typically it consists of variably distributed erythematous to violaceous polygonal papules and plaques. Oral and nail changes may accompany the cutaneous eruption. Although the etiology of lichen planus is unknown, many studies support an
immunologic pathogenesis. Corticosteroids, usually topical, are the treatment of choice in most cases.

Based on the physical characteristics (including the lack of substantial hyperkeratosis and the presence of ulceration on non-weightbearing areas of the hallux), the primary etiology of the ulcers discussed appears to be lichen planus. The immunosuppressant tacrolimus appears to have been effective in treating these foot ulcers. The uniqueness of the case presented is that the patient's ulcer healed each time oral tacrolimus was initiated. Furthermore, reoccurrence or worsening of the ulcerations occurred within a few months after discontinuing tacrolimus.

These observations are similar to previously published case studies. Systemic tacrolimus was instrumental in healing the ulcers of four patients with severe recalcitrant pyoderma gangrenosum unresponsive to conventional therapy. Tacrolimus was started orally at a dose of 0.15 mg/kg twice daily. Dose adjustments were guided by tacrolimus plasma levels or by clinical evidence of incomplete disease control or drug toxicity. All four patients had a dramatic initial response to treatment with a marked reduction in pain, erythema, and drainage by 1 week. Disfiguring open sores were healed within 8 weeks for the three patients who continued to take tacrolimus. Overall, the productivity and the quality of life of these patients who continued to take tacrolimus was greatly improved. Topical application of tacrolimus also has been reported as an effective alternative for pyoderma gangrenosum.

Topical tacrolimus has been shown to have a positive effect in healing lower extremity ulcers. A 65-year-old woman with an 8-year history of severe rheumatoid arthritis developed an ulcer on the lateral side of her ankle. Topical steroids stopped enlargement of the ulcer and oral clindamycin was used to treat a concomitant superinfection of S. aureus. However, healing was not observed during the first 8 months of intensive local treatment, which included 10% cyclosporine solution. Initiating daily topical application of 0.5% tacrolimus solution under a hydrocolloid wound dressing led to almost complete resolution within 5 months. The only side effect noted was a burning sensation during application.

A 79-year-old man with erosive lichen planus on the feet and hands was successfully treated with topical tacrolimus. Tacrolimus 0.5% solution under a hydrocolloid wound dressing was effective in healing a right calf ulcer that developed after an insect bite. An ulceration on the shin of a 62-year-old woman with chronic necrobiosis lipoidica healed in 1 month with twice-daily application of 0.1% tacrolimus ointment. Tacrolimus ointment with oral doxycycline was instrumental in healing long-standing venous ulcerations in three patients.

**Conclusion**

Tacrolimus is an immunosuppressive agent whose range of dermatological indications is likely to expand from atopic dermatitis (eczema) to include other inflammatory disorders. Further
research into the use of tacrolimus for lower extremity skin ulcers, especially those of inflammatory origin, should be conducted.

Acknowledgment
The author thanks Dr. Candace Thrash for her assistance in treating the patient in this study.

References
14. Ring J, Barker J, Behrendt H, et al. Review of the potential photo-