Editorial

Topical Macrolactams: New Indications, Potential Pitfalls

Dirk M. Elston, MD

In this issue, articles highlight both the promise that topical macrolactams can deliver efficacy without the worry of steroid atrophy (page 267) and the reality that they are not without potential side effects (page 237). Over time, we will discover many different uses for this unique class of therapeutic agents. We also will become more familiar with their potential for side effects. Some, like the burning sensation they can provoke, are already well known to dermatologists, and we have already developed strategies for minimizing the undesirable effects. Application of the products to bone-dry skin will minimize the stinging sensation, and pretreatment of the area with a course of a topical corticosteroid may eliminate it entirely. Other side effects, such as tinea incognito, may resemble those of corticosteroids and require vigilance on the part of the clinician and patient.

Off-label indications for which topical macrolactams may be useful include vitiligo, psoriasis, annular erythema, and hand and foot eczema.[1-4] In general, the agents appear well tolerated and lack some important corticosteroid side effects, such as atrophy. On facial areas, corticosteroids may produce steroid-induced rosacea. This effect has not been noted with topical macrolactams, and tacrolimus ointment has been reported as effective in the treatment of steroid-induced rosacea.[5]

Do topical macrolactams have the potential to produce tinea incognito, as has been seen with topical corticosteroids? A report in this issue (page 237) suggests that they may. Topical macrolactams suppress the local immune response, and this suppression may have the potential to alter the clinical expression of tinea infection in a manner similar to corticosteroids. Topical macrolactams have been widely used since they became available. Fujisawa Healthcare, Inc (the manufacturer of tacrolimus) and Novartis (the maker of pimecrolimus) were contacted regarding the finding of tinea incognito. Representatives of both manufacturers indicated that they have received no other reports of tinea incognito (oral communications, 2004). The lack of additional reports suggests that tinea incognito is likely to be a rare occurrence with these agents.

In a review of 1554 patients with atopic dermatitis treated with tacrolimus ointment, the incidence of cutaneous infections was not significantly higher for the tacrolimus group than for the vehicle group, with the exception of folliculitis in adults.[6] The authors concluded that treatment with tacrolimus ointment does not increase the risk of cutaneous bacterial, viral, or fungal infections, at least in the setting of atopic dermatitis.[6] In another study of 631 adult patients and 352 pediatric patients with moderate to severe atopic dermatitis treated with tacrolimus ointment, skin infection was no more common than in control sites.[7]

One case of deep dermatophytosis (Majocchi's granuloma) has been reported in a patient with facial psoriasis treated with topical tacrolimus.[8] The infection cleared with oral terbinafine.[8] This case, together with the report of tinea incognito in the current issue, suggests that topical macrolides may produce some unusual manifestations of cutaneous fungal infections similar to those seen with topical corticosteroids.

Systemic tacrolimus has been associated with occasional reports of invasive fungal disease with organisms including *Trichophyton* and *Scopulariopsis brevicaulis*.[9-11] Invasive cryptococcal infection may be more common in liver transplant patients

From the Departments of Dermatology and Laboratory Medicine, Geisinger Medical Center, Danville, Pennsylvania.
The author reports no conflict of interest.
Reprints: Dirk M. Elston, MD, Department of Dermatology, Geisinger Medical Center, 100 N Academy Ave, Danville, PA 17821 (e-mail: dmelston@geisinger.edu).

receiving tacrolimus as primary immunosuppression than in those treated with other drugs.[12] Topical tacrolimus is poorly absorbed and appears to have a very favorable safety profile for associated cutaneous infection. Any alteration in the manifestations of the infection is likely to be mediated by local effects rather than by systemic absorption.

Topical macrolactams offer a favorable safety profile, but how effective are they in comparison with corticosteroids? Few studies have addressed this question. The answer is likely to vary depending on whether the macrolactam is being applied to eczematous skin (as in atopic dermatitis) or to skin with an intact stratum corneum (as in vitiligo). The potency of a topical corticosteroid depends on its molecular structure and the delivery vehicle. Maximal potency is achieved when steroid receptors are saturated. The vehicle, concentration of the product, regional anatomy, and degree of skin hydration are all important determinants of the ability to saturate steroid receptors. In the case of macrolactams, an intact stratum corneum may be a significant barrier to absorption. In one study, betamethasone 17-valerate 0.12% ointment and tacrolimus 0.1% ointment applied to neck skin were compared for hygroscopicity, water-holding capacity, and the effect of a locally applied vasodilator (0.1% aqueous solution of methyl nicotinate).[13] Changes in these objective parameters were noted in corticosteroid-treated skin but not in the skin treated with tacrolimus ointment, suggesting that poor permeability of tacrolimus may limit its biologic effects in skin with an intact barrier function.[13]

In a study of 570 adult patients with moderate to severe atopic dermatitis, tacrolimus 0.03% and 0.1% ointments were compared with hydrocortisone-17-butyrate 0.1% ointment.[14] In this study, the efficacy of hydrocortisone butyrate 0.1% ointment was similar to that of tacrolimus 0.1% ointment but superior to tacrolimus 0.03% ointment.[14] Other studies have shown both tacrolimus 0.03% and 0.1% ointments to be significantly more effective than hydrocortisone acetate 1% in the treatment of atopic dermatitis and comparable to mometasone furoate 0.1% ointment in the treatment of dyshidrotic palmoplantar eczema.[15,16] Further studies of the relative effectiveness of topical corticosteroids and macrolactams are needed.

Another question to be studied is the effect of combined treatment with a topical macrolactam and a corticosteroid. If the effects are additive or synergistic, combinations of a topical macrolactam with a low or mid potency corticosteroid could provide superior efficacy while minimizing steroid side effects. A 21-day study of 57 patients with atopic dermatitis compared clocortolone pivalate 0.1% cream and tacrolimus 0.1% ointment. Treatment with both agents combined was statistically superior to either agent alone for several studied parameters at a variety of endpoints, suggesting that synergism between a topical macrolactam and a topical corticosteroid is possible.[17] Other possible strategies to achieve synergistic effects while minimizing steroid side effects include pulse application of a potent corticosteroid on weekends combined with daily use of a topical macrolactam. Sequential therapy with a course of a corticosteroid followed by a macrolactam also is likely to be used increasingly. In some settings, corticosteroids will prove superior for initial induction therapy, while topical macrolactams may be more suitable for chronic maintenance therapy.

The macrolactams represent a unique class of therapeutic agents useful in a variety of dermatologic diseases. Future studies should address their relative efficacy compared with corticosteroids in intact or eczematous skin in a variety of anatomic sites. Studies also should address the optimal ways of combining therapy with corticosteroids and macrolactams to maximize efficacy while minimizing side effects. Clinicians must remain alert to the possibility that some steroidlike side effects, including tinea incognito and Majocchi granuloma, may be possible with macrolactam therapy.

REFERENCES

1. Rappersberger K, Meingassner JG, Fialla R, et al. Clearing of psoriasis by a novel immunosuppressive macrolide. *J Invest Dermatol.* 1996;106:701-710.
2. Travis LB, Weinberg JM, Silverberg NB. Successful treatment of vitiligo with 0.1% tacrolimus ointment. *Arch Dermatol.* 2003;139:571-574.
3. Rao NG, Pariser RJ. Annular erythema responding to tacrolimus ointment. *J Drugs Dermatol.* 2003;2:421-424.
4. Thelmo MC, Lang W, Brooke E, et al. An open-label pilot study to evaluate the safety and efficacy of topically applied tacrolimus ointment for the treatment of hand and/or foot eczema. *J Dermatol Treat.* 2003;14:136-140.
5. Goldman D. Tacrolimus ointment for the treatment of steroid-induced rosacea: a preliminary report. *J Am Acad Dermatol.* 2001;44:995-998.
6. Fleischer AB Jr, Ling M, Eichenfield L, et al, and the Tacrolimus Ointment Study Group. Tacrolimus ointment for the treatment of atopic dermatitis is not associated with an increase in cutaneous infections. *J Am Acad Dermatol.* 2002;47:562-570.
7. Kang S, Paller A, Soter N, et al. Safe treatment of head/neck AD with tacrolimus ointment. *J Dermatol Treat.* 2003;14:86-94.

8. Yamamoto T, Nishioka K. Deep dermatophytosis during topical tacrolimus therapy for psoriasis [letter]. *Acta Derm Venereol*. 2003;83:291-292.
9. Corales R, Chua J, Mawhorter S, et al. Significant post-transplant hypogammaglobulinemia in six heart transplant recipients: an emerging clinical phenomenon? *Transplant Infect Dis*. 2000;2:133-139.
10. Martel J, Faisant M, Lebeau B, et al. Subcutaneous mycosis due to *Scopulariopsis brevicaulis* in an immunocompromised patient [in French]. *Ann Dermatol Venereol*. 2001;128:130-133.
11. Yoshimoto T, Yagi K, Inoue M, et al. Leukoencephalopathy probably caused by tacrolimus hydrate after stem cell transplantation in a girl with MDS 7 monosomy [in Japanese]. *Rinsho Ketsueki*. 1997;38:616-621.
12. Singh N, Gayowski T, Wagener MM, et al. Clinical spectrum of invasive cryptococcosis in liver transplant recipients receiving tacrolimus. *Clin Transplant*. 1997;11:66-70.
13. Kikuchi K, Tagami H. Comparison of the effects of daily applications between topical corticosteroid and tacrolimus ointments on normal skin: evaluation with noninvasive methods. *Dermatology*. 2002;205:378-382.
14. Reitamo S, Rustin M, Ruzicka T, et al, and the European Tacrolimus Ointment Study Group. Efficacy and safety of tacrolimus ointment compared with that of hydrocortisone butyrate ointment in adult patients with atopic dermatitis. *J Allergy Clin Immunol*. 2002;109:547-555.
15. Reitamo S, Van Leent EJ, Ho V, et al. Efficacy and safety of tacrolimus ointment compared with that of hydrocortisone acetate ointment in children with atopic dermatitis. *J Allergy Clin Immunol*. 2002;109:539-546.
16. Schnopp C, Remling R, Mohrenschlager M, et al. Topical tacrolimus (FK506) and mometasone furoate in treatment of dyshidrotic palmar eczema: a randomized, observer-blinded trial. *J Am Acad Dermatol*. 2002;46:73-77.
17. Torok HM, Maas-Irslinger R, Slayton RM. Clocortolone pivalate cream 0.1% used concomitantly with tacrolimus ointment 0.1% in atopic dermatitis. *Cutis*. 2003;72:161-166.