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Introduction

IT IS AN EXCITING TIME in dermatology. Tacrolimus and pimecrolimus are the first 2 medications of a new class of compounds, topical immunosuppressive agents that have mechanisms, and pharmacological profiles distinct from topical corticosteroids. Tacrolimus and pimecrolimus appear to be highly useful additions to our armamentarium for the treatment of atopic dermatitis (AD) and other eczematous dermatitis. They may be useful for multiple noneczematous skin conditions as well. A challenge in designing this issue of *Seminars in Cutaneous Medicine and Surgery* was to collect and present a state of the art assessment of our knowledge of these medications for dermatologic use, while acknowledging that our communal experience with them is still fairly limited. Their impact on the evolution of dermatologic therapeutics should be interesting, as our clinical use of these medications increases and as controlled studies and physician informal "trials" are performed. This issue is a collection of preclinical and clinical information on the tacrolimus and pimecrolimus that should be relevant and helpful to dermatologists and other health care professionals treating cutaneous disease.

The history of topical macrolide calcineurin inhibitors is an interesting one. Initially, systemic tacrolimus was used as a potent immunosuppressive agent to prevent rejection of solid organ in transplant recipients. Its beneficial immunosuppressive effects in this population resulted in its subsequent use in a wide variety of immunologic diseases. Experience with cyclosporine for eczema and psoriasis further stimulated interest, and lead to the development and extensive testing of topical tacrolimus as a cutaneous immunosuppressive agent. Pimecrolimus is a similar agent mechanistically, also binding calcineurin. It was derived from ascomycin, a natural macrocyclic product of *Streptomyces hygroscopicus var. ascomyceticus,* and apparently, for uncertain chemical reasons has less systemic immunosuppressive effects relative to skin immunosuppressive effects.

An appreciation of the clinical utility of topical macrolides for eczematous conditions should begin with an understanding of the significance of atopic dermatitis in dermatologic practice and of the pathogenesis of atopic dermatitis. Atopic dermatitis is of tremendous epidemiological importance in the pediatric age group, with a high prevalence that may be increasing. A recent study showed a 17% AD rate in school age children in urban and rural Oregon. Atopic dermatitis patients manifest abnormal cutaneous barrier function and acute and chronic inflammation. Recent work has provided insights into how genetic, environmental, and immunologic factors

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may contribute to atopic dermatitis development and cutaneous inflammation. It is unknown whether early treatment or chronic antinflammatory therapy with tacrolimus or pimecrolimus may influence the course of atopic dermatitis in young children or influence the development of other forms of atopy such as food allergy, allergic rhinitis, or asthma.

In assessing the utility of new medications, clinicians should look to preclinical studies as well as clinical studies. The preclinical work with tacrolimus and pimecrolimus is fascinating, laying the groundwork for development of topical formulations, appropriate dose finding, and display of efficacy and safety in an extensive collection of animal models. The core clinical studies of both tacrolimus and pimecrolimus are discussed in this issue, and are especially interesting for their extensive early study of affected children. The future uses of these medications for non-eczematous processes are fascinating to consider.

Safety assessment is crucial with new medications. To date, topical pimecrolimus and tacrolimus appear very well tolerated, with low levels of systemic absorption. Physicians and other health professionals should be aware of the studies performed to date, the numbers of patients evaluated, and the ages of patients studied. An aphorism I tell my medical students is "You can't have experience until you have experience." Initial data and experience are remarkably positive, although uncommon adverse events may not be appreciated with the number of patients treated with these medications to date. In this issue, discussion of safety also includes systemic side effects of tacrolimus when given systemically. Although these have not been seen with topical use of either tacrolimus or pimecrolimus, it is certainly prudent to be aware of these (although we are hopeful that they won't be part of our future experience).

The ability to use topical macrolides as anti-inflammatory medicine without the limiting side-effect profile of topical corticosteroids may allow a paradigm shift that advances AD management. The ability to use anti-inflammatory, nonsteroidal therapy for the prevention of AD skin flares, for instance, may allow development of guidelines for therapy that emphasize maintenance of noninflamed skin, rather than reactive anti-inflammatory therapy. We should still remember, however, the utility of excellent maintenance skin care, emollients and/or other creams that improve barrier function, and avoidance of irritants or stimulants of cutaneous inflammation. Part of the work ahead is finding the best place for tacrolimus and pimecrolimus in our therapeutic regimens, not just compared to placebo or vehicle, but also compared to and/or in combination with topical steroids and other prescription and non-prescription products and treatments. It is hoped that this issue of *Seminars in Cutaneous Medicine and Surgery* will be a stimulating one, as we work together to find optimal uses for these new medications.

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