# "Topical Immunomodulators?": Introducing old friends and a new ally, tacrolimus

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The supplement accompanying this issue of the JAAD contains a wealth of data on the treatment of atopic dermatitis with topical tacrolimus (pronounced ta•CRO•lim•is and formerly known as FK506). Because of its chronicity and prevalence, atopic dermatitis is the first disease in which topical tacrolimus has been extensively studied. This supplement presents data on the efficacy,[1,2] safety,[2,3] clinical outcomes,[1,4] and long-term use[2] of topical tacrolimus among adults and children with moderate and severe atopic dermatitis.

**Atopic dermatitis therapy will never be the same again**

Tacrolimus and its mechanistically close cousin cyclosporine are potent inhibitors of calcineurin, a calcium-activated enzyme, which cleaves phosphate groups from target proteins. Calcineurin is an excellent target for immunosuppression because it is essential for the transcriptional activation of multiple cytokines as well as processes such as mast cell degranulation. In fact, it was the discovery of the mechanism of action of these potent drugs that taught us how critical calcineurin is to the immune response.

Although these calcineurin inhibitors compare favorably with glucocorticoids in their ability to suppress the immune response, the side effect profiles of these agents when topically applied are very different. Specifically, calcineurin plays no role in collagen synthesis; thus steroid-induced atrophy does not occur with tacrolimus. The combination of good, anti-inflammatory efficacy without worry of atrophy is an exciting prospect in treating chronic inflammatory diseases such as atopic dermatitis.

Abundant evidence suggests that topical tacrolimus is not significantly absorbed into the bloodstream and that systemic side effects are avoided. The most common side effect of topical tacrolimus treatment is a transient burning discomfort on application, which recedes as skin inflammation diminishes. The unique new therapeutic alternative provided by tacrolimus will no doubt revolutionize the approach to the treatment of atopic dermatitis, especially at sites where atrophy is a concern.

**The six(ty?) million dollar supplement**

Although it is unclear how costly the 6 original contributions reported in this supplement were, this work was done well and without cutting corners. Collectively, the data include multiple, randomized, double-blind investigations in patients aged 2 to 79 years after extensive testing in animals. Dozens of rats and micropigs as well as more than 1000 people were followed up for periods up to 1 year in assessments of side effects, skin sensitivity, and anti-inflammatory efficacy. Indeed, the data in this supplement represent the extensive efforts required to demonstrate for the Food and Drug Administration (FDA) that tacrolimus is safe and effective in the treatment of atopic dermatitis.

Given that a study on a much smaller patient population over a shorter period was published on topical tacrolimus and eczema in the *New England Journal of Medicine*,[5] it seems likely that some of the studies in this supplement could have been published in a higher profile setting. It is possible that Fujisawa opted for this supplement format to keep these studies together as a cohesive unit and assure that dermatologists would have ready access to these data.

**Topical immunomodulators: Old and new**

The developer and manufacturer of tacrolimus, Fujisawa, has promoted tacrolimus as "the first in a new class of topical immunomodulators, TIMs." This is a puzzling phrase from two aspects. First, what do they mean by a TIM? The term *immunomodulator* seems

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J Am Acad Dermatol 2001;44:111-3.



0190-9622/2001/$35.00 + 0 **16/1/110902**
doi:10.1067/mjd.2001.110902

designed to avoid the word *immunosuppressant,* which is likely to conjure up images in the prescribing physician's mind of systemic immunocompromise in treated patients. In this regard, the term *TIM* seems very appropriate because there is ample evidence that topical tacrolimus is rarely absorbed enough from the skin even to be detected in blood, and certainly not enough to be immunosuppressive at the systemic level. Indeed, application of topical tacrolimus is likely to be no more systemically immunosuppressive than the use of topical steroids. The term *immunomodulator* also seems to emphasize the reversible nature of the immune effect of tacrolimus on the skin (skin immune function is back to normal within 2-4 weeks after discontinuing application).

What does "the first in a new class of TIMs" mean? Do we have an old class of TIMs? I certainly never recall telling any of my patients, "Slather on this TIM and call me in the morning…." Although we have not referred to them as such, glucocorticoids would surely be considered TIMs were the term to exist. Glucocorticoids potently block cytokine transcription, antigen presentation, and lymphocyte function; they also have effects even more broad, and often more deleterious, than those of tacrolimus. Thus, considering tacrolimus to be "the first in a new class of TIMs" is a reasonable concept, but only if one realizes that the first class of topical immunomodulators contains dozens of familiar hydrocortisone derivatives that have been the trusted allies of dermatologists for decades. It seems it required a second class of TIMs, the calcineurin inhibitors, to apply a label to the first one, the glucocorticoids.

**An ultimate niche for topical tacrolimus**

In most settings, topical steroids will remain the topical immunomodulators of choice for some time because they will be more economical, be familiar to physicians, and have greater skin penetration capacity than tacrolimus. As currently delivered in an ointment, topical tacrolimus is unlikely to be useful in diseases that affect more heavily keratinized skin, such as psoriasis or alopecia areata. Indeed, topical tacrolimus ointment has been found to be ineffective in chronic plaque psoriasis[6] and alopecia areata.[7]

On the other hand, because there is sufficient penetration on inflamed, less heavily keratinized skin and no risk of atrophy, topical tacrolimus will rapidly become the drug of choice for atopic dermatitis on areas such as the face, especially in children. In the studies that have directly compared topical tacrolimus with mid-strength steroids, tacrolimus has equaled or surpassed the efficacy of the steroid in treating atopic dermatitis. No doubt, tacrolimus will be tried in every inflammatory dermatosis, and when capable of traversing the stratum corneum, will likely show some efficacy.

Importantly, new preparations of tacrolimus and its related macrolide immunosuppressants will be compounded in cleverly engineered liposomes and polymers that will improve penetration and efficacy and that will expand the spectrum of diseases in which topical calcineurin inhibitors can be used in the future.

**When will topical tacrolimus be available?**

Topical tacrolimus (apparently to be marketed as Protopic) is not currently available in the United States, but was approved in Japan in November 1999. Fujisawa applied for FDA approval in the United States in September 1999, and early in the year 2001 may be a reasonable time to anticipate approval in the United States.

Because an oral form of tacrolimus (Prograf) is FDA-approved for the prevention of organ transplant rejection, tacrolimus is readily available currently in 1- and 5-mg capsules. The contents of these capsules can be compounded into a 0.1% ointment in a simple ointment such as Eucerin or as described by Aoyama et al[8] by most compounding pharmacies, allowing physicians to prescribe it now if desired.

**The cost question**

Although anticipated pricing information is not available from Fujisawa, it is possible to do arithmetic based on the cost of the oral formulation of tacrolimus. When purchased as a capsule, tacrolimus costs about $3 per milligram. Amazingly, as a testament to the power of modern pharmacology, this is more than 300 times the cost of gold on a per-weight basis. An ounce of pure gold in October 2000 cost $274, whereas an ounce of pure tacrolimus would be $84,900 and enough to prevent organ transplant rejection in a patient for about 16 years. Not to be misleading though, most medicines are costly relative to gold (even generic clobetasol costs many times the price of gold on a per-weight basis.)

In the studies reported in this supplement, about 5 g of a 0.1% tacrolimus ointment was applied each day by patients to control their moderate to severe eczema. This would work out to $15 per day or $450 per month, making it one of the most costly agents in dermatology as it is now compounded extemporaneously from oral capsules. In a conversation with a company spokesman, Fujisawa stated that the high cost of extemporaneously compounded topical tacrolimus is not a relevant predictor of the price of tacrolimus when it will be marketed as an ointment. It thus appears likely that the above scenario is worst case and that topical tacrolimus will be priced

more closely to ultrapotent steroids, its true competition.

**Overview**

In summary, the initial success of tacrolimus will be partly tempered by factors such as lack of familiarity on the part of physicians, transient burning of the patient's skin, and possible financial discomfort to health maintenance organizations. Overall however, dermatologists and their patients will be extremely pleased to have a truly new, carefully studied, effective, and nonatrophogenic ally in the fight against inflammatory disorders such as atopic dermatitis.

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