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In Reply Refer To:

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Dear Drs. Wilkin and Bahtt:

I am among those clinicians eagerly awaiting the addition of topical tacrolimus to the therapeutic armamentarium, because it seems clear that this drug will be particularly useful to induce remissions in severe, recalcitrant atopic dermatitis (AD). Both in severely-affected children and in adults with AD, tacrolimus appears to produce rapid clearing in a majority of patients. However, two recent articles in the *Archives of Dermatology* and other recent publications elsewhere, raise serious concerns that tacrolimus will be prescribed much more widely than is appropriate. Thus, it is very important that the labelling for the drug clearly indicate its proper, intended use and that all known and potential risks be clearly communicated.

The first of the two *Archives* articles, from the European Tacrolimus Ointment Study group, shows that a majority of adults with moderate-to-severe AD markedly improve or clear by one month, and claims to show that improvement increases to 90% if tacrolimus therapy is prolonged to six months or beyond.[1] The second *Archives* paper reports the efficacy of tacrolimus for facial erythema in severe adult AD, if the therapeutic program includes other involved sites.[2] Both studies raise questions about the appropriate indications and uses of tacrolimus, a powerful and potentially toxic, immunosuppressive drug. In the first report, the title and study design themselves suggest: a) that tacrolimus is appropriate for the long-term therapy of adult AD; b) that tacrolimus is appropriate not only for severe AD, but also for moderate disease (i.e., disease which presumably is also responsive to standard therapy); c) that tacrolimus is an effective form of maintenance therapy for AD; and d) that long-term use of tacrolimus is as safe or safer than standard therapy. Each of these premises needs to be examined separately. In fact, once remission is induced in AD, it is likely that other, inherently less toxic therapies, or even emollients alone might sustain the initial tacrolimus-induced response. Indeed, a different study design from the one employed by Reitamo, et al.[1], would be required to assess accurately the efficacy of tacrolimus for long-term therapy of AD. After initial improvement, patients should be randomized either to tacrolimus vs. standard therapy, or to emollients alone, to ascertain whether tacrolimus is superior to or

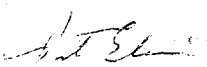
even necessary for maintenance therapy. Until such further studies show that previously recalcitrant patients need to remain on tacrolimus to sustain their remissions, previously refractory patients should be switched to standard therapy or emollients after an initial response is obtained. Moreover, moderate AD probably should not be treated routinely with tacrolimus until further information about long-term side effects, particularly in sun-exposed skin sites, becomes available.

I was also troubled by the second article in the same issue of the *Archives of Dermatology* about the putative 'efficacy of tacrolimus for recalcitrant facial erythema' in AD.[2] By this title alone, the casual reader might think that 'facial erythema' in AD is an appropriate indication for topical tacrolimus. I am concerned that this type of wording represents inappropriate salesmanship that could generalize the use of a limited-indication drug to broader and often inappropriate indications. Obviously, efficacy alone does not justify treating either mild-to-moderate disease, or incidental features, such as facial erythema.

From articles such as these, the practitioner may be left with the inappropriate impression that tacrolimus is indicated, safe, long-term therapy not only for recalcitrant AD, but also for moderate disease, and that it could/should be employed for a specific disease feature, such as facial erythema. Yet, tacrolimus is absorbed into the circulation through inflamed skin, and in low-body weight children it can produce transient, therapeutic (transplant) drug levels. When the barrier is further compromised, as in Netherton's Syndrome, toxic blood levels can occur (see attached submitted manuscript). However, even if blood levels remain low or undetectable, how can we be sure that sub-transplant blood levels do not also induce cumulative nephrotoxic or immunosuppressive side effects? How can we be sure that even very low levels of tacrolimus, percolating into the skin alone, won't increase the risks for either cutaneous T-cell lymphomas, and/or an increased propensity for skin cancers in locally UV-A-irradiated, immuno-suppressed skin?[2] Finally, do we know that local immunosuppression does not increase susceptibility to skin colonization by microbial pathogens, such as *Staphylococcus aureus*?

In summary, I share the excitement that a new therapeutic dimension brings to our capabilities to help suffering patients. Yet, I am alarmed at what appears to be a potentially cavalier and uncritical attitude about the indications and long-term safety of topical tacrolimus. Isn't this current situation reminiscent of the wave of enthusiasm that accompanied the initial release of isotretinoin, that also lead to excessive and inappropriate prescribing?

Sincerely,



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Conflict of Interest Disclaimer: Please note that Dr. Elias is a consultant for cosmetic companies that have developed or are developing emollients as potential alternate, safe therapy for atopic dermatitis.

In Preparation for
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Significant Absorption of Topical Tacrolimus in Two Patients With Netherton Syndrome

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Tacrolimus (FK-506) is a macrolide immunosuppressant that acts through several mechanisms including early inhibition of T-cell activation by blockade of calcineurin phosphatase activity. Oral tacrolimus (Prograf®, Fujisawa, Osaka, Japan) is used for primary immunosuppression following liver and kidney transplantation.[1] Topical 0.1% tacrolimus ointment has recently been shown to be effective in atopic dermatitis for children as young as age 2, with minimal systemic absorption.[2]

Netherton syndrome (NS) is an autosomal recessive disorder characterized by congenital erythroderma, hair shaft defects, frequent infections, poor growth and food allergies. The gene defect was recently localized to chromosome 5q32 and identified as a mutation in the SPINK5 gene, encoding the serine protease inhibitor LEKTI (lympho-epithelial Kazal-type related inhibitor.)[3] The pathognomonic cutaneous finding in NS, ichthyosis linearis circumflexa (ILC), develops in 75% of cases, but is not usually evident in infancy or early childhood.[4] A more common presenting sign is generalized redness and scaling, and often mimics atopic dermatitis. The erythroderma is often widespread and resistant to therapy. A recent report described a 20-year-old man with ILC who improved dramatically with topical tacrolimus.[5] We report 2 cases of children with Netherton syndrome and erythroderma treated with 0.1% tacrolimus ointment who experienced significant percutaneous absorption of the drug with serum levels in the toxic range.

CASE REPORTS

Case 1: A 5 year-old boy initially presented with premature delivery and congenital erythroderma complicated by *Staph aureus* sepsis. Continuing problems beyond the neonatal period included: erythroderma with scaling scalp, sparse hair, frequent otitis media, recurrent sinusitis, and poor growth. The diagnosis of Netherton syndrome was made at 9 months of age by demonstration of the pathognomonic hair shaft defect, trichorrhexis invaginata Initially, his skin care regimen consisted of daily bathing with Cetaphil and frequent use of Aquaphor. He was lost to follow care from ages 3 to 5 years. Recently, his skin has been unresponsive to topical therapies, including: ketoconazole shampoo, topical lactic and salicylic acid lotion, 2.5 % tar ointment, as well as topical 0.1% tazarotene ointment alone and in combination with a Class I topical corticosteroid. We treated this patient in a double-blinded fashion with 0.1% tacrolimus ointment twice daily on one side of the scalp and face and

vehicle on the other side. He had a significant decrease in crusting, scale and erythema on both sides, but the tacrolimus treated side was noted at 3-week and 8-week follow-up visits to have near complete clearing. A total of 15 grams of tacrolimus ointment was then applied sparingly to his trunk, shoulders, scalp and face twice daily over 5 days. A 2-hour post-dose serum tacrolimus level was 37.2 μg/L (post-organ transplant therapeutic range: 5-20 μg/L), drawn from a site that had not been treated for two days prior to the phlebotomy. A second 2-hour post-dose drug level was 19 μg/L on the same dose of medication. Despite these levels, his blood pressure, serum electrolytes, glucose, complete blood count, blood urea nitrogen and serum creatinine remained within normal limits. Subsequently, the drug was applied twice a week, only to the most severely involved areas, i.e., the scalp and face. On this regimen, post-application serum levels monitored at 2-day trough times have been <1.5 μg/L.

Case 2: A 14-year-old girl presented with by trichorrhexis invaginata, short stature, patches of ichthyosis linearis circumflexa and widespread congenital erythroderma associated with severe pruritus and elevated IgE. Her dermatitis and pruritus had been treated with chronic applications of triamcinolone acetonide 0.1% since early infancy. During past 5 years her course has been complicated by recurrent staphylococcal and streptococcal skin infections, flares of her erythroderma, and poor growth falling below the 5th percentile for age. At 10 5/12 years of age her bone age was 6 10/12 years, (2 standard deviations below the mean). Adrenocortical suppression was documented with a low morning cortisol of 0.5 μg/dl (normal > 4.3 μg/dl). She was subsequently placed on a lower potency topical corticosteroid (fluocinolone lotion, [Dermasmoothe F/S; Hill Pharmaceuticals]) and growth hormone replacement with a 6 cm growth spurt over 9 months.

At age 12 she was treated with extemporaneously compounded 0.01% tacrolimus ointment applied to one leg twice a day for one month with significant improvement. For the next 6 months, she applied the compounded ointment to a larger area with excellent response. Blood levels were not monitored. Two months later she was deemed eligible for treatment with proprietary 0.1% tacrolimus ointment (Fujisawa protocol 99-0-054). However, after 3 applications of the 0.1% product yielded intolerable stinging and exudative erythroderma, which subsided one week off medication. Patch tests with the study drug and extemporaneous compound were negative. Another trial of proprietary 0.1% tacrolimus ointment was attempted to one arm twice a day for 7days with the same adverse reaction. A tacrolimus level drawn within 48 hours of the last application was 23 μg/L. Complete blood count, renal and hepatic function were normal. Retreatment with extemporaneously compound 0.03% tacrolimus ointment resultied in a 24 hour post-application drug level of 8.3 μg/L. She elected to discontinue use.

DISCUSSION

Despite dramatic clinical improvement with topical tacrolimus in these two patients, the risk of systemic toxicity from percutaneous absorption is a serious

concern in Netherton syndrome. The therapeutic trough range for oral tacrolimus in organ transplant patients is 5-20 μg/L. Both of our patients experienced blood levels that exceeded the upper limit of this range. Although no clinical signs or symptoms of tacrolimus toxicity were observed, their exposure to high blood levels of drug was brief. In organ transplant patients, toxicity from this drug includes hypertension, renal insufficiency, central nervous system dysfunction, hyperglycemia and GI distress.[1] These complications occur in 10-85% of children with therapeutic trough plasma drug levels, requiring dose reduction in 33%.[add] Lymphoproliferative disorders are an ominous, long-term complication.[add]

In normal skin, multiple lamellar sheets of hydrophobic lipids surround the anucleate corneocytes, providing a waterproofing shield that retards movement of water and water-soluble substances across the stratum corneum.[6] These lipids are delivered to the stratum corneum interstices by a secretory organelle, the epidermal lamellar body. Following secretion, the lipids are further metabolized to hydrophobic species and then organized into repeating membranous arrays, termed lamellar unit structures. A competent skin barrier requires both sufficient layers of stratum corneum and mature extracellular lamellar unit structures.[7] In Netherton syndrome the stratum corneum is thin and parakeratotic. The corneocytes are surrounded by incompletely processed lipids and disorganized lamellae, as well as deposits of amorphous electron-dense materials.[8] These features would be predictive of a defective barrier, although barrier function has not been directly measured. It is well recognized that infants with Netherton syndrome are at risk for hypernatremic dehydration, presumably due to increased free water loss across an impaired skin barrier.[8] Similarly, patients with Netherton syndrome may be particularly vulnerable to increased percutaneous absorption of drugs such as tacrolimus and corticosteroids, as illustrated in our second patient.

The recent identification of the underlying genetic defect in Netherton syndrome, SPINK5, affecting function of an epidermal serine protease inhibitor,[3] is consistent with the pathogenic sequence illustrated in Figure A. Premature activation of the stratum corneum tryptic enzyme would result in activation of phospholipase A2. This may stimulate premature lamellar body secretion, a unique ultrastructural finding in Netherton syndrome,[8] as well as disruption of the plasma membrane, triggering cytolysis or premature cornification. At the same time, unchecked activation of the stratum corneum tryptic enzyme, would lead to premature degradation of corneodesmosomes, premature desquamation and thinning of the stratum corneum. Both of these actions would result in a defective permeability barrier and could account for the increased absorption and high serum levels of tacrolimus in Netherton syndrome patients. Finally, serine proteases may also be involved in releasing stratum corneum IL-1 from its inactive form, which could lead to the marked inflammation characteristic of Netherton syndrome. Interruption of this inflammatory sequence may account for the beneficial effects of topical anti-inflammatory drugs, such as tacrolimus, in this disorder.

Clinical experience with topical tacrolimus has been primarily limited to investigational trials in patients over 2 years of age with atopic dermatitis. In these series, blood levels were occasionally detected within the therapeutic range in subjects with extensive disease.[2] Higher plasma levels invariably occurred

during the first week of therapy, and diminished as patients skin disease improved. Infants and young children with widespread areas of active disease are at highest risk for significant percutaneous absorption of the drug.

Although tacrolimus ointment is not yet commercially available in the United States, approval by the US FDA for the treatment of atopic dermatitis in children as young as 2 years is anticipated in the near future. Meanwhile, an extemporaneously compounded form of the drug is being prescribed in accordance with a recently published formula using Prograf® capsules (Fujisawa, Osaka, Japan).[9] Once the proprietary formulation has been approved and marketed, tacrolimus ointment will likely become the treatment of choice for children with severe or steroid-dependant atopic dermatitis. Because children with Netherton syndrome are often either misdiagnosed as having only atopic dermatitis or assumed to have atopic dermatitis in association with Netherton syndrome, as in our Case 2, it will be important to correctly identify these children prior to initiating topical tacrolimus therapy. Sparse or brittle hair, frequent infections and poor growth in an erythrodermic child should prompt appropriate investigation of Netherton syndrome (11). We also believe that the potential risk of significant systemic absorption with associated acute toxicities must be considered in any child with extensive skin disease, or any infant, regardless of the extent of disease, because of their high ratio of body surface area-to-weight.[10] If topical tacrolimus ointment is prescribed in any of these settings, close monitoring with plasma drug levels is essential. Finally, whether any patients treated with this drug topically will be at increased risk for developing lymphoproliferative disease can only be appreciated after long-term use.

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