

An Appropriate Response to the Black-Box Warning: Corrective, Barrier Repair Therapy in Atopic Dermatitis

Peter M. Elias

Dermatology Service, Veterans Affairs Medical Center, and Department of Dermatology, University of California, San Francisco, CA.

Abstract: Due to years of sophisticated research on T cell function, many dermatologists have viewed atopic dermatitis (AD) largely as an inflammatory disorder of TH1/TH2 imbalance. Hence, therapy has largely consisted of topical immunomodulators and/or steroids. The imposition of “black box” warnings about the potential toxicity associated with prolonged use of the immunosuppressive drugs, tacrolimus 0.1% or 0.3% ointment (Protopic[®], Astellas Pharma U.S., Inc., Deerfield, IL) and pimecrolimus 1% cream (Elidel[®], Novartis, Basel, Switzerland), as well as legitimate concerns about the adverse side effects of potent topical steroids, has stimulated a search for alternate forms of therapy. Recent genetic studies point to the primary role of a defective barrier to water loss and microbial invasion in the provocation of AD, creating a rationale for ‘barrier repair’ therapy. This approach utilizes topical applications of specific combination of the three (3) epidermal lipids that comprise the epidermal permeability barrier in a ratio (ceramide-dominant) that corrects the biochemical abnormality in AD.^{1,2} We review here both recent concerns about the topical immunomodulators, as well as the rationale for barrier repair therapy.

Keywords: atopic dermatitis, barrier function, barrier repair, TH2 cells

Why is the FDA Concerned About Elidel and Protopic?

The direct-to-consumer and physician-to-provider promotional activities that accompanied the marketing of Elidel and Protopic lead to widespread use of these agents in children with AD under the age of two years (outside their approved labeling).³ This prompted the FDA to reconsider the risk/benefit profile of these agents, and their appropriate place in the treatment of AD.^{3,4} Even critics of the FDA’s imposition of “black box” warnings on Elidel[®] and Protopic[®] acknowledge the strong causal link between *systemic* (internal) use of these agents and the development of both lymphatic cancers (lymphomas) and light -induced skin cancers.⁵ The current controversy centers on whether *long-term, topical* use of these immunosuppressive drugs also presents a risk of cancer. It should be noted that long-term use of *topical* steroids poses no increased risk of either lymphoma or sun-induced skin cancer.⁶ We review here general concerns, and the FDA’s specific concerns that led to imposition of the “black box” warning:

- 1) Although the *average* blood concentration of patients using topical Elidel[®] and Protopic[®] is lower than are blood levels of these drugs in organ transplant recipients, some patients, particularly small children with severe AD, demonstrate high blood levels that persist with prolonged use.⁷ Some of these patients may have previously-undiagnosed Netherton syndrome. But regardless, if these agents are employed as *maintenance*, rather than for *short-term*, use as indicated, it is the author’s opinion that physicians should consider monitoring blood levels in order to identify patients at risk.
- 2) The FDA advisory group also noted that *blood* levels do not necessarily reflect *tissue* levels of these drugs. Yet, the marketing companies (Novartis and Astellas) did not provide information from their preclinical studies about drug tissue levels. Nor have these companies provided information about the possible movement of topically-absorbed Protopic[®] or Elidel[®] from the skin to regional lymph nodes (where lymphomas of the type anecdotally-linked to the use of these topical agents can arise).
- 3) Cases have been reported to the FDA in which cancers have developed either *directly at sites* of *prolonged* Elidel[®] and Protopic[®] applications, or in draining, regional lymph nodes. In fact, some

Correspondence: Peter M. Elias, M.D., Dermatology Service (190), VA Medical Center, 4150 Clement Street, San Francisco, CA 94121. Tel: (415) 750-2091; Fax: (415) 751-3927; Email: eliasp@derm.ucsf.edu



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of the reported cases of ‘recalcitrant’ eczema were masquerading for malignant and premalignant disorders, such as Bowen disease, parapsoriasis en plaque, or Paget disease of the nipple. Therefore, it would be advisable to biopsy ‘recalcitrant’ lesions prior to initiating long-term therapy with immunomodulators.

- 4) Finally, in some of the cases reported to the FDA, and in others that the author has since become aware of, tumor incidence has been linked to both the *total applied dose* and *duration* of Elidel/Protopic therapy. Logically, then the longer drug use, or the higher the drug concentration, the greater the likelihood of developing cancer.

Rationale for Barrier Repair Therapy

Even if anti-inflammatory therapies reduce disease severity by suppressing immune function, they do not completely correct the primary underlying barrier abnormality which drives disease pathogenesis in AD.^{8,a} Studies in AD animal models and in patients show that barrier repair interventions promote *normal skin function*, thereby reducing the inflammatory component of disease.^{8,9}

The role of the epidermal barrier in trapping moisture and preventing dry skin is widely appreciated, but less well-known are the numerous other protective functions of the outermost skin layer (stratum corneum, SC). The SC provides not only the permeability barrier, but it also is an antimicrobial, antioxidant, UV-filtering, mechanical and sensory interface.^{8,10} The clinical significance of barrier function begins with the large pool of pre-formed pro-inflammatory cytokines such as IL-1 α and IL-1 β , which are stored in the SC. These molecules then are released into the lower epidermis and dermis when barrier function is perturbed. Although the cytokine cascade helps to restore barrier function in normal skin, it is unsuccessful in AD. Since the barrier is always abnormal in AD, cytokine release is sustained, resulting in the recruitment of additional, pro-inflammatory molecules (hence, the ‘outside-to-inside’ concept of AD causation). In addition to the ongoing cytokine cascade, failure of barrier function triggers/aggravates AD by allowing repeated access of hap- tens, which ultimately stimulate the characteristic

TH2-cytokine response.^{8,10} These two mechanisms, coupled with exotoxins released from colonizing *S. aureus*, together account for downstream inflammation in AD, and provide a strong rationale for barrier repair therapy.

Barrier Repair Therapy in AD

It is commonly assumed that inflammatory skin diseases should be treated with anti-inflammatory or immunosuppressive therapies, and the marketing efforts of pharmaceutical companies have further influenced over-utilization of this approach.^{4,5} Effective, disease-specific formulations that correct the underlying barrier abnormality in AD have not been available until recently. Yet, recent studies show that targeted corrective with a ceramide-dominant form of barrier repair therapy (EpiCeram[®] emulsion) demonstrates efficacy comparable to fluticasone cream (Cutivate[®]).^{2,9} Since this form of therapy displays none of the safety concerns of steroids or immunomodulators, it could therefore assume a central place in the future treatment of AD.^{9,11}

Typical emollient moisturizers, even if they provide some temporary relief through moisturization, actually degrade, rather than improve, barrier function, and by providing partial relief, they actually delay barrier repair.¹¹ This feature of moisturizers explains why atopic patients frequently report that moisturizers provide some immediate relief, but shortly thereafter patients feel worse than before. In contrast, corrective barrier repair requires topical applications of *sufficient quantities* of all three key lipids that mediate barrier function (ie, cholesterol, free fatty acids, and ceramides), further provided in a *proportion that corrects the underlying lipid biochemical abnormality* in AD.¹¹ Under these conditions, restoration of normal skin barrier function alone can then down-regulate inflammation in deeper skin layers. Yet, most currently-available products that make ‘barrier repair’ claims incorporate either *incomplete* mixtures of the three key lipids, *incorrectly formulated* mixtures, *incorrect types* of the three lipids, or in some cases, *insufficient quantities* of the three lipids.¹⁰ Not surprisingly, these products fail to improve barrier repair in animal models of AD.¹⁰

With the recent FDA clearance of EpiCeram[®], physicians and their patients now have an opportunity to assess the potential benefits of a potent, new form of barrier repair therapeutics, developed

^aReductions in inflammation alone can, however, reduce TEWL due to the ‘vicious cycle’ that is operative in AD.⁹

by the author at the University of California, San Francisco.^{6,8,10,11} In AD, there is a global decrease in all three key lipids, with a further reduction in ceramides. This therapy comprises a mixture of the three key physiologic lipids in an appropriate, ceramide-dominant, molar ratio, and at high concentrations (>5%), is designed specifically to correct the lipid biochemical abnormality in AD. In a recent, multicenter, controlled clinical trial in 113 children, aged 6 months to 18 years with moderate-to-severe AD, EpiCeram[®] was highly effective as stand-alone therapy, and comparable in both clinical efficacy and itch reduction to a mid-strength steroid (Cutivate[®] cream) by 28 days of treatment² (Fig. 1) EpiCeram[®] (Promius Pharmaceuticals) cream became available for prescribing in September, 2008.

Since some patients might develop ‘rebound flares’ while being withdrawn from topical steroids, it might be advisable to employ with a combination of EpiCeram[®] with a short-term course of a low-potency steroid (e.g. desonide) which could both yield even faster initial results, and could allow withdrawal from steroids without the risk of rebound flares. After 2–4 weeks, however, EpiCeram[®] alone should suffice. Whether barrier repair therapy will also reduce secondary colonization by pathogenic *S. aureus*, and whether it will prevent emergence of mucosal atopy (‘atopic march’) remains to be determined.

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Conflict of Interest Statement

Dr. Elias is a co-inventor of the optimal ratio, triple-lipid therapy for atopic dermatitis. He is a consultant for Promius Pharmaceuticals, which markets EpiCeram[®] in the United States.

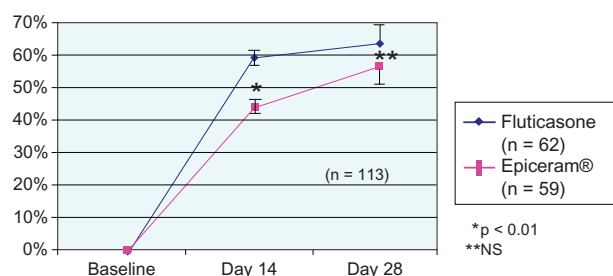


Figure 1. Percent changes in mean SCORAD scores—EpiCeram[®] vs. Fluticasone in moderate-to-severe AD. Both products rapidly improved SCORAD scores. Cutivate rate of improvement was significantly better at 2 weeks, with both products equivalent at 4 weeks.

References

- Chamlin SL, Kao J, Frieden IJ, et al. Ceramide-dominant barrier repair lipids alleviate childhood atopic dermatitis: changes in barrier function provide a sensitive indicator of disease activity. *J Am Acad Dermatol*. 2002;47:198–208.
- Sugarman J, Parish LJ. A topical lipid-based barrier repair formulation (EpiCeram cream) is high-effective monotherapy for moderate-to-severe pediatric atopic dermatitis. *IID 2008 Kyoto, Japan*. 2008.
- Temeck J. Protopic and Elidel Presentation for FDA Regulatory Briefing on January 14, 2005.
- Stern RS. Topical calcineurin inhibitors labeling: putting the “box” in perspective. *Arch Dermatol*. 2006;142:1233–5.
- Fleischer AB Jr. Black box warning for topical calcineurin inhibitors and the death of common sense. *Dermatol Online J*. 2006;12:2.
- Arellano FM, Wentworth CE, Arana A, Fernandez C, Paul CF. Risk of lymphoma following exposure to calcineurin inhibitors and topical steroids in patients with atopic dermatitis. *J Invest Dermatol*. 2007;127:808–16.
- Kameda G, Kramm C, Stege H, Hermsen D, Krutmann J, Niehues T. Unexpected high serum levels of tacrolimus after a single topical application in an infant. *J Pediatr*. 2003;143:280.
- Elias PM, Hatano Y, Williams ML. Basis for the barrier abnormality in atopic dermatitis: outside-inside-outside pathogenic mechanisms. *J Allergy Clin Immunol*. 2008;121:1337–43.
- Elias PM. Barrier-repair therapy for atopic dermatitis: corrective lipid biochemical therapy. *Exp Rev of Dermatol*. 2008;3:441–52.
- Elias PM, Steinhoff M. “Outside-to-inside” (and now back to “outside”) pathogenic mechanisms in atopic dermatitis. *J Invest Dermatol*. 2008;128:1067–70.
- Elias PM. Epilogue: fixing the barrier—theory and rational deployment. IN Elias, P. M., Feingold, K.R. (Ed.) *Skin Barrier*. 2006; New York, Taylor and Francis.