



DERMATOLOGY CME EXPRESS FAX

The Safety of Topical Calcineurin Inhibitors – Consensus Statements

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Expert Commentary

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On February 15, 2006, the Pediatric Advisory Committee of the Food and Drug Administration (FDA) convened a meeting to review safety data concerning the potential cancer risk among pediatric patients treated for atopic dermatitis with topical calcineurin inhibitors, specifically tacrolimus (Protopic) and pimecrolimus (Elidel).¹ As a result of this meeting, the committee recommended that the FDA add “black box” warnings for tacrolimus and pimecrolimus. On January 19, 2006, the FDA approved revisions to the safety labeling for tacrolimus and pimecrolimus which included boxed warnings and a patient medication guide that emphasized the appropriate use of each agent.²

The actions taken by the FDA have generated considerable discussion among clinicians who specialize in the treatment of atopic dermatitis. Concerned that the warnings may confuse and unnecessarily worry patients and their families, as well as healthcare providers, consensus statements from the Topical Calcineurin Inhibitor Task Force of the American College of Allergy, Asthma and Immunology/American Academy of Allergy, Asthma and Immunology,³ the American Academy of Dermatology Association Task Force,⁴ and a group of leading researchers in dermatology have been published in response to the FDA’s recommendations.⁵

As these agents represent a significant advancement in treating atopic dermatitis and are currently the only prescribed anti-inflammatory medications that serve as an alternative to topical corticosteroids, the safety data surrounding their use must be carefully assessed and put into the appropriate context. Due to the similarities among the 3 consensus statements, this *Dermatology Express Report™ Fax* reviews the salient points of the Topical Calcineurin Inhibitor Task Force of the American College of Allergy, Asthma and Immunology/American Academy of Allergy, Asthma and Immunology consensus statement.

FDA Concerns that Led to Recommendations

The Topical Calcineurin Inhibitor Task Force of the American College of Allergy, Asthma and Immunology/American Academy of Allergy, Asthma and Immunology³ recognized several concerns voiced by the FDA in relation to topical calcineurin inhibitor use:

- topical calcineurin inhibitors have been increasingly used due to the perception by physicians and patients that topical tacrolimus and pimecrolimus were safer than topical corticosteroids. Moreover, approximately 25% of new prescriptions were for patients less than 2 years of age.
- the FDA was investigating postmarketing reports of malignancy in patients who had used these agents (Table 1).
- because a definitive answer regarding the risk of carcinogenicity from topical tacrolimus and pimecrolimus would not be known for years, *and if such a risk was real*, the FDA wanted to provide adequate information to assist healthcare providers and patients in their proper use.

Perspective of the Safety Data

The Topical Calcineurin Inhibitor Task Force of the American College of Allergy, Asthma and Immunology/American Academy of Allergy, Asthma and Immunology³ offered the following observations of the current safety data related to tacrolimus and pimecrolimus and treatments for atopic dermatitis:

- after topical application, serum concentrations of tacrolimus and pimecrolimus are low or undetectable,^{1,6-8} with decreased absorption associated with improving atopic dermatitis.

Table 1. Cases Reported to the FDA of Spontaneous Reports of Lymphoma.*³

Agent	Age (years)	Lymphoma Histology	Independent Expert Assessment of Causality
Pimecrolimus	61	Histiocytic lymphoma	Unlikely
Pimecrolimus	53	Subcutaneous panniculitis-like T-cell lymphoma	Unlikely
Pimecrolimus	2.5	Lymphoblastic lymphoma (T cell)	Unlikely
Tacrolimus	52	Non-Hodgkin’s lymphoma	Insufficient evidence
Tacrolimus	50	Anaplastic large cell lymphoma–T-cell type	Insufficient evidence
Tacrolimus	40	Lymphoma “possible”	Insufficient evidence
Tacrolimus	54	Non-Hodgkin’s lymphoma	Insufficient evidence

* Presented February 15, 2005 to the Pediatric Advisory Committee of the FDA.

- based on the malignancy rates in the general population, there is no evidence of increased incidence of lymphoma with the short-term application or intermittent long-term application of topical tacrolimus and pimecrolimus. Moreover, the actual rate of lymphoma formation reported to date with topical tacrolimus or pimecrolimus is *lower* than would be predicted in the general population, although clearly spontaneous reporting is lower than occurrence in a prospective analysis using the medications.
- there are well-recognized features that characterize lymphomas occurring with immunosuppressive therapy. The histology and clinical presentations for the cases of lymphoma identified to date with topical tacrolimus or pimecrolimus are not those associated with post-transplant lymphoproliferative disorder or lymphoma. Moreover, none of the information provided for the cases associated with topical tacrolimus or pimecrolimus use indicated or suggested a casual relationship. An independent expert panel concluded that there was no clear association between topical tacrolimus or pimecrolimus and increased risk of lymphoma.¹
- there is no evidence of systemic immunosuppression from topical tacrolimus or pimecrolimus as measured by response to vaccination^{3,9-12} and delayed hypersensitivity.^{13,14}
- the cutaneous features of cutaneous T-cell lymphoma can be confused with those of atopic dermatitis, leading to misdiag-

nosis and treatment with topical calcineurin inhibitors, despite the existent diagnosis.¹⁵

- there is an increased risk of adverse effects and malignancies associated with oral corticosteroids and other systemic therapies (cyclosporine, psoralen plus ultraviolet A) used for severe atopic dermatitis³ (Table 2).

Conclusions and Recommendations

The Topical Calcineurin Inhibitor Task Force American College of Allergy, Asthma and Immunology/American Academy of Allergy, Asthma and Immunology concluded that there was no evidence to date of systemic immunosuppression after short-term or intermittent long-term application of topical tacrolimus and pimecrolimus. Moreover, lymphoma formation was generally associated with high-dose and sustained *systemic* exposure to *oral* tacrolimus and pimecrolimus and the reported cases of lymphoma from topical tacrolimus and pimecrolimus were anecdotal and not consistent with lymphoma observed with systemic immunosuppressive therapy. However, the long-term effect of topical tacrolimus and pimecrolimus on developing immune systems is not known. Therefore, the Task Force recommended that immunocompromised children and adults should not use these agents. Furthermore, topical tacrolimus and pimecrolimus should be used only in an amount to control patients' symptoms and that patients should be thoroughly

educated on the risks and benefits of all therapies used to treat atopic dermatitis. In addition, clinicians should reinforce the need for adjunctive therapy to control their atopic dermatitis (eg, liberal moisturization, treatment of infections, optimal skin care). The Task Force stressed the importance of vigilance and education on the prudent use of all therapies to manage atopic dermatitis.

Table 2. Malignancy Risks of Therapies Used to Treat Atopic Dermatitis.^[adapted from 3]

Therapy	Malignancy Risk	Adverse Event
Topical corticosteroids	Evidence-based: no evidence of immunosuppressive malignancy	HPA axis suppression, skin atrophy, telangiectasias, ↓ bone mineral density
Oral corticosteroids	↑ risk of squamous cell-basal cell carcinoma; non-Hodgkin's lymphoma	↑ infection, hypertension, myopathy, glaucoma, Cushing syndrome, osteopenia
Topical calcineurin inhibitors	Evidence-based: no evidence of immunosuppressive malignancy	Skin irritation at application site
Oral immunosuppressive agents (cyclosporine)	↑ lymphoproliferative disease (esp. B cell)/skin cancer	Nephrotoxicity, hepatotoxicity
Phototherapy	↑ risk of squamous cell and basal cell carcinoma and malignant melanoma	Erythema, pruritus, chronic actinic skin damage, dyskeratotic and precancerous skin conditions

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