



Balancing Clinical Benefit and Possible Risks of Topical Calcineurin Inhibitors

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Expert Commentary

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The topical calcineurin inhibitors, tacrolimus (Protopic) and pimecrolimus (Elidel) are approved by the Food and Drug Administration (FDA) for the treatment of atopic dermatitis.^{1,2} Topical calcineurin inhibitors were developed in response to concern over prolonged use of topical corticosteroid treatment which has been associated with significant side effects, such as skin atrophy, telangiectasias, hypopigmentation and potential suppression of the hypothalamic-pituitary-adrenal axis.³⁻⁵ In contrast to topical corticosteroids, tacrolimus has demonstrated no effect on collagen synthesis and causes no skin atrophy.⁶ Similarly, pimecrolimus has also displayed a lack of atrophogenic properties.⁷ Tacrolimus and pimecrolimus have demonstrated safety and efficacy in treating children and adults with atopic dermatitis.

On February 15, 2005, the Pediatric Advisory Committee of the FDA convened a meeting to review safety data concerning the potential cancer risk among pediatric patients treated for atopic dermatitis with topical calcineurin inhibitors.⁸ As a result of this meeting, the FDA approved revisions to the prescribing information for tacrolimus and pimecrolimus which included boxed warnings and a patient medication guide.⁹

The revised prescribing information for tacrolimus and pimecrolimus has generated extensive debate among clinicians who specialize in the treatment of atopic dermatitis. Concerned that these warnings may confuse and unnecessarily worry patients, as well as their healthcare providers, consensus statements have been issued in response to the FDA's recommendations.¹⁰⁻¹² It is critical for healthcare providers to fully understand the background and implications of the FDA warnings in order to provide optimal care for their patients with atopic dermatitis.

The basis of the recent FDA labeling revisions was derived from oral systemic calcineurin inhibitors following organ transplantation. Although the prolonged use of oral systemic immunosuppressive agents has been associated with an increased rate of skin cancer formation,¹³ the role of topical calcineurin inhibitors and increased risk of skin cancer is less clear. Indeed, a large retrospective analysis of 9,813 pediatric and adult patients with moderate-to-severe atopic dermatitis demonstrated no increased risk of non-melanoma skin cancer (NMSC) with tacrolimus ointment treatment.¹⁴

This *Dermatology Express Report™* reviews the consensus statement from The Topical Calcineurin Inhibitor Task Force of the American College of Allergy, Asthma and Immunology/American Academy of Allergy, Asthma and Immunology concerning the use of topical calcineurin inhibitors in treating atopic dermatitis and the results of the retrospective safety analysis of tacrolimus ointment therapy.

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 Immunology¹⁰ 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).

Table 1. FDA Cases of Spontaneous Reports of Lymphoma.¹⁰

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

- 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.

Task Force Perspective of the Safety Data

The Topical Calcineurin Inhibitor Task Force¹⁰ 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,^{8,15-17} with decreased absorption associated with improving atopic dermatitis
- 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
- there are features that characterize lymphomas occurring with immunosuppressive therapy. The histology and clinical presentations for the cases of lymphoma identified 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 lymphoma⁸
- there is no evidence of systemic immunosuppression from topical tacrolimus or pimecrolimus as measured by response to vaccination^{10,18-21} and delayed hypersensitivity^{22,23}
- atopic dermatitis itself, has been associated with malignancy, such as cutaneous T-cell lymphoma²⁴
- 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 dermatitis¹⁰ (Table 2)

Table 2. Malignancy Risks of Therapies Used to Treat Atopic Dermatitis.^[adapted from 10]

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 (eg, cyclosporine)	↑ B-cell lymphoproliferative disease/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

Task Force Conclusions and Recommendations

The Topical Calcineurin Inhibitor Task Force concluded that there was no evidence 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.

Topical Tacrolimus Does Not Increase Risk of Non-melanoma Skin Cancer

A retrospective analysis examined the incidence of NMSC (eg, basal cell epithelioma, squamous cell carcinoma) in patients with atopic dermatitis treated with tacrolimus ointment. This analysis included 9,813 pediatric and adult patients with moderate-to-severe atopic dermatitis enrolled in randomized, double-blind, vehicle-controlled and open-label safety studies between 1995–2001 and treated with tacrolimus ointment (0.03% or 0.1%) twice daily until 1 week after resolution of lesions.¹⁴

The incidence of NMSC was calculated by dividing the number of patients with NMSC by the total patient-years of exposure for all patients ≥40 years of age. This age group was selected because the incidence of NMSC increases after age 40 and data with similar age groups were available for comparison (Physician's Health Study,²⁵ n = 22,071, 12-year follow-up and Danish National Hospital Register,²⁶ n = 2,030, 19-year follow-up). Data from 9,813

patients were included in the analysis (Table 3). Overall, 1,718 patient-years of tacrolimus ointment exposure was accrued in patients ≥40 years of age (Figure 1).

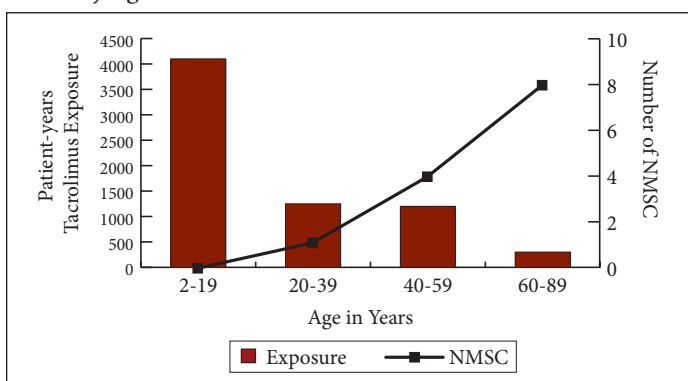
The analysis showed that 13 patients developed NMSC (10 basal cell epithelioma and 3 squamous cell carcinoma).

Table 3. Selected Demographics and Treatment Characteristics for All Patients.^[adapted from 14]

Parameter	Age in Years			
	2-19 (n = 5,052)	20-39 (n = 2,144)	40-59 (n = 1,929)	≥60 (n = 688)
Male	45.9%	37.2%	40.2%	45.5%
White	68.7%	68.2%	78.9%	85.6%
African-American	18.1%	19.5%	13.6%	7.7%
% Body surface area treated (mean)	37.0	31.4	30.2	33.3
Patient-years of exposure	4,103.0	1,291.4	1,290.9	426.9
No. of patients with NMSC	0	1	4	8

NMSC = non-melanoma skin cancer.

Figure 1. Patient-years of Tacrolimus Exposure and Number of NMSC by Age.¹⁴



Their mean percentage of body surface area treated was 42.7% (median 37%). The enrolling physicians did not consider any of the NMSC cases to be related to the use of tacrolimus ointment.

The patients diagnosed with NMSC in this analysis exhibited known risk factors for developing skin cancer:

- All 13 patients were white
- 7 of 13 patients resided in geographic areas associated with prolonged sun exposure (Florida, North Carolina, California, New Mexico, Texas)

- 6 of 13 patients had NMSC on skin areas chronically exposed to the sun, while the remainder had NMSC on skin areas which potentially receive substantial sun exposure
- 10 of 13 patients were over 55 years of age (>30% of patients >55 years of age have a history of skin cancer²⁷)
- 7 of 13 patients had prior history of skin cancer and/or prior ultraviolet light therapy or systemic immunosuppressive therapy

No NMSC was diagnosed in pediatric patients with atopic dermatitis; only 1 case was diagnosed in 7,196 patients <40 years of age. Eight patients had NMSC at a non-application site. Since topical tacrolimus results in minimal systemic exposure and studies have shown no systemic effect from topical tacrolimus, NMSC at non-application sites is unlikely to be related to topical tacrolimus.

All the patients with NMSC were diagnosed within 11.5 months of the initiation of topical tacrolimus therapy and 10 were diagnosed within 113 days. Since these were primarily patients with moderate-to-severe atopic dermatitis, investigators theorized that the clinical manifestations of their atopic dermatitis may have obscured NMSC present at study entry that became apparent as their atopic dermatitis resolved. Therefore, the relatively short time between the start of topical tacrolimus therapy and the development of NMSC in these patients also argues against the likelihood that topical tacrolimus contributed to the development of NMSC.

Treatment Recommendations

The appropriate use of topical calcineurin inhibitors is necessary to provide safe and effective treatment for patients with atopic dermatitis. Based on currently available data, there is no evidence to suggest that topical calcineurin inhibitors are associated with development of skin cancer or malignancies. Prudent and judicious use of topical calcineurin inhibitors, in combination with educational counseling of patients on potential long-term safety issues associated with topical calcineurin inhibitors, is warranted to provide optimal care for patients with atopic dermatitis.

References

1. Protopic prescribing information [package insert]. Astellas Pharma US, Inc. Available at www.protopic.com. Accessed September 22, 2006.
2. Elidel prescribing information [package insert]. Novartis Pharmaceuticals Corp. Available at www.elidel.com. Accessed September 22, 2006.
3. Ahuja A, Land K, Barnes CJ. Atopic dermatitis. *South Med J*. 2003;96:1068-1072.
4. Ellis C, Luger T, on behalf of the ICCAD II faculty. International Consensus Conference on Atopic Dermatitis II (ICCAD II): clinical update and current treatment strategies. *Br J Dermatol*. 2003;148(Suppl 63):3-10.
5. Stone KD. Atopic diseases of childhood. *Curr Opin Pediatr*. 2003;15:495-511.
6. Reitamo S, Rissanen J, Remitz A, et al. Tacrolimus ointment does not affect collagen synthesis: results of a single-center randomized trial. *J Invest Dermatol*. 1998;111:396-398.
7. Queille-Roussel C, Paul C, Duteil L, et al. The new topical ascomycin derivative SDZ ASM 981 does not induce skin atrophy when applied to normal skin for 4 weeks: a randomized, double-blind controlled study. *Br J Dermatol*. 2001;144:507-513.
8. Briefing Information from the Pediatric Advisory Committee of the US Food and Drug Administration, Washington, DC, February 15, 2005. Available at www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4089b2.htm. Accessed September 22, 2006.

9. FDA News P06-09. FDA approves updated labeling with boxed warning and medication guide for two eczema drugs, Elidel and Protopic. Available at www.fda.gov/bbs/topics/news/2006/NEW01299.html. Accessed September 22, 2006.
10. Fonacier L, Spergel J, Charlesworth EN, et al. Report of the Topical Calcineurin Inhibitor Task Force of the American College of Allergy, Asthma and Immunology and the American Academy of Allergy, Asthma and Immunology. *J Allergy Clin Immunol*. 2005;115:1249-1253.
11. Bieber T, Cork M, Ellis C, et al. Consensus statement on the safety profile of topical calcineurin inhibitors. *Dermatology*. 2005;211:77-78.
12. Berger TG, Duvic M, Van Voorhees AS, VanBeek MJ; American Academy of Dermatology Association Task Force. The use of topical calcineurin inhibitors in dermatology: safety concerns. Report of the American Academy of Dermatology Association Task Force. *J Am Acad Dermatol*. 2006;54:818-823.
13. Berg D, Otley CC. Skin cancer in organ transplant recipients: epidemiology, pathogenesis, and management. *J Am Acad Dermatol*. 2002;47:1-17.
14. Naylor M, Elmets C, Jaracz E, Rico MJ. Non-melanoma skin cancer in patients with atopic dermatitis treated with topical tacrolimus. *J Dermatolog Treat*. 2005;16:149-153.
15. Harper J, Green A, Scott G, et al. First experience of topical SDZ ASM 981 in children with atopic dermatitis. *Br J Dermatol*. 2001;144:781-787.
16. Van Leent EJ, Ebelin ME, Burtin P, Dorobek B, Spuls PI, Bos JD. Low systemic exposure after repeated topical application of pimecrolimus (Elidel, SDZ ASM 981) in patients with atopic dermatitis. *Dermatology*. 2002;204:63-68.
17. Protopic (tacrolimus) Ointment New Drug Application 050777. Approval date 12/8/2000. Available at www.fda.gov/cder/foi/nda/2000/50777_protopic.htm. Accessed September 22, 2006.
18. Papp KA, Breuer K, Meurer M, et al. Long-term treatment of atopic dermatitis with pimecrolimus cream 1% in infants does not interfere with the development of protective antibodies after vaccination. *J Am Acad Dermatol*. 2005;52:247-253.
19. Stiehm ER, Roberts RL, Kaplan MS, Corren J, Jaracz E, Rico MJ. Pneumococcal seroconversion after vaccination for children with atopic dermatitis treated with tacrolimus ointment. *J Am Acad Dermatol*. 2005;53:S206-S213.
20. Cranswick N. Vaccination response is equivalent in children with atopic dermatitis treated with 0.03% tacrolimus ointment or a hydrocortisone ointment regimen. *J Am Acad Dermatol*. 2006;54(Suppl):AB84. [Abstract P817].
21. Hofman T. Tacrolimus ointment application does not affect the immediate response to vaccination, the generation of immune memory, or humoral and cell-mediated immunity in children. *J Eur Acad Dermatol Venerol*. 2005;19(Suppl 2):1-32. [Poster P17.41].
22. Reitamo S, Wollenberg A, Schopf E, et al. Safety and efficacy of 1 year of tacrolimus ointment monotherapy in adults with atopic dermatitis. The European Tacrolimus Ointment Study Group. *Arch Dermatol*. 2000;136:999-1006.
23. Wahn U, Bos JD, Goodfield M, et al. Efficacy and safety of pimecrolimus cream in the long-term management of atopic dermatitis in children. *Pediatrics*. 2002;110:e2.
24. Prior medical conditions and medication use and risk of non-Hodgkin lymphoma in Connecticut United States women. *Cancer Causes Control*. 2004;15:419-428.
25. Frieling UM, Schaumberg DA, Kupper TS, Muntwyler J, Hennekens CH. A randomized, 12-year primary-prevention trial of beta carotene supplementation for nonmelanoma skin cancer in the physician's health study. *Arch Dermatol*. 2000;136:179-184.
26. Olesen AB, Engholm G, Storm HH, Thestrup-Pedersen K. The risk of cancer among patients previously hospitalized for atopic dermatitis. *J Invest Dermatol*. 2005;125:445-449.
27. Serrano H, Scotto J, Shornick G, Fears TR, Greenberg ER. Incidence of nonmelanoma skin cancer in New Hampshire and Vermont. *J Am Acad Dermatol*. 1991;24:574-579.

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