



DERMATOLOGY CME EXPRESS FAX

Safety of Topical Calcineurin Inhibitors – Analysis of Non-melanoma Skin Cancer

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Expert Commentary

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In February 2005, the Pediatric Advisory Committee of the Food and Drug Administration (FDA) convened a meeting to review safety data concerning the potential cancer risk associated with the use of topical calcineurin inhibitors (tacrolimus, Protopic; pimecrolimus, Elidel) in treating patients with atopic dermatitis.¹ As a result of this meeting, the FDA approved revisions to the safety labeling for tacrolimus and pimecrolimus which included boxed warnings and a patient medication guide.² The revised labeling approved by the FDA has generated considerable debate amongst clinicians who specialize in the treatment of atopic dermatitis. Indeed, consensus statements have voiced opposition to the FDA's recommendations.³⁻⁵

Although the prolonged use of *oral* systemic immunosuppressive agents following organ transplantation has been associated with an increased rate of skin cancer formation,⁶ the role of *topical* calcineurin inhibitors and increased risk of skin cancer is less clear. Importantly, data from 23 comparative, randomized, worldwide clinical trials that used topical tacrolimus as a comparator (n = 7,000) indicate that no malignancies were reported with topical calcineurin inhibitors studied, whereas malignancies including skin cancer and lymphoma were reported for both vehicle and corticosteroid treatment groups.⁷ Very similar data were presented to the FDA for topical pimecrolimus, showing decreased cancer rates in randomized controlled trials using pimecrolimus versus for both vehicle and corticosteroid treatment groups.¹

This *Dermatology Express Report™ Fax* reviews the results of a retrospective analysis⁸ that examined the incidence of non-melanoma skin cancer (NMSC; eg, basal cell epithelioma, squamous cell carcinoma) in patients with atopic dermatitis treated with tacrolimus ointment.

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

A retrospective analysis was conducted of 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.⁸ Enrolling physicians (the majority dermatologists) evaluated patients every 3 months for up to 4 years.

Additional information (location of skin cancer, relationship to tacrolimus exposure, time from tacrolimus exposure to NMSC diagnosis, presence/absence of risk factors) was collected from all patients who developed NMSC during the studies, regardless of the relationship between NMSC and tacrolimus treatment.

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,⁹ n = 22,071, 12-year follow-up and Danish National Hospital Register,¹⁰ n = 2,030, 19-year follow-up).

Data from 9,813 patients were included in the analysis (Table 1). Overall, 1,718 patient-years of tacrolimus ointment exposure was accrued in patients 40 years of age (Figure 1).

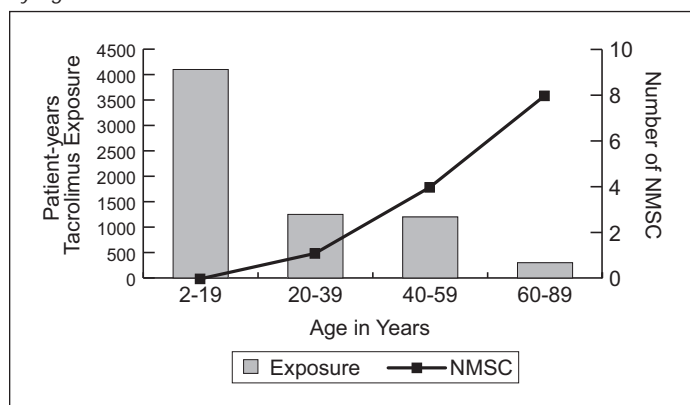
The analysis showed that 13 patients developed NMSC (10 basal

Table 1. Selected Demographics and Treatment Characteristics for All Patients, [adapted from 8]

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.⁸



cell epithelioma and 3 squamous cell carcinoma). 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 13 cases of NMSC were reported in 4,761 adult patients with atopic dermatitis (>20 years old; 0.27% incidence). These results were lower to the 16 cases of NMSC reported among 2,030 adult patients previously hospitalized for atopic dermatitis from the Danish National Hospital Register (>18 years old; 0.79% incidence).¹⁰

The incidence (95% Exact Confidence Intervals) of NMSC in patients >40 years of age in the analysis study was estimated to be between 361 and 1,217 per 100,000 person-years. These results compared to an age-specific incidence of first NMSC of 533 per 100,000 person-years in the Physician's Health Study.⁹ Thus, the results of this analysis do not support an increased risk of first NMSC over that of a similarly aged cohort.

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 cancer¹¹)
- 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.

Conclusion

The prolonged use of *oral* systemic immunosuppressive agents following organ transplantation has been associated with an increased rate of skin cancer formation. However, the role of *topical* calcineurin inhibitors (tacrolimus, pimecrolimus) and increased risk of skin cancer is less clear.

According to the results of a large retrospective analysis of 9,813 pediatric and adult patients with moderate-to-severe atopic dermatitis, the use of tacrolimus ointment was not associated with an increased risk of NMSC. Until additional longer-term studies and analyses are conducted, patients using topical calcineurin inhibitors to treat their atopic dermatitis should continue to use appropriate sun protection.

References

1. 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.
2. 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.
3. 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.
4. Bieber T, Cork M, Ellis C, et al. Consensus statement on the safety profile of topical calcineurin inhibitors. *Dermatology*. 2005;211:77-78.
5. 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.

6. Berg D, Otley CC. Skin cancer in organ transplant recipients: epidemiology, pathogenesis, and management. *J Am Acad Dermatol*. 2002;47:1-17.
7. Jaracz E, Maher R, Simon D, Kristy R, Park SL, Rico J. Safety profile of tacrolimus ointment: data from five years of post-marketing experience. Presented at the American Academy of Dermatology 64th Annual Meeting, March 3-7, 2006, San Francisco, California. Poster P14.
8. 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.
9. 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.
10. 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.
11. 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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