

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

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Atopic dermatitis (AD) is a common chronic inflammatory skin disease that causes significant suffering and has limited treatment options.^{1,2} It is often the first step in the atopic march and might contribute to the severity-persistence of asthma.²⁻⁴ On February 15, 2005, the Pediatric Advisory Committee of the US Food and Drug Administration (FDA) recommended “black box” warnings for pimecrolimus (Elidel; Novartis, Basel, Switzerland) and tacrolimus (Protopic; Astellas Pharma, Tokyo, Japan) because of a potential risk of cancer. The American College of Allergy, Asthma and Immunology and the American Academy of Allergy, Asthma and

Abbreviations used

AD: Atopic dermatitis
FDA: US Food and Drug Administration
MRHD: Maximum recommended human dose

Immunology formed a Joint Task Force to review the data and present it to their membership with the following objectives:

1. to review current FDA concerns regarding the safety of the use of topical pimecrolimus (Elidel) and tacrolimus (Protopic) in patients with AD;
2. to assist the allergist in providing their patients with appropriate information and to assist them in proper use of these products; and
3. to address the black box warning and its effect on the treatment of AD at this time

I. FDA CONCERNS

- A. Because of a perception by physicians and patients that topical pimecrolimus and tacrolimus are safer than steroid preparations, they have increasingly been used as first-line therapy and off label. There were almost 2 million prescriptions written for these topical medications for children between June 2003 and May 2004, and approximately half a million were for those less than 2 years of age. There is also heavy direct-to-consumer advertising, which might be related to its increasing use.
- B. The FDA is investigating postmarketing reports of malignancy in children and adults who have used these medications (Tables I and II).⁵ A postmarketing nonhuman primate study with an oral formulation of pimecrolimus demonstrated an occurrence of lymphoma in monkeys exposed to the lowest dose, which represented 30 times the maximum recommended human dose (MRHD).⁵

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TABLE I. Postmarketing total tumor adverse events as of December 31, 2004

		Total tumor ⁵	Total US cases of lymphoma ⁵	Median time from initial treatment until diagnosis ⁵
Pimecrolimus	Children ≤16 y	1	1	90 (7-300 d)
	Adult	5†	3†	
Tacrolimus	Children ≤16 y	3	0	240 (21-940 d)
	Adult	18	4	

†There is one non-US case of lymphoma that is poorly documented.

C. A definitive answer regarding the risk of carcinogenicity from topical pimecrolimus and tacrolimus will not be known for years, and if such a risk was real, the advisory panel was concerned that people might think they were not provided adequate information to assist them in the proper use of these products.

II. CURRENT DATA

- A. After topical application of tacrolimus and pimecrolimus, serum concentrations are usually low or undetectable,⁵⁻⁸ and absorption decreases as dermatitis improves. Additional absorption studies are needed in infants and young children.
- B. Although there are animal data showing dose-dependent carcinogenicity, it should be noted that the lymphoma formation was only reported in mice with the application of tacrolimus and pimecrolimus dissolved in ethanol at 26 and 47 times the MRHD.⁵
- C. On the basis of the malignancy rates in the general population of the United States for tacrolimus (Table III)^{5,10,11} and the incidence of non-Hodgkin's lymphoma on the basis of the person-years of exposure for pimecrolimus (Table IV),^{5,11,11a} there is no evidence of increased incidence of lymphoma with the short-term or intermittent long-term application of topical tacrolimus and pimecrolimus at this time, despite the use of these drugs in nearly 7 million persons.
- D. There are features that characterize lymphomas occurring in the setting of immunomodulatory or immunosuppressive therapy. These are (1) frequent occurrence in unusual sites, including soft tissue, joint spaces, and lungs; (2) polymorphous and pleomorphic large cell or Hodgkin's-like morphology; (3) presence of the Epstein-Barr genome in lymphoma cells; (4) B-cell lymphomas developing weeks, months, or, less commonly, up to several years after receipt of immunomodulatory therapy; and (5) lymphomas spontaneously regressing after withdrawal of immunomodulatory therapy without the need for chemotherapy or radiation

TABLE II. US FDA cases of spontaneous reports of lymphoma^{5*}

Drug	Age (y)	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

*There is one non-US case of lymphoma.

TABLE III. Tacrolimus analysis of malignancy rates

	Malignancy rates in the general US population	Malignancies reported in tacrolimus-treated patients*
Lymphoma	22/100,000 ^{10†}	0.65/100,000 ⁵
Nonmelanoma skin cancer	533/100,000 ^{11‡}	0.94/100,000 ⁵

*For the time period up to December 2004, 1,700,000 patients have been treated with tacrolimus.⁹ Eleven lymphomas, including 6 cutaneous T-cell lymphomas, and 16 nonmelanoma skin cancers have been reported in the United States.⁵

†Surveillance Epidemiology and End Result (SEER).

‡Public Health Service (Department of Health and Human Services).

therapy in a significant percentage of cases (30% to 50%).

None of the information provided for the cases of lymphoma associated with the use of topical pimecrolimus or tacrolimus in patients with AD indicate or suggest a causal relationship. The histology reported and the clinical presentations are not those usually associated with posttransplant lymphoproliferative disorder or of lymphoma occurring in the immunocompromised setting. Five independent external experts in the areas of dermatology, epidemiology, posttransplantation lymphoproliferative disorders-oncology, and pediatric oncology concluded that there was no clear-cut link between pimecrolimus or tacrolimus⁵ and increased risk of lymphoma.

- E. There is no evidence of systemic immunosuppression from topical pimecrolimus or tacrolimus, as measured on the basis of response to childhood immunizations (B cell)^{12,13} and delayed hypersensitivity (T cell).^{9,14}
- F. In clinical trials infants and children younger than 2 years of age treated with topical pimecrolimus were reported to have higher rates of upper respiratory tract infections than those treated with placebo cream.

TABLE IV. Pimecrolimus analysis of malignancy rates⁵

	<5	5-9	10-14	15-19	Total children	Total adults	Total (US)
Person-years of exposure	278,842	118,196	65,224	33,431	495,694	237,030	732,724
Expected no. of cases (SEER) ^{11,11a}	1.8	1.0	0.7	0.5	4.0	42.1	46.1
Reported cases ⁵	1	0	0	0	1	2	3

On the basis of the person-years of exposure, there is no evidence of increased incidence of non-Hodgkin's lymphoma in any age group in patients receiving pimecrolimus.

SEER, Surveillance Epidemiology and End Result.

TABLE V. Malignancy risks of anti-inflammatory therapy used in AD

Therapy	Malignancy risk	Adverse event
Topical corticosteroids*	Evidence-based: no evidence of immunosuppressive malignancy	HPA axis suppression, skin atrophy, telangiectasia, percutaneous absorption, ↓ bone mineral density ^{33,36-43}
Oral corticosteroids†	Increased risk of squamous cell–basal cell carcinoma; increased risk of non-Hodgkin's lymphoma ^{20,21}	↑ infection, hypertension, myopathy, glaucoma, aseptic necrosis of the hip, cataracts, Cushing syndrome, weight gain, osteopenia ^{44,45}
Topical calcineurin inhibitors	Theoretical: topical dosing can induce cancer in mice at >40× maximum human recommended dose ^{5,7} ; Evidence-based: no evidence of immunosuppressive malignancy	Skin irritation at application site ^{6,7,9,44-48}
Oral immunosuppressives (cyclosporin A)†	Increases B-cell lymphoproliferative disease and skin cancer; no significant risk if therapy less than 2 y ^{23,28,31,32}	Nephrotoxicity, hepatotoxicity ^{26,45,49,50}
Phototherapy (UVA and UVB), photochemotherapy (PUVA)	Increased risk of squamous cell and basal cell carcinoma and malignant melanoma ^{22,25,29,30,35} (UVB < PUVA) ²⁴	Erythema, pruritis, nausea, headache, chronic actinic skin damage, dyskeratotic and precancerous skin conditions ^{22,25,27,34}

UVA, Ultraviolet A; UVB, ultraviolet B; PUVA, psoralen plus ultraviolet A.

*Adverse effects relate to corticosteroid potency, occlusiveness of the preparations, site of application, percentage of the body surface covered, and duration of treatment.

†Occasionally required for treatment of severe AD.

However, when data were adjusted for time on medication, pimecrolimus was not associated with increased prevalence of systemic infection. There was also no difference in systemic infections in children 2 to 17 years of age or adults.^{5,12,14-18}

- G. AD itself has been associated with malignancy, such as cutaneous T-cell lymphoma.¹⁹
- H. There is an increased risk of adverse effects and malignancies among users of oral corticosteroids^{20,21} and other systemic therapies, such as cyclosporin and psoralen plus ultraviolet A for AD, that are occasionally required for the treatment of severe AD (Table V).^{6,7,9,10,20-50}

III. CONCLUSIONS AND RECOMMENDATIONS

- A. Guidelines for the use of pimecrolimus cream 1% and tacrolimus ointment 0.03% and 0.1%.
1. Current FDA guidelines recommend that topical pimecrolimus and tacrolimus are indicated for the short-term or intermittent long-term treatment of AD in patients 2 years of age or older who are

unresponsive to or intolerant of other conventional therapies or in whom these therapies are inadvisable because of potential risks.

2. The long-term effect of pimecrolimus and tacrolimus on the developing immune system in infants and children is not known. Children and adults with a compromised immune system should not use pimecrolimus or tacrolimus.
3. On the basis of information available, it would be prudent to use these medications as has been previously recommended and approved and at the amount needed to control the patient's symptoms. Animal data suggest that the risk of cancer increases with increased exposure to pimecrolimus or tacrolimus. However, the doses in which cancers occur were substantially higher than the levels used in human subjects.
4. It is important to reinforce the need for adjunctive treatment for AD, including liberal moisturization, evaluation for food and inhalant allergies, treatment of infections, and referral to an allergist-immunologist or a dermatologist for identification of triggers and optimal skin care.

5. There is no evidence to date of systemic immunosuppression after short-term or intermittent long-term topical application of FDA-approved formulations of pimecrolimus and tacrolimus in patients with AD.
- B. Patient information should be adequate and must include the risks and benefits of the drug and the proper use of these products. This includes:
 1. addressing the chronic, relapsing nature of AD and its complications, such as infection, associated allergies, skin barrier dysfunction, and risk of asthma;
 2. acknowledging that topical calcineurin inhibitors have significantly improved the clinical management of patients with AD;
 3. discussing current product label in the use of these drugs on patients:
 - a. younger than 2 years of age,
 - b. with compromised immune system,
 - c. treated with concurrent phototherapy,
 - d. pregnant or breast-feeding, and
 - e. with severely impaired skin barrier function (eg, Netherton syndrome) that might result in immunosuppressive blood levels of the drug;
 4. discussing treatment options for AD, including topical corticosteroids that might have adverse effects relating to potency, occlusiveness of the preparation, site of application, percentage of body surface covered, and duration of treatment, including skin atrophy; and
 5. discussing alternative treatments for moderate-to-severe AD, which include oral corticosteroids, cyclosporin A, and phototherapy, all of which have significant potential for causing serious adverse events, including malignancy.
- C. The Topical Calcineurin Inhibitor Task Force of the American College of Allergy, Asthma and Immunology and the American Academy of Allergy, Asthma and Immunology concludes that on the basis of current data, the risk/benefit ratios of topical pimecrolimus and tacrolimus are similar to those of most conventional therapies for the treatment of chronic relapsing eczema.

In children less than 2 years of age with poorly controlled persistent AD who require more than hydration and use of emollients to keep their skin disease under control, use of off-label therapy might be necessary because most topical steroids or other immunomodulators have not been studied or approved in this age group.

IV. BLACK BOX WARNING

Current data do not support the use of the black box warning on topical pimecrolimus and tacrolimus on the basis of the following facts:

1. Lymphoma formation is generally associated with high-dose and sustained systemic exposure to pimecrolimus and tacrolimus.

2. The reported cases of lymphoma from topical pimecrolimus and tacrolimus are not consistent with lymphomas observed with systemic immunomodulator therapy.
3. The actual rate of lymphoma formation reported to date for topical calcineurin inhibitors is lower than predicted in the general population.

Current labeling and product package inserts for both topical pimecrolimus and tacrolimus clearly state the potential of malignancy in animal studies. There are no new data, except for a few cases of postmarketing adverse events that are anecdotal at this time and a nonhuman primate study with an oral formulation of pimecrolimus demonstrating an occurrence of lymphoma in the lowest dose representing 30 times MRHD.

V. RECOMMENDATION

1. More controlled studies are needed on the use of topical calcineurin inhibitors, especially in patients less than 2 years of age.
2. Controlled long-term safety studies are also needed for topical corticosteroids in patients with AD, especially those younger than 2 years.
3. Likewise, warnings regarding the use of unproved treatments perceived to be safer than conventional therapies are warranted.
4. Vigilance and education on the prudent use of all products for the management of AD are needed.

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