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REVIEW ARTICLE

Topical Calcineurin Inhibitors and Lymphoma Risk: Evidence Update with Implications for Daily Practice

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Abstract Topical calcineurin inhibitors (TCIs), commercially available since 2000–2001, are the first and only topical medications approved for chronic treatment of atopic dermatitis (AD) in pediatric patients and remain a welcomed alternative to topical corticosteroids. In January 2006, the US Food and Drug Administration (FDA) issued a boxed warning requirement based on a theoretical risk of malignancy (including lymphoma) with TCI use. However, in the years since, analyses of epidemiologic and clinical data have failed to demonstrate a causal relationship between TCI use and malignancy or lymphoma risk, especially for pimecrolimus cream. In fact, the observed number of malignancies and lymphomas observed both in post-marketing surveillance and reported to the FDA using its adverse events reporting system is much lower among TCI-exposed patients than the expected number for the general population. Furthermore, among children enrolled in post-marketing pediatric registry studies for both tacrolimus and pimecrolimus followed for up to 5.5 years [10,724 patient-years (PY)] or 6.5 years (16,219 PY), respectively, the observed number of malignancies and lymphomas is very low and similar to the number expected for a sample of similar size in the general population. In addition to reporting these comparative malignancy and lymphoma data, this article provides a historical overview of the boxed warning requirement and critically evaluates the preclinical, clinical, and epidemiological evidence that has thus far failed to substantiate a relationship between TCI use and malignancy. The authors also provide practical clinical advice for optimizing AD management and patient care in the context of the boxed warning.

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1 Introduction

Topical tacrolimus ointment and pimecrolimus cream have been commercially available for more than a decade and are the first and only drugs approved for chronic treatment of atopic dermatitis (AD) in pediatric patients. These topical calcineurin inhibitors (TCIs) have been a welcomed alternative to topical corticosteroids because their chronic use is not associated with skin barrier compromise or increasing percutaneous absorption. However, in January 2006, the US Food and Drug Administration (FDA) instituted a boxed warning for both TCIs based on a theoretical risk of malignancy (including lymphomas) that sparked an ongoing debate over the safety of these drugs. Since then, despite a number of epidemiological and clinical studies, no clear link between TCI use and lymphoma risk has been established. Yet, the boxed warning remains, leaving many physicians hesitant to prescribe TCIs and countless patients (including infants and children) exposed to other anti-inflammatory agents with proven adverse effects. This review will (1) present a historical overview of the basis for the boxed warning, (2) review and critically evaluate the evidence for lymphoma risk, (3) provide practical clinical and evidence-based advice on using TCIs in the management of AD, and (4) offer advice on addressing obstacles to patient access to these drugs.

2 Background

2.1 Regulatory History of the Boxed Warning for TCIs

Tacrolimus ointment 0.03 and 0.1 % [Protopic®; owned and developed by Fujisawa (now Astellas)] and pimecrolimus cream 1 % (Elidel®; developed by Novartis, Meda acquired global rights to Elidel® in 2011 and immediately licensed North American rights to Valeant) are TCIs, which inhibit transcription and release of inflammatory cytokines and mediators from T cells [1]. In December 2000, tacrolimus ointment was approved for "short-term and intermittent long-term therapy in the treatment of patients (≥2 years of age) with moderate to severe AD in whom the use of alternative, conventional therapies is deemed inadvisable because of potential risks, or in the treatment of patients who are not adequately responsive to or are intolerant of alternative, conventional therapies" [2]. At that time, no efficacy or safety studies had been conducted with tacrolimus in infants, and the approved indication was limited to patients at least 2 years of age. One year later, in December 2001, pimecrolimus cream was approved with a similar indication for mild-to-moderate AD with similar warnings and contraindications based on pharmacological class [3]. In contrast to tacrolimus, data demonstrating the safety and efficacy of pimecrolimus were available at the time of application for 436 infants who had participated in clinical trials. On the basis of the "disproportionately higher incidence of adverse events, particularly viral infections in infants," seen in these trials, the approved indication was limited to patients 2 years of age and older. To further investigate the long-term safety of both drugs, the FDA requested post-approval commitments from both companies to establish pediatric registries [4, 5].

At the time of drug approval, the FDA requested that Astellas perform additional studies of topical tacrolimus including: a retrospective analysis to explore any demographic and disease factors possibly associated with persistently detectable blood concentrations [6]; bioavailability of 0.03 and 0.1 % ointments following long-term intermittent treatment of AD [7]; and pharmacokinetics of 0.03 % ointment in patients 2–5 years of age with moderate-to-severe AD [7].

Upon pimecrolimus cream approval, the FDA also requested that Novartis conduct two case-control epidemiological studies to assess the risk of non-melanoma [8] and melanoma skin cancers (protocol under FDA review) in adults; a controlled safety and efficacy study in HIV-positive patients; and a pregnancy registry. The last two requests were waived/fulfilled via labeling change or provision of additional preclinical data. In addition, Novartis initiated two ambitious long-term randomized clinical studies to assess the effects of pimecrolimus cream in infants as young as 3 months of age: a 6-year study ($N = 1{,}091$) designed to evaluate long-term safety and the impact of AD treatment on the progression of atopy; and a 5-year study ($N = 2{,}418$) designed to evaluate long-term safety including growth velocity and immune system development effects [9–13].

In October 2003, the FDA Pediatric Advisory Committee (PAC) met to review the products' registry protocols. However, the focus of the meeting was shifted by recognition of increasing off-label use among infants younger than 2 years of age (11 % of all TCI prescriptions by the end of 2003; Fig. 1) [14] as well as by malignancy reports made to the FDA's adverse event reporting system (AERS): two reports for pimecrolimus cream and five for tacrolimus ointment. Following this meeting, two 10-year prospective registries (planned $N = 8{,}000$ for each) were created to assess the risk of malignancies in children with tacrolimus ointment [A Prospective Pediatric Longitudinal Evaluation to Assess the Long-Term Safety (APPLES) of tacrolimus ointment for the treatment of AD] and pimecrolimus cream [Pediatric Eczema Elective Registry (PEER)]. APPLES includes patients no older than 16 years of age and was initiated in 2005; PEER includes patients 2–17 years of age and was initiated in 2004.

The PAC convened 15 months later in February 2005 to review the results of a newly completed oral carcinogenicity study conducted in monkeys (the results of which are discussed in detail in Sect. 3.1) as well as additional AERS malignancy reports. The concerns of the PAC were elevated in part by the manufacturers' marketing efforts, escalating TCI sales, and a higher rate of off-label use. On the basis of the recommendation made at this meeting, the FDA issued a public health advisory in March 2005 and a requirement in January 2006 for revised labeling for both products to include a boxed warning ('black box') and medication guide ('patient medi guide') to address a theoretical risk of lymphoma and to emphasize that the safety of long-term continuous use and use in patients 2 years of age and younger had not been established [14, 15]. In addition, the indications were modified to specify that TCIs are "*second-line* [emphasis added] therapy for short-term and non-continuous chronic treatment…of [AD] in non-immunocompromised adults and children [≥2 years of age] who have failed to respond adequately to other topical prescription treatments, or when those treatments are not advisable" [3, 16]. This was the first time that the FDA required that a boxed warning be issued on the basis of a theoretical risk rather than proven safety concerns.

At subsequent meetings held in March 2010 and May 2011, the PAC reviewed post-marketing surveillance (PMS) and epidemiological data for both drugs and found it to be inconclusive with regards to both long-term safety

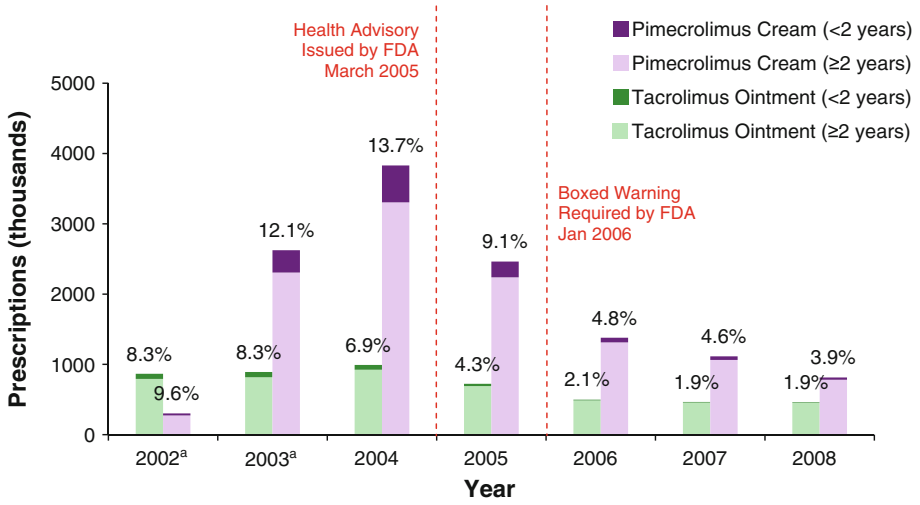

Fig. 1 US pimecrolimus cream and tacrolimus ointment prescriptions (2002–2008). Interval for each year is January 1–December 31 except where noted. Values are percent of prescriptions dispensed for infants (<2 years of age). Data source (2004–2008): SDI Vector One® National in briefing document from Patty Greene, Drug Use Data Analyst, Division of Epidemiology, Office of Surveillance and Epidemiology, FDA Center for Drug Evaluation and Research. BPCA drug use review: Comparison of Elidel® cream and Protopic® ointment utilization trends following 2006 labeling changes, 17 July 2009. Available from http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/UCM204723.pdf. Accessed 2 April 2012. Data source (2002–2003): IMS Health National Prescription Audit Plus™ in briefing document from David Moeny, Pharmacist/Drug Use Specialist, Division of Surveillance, Research and Communication Support, FDA Center for Drug Evaluation and Research. Pediatric drug use analysis for topical calcineurin inhibitors, 16 July 2004. Available from http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4089b2_01_05_Cleared%20version%20Elidel-Protopic%20Drug%20Use%20Review%20D040389%207-2004.pdf. Accessed 23 May 2012. [a]Interval is June 1–May 31

concerns and malignancy risk [17, 18]. At both meetings, the committee requested that the FDA continue to monitor the literature, AERS, and product registries and maintain the boxed warning until conclusive evidence was found [18]. In light of these inconclusive findings, this re-examination of a possible link between TCI use and lymphoma was undertaken.

2.2 Response from the Public and the Medical Community

News coverage of the boxed warnings was widespread, with stories appearing in notable publications, including *USA Today* [19], *Washington Post* [20], *BBC News* [21], and *Consumer Reports* [22]. The resulting patient concerns led some patients and caregivers to dispose of their TCIs and opt for other treatments or forgo treatment altogether. Law firms began posting websites dedicated to soliciting litigations against the makers of TCIs [23–27], further adding to the anxiety among patients and caregivers.

Members of the medical community criticized the FDA's action and suggested that an unintended result was to jeopardize the chances of ever clarifying the risks due to decreased participation in clinical trials [28]. Some argued that the FDA did not fairly weigh the data with respect to low systemic exposure seen in humans, lack of cancer adverse events in clinical studies, overall low rate of malignancy reports, and lack of evidence for systemic immune suppression with topical application of market formulations in preclinical studies. Critics also argued that the FDA overlooked the unmet medical need for these agents as an alternative to topical corticosteroids, especially for infants and patients with facial involvement [28–42]. Furthermore, some members of the medical community questioned the plausibility of a biological link between immunosuppression and the types of cancers observed [40–42]. On the other hand, the FDA did not rescind either drug's approval or request the termination of any of the ongoing clinical trials for either of these drugs.

2.3 Consequences of the Boxed Warning

As might be expected, TCI sales and off-label use among infants decreased dramatically within a year of the public health advisory (Figs. 1, 2). Payers responded to the boxed warning by creating hurdles for both healthcare providers and patients including limiting reimbursement, changing formulary status, and/or requiring pre-authorization or step-edits. Thereafter, sales of pimecrolimus cream continued to decline, possibly due to curtailed marketing efforts by Novartis. On the other hand, sales of tacrolimus ointment slightly increased despite little change in marketing efforts by Astellas. However, a survey conducted within 2 years after the labeling change reflected a negative

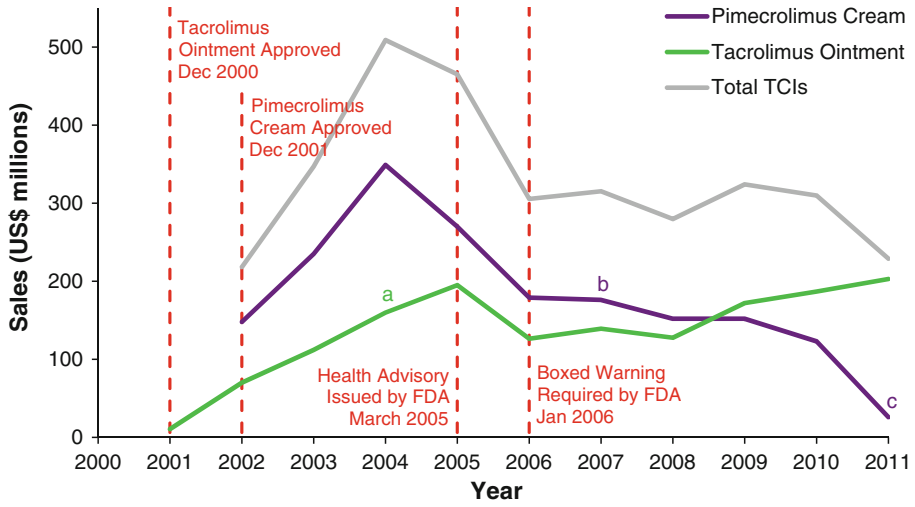

Fig. 2 Worldwide pimecrolimus cream and tacrolimus ointment sales (2000–2011). Data source for pimecrolimus cream: Novartis 2002–2003 corporate annual reports. Available from http://www.unglobalcompact.org/participant/7016-Novartis-International-AG. Accessed 2 April 2012; Novartis 2004–2008 corporate annual reports. Available from http://www.novartis.com/newsroom/corporate-publications/archive.shtml. Accessed 2 April 2012. Elidel worldwide sales 2009–2011. Available from http://www.evaluatepharma.com/Universal/View.aspx?type=Search&query=elidel. Accessed 29 March 2012. Data source for tacrolimus ointment: Astellas and Fujisawa 2001–2011 corporate annual reports. Available from http://www.astellas.com/en/ir/library/annual_report.html. Accessed 2 April 2012. (Using yearly conversion rates available from http://www.mac.doc.gov/japan-korea/statistics/exchange.htm. Accessed 29 March 2012.) [a]Fujisawa merged with Yamanouchi to become Astellas in 2004. [b]Novartis promotion scaled back Q1 2007, ceased Q3 2007. [c]Meda acquired global rights to pimecrolimus cream Q2 2011 and immediately licensed North American rights to Valeant

impact on long-term control among a significant minority of patients. In place of TCIs, 35 % of these dermatologists prescribed chronic topical corticosteroids; 12 % systemic corticosteroids; 4 % cyclosporine; 4 % other systemic immunosuppressants; and 20 % ultraviolet (UV) B or psoralen plus UVA for AD [43].

3 Summary of the Evidence for Lymphoma Risk

3.1 Preclinical Data

At the time of approval for both drugs, malignancy signals were detected in preclinical repeat-dose and carcinogenicity studies only when systemic exposure to pimecrolimus or tacrolimus was sufficient for systemic immune suppression (Table 1) [16, 44–46]. Given the known malignancy risk with systemic immune suppressants (which increases with the intensity and duration of immune suppression) [47, 48], these results were not unexpected. When systemic exposure was lower (drug given to animals in their feed or topically applied using marketed formulation), there were no neoplastic findings. In human studies using topical administration (discussed in detail in Sect. 4.5.1), systemic exposure is minimal.

The most common forms of malignancy seen in transplant patients treated with systemic (oral or intravenous) tacrolimus for graft-versus-host prophylaxis are skin carcinomas and non-Hodgkin's lymphomas (NHL) associated with Epstein–Barr virus infection, which may regress with treatment discontinuation [47]. In order to determine if systemically administered oral pimecrolimus can act through a similar mechanism, a 39-week oral (gavage) toxicity study was conducted in monkeys. The results of this study, reviewed by the FDA in February 2005, confirmed that oral pimecrolimus, given at doses sufficient to result in systemic immune suppression (~30-fold greater than the maximal exposure in humans with topical application), can elicit lymphomas associated with Epstein–Barr-like primate viruses similar to oral tacrolimus [49]. These results were cited as part of the basis for the boxed warning requirement for topical application [14, 50] despite the fact that administration was oral rather than topical and that evidence of systemic immune suppression was not detected following topical administration.

3.2 Epidemiological Data

The literature review considered at the March 2010 PAC meeting [51, 52] included conflicting data, summarized by Tennis et al. [53]. In comparison to untreated AD patients, Hui et al. [54] reported an increased risk of T cell lymphoma among tacrolimus ointment users (hazard ratio [95 % CI]; 3.13 [1.41–6.94]), but not among pimecrolimus cream users [1.86 (0.71–4.87)]. On the other hand, Arellano et al. [55] found no association between TCI use

Table 1 Relevant repeat-dose toxicity and carcinogenicity studies in animals as reviewed by the FDA (at approval)

Study	Conclusions	Systemic immune suppression observed? (AUC; safety margin[a])	Malignancy findings
Tacrolimus			
80-week carcinogenicity of oral (in feed) tacrolimus in CD-1 mice[b] [16, 44]	No relationship of tumor incidence was found	No (NA; threefold)	NA
104-week carcinogenicity of oral (in feed) tacrolimus in CD rats[b] [16, 44]	No relationship of tumor incidence was found	No (NA; ninefold)	NA
104-week oncogenicity of topical tacrolimus ointment (marketed formulation) in B6C3FI mice [44]	The increased incidence of pleomorphic and undifferentiated lymphomas are probably due to the established pharmacologic effect of tacrolimus, but the safety factor is sufficient that "human patients would not have a high risk"	Yes (~180 ng·h/mL; tenfold)	• Topical tacrolimus ointment 0.1 % was associated with a statistically significant increase in the incidence of pleomorphic lymphoma (males and females) and undifferentiated lymphoma (females) mostly of B cell type • No skin carcinomas were noted
Pimecrolimus [45, 46]			
13-week toxicity of topical pimecrolimus in ethanol in CD-1 mice	The increased incidence of pleomorphic lymphomas observed in this study may be related to the pharmacological action of and systemic exposure to pimecrolimus	Yes; assumed related to ethanol vehicle (males: 643 ng·h/mL; 17-fold; females: 675 ng·h/mL; 18-fold)	• Topical pimecrolimus 25 and 50 mg/kg/day were associated with lymphoproliferative changes, including malignancies
Oncogenicity of oral (gavage) pimecrolimus in CD-1 mice for their life-span	The increased incidence of malignant lymphoma was most likely a consequence of systemic immunosuppression, but the safety factor is "adequate" for use in humans	Yes (males: 2,260 ng·h/mL; 60-fold/females: 5,059 ng·h/mL; 133-fold)	• Oral pimecrolimus 45 mg/kg/day was associated with a statistically significant increase in the incidence of follicular center cell lymphoma, pleomorphic lymphoma, and combined lymphoma in both males and females
104-week oncogenicity of oral (gavage) pimecrolimus in Wistar rats (2 replicates)	The increased incidence of benign thymoma is a significant finding but may not be relevant to humans; the safety factor for females is "adequate" for use in humans, but not for males	Yes (males: 42 ng·h/mL; 1.1-fold/females: 805 ng·h/mL; 21-fold)	• Oral pimecrolimus 5 mg/kg/day (males) and 10 mg/kg/day (males and females) were associated with a "biologically significant" increase in the incidence of benign thymoma
104-week carcinogenicity of topical pimecrolimus cream (marketed formulation) in Wistar rats[c]	The increased incidence of follicular cell adenoma of the thyroid is a significant finding but may not be relevant to humans; the safety margin is not as great as noted in other carcinogenicity studies, but since the highest feasible dose was used, the study was considered adequate	Not clear; but no significant toxicity was noted (57 ng·h/mL based on highest feasible dose; 1.5-fold)	• A statistically significant increase in the incidence of follicular cell adenoma in the thyroid in all topical pimecrolimus cream dose groups (0.2, 0.6, and 1.0 %) was noted in males only[d] • A slight (non-significant) increase in benign thymoma was seen in males at all doses and in females at the 0.2 % dose level[e] • Non-neoplastic minimal-to-moderate application site epithelial hyperplasia was noted for both pimecrolimus cream and vehicle; this was attributed to vehicle effects • No lymphomas were noted

AUC area under concentration–time curve, *NA* not available, *NOAEL* no observed adverse effect level

[a] AUC is based on NOAEL unless otherwise noted; safety margin is in comparison to highest AUC seen with topical administration in humans

[b] Both the mouse and rat oral (in feed) studies were deemed as inadequate because of inadequate duration and low systemic exposure; however, since these studies are heavily referenced in the FDA toxicology review, they are included in this table

[c] No malignancies were found in an additional 104-week carcinogenicity study of topical pimecrolimus in ethanol in CD-1 mice; however, the study was deemed unacceptable by the FDA because of inadequate high dose and is not included in this table

[d] Male rats are more sensitive to thyroid effects than female rats or humans because of lower T4 hormone levels; this finding may not be relevant to humans

[e] Values fell within the historical range for Wistar rats and/or showed no dose dependence; this finding was determined to be not significant

(pimecrolimus cream or tacrolimus ointment) and lymphoma of any type (adjusted odds ratio [95 % CI]; 0.82 [0.42–1.61] and 0.79 [0.37–1.71], respectively) compared with untreated AD patients. Schneeweiss et al. [56] also report no significant increase in risk for lymphoma of any type (rate ratio [95 % CI]; pimecrolimus cream: 1.79 [0.92–3.48]; tacrolimus ointment: 1.97 [0.87–4.50], respectively) nor for cutaneous lymphomas (1.49 [0.36–6.24]; 2.53 [0.51–12.6], respectively) when TCI users were compared with untreated AD patients. As with all retrospective studies, each of these reports has significant limitations, including low numbers of pediatric patients, short duration, potential association between AD and lymphoma, no assessment by lymphoma subtype, exclusion of a lag period, and lack of case verification.

A full report of an additional long-term study was available for the May 2011 PAC meeting [52]. This study found no evidence for increased risk of lymphoma of any type for the overall population (625,915 patients; adjusted odds ratio [95 % CI]; pimecrolimus cream: 0.76 [0.54–1.08]; tacrolimus ointment: 1.24 [0.80–1.91]) or among those patients younger than 20 years of age (396,069 patients; pimecrolimus cream: 0.64 [0.34–1.21]; tacrolimus ointment: 0.96 [0.38–2.45]) compared with untreated AD patients (patients were followed from 6 months to over 10 years). Among patients exposed to the highest cumulative dose of tacrolimus ointment (≥0.10 g), the risk of lymphoma was significantly increased (2.08 [1.24–3.49]); however, no association was evident for pimecrolimus cream. When T cell lymphomas were evaluated alone, they found an increased risk of T cell lymphoma among tacrolimus ointment users (4.95 [1.86–13.19]), which was dose-dependent (<0.03 g: 4.27 [0.24–75.49]; ≥0.03 to <0.06 g: 5.36 [0.78–37.05]; ≥0.06 to <0.10 g: 6.03 [1.31–27.70]; ≥0.10 g; 12.76 [3.35–48.68]). T cell lymphoma risk was not elevated among pimecrolimus cream users (0.85 [0.25–2.90]) and showed no dose-dependence. Dose-dependence results for T cell lymphoma should be interpreted with caution, however, because of the low number of cases in each category.

3.3 Clinical Databases

Relative cancer risk may be best appreciated by comparing the actual number of reports in the entire exposed population compared with the general population. In order to make such a comparison, the cumulative worldwide exposure was calculated by dividing the total amount (in grams) of cream or ointment sold worldwide since launch by the average amount of drug dispensed per year per patient in the USA to obtain cumulative 'patient-years' (PY) of exposure (Eq. 1). Thus, cumulative exposure, expressed as PY accounts not only for the number of patients exposed but also for duration of exposure. This method assumes constant distribution of tube sizes and number of 'fills' over time, in different countries, and for all age ranges.

$$\frac{\text{Amount sold worldwide since launch (g)}}{\text{Average amount dispensed (g/patient/year)}} = \text{Cumulative exposure (PY)} \quad (1)$$

The number of reports that would be expected in the general population (of similar age range) over the same duration of observation (PY) was calculated on the basis of age-adjusted incidences (per 100,000 PY) found in the Surveillance, Epidemiology and End Results (SEER) database (Eq. 2). In comparing these numbers, the rate of malignancies and lymphomas with TCIs observed in several clinical databases, including AERS, is similar to or lower than the rate seen in the general population (Table 2) [57–65]. In cases where only the number of exposed patients is known (e.g., sponsored clinical trials databases), and no information is available about the duration of exposure, the expected number of malignancies cannot be calculated in a manner that would allow for a comparison across different study durations.

$$\frac{\text{Age}-\text{adjusted SEER incidence}}{100{,}000\,\text{(PY)}} \times \text{cumulative exposure (PY)} = \text{Expected reports} \quad (2)$$

4 Critical Evaluation of the Evidence

A number of generally confounding factors must be considered when evaluating the strength of the evidence that led to the FDA decision to apply the boxed warning—the difficulty in assessing the risk of rare events, possible confounding effects of disease state and severity, and a consideration of risks and benefits across a number of alternative therapies. Confounding factors specific to this examination include the relative importance of preclinical versus clinical data and the intrinsic properties of each of the compounds.

4.1 Inherent Difficulties in Assessing the Risk of Rare Events

Assessing risk based on spontaneous adverse event reports (such as AERS) is complicated because of variable under-reporting, indeterminate population size, and inconsistent data quality, especially for details on drug exposure and underlying diseases [66]. Spontaneous reporting might be especially problematic for adverse events with long latency times. Adverse events are believed to be under-reported to the FDA by a factor of as much as 10 and the reporting rate changes for the same product over time, with new and

Table 2 Actual number of malignancy and lymphoma (Hodgkin's and Non-Hodgkin's) reports in clinical databases compared with the expected number of reports in the general population (based on SEER [57])

Data source	Cumulative Exposure, PY[a]	Age Range, years	Any Malignancy		Hodgkin's Lymphoma (HL)		Non-Hodgkin's Lymphoma (NHL)	
			Actual	Expected (95% CI)[b]	Actual	Expected (95% CI)[b]	Actual	Expected (95% CI)[b]
TACROLIMUS OINTMENT								
Sponsored Comparative Clinical Trials in AD[58] (as of December 2005)	(~4,200 pts)	all ages	**0**	--	**0**	--	**0**	--
US Post-Marketing Surveillance (PMS)[59] (as of December 2009)	**~1,600,000**[c] (~927,000 pts)	pediatric[d]	**18**	**276** (267-285)	NA	--	NA	--
US Post-Marketing Surveillance (PMS)[60] (as of February 2005)	**~3,000,000**[c] (~1,700,000 pts)	all ages	NA	--	**HL and NHL Lymphoma**[e]	**Actual**	**Expected (95% CI)**[b]	
						11 (incl. 6 CTCL, 0 in <16 YO)	**659** (646-672)[f]	
APPLES[61] (as of September 2010)	**10,724** (5,872 pts)	<16	**2**	**1.9** (1-2)	**0**	**0.1** (0-1)	**0**	**0.1** (0-1)
AERS[62] (as of May 2011)	**~1,600,000**[c,g] (~927,000 pts)	<16	**22**	**276**[g] (267-285)	**0**	**21**[g] (18-24)	**9** (incl. 4 CTCL, 1 CT/BCL)	**19**[g] (16-22)
PIMECROLIMUS CREAM[63]								
Sponsored Controlled Clinical Trials in AD (as of March 2011)	(>55,000 pts)	all ages	**5**	--	**0**	--	**1** (CTCL)	--
Worldwide Post-Marketing Surveillance (PMS)[h] (as of March 2011)	**>19,000,000**	all ages[i]	**163**	**86,720** (86,447-86,995)	**19** (incl. 5 in <20 YO)	**508** (487-530)	**61**[j] (incl. 8 CTCL, 13[k] in <20 YO)	**3,663** (3,606-3,721)
PEER (as of October 2011)	**16,219** (6,073 pts)	2-17	**2**	**2.8** (2-3)	**0**	**0.2** (0-1)	**0**	**0.2** (0-1)
AERS[62] (as of May 2011)	**>9,000,000**[l]	<16	**43**	**1,554** (1,506-1,602)	**4**	**119** (106-134)	**11**	**106** (93-119)
TACROLIMUS OINTMENT & PIMECROLIMUS CREAM								
AERS[62] (as of May 2011)	--	<16	**7**	--	**0**	--	**1**	--

APPLES and PEER are the ongoing 10-year prospective registries (planned $N = 8{,}000$ for each) designed to assess the risk of malignancies in children

AD atopic dermatitis, *AERS* FDA's adverse event reporting system, *CI* confidence interval, *CTCL* cutaneous T cell lymphoma, *CT/BCL* cutaneous T cell and B cell lymphoma, *HL* Hodgkin lymphoma, *incl.* includes, *NA* not available, *NHL* non-Hodgkin lymphoma, *pts* patients, *PY* patient-years, *TCI* topical calcineurin inhibitor, *YO* year olds, – not calculable

[a] Calculated by dividing the total amount (g) of cream or ointment sold worldwide since launch by the average amount of drug dispensed per year per patient (g/year/patient)

[b] Estimated based on age-adjusted incidences (per 100,000 PY) for 2009 (the most recent estimate available) in the SEER database [57]; estimates were rounded to the nearest whole number unless estimate was <10, then estimate was rounded to the nearest tenth; Lower limits of 95 % confidence intervals were rounded to the next lower whole number, upper limits were rounded to the next higher whole number)

[c] Estimated by multiplying the approximate number of patients exposed by the factor (3,000,000 PY/1,700,000 patients) given in the Tacrolimus Ointment February 2005 PAC Briefing Book [64]

[d] Age range not further specified

[e] Only incidence of overall lymphoma available

[f] Calculated by adding the expected (95 % CI) number of reports for HL and NHL to obtain expected (95 % CI) number of reports for all lymphomas

[g] Based on exposure data as of December 2009, the most recent estimate available

[h] Includes clinical trial (solicited), spontaneous, and literature reports

[i] Actual reports were in patients ranging in age from 11 months to 70 years

[j] Includes 13 unspecified lymphomas

[k] Includes 4 unspecified lymphomas in patients <20 YO

[l] Calculated by multiplying the cumulative exposure (PY) by the proportion of prescriptions dispensed to <17 YO estimated using SDI Vector One® data from 2004 to 2008 [65] (assuming that number and distribution of prescriptions were similar between 2002–2003 and 2004 and between 2009–2011 and 2008)

highly publicized drugs susceptible to increased reporting rates.

4.2 Confounding Factors: Disease State and Severity

The interpretation of results of studies examining risk associated with TCI exposure alone may be challenging because of several confounding factors. Namely, that AD like psoriasis (another inflammatory skin disease) may be independently associated with a risk of developing lymphoma, which increases with severity [53, 67–71]. On the other hand, in some cases, cutaneous T cell lymphoma may be misdiagnosed as AD (and treated as such) owing to similar clinical signs and symptoms [29, 72–74]. In

addition, patients receiving TCIs as second-line therapy or at higher doses may bias the patient population toward more severe disease and greater exposure, thereby also increasing the potential for misleading results.

4.3 Benefit–Risk Analysis: Considering Alternative Therapies

In order to properly weigh the risks and benefits of AD treatment, one must consider the benefits and adverse effects of all possible treatments. Topical corticosteroids (TCS) are the mainstay of treatment for AD flares. However, no TCSs are indicated for long-term (>4 weeks) use and few are approved for patients younger than 2 years of age [75] because of skin-thinning potential and rebound effects. TCIs, on the other hand, have low atrophogenic potential [76] and skin permeation (as discussed in Sect. 4.5.1) and can be used for long periods, even on sensitive skin areas, without risk of developing tachyphylaxis [77–86].

There are no preclinical carcinogenicity studies of TCS due to rapid toxicity in mice and rats, although, as an immune suppressant, there is a plausible link. In fact, other alternative anti-inflammatory AD treatments (i.e., oral corticosteroids, oral immunosuppressives, and phototherapy) all carry a risk of cancer [42, 71], and malignancy risk with TCS is unclear [56, 87–89].

4.4 Sufficient Evidence for TCI Boxed Warning?

According to FDA guidance, boxed warnings are ordinarily applied when (a) there is an adverse reaction so serious in proportion to the potential benefit from the drug (e.g., fatal, life-threatening, or permanently disabling) that it is essential that it be considered when assessing the benefit–risk ratio of prescribing the drug; (b) there is a serious adverse reaction that can be prevented or reduced in frequency or severity by appropriate use of the drug (e.g., patient selection, careful monitoring, avoiding use in a specific clinical situation); or (c) the FDA approved the drug with restrictions to ensure safe use [90]. According to the guidance, a boxed warning can also be used to highlight information that is considered especially important to the prescriber (e.g., reduced effectiveness in certain patient populations). Boxed warnings are most often based on observed serious adverse reactions (i.e., clinical data) or, in some cases, based on anticipated adverse reactions [i.e., an expected adverse reaction based on pharmacologic action of the drug (preclinical data)]. Beach et al. [91] found that over 80 % of boxed warnings (in the 1995 *Physicians' Desk Reference*) were based on clinical data including adverse event reports obtained through clinical trials and spontaneous reports. Only 9 % of warnings were based on 'other' evidence.

The boxed warning for TCIs was implemented despite the fact that "a causal relationship has not been established" [3, 16]. While no specific risks have been identified, the label indicates that "long-term safety of topical calcineurin inhibitors has not been established…[and] rare cases of malignancy (e.g., skin and lymphoma) have been reported in patients treated with [TCIs]" [3, 16]. In contrast, the boxed warning for long-acting β-agonists for childhood asthma is based on data from large placebo-controlled trials that showed an increase in asthma-related deaths [92].

There is some precedent for removing a boxed warning based on differences in systemic exposure between oral and topical formulations and/or new clinical data [93–95]. Given the inconclusive nature of prior evidence, the clinical value of TCIs, and the negative impact of limiting patients' access to TCIs, significant weight should be given to more recent epidemiological and clinical data when considering the ongoing need for the boxed warning.

4.5 Justification for a Class Labeling?

The FDA applies pharmacological classes to drugs in order to help prescribers avoid duplicative therapy and drug interactions. In order to maintain consistency, the agency considers applying warnings, contraindications, and boxed warnings to all members of a pharmacological class; however, it does allow for these to be applied to a single member of a class if the benefit–risk ratio is shown to apply to only one member [90]. Low systemic exposure with TCIs and striking differences between pimecrolimus cream and tacrolimus ointment in terms of pharmacology and clinical development programs might justify reconsideration of class labeling and/or warnings.

4.5.1 Low Systemic Exposure

Many studies with both pimecrolimus cream and tacrolimus ointment have shown systemic exposure to be low after topical treatment in AD patients as young as 3 months of age [7, 96–106]. In a head-to-head comparison study, the highest blood concentrations detected in adults with moderate-to-severe AD were 1.51 ng/mL in the pimecrolimus cream group and 2.39 ng/mL in the tacrolimus ointment group, both of which are substantially below target trough concentrations for systemic immunosuppression for tacrolimus (5–20 ng/mL) in transplant patients [107]. In infants, blood concentrations are similar to those seen in adults with no evidence of accumulation for up to 1 year [101–106]. The highest blood concentrations reported for infants with pimecrolimus cream 1 % range from 1.8 to 4.14 ng/mL [101–105] and the average maximum

concentration with tacrolimus ointment 0.03 % was 3 % of that observed in pediatric liver-transplant patients receiving oral tacrolimus [106].

In vitro skin penetration (into) for each compound is approximately equal, but skin permeation (through) is greater for tacrolimus ointment than pimecrolimus cream [108, 109]. When comparing relative permeation in normal versus inflamed or corticosteroid-pretreated skin, both compounds permeated inflamed and corticosteroid-pretreated skin to a greater extent (up to a factor of 6 times greater than normal skin) [108]. Thus, exposure to TCIs is self-limiting—as skin barrier function is restored, exposure decreases. There is also the argument that pediatric patients may have greater systemic exposure because of their greater body surface area to weight ratio. In the head-to-head trial, when blood concentrations after tacrolimus ointment application were analyzed by total body surface area (TBSA) affected by AD, they were detectable in more patients as TBSA affected by AD increased [107].

4.5.2 Differences in Pharmacology

Unlike tacrolimus, which was originally developed for its antirejection activity, pimecrolimus was developed specifically to target inflammatory skin diseases on the basis of its pharmacology [110]. After oral administration in rats, skin concentrations of pimecrolimus were consistently greater (twofold) than that of tacrolimus whereas in other tissues tested (blood, lymph nodes), concentrations of tacrolimus were greater (6-fold and 50-fold, respectively) [111]. In several animal models, pimecrolimus demonstrated much lower immunosuppressive potential than tacrolimus [1, 110, 112–115].

4.5.3 Differences in Clinical Programs

In addition, there are substantial differences in the number of patients studied (and duration of treatment) with each drug (Table 3) [63, 81, 116–118]. At the time of approval, pimecrolimus cream had been studied in more pediatric patients, including infants, for significantly longer durations, yet the indications for both drugs in these regards are remarkably similar.

5 Implications for Daily Practice

5.1 Increased Burden on Medical Providers and their Patients

Practicing physicians and their office staff bear the bulk of administrative burden generated by the boxed warning, while patients assume additional personal and financial burden. In response to the warning, third-party payers restricted off-label access to TCIs for children with conditions other than TCS-failing AD, and for all infants. Most third-party payers require time-consuming prior authorization for all TCI prescriptions. In many states, Medicaid-insured children have no access to these corticosteroid-sparing medications [119] based on disease and age-specific labeling, amounting to discriminatory denials. Some physicians may be hesitant to prescribe TCIs because of a higher perceived medicolegal liability [120].

5.2 Consequences of Inaccurate Diagnosis

Cutaneous T cell lymphoma is a chronic condition with insidious onset that may be misdiagnosed as AD, complicating assessment of a true lymphoma risk associated with TCIs.

5.3 Consequences of Inadequate Treatment

Active AD can have significant negative impact on quality of life for patients and their caregivers. Adequate treatment has been shown to significantly improve quality of life and patient satisfaction [121, 122]. In addition, early disease control may slow or prevent the "atopic march" to subsequent allergic rhinitis, food allergy, and asthma [123]. Suboptimal management of AD leads to more frequent flares and greater likelihood of exposure to medications like systemic corticosteroids, cyclosporine, or other immunosuppressants with higher toxicity risks [42]. And in contrast to frequent application of TCS, daily maintenance therapy with TCIs does not interfere with skin barrier integrity or enhance percutaneous absorption. Recommendations to limit exposure to topical therapy with TCIs places disproportionate importance on theoretical drug-related risks compared with well-established risks of chronic skin disease.

In addition, the costs of inadequately treated AD are substantial [124–127]. Dermatology is among the most difficult subspecialty to gain access to for publically insured children [128]. The frequency of emergency department (ED) visits for AD observed in one Midwest urban hospital suggests restricted access to outpatient care and suboptimal maintenance treatment, adding significant cost [119]. Emergency medicine providers receive limited training in the management of dermatological issues [119, 129]. Furthermore, prescription assistance programs (including the Allergy and Asthma Foundation, the Health Well Foundation, and the Chronic Disease Fund) do not include AD as an eligible indication.

5.4 Optimal Use of TCIs

Most treatment algorithms recommend regular use of emollients for control of dry skin with short-term TCS for

Table 3 Pimecrolimus cream and tacrolimus ointment clinical development programs in atopic dermatitis

Age Group	Duration	Subjects exposed
TACROLIMUS OINTMENT		
Clinical trials reviewed at approval[116]		
Phase 3 controlled studies/pivotal		
Children (2-15 years)	*12 weeks*	*235*
Adults (≥15 years)	*12 weeks*	*202*
Adults (≥16 years)	*12 weeks*	*218*
Phase 2 or 3 supportive safety		
Children (3-6 years)	*3 weeks*	*25*
Children (6-16 years)	*3 weeks*	*136*
Adults (≥13 years)	*3 weeks*	*159*[a]
Adults (≥16 years) x 2 trials	*1 week*	*226*
Adults (≥16 years) x 4 trials	*3 weeks*	*424*
Adults (≥17 years)	*3 weeks*	*20*
Uncontrolled long-term safety		
Children (2-15 years)	*1 year*	*255*
Adults (≥18 years)	*1 year*	*318*
Uncontrolled supportive safety		
Adults (≥16 years)	*2 years*	*569*
Adults (≥18 years)	*6 weeks*	*62*
Total		**2,849**
Infants (<2 years)	NA	0
Children (2-17 years)	3 weeks – 1 year	651
Adults (≥16 years)	1 week – 2 years	2,198
All clinical trials (as of May 2011[b])		
Total		**>36,000**
Infants (<2 years)[81]	≤2 years	~50
Children (2-17 years)[117]	≤10 years[d]	~9,000
Adults (≥16 years)[117]	≤4 years[d]	~27,000
PIMECROLIMUS CREAM		
Clinical trials reviewed at approval[118]		
Phase 3 controlled studies/pivotal		
Infants (<2 years)	*26 weeks*	*123*
Children (2-17 years) x 2 trials	*26 weeks*	*267*
Controlled supportive safety		
Infants (<2 years)	*6 months*[c]	*204*
Children (2-17 years)	*1 year*	*474*
Adults (≥18 years)	*1 year*	*328*
Total		**1,396**
Infants (<2 years)	6 months – 1 year	327
Children (2-17 years)	6 months – 1 year	741
Adults (≥18 years)	1 year	328
All clinical trials (as of May 2010[b])[63]		
Total		**>55,000**
Infants (<2 years)	≤6 years	~4,000
Children (2-17 years)	≤10 years[d]	~27,000
Adults (≥18 years)	≤3 years	~16,000
Other (≥3 months)	≤27 weeks	~8,000
Unspecified	≤3 years	~450

NA not applicable

[a] Included in total adult subjects despite overlapping age range

[b] Time frames differ due to data availability

[c] Includes duration of ongoing registry studies (APPLES and PEER); current duration of exposure is shorter

[d] Interim analysis

treatment of AD flares. Under certain circumstances, TCIs are a more appropriate first-line choice and/or useful adjunct to TCS.

1. *As a corticosteroid-sparing agent*: Reducing the risks of chronic TCS exposure is important, especially in children treated with intranasal, inhaled, or systemic corticosteroids for other atopic diseases such as asthma or allergic rhinitis. The corticosteroid-sparing effect of pimecrolimus cream has been demonstrated in clinical trials [77–79, 130–134]. A reduced number of flares and prolonged time-to-flare quantified in tacrolimus ointment clinical trials also supports a corticosteroid-sparing effect [135–140].
2. *To treat face and skin fold disease*: Skin atrophy, perioral dermatitis, and increased percutaneous absorption are TCS risks prompting greatest concern in patients with inflammatory skin disease involving sensitive skin areas on the face, eyelids, and diaper area. TCIs are well suited for use in these areas due to low acnegenic and atrophogenic potential [76, 78, 83, 131, 141–152].
3. *To simplify treatment regimens*: Risks associated with TCS use are highest with more potent products, especially when applied to sensitive skin areas. To minimize these risks, a popular approach is to recommend a two-drug treatment regimen using a lower potency TCS on the face and a higher potency product on the body. Patients are

often confused about the appropriate drug to use on the affected sites, and monitoring the optimal quantity used can also be complicated. Maintenance treatment with a TCI requires use of only one product on all affected sites. This not only simplifies treatment for the patient, but also allows easier monitoring of drug quantity used over time.

4. *For children who require daily treatment*: Safety of TCS has been studied for durations of no longer than 4 weeks for a limited number of products. In contrast, safety of TCIs for durations of up to 1 year has been documented in several prospective trials and registries [83–86].
5. *In patients who are TCS intolerant or dependent*: Well-described but under-recognized complications of long-term use of TCS include delayed-type hypersensitivity reactions, and rebound erythroderma. Neither pimecrolimus cream nor tacrolimus ointment carry these risks [150–153].
6. *In patients with confirmed or suspected skin infection*: 'In cognito' TCS-associated skin infections are another complication that has been well-described but underappreciated [154]. The proposed mechanism of action is via dendritic cells and antigen presentation [155]. In contrast, TCIs do not affect the differentiation, maturation, or function of dendritic cells [156–162]. Clinical trials have not identified an increased incidence of skin infection for either TCI [82, 163, 164].

5.5 Effective Communication with Patient About the Benefit–Risk Ratio

Even when a physician has weighed the risks and benefits and determined that TCIs are the appropriate therapy for a particular patient, an additional hurdle remains—discussing the boxed warning and medication guide. The 'real' risk of lymphoma with TCIs can be made more understandable to patients and caregivers by using some reassuring language. Suggested talking points include

1. The risk of lymphoma and other cancers is no higher than what you see in the general population.
2. TCI molecules are about twice the size of corticosteroids, which makes it more difficult for them to permeate the skin and cause systemic adverse effects.
3. All drugs, including TCIs and corticosteroids, have risks and benefits.
4. The American Academy of Dermatology (AAD) and other professional organizations do not support the boxed warning.
5. Pharmacists and other healthcare professionals may provide you with information that conflicts with what we have discussed.
6. As your physician, I have carefully weighed the risks and benefits of prescribing a TCI and feel that this drug is well suited to manage your skin condition.

6 Conclusions

The TCIs were a welcome therapeutic option for the management of AD when they were approved over 10 years ago, and they remain the only approved treatment for long-term use in children 2 years of age and older. Physicians quickly adopted the TCIs as a corticosteroid-sparing adjunct to topical corticosteroids. Despite the utility of TCIs, in January 2006, the FDA implemented a boxed warning regarding the safety of long-term use and a possible risk of lymphoma and limited the indication to "second-line therapy for the short-term and noncontinuous chronic treatment of (mild-to-moderate or moderate-to-severe AD) in nonimmunocompromised adults and children (≥2 years of age) who have failed to respond adequately to other topical prescription treatments for (AD), or when those treatments are not advisable" [3, 16]. This had a significant impact on physician prescribing patterns and patient access to these medications, leading to decreased disease control and quality of life for patients and their families. Many members of the medical community criticized the actions of the FDA. They questioned the validity of the boxed warning in large part because no definitive human clinical trial data has demonstrated an increased risk of malignancy with TCI exposure. In addition, several epidemiological studies have shown no association between TCI use and lymphoma risk in clinical practice, and the incidences of malignancy and lymphoma in clinical databases are below that of the general population. In addition, a possible association between AD itself and malignancy further erodes the basis for the warning. In order to provide patients with optimal care, physicians must have strategies for mitigating the impact of the boxed warning on the quality and costs of AD management. These include using TCIs appropriately as corticosteroid-sparing agents and proactively communicating the relative risks and benefits of TCIs to patients and their caregivers.

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