

## Original Investigation

# Association Between Malignancy and Topical Use of Pimecrolimus

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**IMPORTANCE** A black box warning describes a potential risk of malignancy associated with topical use of pimecrolimus to treat atopic dermatitis due to its similarity to oral calcineurin inhibitors used in solid-organ transplantation and spontaneous reporting of malignancies, including lymphomas and cutaneous malignancies.

**OBJECTIVE** To evaluate the risk of malignancy in a postmarketing study of children exposed to pimecrolimus.

**DESIGN, SETTING, AND PARTICIPANTS** A longitudinal cohort study among a nationwide ongoing long-term cohort of children enrolled in the Pediatric Eczema Elective Registry (PEER) who had a history of atopic dermatitis and pimecrolimus use with data available up through May 2014.

**MAIN OUTCOMES AND MEASURES** Reports of malignancy among those in the PEER compared with expected rates from the Surveillance, Epidemiology, and End Results (SEER) program.

**RESULTS** Overall, 7457 children were enrolled in the PEER, for a total of 26 792 person-years. Children used a mean (SD) of 793 (1356) g of pimecrolimus when enrolled in the study. As of May 2014, five malignancies had been reported. These include 2 leukemias, 1 osteosarcoma, and 2 lymphomas. No skin cancers were reported. The standardized incidence ratio for all malignancies (primary outcome) based on the age-standardized SEER population was 1.2 (95% CI, 0.5-2.8). As secondary analyses, the standardized incidence ratios (based on 2 cases for each) were 2.9 (95% CI, 0.7-11.7) for lymphoma and 2.0 (95% CI, 0.5-8.2) for leukemia. None of these findings were statistically significant.

**CONCLUSIONS AND RELEVANCE** Based on more than 25 000 person-years of follow-up, it seems unlikely that topical pimecrolimus as it was used in the PEER cohort to treat atopic dermatitis is associated with an increased risk of malignancy.

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**A**topic dermatitis (AD) is a common chronic inflammatory dermatitis of the skin. It most frequently occurs in the first decade of life and is often associated with other allergic diseases such as asthma, seasonal allergies, and food allergies.<sup>1</sup> It was reported in 2014 to be one of the most burdensome of all dermatologic illnesses.<sup>2</sup> Guidelines for the diagnosis and treatment of this disease were recently published.<sup>1</sup> Few topical agents have been approved by the US Food and Drug Administration (FDA) or the European Union Medicines Agency for the treatment of AD in children. Topical calcineurin inhibitors (TCIs) were approved about a decade ago.<sup>3</sup>

Systemic calcineurin inhibitors were originally approved as immunosuppressive agents to be used after solid-organ transplantation to prevent organ rejection. Agents in this class

inhibit calcineurin activity or production, thereby interfering with the activity of effector T cells, as well as the production of lymphokines and interleukin, thus preventing organ rejection.<sup>3-7</sup> The most frequently used oral agents in this class are cyclosporine and tacrolimus. An unfortunate adverse event associated with the use of these agents is an increased risk of malignancy, especially skin cancer and lymphoma.<sup>6,7</sup>

Pimecrolimus was approved in December 2001 by the FDA for the treatment of mild to moderate AD in children at least 2 years old. It was approved by the European Union Medicines Agency in 2002. The Pediatric Eczema Elective Registry (PEER) study was established as part of the postmarketing commitments for the approval of this drug. These commitments were originally to Novartis Pharmaceuticals and are now to Valeant

Pharmaceuticals International. The purpose of the PEER study was to follow up children with AD for 10 years who had at least 6 weeks of exposure to pimecrolimus to determine their incidence of malignancy. The original study commenced in 2004. However, because of concerns about the overall sample size, the original study was enlarged from 4000 participants, with an original expectation of accruing 20 000 person-years of follow-up, to 8000 participants and an anticipated 40 000 person-years of follow-up. The present study is an evaluation of the risk of malignancy in approximately the first 20 000 person-years of PEER follow-up. Observed rates are compared with standardized rates from the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute.

## Methods

### Study Population

Informed consent (or assent) was obtained for all participants from the participant or his or her caregiver. The informed consent process was approved by Concordia Institutional Review Board. Our research protocol was approved by the Institutional Review Board at the University of Pennsylvania. The PEER is an ongoing prospective observational cohort study. The total enrollment is expected to reach 8000 children with mild to moderate AD at the time of enrollment, who will be followed up for 10 years, with a goal of accruing at least 40 000 person-years of follow-up. The present study was based on data received up to May 2014. The enrollment criteria and goals of the PEER study have been described in detail elsewhere.<sup>8-11</sup> Eligible participants were between 2 and 17 years old at the date of enrollment. All participants had a diagnosis of AD by their treating physicians, most of whom were pediatricians, allergists, or dermatologists.<sup>8-10</sup> The enrollment diagnosis was confirmed using the United Kingdom Working Party's Diagnostic Criteria for Atopic Dermatitis.<sup>12</sup> All participants had used pimecrolimus cream for at least 42 days out of the preceding 180 days before enrollment. However, no child after enrollment had to continue to use pimecrolimus, and all treatment decisions were made by the participant, his or her parents, or the health care providers independent of the study. Participants were excluded if at the time of enrollment they had a history of or current lymphoproliferative disease, systemic malignancy, or skin malignancy or a history of the use of oral immunosuppressive therapy. As noted, children were not required to continue to use pimecrolimus once they were enrolled in the PEER.<sup>10</sup>

### Primary and Secondary Outcomes and the Measurement of Time

The primary outcome for this study was onset of any malignancy after enrollment into the PEER study. All study participants were queried every 6 months to determine if they had developed a malignancy. Any affirmation consistent with a malignancy or the possibility of a malignancy was then referred to the Medical Affairs program at Novartis Pharmaceuticals and, more recently, Valeant Pharmaceuticals International to determine and confirm the diagnosis. All serious adverse events

were reported to the appropriate federal regulatory authority. All participants received monetary reimbursement after the completion of each 6-month survey. Comparison data were obtained from the SEER program by request after submitting a signed data use agreement in July 2013. In addition to total malignancy rates, we report separately on leukemia, lymphoma, and skin cancers as secondary outcomes. Skin cancers are not reported in the SEER program.

Time was measured from the date of enrollment to the date of the last survey received by the study team (D.J.M. and O.J.H.) for each participant. Individuals who failed to return a survey were contacted by mail and by phone.

### Statistical Analysis

The incidence (95% Poisson CI) of malignancy was estimated per 100 000 person-years. The total number of malignancies in the PEER was compared with that in the SEER database. Comparisons of observed and expected malignancies were made using the standardized incidence ratio (SIR), which is the ratio of observed to expected cases. Cancer rates are known to vary by age, sex, and race. The expected number of cancers from the SEER database was calculated in 2 ways, by standardizing the SEER data to age at the time of reporting (by 5-year intervals) and standardizing by age, sex, and race at the time of reporting for the PEER population. Estimates were obtained from the SEER data for all malignancies and then specifically for lymphoma and leukemia. This form of standardization of the SEER data to time at risk (in person-years) in the PEER was done using the indirect standardization method, and the 95% CIs were estimated using the method by Woolf.<sup>13</sup> The analytic plan was originally submitted to the FDA as part of the postmarketing commitment several years ago. To determine the power of our projected sample size, we had previously used the SEER data to estimate an expected incidence of malignancy of 28.2 cases per 100 000 person-years for individuals 0 to 29 years old. The initial power calculation revealed that 20 000 person-years of follow-up would provide more than 80% power to exclude an SIR of less than 2.8.

## Results

As of May 2014, a total of 7457 children were enrolled and followed up for 26 792 person-years based on the PEER data received, stored, and analyzed by us. There were 3969 girls (53.2%) and 3952 African Americans (53.0%). The mean (SD) age at onset of AD was 2.3 (3.0) years (median, 6 months; interquartile range, 9 months to 3 years), and the mean (SD) age at enrollment into the PEER study was 7.2 (4.0) years (median, 6.2 years; interquartile range, 3.9-9.9 years). **Table 1** lists person-years of follow-up by participant age at the time of each survey response. The age categories were grouped to be compatible with data available from the SEER program. Asthma was noted in 4638 children (62.2%), and seasonal allergies were reported in 3952 children (53.0%). Children used a mean (SD) of 793 (1356) g of pimecrolimus, with a median use of 360 g (interquartile range, 60-900 g). During the study, the use of pimecrolimus substantially decreased (**Table 2**).

**Table 1. Accrued Person-years in the Pediatric Eczema Elective Registry Cohort Based on Age at the Time of Each 6-Month Survey Response**

Age, y	Follow-up, Person-years	Proportion of Total
0-4	2585.10	0.10
5-9	10 580.43	0.39
10-14	8845.06	0.33
15-19	3969.16	0.15
20-24	785.07	0.03
25-29	26.85	0.00
<b>Total</b>	<b>26 791.67</b>	<b>1.00</b>

**Table 4. Expected Surveillance, Epidemiology, and End Results Rates of Malignancy by Age Group and Diagnosis**

Age, y	Per 100 000 Person-years		
	All Malignancies	Lymphoma	Leukemia
0-4	22.3	0.7	7.9
5-9	11.8	1.6	3.7
10-14	13.2	2.6	2.9
15-19	21.6	5.1	2.6
20-24	38.2	7.8	2.5
25-29	61.2	8.7	2.6

**Table 2. Percentage of Participants Based on Age at Enrollment Reporting No Pimecrolimus Use in the Previous 6-Month Interval Since Enrollment**

Age, y	Time, mo								
	6	12	18	24	30	36	42	48	54
2-5	19.8	28.2	33.2	36.7	38.9	44.5	47.5	51.0	55.3
6-8	16.7	23.3	27.4	30.8	32.2	37.7	39.9	43.7	44.6
9-11	19.2	25.2	31.8	32.1	35.9	42.8	43.6	46.1	50.9
12-14	17.9	28.0	31.6	36.1	39.8	41.7	45.7	49.4	48.6
15-17	23.7	30.4	29.8	27.6	36.2	32.8	40.7	46.4	49.6
<b>Total</b>	<b>19.1</b>	<b>26.8</b>	<b>31.3</b>	<b>34.1</b>	<b>36.9</b>	<b>41.8</b>	<b>44.7</b>	<b>48.0</b>	<b>51.3</b>

**Table 3. Reported Malignancies in the Pediatric Eczema Elective Registry Cohort**

Age at Malignancy Diagnosis, y	Study Time, y	Sex	Race	Malignancy	Total Reported Pimecrolimus Use, g
0-4	0.4	Male	African American	Acute lymphoblastic leukemia	30
0-4	0.2	Female	African American	Acute lymphoblastic leukemia	60
10-14	4.5	Male	African American	Osteosarcoma	150
5-9	1.2	Female	White	Burkitt lymphoma	60
15-19	7.0	Male	White	Lymphoma	2280

As of May 2014, 5 malignancies had been reported (Table 3). These include 2 leukemias, 1 osteosarcoma, and 2 lymphomas. Rates for overall malignancies (primary outcome), lymphoma, and leukemia were estimated from a PEER-standardized SEER population. Standardization was done by age alone and by age, sex, and race. These rates are listed in Table 4.

The overall rate of observed malignancies in the PEER population was 18.7 (95% CI, 6.1-43.6) per 100 000 person-years (calculated as 5 cases per 26 791.67, times 100 000). The overall rate of lymphoma was 7.5 (95% CI, 0.9-26.9) per 100 000 person-years (calculated as 2 cases per 26 791.67, times 100 000). The overall rate of leukemia was also 7.5 (95% CI, 0.9-26.9) per 100 000 person-years (calculated as 2 cases per 26 791.67, times 100 000). No skin cancers were reported. Therefore, the overall rate of skin cancers (melanoma and keratinocyte cancers) was 0.0 (95% CI, 0.0-3.7) per 100 000 person-years. The expected rates based on the age-standardized SEER population were 15.6 per 100 000 person-years for all malignancies, 2.6 per 100 000 person-years for lymphoma, and 3.6 per 100 000 person-years for leukemia (Table 5). The SIR for all malignancies based on the age-standardized SEER population was 1.2 (95% CI, 0.5-2.8) (18.7 of 15.6), which was the primary end point of the study and was less than the prespecified ratio of 2.8 (from the power estimate). The SIRs (based on

2 cases for each) were 2.9 (95% CI, 0.7-11.7) for lymphoma and 2.0 (95% CI, 0.5-8.2) for leukemia. If the SEER data were standardized based on age, sex, and race, the SIRs changed minimally and were 1.2 (95% CI, 0.5-2.9), 2.9 (95% CI, 0.7-11.7), and 2.1 (95% CI, 0.6-8.2) for all malignancies, lymphoma, and leukemia, respectively. Because these estimates are so similar to the age-standardized rates, we will use the age-standardized rates for the remainder of the discussion herein.

## Discussion

Topical calcineurin inhibitors have been used to treat children with AD for more than a decade. Approximately 8 years ago, because of concerns about the theoretical increased risk of malignancy, the FDA revised the labeling for the TCI class of medication to include a black box warning addressing this concern.<sup>3,10</sup> The present study was based on more than 25 000 person-years of follow-up from a postmarketing cohort study designed to evaluate the risk of malignancy in children exposed to pimecrolimus. This is one of the largest prospective longitudinal studies ever conducted on a dermatologic illness and probably is the largest to date of a pediatric dermatologic illness in the United States. Nevertheless, it is impor-

Table 5. Expected Surveillance, Epidemiology, and End Results Rates of Malignancy Standardized by Age to the Pediatric Eczema Elective Registry Population<sup>a</sup>

Cancer Type	Pediatric Eczema Elective Registry Cohort		Race		Sex	
	Standardized by Age	Standardized by Age, Sex, and Race	African American	White	Male	Female
All malignancies	15.6	15.2	13.5	8.2	15.9	15.2
Lymphoma	2.6	2.5	2.6	1.4	2.8	2.2
Leukemia	3.6	3.5	2.9	1.9	4.1	3.2

<sup>a</sup> Rates are per 100 000 person-years standardized for the full Pediatric Eczema Elective Registry cohort or for a specified subcohort.

tant to note that individuals who were enrolled in this study were unlikely to have continuously used pimecrolimus. In fact, as the study proceeded, many had not used it at all in the previous 6-month period. However, our study likely replicates how pimecrolimus and other topical agents are used to treat mild to moderate AD in general practice in the United States because AD waxes and wanes over time. Compared with the SEER data, the SIR for all malignancies herein was 1.2 (95% CI, 0.5-2.9) when standardized based on age, sex, and race. This estimate is close to unity (no risk), and the 95% CI overlaps with 1. Based on this estimate, it is unlikely that those who were exposed to pimecrolimus are at an increased risk of developing a malignancy.

We presented separate estimates for lymphoma and skin cancers (melanoma and keratinocyte cancers) because they have been associated with oral calcineurin use and separately for leukemia because 2 studies<sup>3,5</sup> were noted in our data set. Our study was not originally designed to be large enough to present stable estimates for these secondary outcomes. However, skin cancers are among the most common malignancies noted in patients who have undergone solid-organ transplantation.<sup>4,14</sup> The incidence of keratinocyte malignancy in the solid-organ transplantation population is thought to be associated with the intensity of immunosuppression and the duration of treatment.<sup>4,14</sup> The risk of keratinocyte cancers in patients after solid-organ transplantation receiving immunosuppression that includes systemic calcineurin inhibitors has been estimated to be more than 10 times to as high as 65 times greater than that in the general population.<sup>4,6,7,14</sup> Five years after commencing transplantation immunosuppression regimens, approximately 5% of patients will have a keratinocyte cancer.<sup>4,14</sup> These tumors are also thought to be aggressive.<sup>4,6,7,14</sup> In the PEER study reported herein, no skin cancers (basal cell, squamous cell, or melanoma) of any type have been noted after more than 25 000 person-years of follow-up. Our estimate is 0.0; however, the upper bound of the 95% CI is 0.0 (0.01% per year or 0.07% per 5 years), which is markedly smaller than the estimated 5% incidence of skin cancers at 5 years after transplantation.

Patients after solid-organ transplantation also have an increased risk of lymphoma.<sup>3,5</sup> In a recent US-based study,<sup>5</sup> there was a 6-fold increased risk of non-Hodgkin lymphoma (NHL) in those undergoing solid-organ transplantation compared with the general population. However, the largest risks were measured with SIRs, approaching a 100-fold increase for hepatosplenic T-cell lymphoma, Burkitt lymphoma, natural killer cell or T-cell lymphoma, diffuse large B-cell lymphoma, and ana-

plastic large cell lymphoma.<sup>5</sup> The highest rates of lymphoma are seen shortly after exposure to calcineurin inhibitors and then again more than 5 years after transplantation.<sup>5</sup> Except for cutaneous T-cell lymphoma, which may represent a diagnostic dilemma with respect to AD, previous studies<sup>3,15-17</sup> reporting on the association between AD treatment with TCIs and NHL have generally not reported an increased risk, with non-significant risk ratios ranging from 0.82 to 2.53. In our study, the rate of lymphoma was 7.5 (95% CI, 0.9-26.9) per 100 000 person-years, with an SIR of 2.9 (95% CI, 0.7-11.7). Our SIR is not statistically significant. Based on the width of the CI, our estimate lacks precision (ie, a larger study is needed). However, our estimates are similar to the previously published risk ratios,<sup>3,15-17</sup> finding no increased risk. Furthermore, our estimated SIR is lower than the SIR of 6 that was recently reported as the risk thought to be due to immunosuppression after solid-organ transplantation.<sup>5</sup> A fair conclusion is that pimecrolimus use is not statistically associated with an increased risk of lymphoma. However, it would be prudent to note that our sample size is too small to exclude all risk. Furthermore, if no more cases of lymphoma are reported, a final report after 40 000 person-years of follow-up (as requested by the FDA and the present goal of the PEER study) would likely not markedly improve the precision (ie, the width of the 95% CI) of this estimate or markedly change the incidence estimate (ie, 5.0; 95% CI, 0.6-18.1 per 100 000 person-years). A final concern is that pruritus can be a feature of both AD and NHL. One of the 2 participants diagnosed as having NHL reported little pimecrolimus use (one 60-g tube) before her NHL diagnosis, and it occurred within approximately 1 year of enrollment. It is possible that pimecrolimus was used to treat pruritus due to NHL.

Two individuals developed acute lymphoblastic leukemia. In both patients, the diagnosis of malignancy occurred within less than 6 months of enrollment, and the children received minimal exposure to a TCI (Table 3). Acute lymphoblastic leukemia has not been associated with oral calcineurin use.<sup>3,17</sup> The cause and effect of these malignancies with respect to the timing of TCI use may not be apparent.

In general, the causal mechanism of action relating the use of systemic calcineurin inhibitors to malignancy is not fully understood. The earliest explanations centered on the notion that calcineurin inhibition, as occurs with systemic use of these agents for organ transplantation, resulted in the inability of normal-functioning T cells to mount a response to prevent the malignant transformation of B cells infected with Epstein-Barr virus.<sup>18</sup> With respect to skin carcinogenesis, the

use of systemic calcineurin inhibitors is thought to have a direct effect on keratinocytes and to diminish the need for immunosurveillance, which normally leads to irradiation of premalignant changes.<sup>14</sup> Unlike the expectation of the administration of systemic calcineurin inhibitors, the systemic absorption of calcineurin inhibitor from the application of a TCI as used to treat AD is generally low or undetectable.<sup>3,17,19</sup> Furthermore, unlike the systemic administration of calcineurin inhibitors as used after organ transplantation, there is no evidence of extracutaneous immunosuppression after the administration of a TCI for the treatment of AD.<sup>3,17,20,21</sup>

Like all studies of this design, there are limitations. We only know of malignancies that have been reported to us by study participants. Not all participants responded to our surveys or other queries. It is possible that the PEER participants developed cancers that are currently not known by us. Part of the protocol was to contact participants by mail and phone, as well as to contact their health care providers. When other attempts failed, third-party search firms contacted study participants who were lost to follow-up. All participants were paid to respond to our surveys. During the time frame described in this study, more than 75% of eligible participants responded on average at each time point.<sup>11</sup> We also only assessed time based on those reporting.<sup>11</sup> All study participants were informed that the objective of this study was to determine if there is an association between malignancy and pimecrolimus use, and all study participants received pimecrolimus from a pharmacy that included the black box warning describing this risk. These events possibly reduced the likelihood that a participant who developed a malignancy would not have made an association between his or her illness and pimecrolimus use and then failed to contact the study or the company. We used the SEER data as our standard of comparison. The SEER program is often used as a standard for US studies of malignancy rates. The PEER participants represent most states in the United States.<sup>11</sup> However, the SEER program captures data only from SEER centers; therefore, it is possible that the SEER data might not properly reflect the geographic risk of our study popula-

tion. Also, the SEER program does not have data on keratinocyte cancers, although we recorded none in our study population. Participants in our study did not use pimecrolimus continuously. Their treatment was not predicated on their enrollment in the study but was determined by interactions with their health care providers in a fashion that is likely generalizable to the treatment of AD in the United States. The PEER study and the present study represent children and not adults. It may be possible that pimecrolimus use has different risks in adults. Finally, the study was originally designed and powered in consultation with the FDA as part of a postmarketing commitment to discover SIR differences of 2.8 or greater. It is possible that a smaller difference could be important and would not be found to be statistically significant by our current study design. For this reason, we provided point estimates (95% CIs) for our observations whether statistically significant or not.

## Conclusions

In summary, AD is a disease that waxes and wanes. Pimecrolimus is a TCI that is used intermittently to treat AD. Based on its similarity to oral medications used after organ transplantation, a theoretical association with malignancy has been postulated, but the treatment duration and pattern of use, the blood level achieved, and the ability of pimecrolimus to achieve an immunosuppressed state all differ greatly from the oral calcineurin inhibitors.<sup>3</sup> As in the general care of AD, all therapeutic decisions in the PEER study were made by local health care providers and the patients and families. Compared with the SEER data, pimecrolimus as used in the PEER study does not appear to be associated with an increased risk of malignancy. Furthermore, no skin cancers were reported in the PEER study. Based on more than 25 000 person-years of follow-up, it seems unlikely that topical pimecrolimus as it was generally used in the PEER cohort to treat AD<sup>3-5,14-17</sup> is associated with an increased risk of malignancy.

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**Study concept and design:** Margolis, Hoffstad, Bilker.  
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**Study supervision:** Margolis.

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