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No significant association between malignancy and topical use of pimecrolimus

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Abstract

Importance—A black box warning describes a potential risk of malignancy associated with the topical use of pimecrolimus to treat atopic dermatitis (AD) due to its similarity to oral calcineurin inhibitors used in solid organ transplantation and spontaneous reporting of malignancies including lymphomas and cutaneous malignancies.

Objective—The goal of this study was to evaluate the risk of malignancy in a post marketing study of children exposed to pimecrolimus.

Design—A longitudinal cohort study.

Setting—A nation-wide ongoing long-term cohort of children with AD.

Participants—Children enrolled in the Pediatric Eczema Elective Registry (PEER) who had a history of AD and pimecrolimus use.

Main outcome—Reports of malignancy in those in PEER as compared to expected rates from the Surveillance Research (SEER) Program.

Results—7,457 subjects were enrolled in the PEER study for a total of 26,792 person-years. Children used a mean of 793 (SD 1356) grams of pimecrolimus while enrolled in the study. As of May 2014, 5 malignancies had been reported. These include **2** leukemias, 1 osteosarcoma, and 2 lymphomas. No skin cancers were reported. The Standardized Incidence Ratio (SIR) for all

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malignancies (primary outcome) based on the age standardized SEER population was 1.2 (0.5, 2.8). As secondary analyses, the SIR (based on 2 cases for each) for lymphoma was 2.9 (0.7, 11.7) and for leukemia was 2.0 (0.5, 8.2). 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 AD is associated with an increased risk of malignancy.

Atopic 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[1]. It was recently shown to be one of the most burdensome of all dermatologic illnesses[2]. Guidelines for the diagnosis and treatment of this disease were recently published[1]. Very few topical agents have been approved by the Food and Drug Administration (FDA) or European Union Medicines Agency (EUMA) for the treatment of AD in children. Topical calcineurin inhibitors (TCI) were approved about a decade ago[3].

Systemic calcineurin inhibitors were originally approved as immunosuppressive agents to be used after whole 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, and thus preventing organ rejection[3–7]. The most frequently used oral agents in this class are cyclosporine and tacrolimus. An unfortunate adverse event associated with these agents is an increased risk of malignancy especially skin cancer and lymphoma[6;7].

Pimecrolimus (trademark Elidel) was approved by the FDA for the treatment of mild to moderate AD in children of at least 2 years of age in December of 2001. Pimecrolimus was approved by EUMA in 2002. The Pediatric Elective Registry (PEER) study was established as part of the post-marketing commitments for the approval of this drug. The post-marketing commitments were originally to Novartis Pharmaceuticals and are now to Valeant Pharmaceuticals International. The purpose of PEER was to follow children with AD for 10 years who had at least 6 weeks of total exposure to pimecrolimus in order to determine their incidence of malignancy. The original study commenced in 2004. However, due to concerns about the overall sample size the original study was enlarged from 4,000 subjects with an original expectation of accruing 20,000 person-years of follow-up to 8,000 subjects and an expectation of 40,000 person-years of follow-up. This report is an evaluation of the risk of malignancy in approximately the first 20,000 person-years of PEER follow-up. Observed rates are compared to standardized rates from the Cancer Surveillance, Epidemiology and End Results program of the National Cancer Institute (SEER).

Methods

Population

PEER is an ongoing prospective observational cohort study. The total enrollment is expected to reach 8,000 children with mild to moderate AD at the time of enrollment who will be followed for 10 years with a goal of accruing at least 40,000 person-years of follow-up. The current report was based on data received up to May 2014. The enrollment criteria and goals

of the PEER study have been described in detail elsewhere[8–11]. Eligible subjects were ≥ 2 and < 18 years of age at the date of enrollment. All subjects had a diagnosis of AD by a treating physician, the majority of who were pediatricians, allergists, or dermatologists[8–10]. The enrollment diagnosis was confirmed by the Working Party Diagnostic Criteria[12]. All subjects used pimecrolimus cream for at least 42 days out of the preceding 180 days prior to enrollment. However after enrollment no child had to continue to use pimecrolimus and all treatment decisions were made by the participant, their parents, and/or their healthcare providers independent of the study. Finally, informed consent (and/or assent) was obtained for all participants either from the participant or their caregiver. The informed consent process was approved by Concordia Institutional Review Board (IRB). Participants were excluded if at the time of enrollment they had a previous or current history of lymphoproliferative disease, systemic malignancy, skin malignancy, and/or history of the use of oral immunosuppressive therapy. As noted, children were not required to continue to use pimecrolimus once they were enrolled in PEER[10]. Our research protocol was approved by the IRB at the University of Pennsylvania.

Outcome and the measurement of time

The primary outcome for this study was the onset of any malignancy after enrollment into the PEER study. All study participants were queried every 6 months in order 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 and more recently Valeant in order to determine and confirm the diagnosis. All serious adverse event reports were reported to the appropriate federal regulatory authority. All participants received monetary reimbursement after the completion of each 6 month survey. Comparison data was obtained from the Surveillance Research (SEER) Program, National Cancer Institute (NCI) by request after submitting a signed data use agreement on July 2013. In addition to total malignancy rates as secondary outcomes we report separately on leukemia, lymphoma, and skin cancers. Skin cancers are not reported in SEER.

Time was measured from date of enrollment to the date of the last survey received by the study team for that subject. Individuals who failed to return a survey were contacted by the mail and by the phone.

Analysis Plan

Incidence of malignancy was estimated per 100,000 person-years with 95% Poisson confidence intervals. The total number of malignancies in PEER was compared to that in the SEER database. The comparisons of observed and expected malignancies were made using the Standardized Incidence Ratio (SIR), which was the ratio of observed to expected cases. Cancer rates are known to vary by age, gender, and race. The expected number of cancers from SEER was calculated in two ways by standardizing SEER data to the age at the time of reporting (by 5-year intervals) and standardized by gender, race, and age 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 SEER to the time at risk (person-years) in PEER was done using the indirect standardization method and the 95% confidence intervals were estimated using the

method of Woolf[13]. The analytic plan was originally submitted to the FDA as part of the post-marketing commitment several years ago. In order to determine the power of our projected sample size, we previously used SEER to estimate an expected incidence of malignancy for individuals aged 0 to 29 years, 28.2 per 100,000 person-years. 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, based on PEER data received, stored, and analyzed by the authors, 7,457 children were enrolled and followed for 26,792 person-years. There were 3,969 (53.2%) girls and 3,952 (53.0%) African-Americans. The average age at the onset of AD was 2.3 years (SD (standard deviation) 3.0, median 6 months (interquartile range (IQR): 9 months, 3 years)) and the average age of enrollment into PEER was 7.2 (SD 4.0, median 6.2;(IQR:3.9, 9.9)). Table 1 presents person-years of follow-up by the subject's age at the time of each survey response. The age categories were grouped to be compatible with data available from SEER. Asthma was noted in 4,638 (62.4%) and seasonal allergies were reported in 3,952 (53.0%) of the children. Children on average used 796 (SD 1356) grams with a median use of 360 (IQR:60,900) grams of pimecrolimus. Over the course of the study, the use of pimecrolimus substantially decreased (Table 2).

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

The overall rate of observed malignancy in the PEER population is **18.7** (95% Poisson confidence interval: **(Confidence interval (CI): 6.1, 43.6)** per 100,000 person-years ((calculated as 5 cases/26791.67) * 100,000), for lymphoma is **7.5 (.9, 26.9)** per 100,000 person-years ((2 cases/26791.67) *100,000), and for leukemia is **7.5 (0.9, 26.9)** per 100,000 person-years ((2 cases/26791.67) *100,000). No skin cancers were reported. Therefore, the overall rate of skin cancers (melanoma and keratinocyte cancers) was 0 (0, 3.7) per 100,000 person-years. The expected rates based on the age standardized SEER population are **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. The SIR for all malignancies based on the age standardized SEER population is **1.2 (0.5, 2.8) (18.7/15.6)**, which was the primary endpoint of the study and was less than the pre-specified ratio of **2.8** (from the power estimate) (Table 5). The SIR (based on 2 cases for each) for lymphoma is **2.9 (0.7, 11.7)** and for leukemia is **2.0 (0.5, 8.2)**. If SEER were standardized based on age, gender, and race the SIRs changed minimally and were **1.2(0.5, 2.9), 2.9(0.7, 11.7)**, and **2.1(0.6, 8.2)**, for any malignancy, lymphoma, and leukemia, respectively (Table 5). Because these estimates are so similar to the age standardized rates, we will use the age standardized rates for the remainder of this report.

Discussion

TCIs have been used to treat children with AD for more than a decade. About 8 years ago, due to concerns about the theoretical increased risk of malignancy, the FDA revised the labeling for the TCI class of medication to include a boxed warning addressing this concern[3;10]. Our current report was based on more than 25,000 person-years of follow-up from a post-marketing 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 likely the largest prospective longitudinal study of a pediatric dermatologic illness in the US. First, it is important to realize 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 US, because AD waxes and wanes over time. As compared to SEER, the SIR for all malignancies was 1.2 (0.5, 2.9). This estimate is very close to unity (no risk) and the confidence interval overlaps with one. Based on this estimate it is very 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 leukemia because 2 reports were noted in our dataset[3;5]. 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 received solid organ transplants[4;14]. The incidence of keratinocyte malignancy in the solid organ population is thought to be associated with the intensity of immunosuppression and duration of treatment[4;14]. The risk of keratinocyte cancers in solid organ transplant patients receiving immunosuppression that includes systemic calcineurin inhibitors has been estimated to be more than 10-times higher and as high as 65-times greater than the general population[4;6;7;14]. Five years after commencing transplantation immunosuppression regimens, about 5% of patients will have a keratinocyte cancer[4;14]. These tumors are also thought to be more aggressive[4;6;7;14]. In the PEER study, after more than 25,000 person-years of follow-up, no skin cancers (basal cell, squamous cell or melanoma) of any type have been noted. Our estimate is 0, however, the upper bound of the 95% confidence interval is 0.0, 0.014% per year or 0.07% per 5 years, which is markedly smaller than 5% incidence of skin cancers 5 years post transplantation.

Patients with solid organ transplants also have an increased risk of lymphoma[3;5]. In a recent US-based study there was a 6-fold increased risk of non-Hodgkin Lymphoma (NHL) in those receiving a solid organ transplant as compared to the general population[5]. However, the largest risks were measured with SIRs approaching an 100-fold increase for; hepatosplenic T-cell lymphoma, Burkitt's lymphoma, NK/T-cell lymphoma, diffuse large B-cell lymphoma, and anaplastic large-cell lymphoma[5]. The highest rates of lymphoma are seen shortly after exposure to calcineurin inhibitors and then again more than 5 years post transplantation[5]. With the exception of cutaneous T-Cell Lymphoma, which may represent a diagnostic dilemma with respect to AD, previous studies reporting on the association

between AD patients treated with TCI and NHL have generally not reported an increased risk with non-significant risk ratios ranging from 0.82 to 2.53[3;15–17]. In our study the rate of lymphoma was 7.5 (0.9, 26.9) per 100,000 person-years, with an SIR of 2.9 (0.7, 11.7). Our SIR is not statistically significant. Based on the width of the confidence interval our estimate lacks precision (i.e. a larger study is needed). Our estimates are however similar to the previous published risk ratios that concluded no increased risk[3;15–17]. Furthermore, our estimated SIR is lower than the SIR of 6, recently reported as the risk thought to be due to immunosuppression after solid organ transplantation[5]. A fair conclusion is that pimecrolimus 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, it is important to realize that, 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 current goal of the PEER study, would likely not markedly improve the precision (i.e., width of the confidence interval) of this estimate or markedly change the incidence estimate (e.g., 5.0 (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 two subjects diagnosed with NHL reported very little pimecrolimus use (one 60 gram tube) before her NHL diagnosis and it occurred within about a year of enrollment. It is possible that pimecrolimus was used to treat pruritus due to NHL.

Two individuals developed acute lymphoblastic leukemia (ALL). In both cases the diagnosis of malignancy occurred within less than 6 months of enrollment and the children received minimal exposure to a TCI (Table 3). ALL has not been associated with oral calcineurin use[3;17]. 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 the 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[18]. With respect to skin carcinogenesis, systemic calcineurin inhibitors are thought to have a direct effect on keratinocytes and to diminish the immunosurveillance that normally leads to the irradiation of premalignant changes[14]. 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 very low or undetectable[3;17;19]. Furthermore, unlike the expectation of 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[3;17;20;21].

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 study subjects responded to our surveys or other queries. It is possible that PEER participants developed cancers that are currently not known by us. Part of the protocol was to contact subjects by mail and phone as well as to contact the subject's healthcare providers and, when other attempts have failed, to employ third party search firms to contact "lost" study participants. All participants were paid to respond to our surveys. We do know that during the time frame described in this study on

average more than 75% of eligible subjects responded at each time point[11]. We also only assessed time based on those reporting[11]. All study subjects were informed that the purpose of this study was to determine if there is an association between malignancy and pimecrolimus and all study subjects received pimecrolimus from a pharmacy that included the boxed warning describing this risk. These events possibly reduced the likelihood that a subject who developed a malignancy would not have made an association between their illness and pimecrolimus and then failed to contact the study or the company. We used SEER as our standard of comparison. SEER is often used as a standard for US studies of malignancy rates. PEER subjects are from the majority of the states in the US[11]. SEER however captures data only from SEER centers and it is therefore possible that SEER might not properly reflect the geographic risk of our study population. Also, SEER does not have data on keratinocyte cancers, although we recorded none in our study population. Subjects 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 healthcare providers in a fashion that is likely generalizable to the treatment of AD in the US. The PEER study and our report is on children and not adults. It may be possible that pimecrolimus has different risks in adults. Finally, the study was originally designed and powered in consultation with the FDA as part of a post-marketing commitment to discover differences in SIR of about 3 or greater. It is certainly possible that smaller difference could be important and would not be found to be statistically significant by our current design. For this reason we provided point estimates and confidence intervals for our observations whether statistically significant or not.

In summary, atopic dermatitis is a waxing and waning disease. Pimecrolimus is a TCI that is used intermittently to treat AD. Based on its similarity to oral medications used in the treatment of organ transplantation a theoretic association with malignancy has been postulated but treatment duration and pattern of use, blood level achieved, and the ability of pimecrolimus to achieve an immunosuppressed state all differ greatly from the oral calcineurin inhibitors[3]. Like in the general care of AD, all therapeutic decisions in the PEER study were made by the local providers and the patients/family. As compared to SEER, pimecrolimus as used in PEER does not appear to be associated with an increased risk of malignancy. Further, 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 is associated with an increased risk of malignancy[3–5;14–17].

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Table 1

Accrued person-time in PEER cohort based on age at the time of a 6 month survey response

Age Groups	Person-years of follow-up	Proportion of total
0–4	2585.1	0.10
5–9	10580.43	0.39
10–14	8845.06	0.33
15–19	3969.16	0.15
20–24	785.07	0.029
25–29	26.85	0.001
Total	26791.67	1.00

Table 2

Percent of subjects based on age at enrollment reporting **no** pimecrolimus used in the previous 6 month (mo) interval since enrollment

Age Group	Enroll	6 mo	12 mo	18 mo	24 mo	30 mo	36 mo	42 mo	48 mo	54 mo
2 to 5	0	19.8	28.2	33.2	36.7	38.9	44.5	47.5	51.0	55.3
6 to 8	0	16.7	23.3	27.4	30.8	32.2	37.7	39.9	43.7	44.6
9 to 11	0	19.2	25.2	31.8	32.1	35.9	42.8	43.6	46.1	50.9
12 to 14	0	17.9	28.0	31.6	36.1	39.8	41.7	45.7	49.4	48.6
15 to 17	0	23.7	30.4	29.80	27.6	36.2	32.8	40.7	46.4	49.6
Total	0	19.1	26.8	31.3	34.1	36.9	41.8	44.7	48.0	51.3

Table 3

PEER reported malignancies (M-male; F-female; AA-African-American; W-white)

Age category at malignancy diagnosis	Time in study (yrs)	Gender	Race	Malignancy	Total reported Pimecrolimus used (grams)
0–4	0.4	M	AA	Acute Lymphobastic Leukemia	30
0–4	0.2	F	AA	Acute Lymphobastic Leukemia	60
10–14	4.5	M	AA	Osteosarcoma	150
5–9	1.2	F	W	Burkitt's lymphoma	60
15–19	7.0	M	W	Lymphoma	2280

Table 4

Expected SEER rates of malignancy by age group and diagnosis

Age Groups	All malignancies per 100,000 person-years	Lymphoma per 100,000 person-years	Leukemia per 100,000 person-years
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 5

Expected SEER rates standardized by age to the PEER population. Rates listed as per 100,000 person-years standardized for the full PEER cohort or for a specified sub cohort.

Cancer type	PEER Cohort	PEER Cohort*	African Americans	White	Male	Female
Overall	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

* standardized by age, gender, and race.

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