Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	May 10, 2011
To:	Dianne Murphy, M.D. Director, Office of Pediatric Therapeutics FDA Center for Drug Evaluation and Research
Through:	Solomon Iyasu, M.D., M.P.H Director, Division of Epidemiology Office of Surveillance and Epidemiology FDA Center for Drug Evaluation and Research Simone Pinheiro, Sc.D., M.Sc. Team Leader, Division of Epidemiology Office of Surveillance and Epidemiology FDA Center for Drug Evaluation and Research
From:	Angelika Manthripragada, Ph.D., M.P.H, Epidemiologist, Division of Epidemiology Office of Surveillance and Epidemiology FDA Center for Drug Evaluation and Research
Subject:	Addendum: Update on Calcineurin Inhibitor Pediatric Literature Review
Drug Name(s):	Tacrolimus (Protopic) and Pimecrolimus (Elidel)
Submission Number:	
Application Type/Number:	NDA 21-302 and 50-777
Applicant/sponsor:	Novartis, Astellas
OSE RCM #:	2010-996

This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.

Contents

1 EXECUTIVE SUMMARY

In this addendum, we update a literature review conducted by the Office of Surveillance and Epidemiology, Division of Epidemiology (OSE, DEPI) that evaluated the risk of systemic infections and malignancies in pediatric patients using pimecrolimus (PIM, Elidel, NDA 021302) or tacrolimus (TAC, Protopic, NDA 050777), which are both topical calcineurin inhibitors (TCI). The update incorporates study results and additional analyses of previously reviewed studies submitted by the sponsor and study authors subsequent to the completion of the previous OSE review.[1]

The Agency requested that the authors/sponsors of the previously reviewed studies provide analyses restricted to pediatric users. Additionally, the sponsor submitted a final study report for a nested case-control study; OSE had previously reviewed only an abstract of this study. The reviewed results provided little information specific to the pediatric population. The additional information on pediatric sub-analyses obtained from the Hui (2009), Schneeweiss (2009) and Arellano (2007) studies provided little new pediatric information since analyses were limited due to small sample size. The additional data obtained from the Arana (2010) nested case-control study also provided little information specific to the pediatric population, with most analyses not being stratified by age.

The additional data from the sponsor on the Arana (2010) study support the conclusions of the previous OSE review. This study suggests the possibility of an association between TAC use and an increased risk of t-cell lymphoma. However, given the study limitations, including the possibility of protopathic bias and confounding by indication, causality is difficult to confirm. Also, given that most analyses were not stratified by age and that the study was of relatively short duration, the applicability of the reported results specifically to the pediatric population and to the long-term safety profile of the drug remains in question.

2 INTRODUCTION

On September 29, 2010, the Office of Surveillance and Epidemiology, Division of Epidemiology (OSE, DEPI) completed a literature review of published observational studies evaluating the risk of systemic infections and malignancies in pediatric patients using the topical calcineurin inhibitors (TCI) pimecrolimus ("PIM," Elidel, NDA 021302) or tacrolimus ("TAC," Protopic,

NDA 050777).[1] PIM 1% and TAC 0.03% ointment are indicated for adults and children ≥2 years of age or older while TAC 0.1% ointment is indicated for adults.[2]

The OSE literature review, which was completed in preparation for the May 2011 Pediatric Advisory Committee (PAC) meeting, included a review of six epidemiologic studies evaluating the risk of malignancies, and eleven noncomparative studies evaluating the risk of systemic infections. In this addendum, we update the malignancies literature review with any newly published studies and new information on previously reviewed studies. The Agency requested that the authors/sponsors of the previously reviewed studies provide analyses restricted to pediatric users. Additionally, the sponsor submitted a final study report for a nested case-control study; OSE had previously reviewed only an abstract of this study.

3 MATERIAL REVIEWED

To update the initial literature review, we searched the medical literature using PubMed@FDA [October 2010 - April 1, 2011; search terms: (elidel OR protopic OR pimecrolimus OR tacrolimus) AND (epidemiology OR observational OR safety) AND (atopic dermatitis OR eczema)]. Our search yielded no new observational studies of malignances. Although we did not find any additional literature, we reviewed the following information provided to us by the sponsors and study authors since the completion of the previous review:

- "Nested case-control study to assess the risk of lymphoma following exposure to topical pimecrolimus (Elidel cream 1%) among patients with atopic dermatitis." Final Study Report, Risk Management Resources. Funded by Novartis Pharmaceuticals Corporation, East Hanover, New Jersey.
- Email correspondence between Rita Hui (Kaiser Permanente), and Angelika Manthripragada (OSE), November 8, 2010, regarding additional data on the following published study: Hui RL, Lide W, Chan J, Schottinger J, Yoshinaga M, Millares M. Association Between Exposure to Topical Tacrolimus or Pimecrolimus and Cancers. Annals of Pharmacotherapy 2009;43:1956-1962.
- "Response to FDA request for Information." Elidel (PIM). November 29, 2010. Submitted by Novartis.

[1] Manthripragada, AD. OSE Review: Calcineurin Inhibitor Pediatric Literature Review. September 29, 2010. Communication PK# 2842634

[2] We clarify here that pimecrolimus 1% is indicated for both adults and children to dispel any ambiguity in the OSE September 29, 2010 review, page 4.

4 RESULTS

4.1 HUI (2009) STUDY

We received additional data on pediatric sub-analyses from the lead study author of this Kaiser Permanente study.[3] Although the study author did not perform analyses by age strata, she reports that only one of the 12 confirmed lymphoma cases was ≤20 years old. This case was exposed to both TAC and PIM.

4.2 SCHNEEWEISS (2009) STUDY

We received additional data related to the previously reviewed Schneeweiss (2009) study regarding pediatric sub-analyses from the sponsor.[4] A secondary analysis limited to patients aged 5 years and younger was conducted. No cases of lymphoma were reported in the 6 month period after enrollment among PIM initiators, initiatiors of medium or high potency topical corticosteroids (TCS), patients with untreated dermatitis, or the general population. Two cases of lymphoma, one cutaneous and the other classified as "any lymphoma," were identified among TAC users ≤ 5 years of age. Sample size precluded any formal analyses.

4.3 ARELLANO (2007) STUDY

We received additional data related to the previously reviewed Arellano (2007) study regarding pediatric sub-analyses from the sponsor.[3] Of the 294 lymphoma cases identified in the PharMetrics database, 81 occurred in patients under < 20 years of age. Of these pediatric cases, 4 were exposed to TAC, 4 were exposed to PIM, and 1 was exposed to both PIM and TAC. Sample size precluded any formal analyses.

4.4 ARANA (2010) STUDY

In the previous OSE literature review, we summarized an abstract of the Arana (2010) study, which provided us with few details regarding study methodology and results. The complete study report and results were subsequently submitted to the Agency by the sponsor. The following is a more complete summary of the nested case-control US Pharmetrics study based on the sponsor's final study report, dated July 30, 2010.

4.4.1 Methods

This study enrolled atopic dermatitis (AD) patients from July 1, 1995 to March 31, 2009, and is an extension of the previous US-based Arellano (2007) Pharmetrics study, which enrolled

[3] Email correspondence with Rita Hui, Kaiser Permanente, November 8, 2010.

patients from July 1995 to January 2005. Participants were identified using ICD-9 codes 691 ("atopic dermatitis and related conditions," excluding 691.0 "Diaper or napkin rash") and 691.8 ("Other atopic dermatitis and related conditions"). Subjects were required to have at least 6 months of continuous enrollment in the database, with cohort entry defined as the first AD diagnosis date in the database (index date). Exclusion criteria included a history of systemic malignancy, a history or present use of systemic immunosuppressive therapy or cancer drugs, or a history of a compromised immune system (including transplant patients, HIV infection/AIDs diagnosis, disorders of the immune mechanism, psoriasis, rheumatoid arthritis, systemic lupus erythematosus, Sjorgen's syndrome, or Celiac sprue). Among the cohort of eligible AD patients, cases of lymphoma first recorded after the index date were identified using ICD-9 codes (200.x, 201.x, 202.x, 204.x). Cases were ascertained as lymphoma cases by a hematologist review based on the presence of claims or diagnosis codes for lymphoma and compatible treatment or related procedures following the first diagnosis, and subdivided into type of lymphoma based on diagnostic coding. Controls were selected using risk-set sampling, and were matched by age (± 2 years) and index date. Exposure to TCIs and other medications was determined from prescription records, which included the National Drug Code (NDC) as well as days supplied and quantity dispensed.

Incidence rates and hazard ratios (calculated using Cox proportional hazard models) of overall lymphoma by exposure were determined for the study cohort. In the nested case-control study, conditional multivariable logistic regression was used to estimate odds ratios of lymphoma overall, and by lymphoma subtype for both TCS and TCI users. Odds ratios were adjusted for age, sex, index date, AD index year, region, specialty, presence of infectious mononucleosis, asthma diagnosis, asthma drug use, oral corticosteroids use, and severity of AD. Severity of AD was defined by the number of physician visits per year.[5] Sub-analyses in patients <20 years of age were conducted. Main analyses were unlagged; however, sensitivity analyses using a 6 month lag time were performed.

4.4.2 Results

There were 625,915 AD patients included in the cohort, with 396,069 (63%) of the cohort < 20 years old. 147 (16%) of the 907 potential cases with a recorded lymphoma diagnosis were excluded after review by a hematologist. The remaining 760 cases of lymphoma consisted of the

---

[4] "Response to FDA request for Information." Elidel (PIM). November 29, 2010. Submitted by Novartis.

[5] Patients ≥3 years old were classified as having severe AD if they had at least 4 physician visits for AD per year and patients < 3 years were classified as having severe AD if they had at least one dermatologist visit during the follow-up period.

following: 106 cases of Hodgkin's disease; 200 cases of Non-Hodgkin's lymphoma (118 t-cell lymphoma, 30 b-cell lymphoma, 52 indeterminate); and 454 cases that could not be further classified. 3,040 controls were selected from the cohort. Of the 760 lymphoma cases, 247 occurred during the first six months after the index date, and 180 cases occurred 2 or more years after the index date. The mean time (SD) from first exposure to recorded diagnosis of lymphoma was 2.06 (1.63) years for patients exposed to PIM, 1.87 (1.64) years for patients exposed to TAC, and 3.05 (1.84) years for patients exposed to both PIM and TAC. The incidence rates of overall lymphoma in all AD patients was 8.55 per 10,000 (95% CI 5.96 , 11.89) for topical TAC users, 5.06 per 10,000 (95% CI 3.76, 6.68) for PIM users, 6.29 per 10,000 (95% CI 5.60, 7.04) for TCS users only, and 7.83 per 10,000 (95% CI 7.05 to 8.67) for non-users. Hazard ratios showed an increased risk of overall lymphoma only among users of TAC in combination with TCS (HR=1.61; 95% CI 1.14, 2.27).

The nested case-control study reported no association with overall lymphoma in patients of all ages (TAC adjusted OR=1.24; 95% CI 0.80, 1.91; PIM adjusted OR=0.76; 95% CI 0.54, 1.08), or in those <20 years old (TAC adjusted OR=0.96; 95% CI 0.38, 2.45; PIM adjusted OR= 0.64; 95% CI 0.34, 1.21). Six month lagged analyses in the entire study population showed no association between either TAC or PIM use and overall lymphoma. There were no reported associations with TCI use and Hodgkin's disease. However, the study reported an increased risk of non-hodgkin's lymphoma and TAC (adjusted OR=2.46; 95% CI 1.11, 5.47) but not for PIM (adjusted OR=0.65; 95% CI 0.29, 1.45). Similarly, the study reported an association between t-cell lymphoma and TAC use versus untreated AD (adjusted OR=4.95; 95% CI 1.86, 13.19) but no association with t-cell lymphoma and PIM use versus untreated AD and t-cell lymphoma (adjusted OR=0.85; 95% 0.25, 2.90). Results of b-cell lymphoma analyses were not interpretable due to small sample size. Results for patients <20 years of age were not presented for these analyses.

The sponsor also presented results by cumulative use, which was defined as grams of cream dispensed times the concentration of the active principle. Adjusted estimates show an increased risk of overall lymphoma in high cumulative TAC use versus non-use (TAC ≥0.10 g: adjusted OR=2.08; 95% CI 1.24, 3.49), and an increased risk of t-cell lymphoma with increasing TAC use versus non-use (TAC < 0.03 g: adjusted OR=4.27; 95% CI 0.24, 75.49; TAC ≥ 0.03-< 0.06 g: adjusted OR=5.36; 95% CI 0.78, 37.05; TAC ≥ 0.06-< 0.10 g: adjusted OR=6.03; 95% CI 1.31, 27.70; TAC ≥ 0.10 g: adjusted OR=12.76; 95% CI 3.35, 48.68). No associations with cumulative use were reported for PIM, and no results for <20 years of age were presented.

5 DISCUSSION

The results of the Arana (2010) study suggest an increased risk of t-cell lymphoma for TAC users. Furthermore, increased cumulative use of TAC was associated with an increasing risk of t-cell lymphoma. The highest category of cumulative use versus non-use was associated with a 12-fold increased risk of t-cell lymphoma, although the lack of precision is reflected in the wide 95% confidence intervals (OR= 12.76; 95% CI 3.35, 48.68). The results of the Arana (2010) study are in agreement with the findings of the previous OSE review, which concluded that the reviewed studies suggested an increased risk of t-cell lymphoma among TAC users.

We now have enough information on the Arana (2010) study to comment on study methodology. There were several limitations in this study which limit the interpretation of the data. A major limitation of this study is the lack of adjudication of cases identified using ICD-9 codes through medical record review or linkage to a cancer registry. This method of case identification could lead to significant misclassification of cases (see previous OSE review #2842634). Additionally, classification of lymphoma by subtype was hampered by the lack of further information on cases. Of the 760 identified cases, the type of lymphoma was classified as indeterminate in 60% of cases. Another limitation is the possibility of prothopathic bias.[6] The study incorporated a 6 month lag only in a very limited number of sensitivity analyses, and reported cases could be a result of a physician applying topical cream to a lymphoma lesion (117 of the 118 t-cell lymphoma cases included skin involvement). If this were the case, we would observe an association suggesting an increased risk of t-cell lymphoma among TAC users even if there was not a true casual relationship. However, if protopathic bias did account for the reported association between t-cell lymphoma and TAC, one would expect to see associations between PIM or TCS and malignances since these would also be prescribed for an early manifestation of lymphoma, such as a skin lesion, before the lymphoma has diagnostically been detected; however, this was not the case. Lastly, although the study comparator group was comprised of AD patients, confounding by indication[7] remains an issue if severity of AD is related to the risk of lymphoma. Data regarding this relationship is currently mixed although this study reported an association with AD severity among patients > 3 years old (OR=1.99; 95% CI 1.42, 2.77). Both TAC and PIM are second-line therapies and thus may be used for more severe AD than other AD medications or untreated AD. Although Arana (2010) controlled for this in their study, residual confounding remains a possibility. The fact that TAC, which is indicated for moderate to severe

[6] Bias that can arise from a drug being unintentionally prescribed for an early manifestation of an undiagnosed disease.

[7] Bias that can arise from differing baseline risks, comorbidities, and prognostic factors between patients who received a particular treatment and those who do not receive this treatment.

AD, was found to be associated with AD, and PIM, which is indicated for mild to moderate AD, was not found to be associated with lymphoma, could suggest that confounding by indication could be a present if more severe disease is associated with greater risk of lymphoma. Alternatively, this relationship may be biologically plausible given that there are data which suggest that t-cell inhibition is eight times higher with TAC versus PIM.[8]

The Arana (2010) study stratified by age (<20 years) only in the analysis pertaining to overall lymphoma risk. Results presented for t-cell lymphoma included both the pediatric and adult populations. The additional information on pediatric sub-analyses obtained on the Hui (2009), Schneeweiss (2009) and Arellano (2007) studies provided little new pediatric information, with analyses being limited due to small sample size.

6 CONCLUSIONS AND RECOMMENDATIONS

The sponsor and study authors response to the Agency's request for additional data on pediatric sub-analyses for the previously reviewed studies (OSE review #2842634) provided us with little additional information specific to the pediatric population given the limited sample size in these analyses. The additional data on the Pharmetrics nested case-control study (Arana, 2010) submitted by the sponsor support the conclusions of the previous OSE review. Study results suggest the possibility of an association between TAC and an increased risk of t-cell lymphoma; however, causality is difficult to determine in light of the potential study biases (e.g,. misclassification of lymphoma, protopathic bias, and confounding by indication). Also, given that most analyses were not stratified by age and that the study was of relatively short duration, the applicability of the reported results specifically to the pediatric population and the long-term safety profile of the drug remains in question.

[8] Kalthoff, FS et al. Differential inhibition of primary versus preactivated t cells by pimecrolimus but not by tacrolimus in vitro. Int Arch Allergy Immunol 2007;142:255-264.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANGELIKA D MANTHRIPRAGADA
05/10/2011

SOLOMON IYASU
05/10/2011