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Contents

1 EXECUTIVE SUMMARY

The Office of Pediatric Therapeutics (OPT) and the Pediatric and Maternal Health Staff (PMHS) have requested that the Office of Surveillance and Epidemiology, Division of Epidemiology (OSE, DEPI) conduct a literature review of observational studies evaluating the risk of systemic infections and malignancies in pediatric patients using the topical calcineurin inhibitors (TCI) pimecrolimus (Elidel, NDA 021302) or tacrolimus (Protopic, NDA 050777). Pimecrolimus and tacrolimus are approved as second-line therapies in atopic dermatitis (AD) patients. In this review, we evaluated the methodology and results from five epidemiologic association studies and eleven noncomparative studies, which provided information on the risk of malignancy or infections among pimecrolimus or tacrolimus users.

When considered together, the reviewed association studies suggest an increased risk of lymphoma, particularly t-cell lymphoma, among TCI users when compared against untreated atopic dermatitis (AD) patients. The risk of lymphoma was greatest among tacrolimus users (Hui (2009): $HR_{\text{t-cell lymphoma}}$=3.13 95% CI 1.41, 6.94; Arana (2010): $OR_{\text{t-cell lymphoma}}$=5.38 95% CI 2.04-14.20; Schneeweiss (2009): $RR_{\text{any lymphoma}}$=1.97 95% CI 0.87, 4.50), but pimecrolimus users were also at an increased risk of lymphoma (Hui (2009): $HR_{\text{t-cell lymphoma}}$=1.86 95% CI 0.71, 4.87; $HR_{\text{b-cell lymphoma}}$ =1.58 95% CI 0.95, 2.63; Schneeweiss (2009): $RR_{\text{any lymphoma}}$ =1.79 95% CI 0.92, 3.48). However, the applicability of these results specifically to the pediatric population is questionable, as is the contribution to our understanding of the long-term safety profile of the drug. Although all of the studies included pediatric patients (~29% to 63% of study population), none of the studies provided results for pediatrics patients only. Furthermore, studies were of short duration (<2.5 years), an important consideration given the long latency of the outcome.

Non-melanoma skin cancer (NMSC), melanoma, and other cancers (e.g., breast, adenocarcinoma, and prostate cancers) were less frequently studied; no more than one study result per outcome was found. Although these studies did not report an increased risk of NMSC, melanoma, or other cancer outcomes among TCI users, given the dearth of epidemiologic studies and the limitations of the existing studies (e.g., confounding by indication, lack of case validation, exclusion of pediatric patients, self-reported exposure), we can not draw conclusions regarding the risk of these other cancers, including melanoma and non-melanoma, in pediatric TCI users.

There were no epidemiologic association studies examining the risk of systemic infection among TCI users; however, there were a number of noncomparative observational studies (n=11) which provided information regarding the frequency of these infections. But whether pimecrolimus or

tacrolimus is associated with an increased risk of infection remains difficult to ascertain from these studies given the broad outcome of systemic infections, lack of comparison group, practice of not confirming the causality of drug exposures to all reported events, and failure to take discontinuation of drugs into account. Since there are no epidemiologic association studies evaluating this potential association, clinical trials or case reports may provide further information in this area.

2 INTRODUCTION

The Office of Pediatric Therapeutics (OPT) and the Pediatric and Maternal Health Staff (PMHS) have requested that the Office of Surveillance and Epidemiology, Division of Epidemiology (OSE, DEPI) conduct a literature review of observational studies evaluating the risk of systemic infections and malignancies in pediatric patients using the topical calcineurin inhibitors (TCI) pimecrolimus (Elidel, NDA 021302) or tacrolimus (Protopic, NDA 050777). Pimecrolimus and tacrolimus were approved in the United States in December 2001 and 2000, respectively, as second-line therapies for the short and non-continuous treatment of mild to moderate atopic dermatitis (AD) in patients who failed to respond adequately to other topical prescription treatments for AD, or when these treatments are not advisable. Pimecrolimus 1% cream and tacrolimus 0.1% ointment are indicated for adults while tacrolimus 0.03% ointment is indicated for adults and children 2 years of age or older.

Pimecrolimus and tacrolimus inhibit calcineurin, which in turn reduces both T lymphocyte proliferation and the release of proinflammatory cytokines. Additionally, these drugs prevent the release of mediators from mast cells.[1] As a result of these immunosuppressive properties, TCIs alleviate skin inflammation;[2] the exact mechanism of action in AD, however, is unknown. The long-term safety profile of both drugs in humans also remains unknown. Pre-clinical animal studies performed with both products have shown evidence of immune suppression mediated carcinogenicity. Additionally, orally or intravenously administered tacrolimus is associated with an increased risk of lymphoproliferative disorders and skin cancer in transplant recipients. And, although pimecrolimus and tacrolimus are both topical agents, studies have shown that active compound may be absorbed systemically.[3] Systemic absorption is of particular concern in the pediatric population since this population has a higher body surface area to weight ratio.

In January 2006, a public health advisory and black box warning for long-term safety and the risk of malignancies (e.g. lymphoma and skin cancer) and a Medication Guide were issued for both products. These changes were prompted by increasing concern surrounding the use of TCIs as first-line and off-label therapy, postmarketing reports of malignancy in children and adults, and

studies showing malignancies in animal models.[3] In March 2010, the Pediatric Advisory Committee (PAC) recommended that the FDA continue to monitor the occurrence of cancer cases in pediatric patients using TCIs. Additionally, FDA was advised to complete a current literature review and provide a follow-up report on the sponsor's cancer registries at the March 2011 PAC meeting.[3]

3 MATERIAL REVIEWED

We searched the medical literature using PubMed@FDA [2005-2010, search terms: (elidel OR protopic OR pimecrolimus OR tacrolimus) AND (epidemiology OR observational OR safety) AND (atopic dermatitis OR eczema)]. Our search yielded 127 publications. Although this review is focused on the pediatric population, given the limited number of association studies, we included all cohort and case-control studies (n=6).[2;4-8] However, for noncomparative studies (studies following only treated individuals), we included only studies that presented separate results for the pediatric population (n=11).[9-19] We did not include randomized clinical trials, meta-analyses of randomized clinical trials, case reports, or review articles in our review.

4 RESULTS: MALIGNANCIES

Table 1 (Appendix 1) provides an overview of the reviewed studies investigating a potential association between pimecrolimus or tacrolimus use and malignancies. Additionally, the noncomparative studies in Table 2 (Appendix 2) were reviewed for any mention of malignancy. All of these studies are discussed below in greater detail.

4.1 HUI (2009) STUDY[2]

4.1.1 Methods

This retrospective cohort study used health insurance claims data from Kaiser Permanente Northern and Southern California to examine whether pimecrolimus or tacrolimus is associated with an increased risk of various types of cancer.* The study population included 953,064 individuals diagnosed with AD or eczema (ICD-9 codes 691.X or 692.2) between January 2001 and December 2004 in the Kaiser database. 278,551 pediatric patients (<20 years) were identified (260,744 unexposed; 5,768 tacrolimus exposed; 12,039 pimcrelimous exposed), with

* Acute myeloblastic leukemia, adenocarcinoma, B-cell lymphoma, breast cancer, bronchus and lung cancer, chronic lymphocytic leukemia, female reproductive system cancer, kidney cancer, male reproductive system cancer, melanoma, other cancer, other leukemia, prostate cancer, squamous cell cancer (non-skin location), t-cell lymphoma, and thyroid cancer.

9.4% of the unexposed group, 9.2% of the tacrolimus exposed group, and 14.0% of the pimecrolimus exposed group between 0-2 years of age. The study entry date was defined as the date of first recorded AD or eczema diagnosis. Patients could be of any age, had to be enrolled in a Kaiser health plan for at least 6 months (or from birth if <6 months of age), and could not have had a recorded history of any cancer prior to study entry date. Participants were followed until cancer diagnosis, disenrollment from the health plan (gap in membership >60 days), death, or the end of the study on December 31, 2005. Data on duration, number of prescriptions, and strength of ointment was collected using outpatient pharmacy records. Person-time before the first identified exposure to topical tacrolimus or pimecrolimus during follow-up was classified as being off therapy. Cancer cases occurring at least 6 months after drug exposure in the exposed group, or anytime after the diagnosis of AD or eczema in the unexposed group, were identified using the Kaiser Permanente Northern and Southern California Cancer Registries (KPNCCR, KPSCCR). Cancer identification in KPNCCR and KPSCCR is primarily through pathology reports (≥80%) and medical records disease indices (10-20%), supplemented by death clearance (1-2%) conducted retrospectively. The authors performed chart reviews on exposed t-cell lymphoma cases to determine linkage between the use of tacrolimus and pimecrolimus and occurrence of the malignancy based on the timing and site of drug application. Cox proportional hazard models were used to estimate hazard ratios (HR).

4.1.2 Results

The mean ages of the study cohorts were 36.8 +/-23.2 years in the unexposed, 34.1 +/-23.5 years for those exposed to tacrolimus, and 29.7 +/-23.8 years for those exposed to pimecrolimus. 28.6% of the population was <20 years old. The authors identified 11,061 unique cases of cancer reported within the cohorts during 2001-2005. The median follow-up time from drug exposure to the end of follow-up was 1.9 years (interquartile range (IQR) 1.3-2.5) and 2.4 years (IQR 1.5-3.6) for pimecrolimus and tacrolimus, respectively, and 2.6 years (IQR 1.5-3.8) from date of diagnosis to end of follow-up in the unexposed. AD or eczema patients using pimecrolimus or tacrolimus were at an increased risk of t-cell lymphoma compared to untreated AD or eczema patients, although after chart review and adjustment for exposure to systemic immunosuppressants or psoriasis-specific therapy, only the effect estimate for tacrolimus use remained statistically significant (tacrolimus: HR=3.13 95% CI 1.41, 6.94; pimecrolimus: HR=1.86 95% CI 0.71, 0.87) (Table 1, Appendix 2). Four of the 16 TCI exposed cases of t-cell lymphoma were excluded because the clinician suspected they had cutaneous t-cell lymphoma (CTCL) before exposure to tacrolimus or pimecrolimus. Of the remaining 12 exposed cases, 7 were exposed only to

tacrolimus, 3 were exposed only to pimecrolimus, and 2 were exposed to both drugs. The authors do not specify the age of the t-cell lymphoma cases and no sub-analysis on pediatric patients was performed. The median time from tacrolimus exposure to t-cell lymphoma diagnosis was 1.4 years (IQR 0.8-3.5), and the median time from pimecrolimus exposure to t-cell lymphoma diagnosis was 1.7 years (IQR 1.0-2.0). There was not a significant difference in the number of subjects exposed to the higher tacrolimus 0.1% ointment (89% vs. 78%) or in the median number of tacrolimus or pimecrolimus prescriptions between t-cell lymphoma cases and t-cell lymphoma free individuals (Table 2, Appendix 2). Pimecrolimus users were also at an increased risk of b-cell lymphoma although the effect estimate was not statistically significant and only minimally adjusted (HR=1.58 95% CI 0.95, 2.63 adjusted for age and sex). Tacrolimus and pimecrolimus were not associated with an increased risk of any other studied cancers (Table 1, Appendix 2). However, tacrolimus users had a decreased age and sex-adjusted risk of melanoma (HR=0.32 95% CI 0.12, 0.84), and pimecrolimus users had a decreased age and sex-adjusted risk of bronchus and lung cancer (HR=0.52; 95% CI 0.28 to 0.94). None of the cancer outcomes except t-cell lymphoma were validated via medical record review.

4.2 SCHNEEWEISS (2009) STUDY[8]

4.2.1 Methods

This cohort study and nested case-control study assessed the potential risk of lymphoma associated with the use of pimecrolimus and tacrolimus using the Ingenix Data Research Mart health insurance claims database. From January 1, 2002 to June 30, 2006, the study identified cohorts of initiators of topical pimecrolimus, tacrolimus and corticosteroid treatment, along with cohorts of unexposed (not dispensed a TCI on date of diagnosis or during the 6 preceding months) patients with untreated dermatitis (ICD-9 codes 690.x, 691.x, 692.x, and excluding 692.7) and dermatitis-free enrollees. Drug initiation was defined as no topical pimecrolimus, tacrolimus or medium/high potency topical corticosteroid in the 6 months prior to cohort entry. Patients with untreated dermatitis and dermatitis-free patients were matched to pimecrolimus initiators by age, sex, and calendar year. Participants could not have been diagnosed with any cancer, congenital immunodeficiency, transplantation, HIV infection or AIDS during the 6 month period prior to study enrollment. Cases of incident lymphomas were identified in the claims database (ICD-9 codes 201.x (Hodgkin's lymphoma), 200.x, 202.x (non-Hodgkins lymphoma), 204.x (lymphocytic leukemia) and adjudicated by oncologists using medical records. Only confirmed cases were used in the analyses.

For the cohort study, follow-up began 6 months after the cohort entry date and continued until an ICD-9 diagnosis of lymphoma, disenrollment from the health plan, death or the end of the study period. Events occurring within 6 months after cohort entry were recorded but not included in primary outcome analyses since the duration of drug exposure was likely too short to be related to the outcome. Potential confounders including preexisting conditions that may interact with the immune system, prior drug use and procedures, healthcare utilization variables, and demographic factors were all considered for inclusion in a propensity model. Confounding by indication was addressed by using propensity score matching. Analyses consisted of proportional hazard models and Kaplan Meier plots.

A nested case-control study was conducted within the cohort study to more closely examine drug use in relation to the study outcomes. Cases included individuals diagnosed with lymphoma at least 6 months after cohort entry, while controls were selected using risk-set sampling. Exposure was categorized as ever/never use (at least one dispensing of the drug in the pre-index date period), total cumulative dispensed amount of the drug, and time between the earliest and latest drug dispensing for each drug. Logistic regression analyses, which included baseline propensity scores as a single continuous covariate in the model, were conducted.

4.2.2 Results

The primary outcome analysis included 92,989 pimecrolimus initiators (121,289 person-years), 29,870 tacrolimus initiators (40,548 person-years), 89,601 untreated dermatitis patients (110,454 person-years), and 88,820 non-dermatitis patients (107,902 person-years). 48% of the cohort was <20 years old. Both pimecrolimus and tacrolimus initiators were followed for an average of 1.5 years after cohort entry (including the 6 month period following cohort entry not considered in the primary outcome analysis). Medical records were reviewed for 664 (74%) of the 900 incident lymphoma cases identified using claims data. Of these 664 cases, only 197 cases were confirmed. Only 57 of these confirmed cases occurred at least 6 months after cohort entry and were subsequently included in the primary outcome analysis (pimecrolimus n=26, tacrolimus n=10, untreated dermatitis n=13, non-dermatitis n=8).

The adjusted (age, sex, calendar year) incidence rate of pimecrolimus compared to untreated dermatitis patients suggested an increased risk of lymphoma, although the confidence intervals included the null value (RR=1.79 95% CI 0.92, 3.48). Pimecrolimus initiators also had an increased risk of lymphoma compared to the general population (age, sex, calendar year adjusted RR=2.89 95% CI 1.32, 6.32). These results were similar for tacrolimus (tacrolimus vs.

untreated dermatitis: RR=1.97 95% CI 0.87, 4.50; tacrolimus vs. general population: RR=2.82 95% CI 1.08, 7.39) (Table 3, Appendix 2). Propensity-score-matched analyses were only performed for pimecrolimus initiators, using tacrolimus initiators and CS initiators as comparison groups. These estimates did not show an increased risk of malignancies for any type of lymphoma (data not shown). Subanalyses in children ≤ 5 years of age were too small to draw any conclusions; no lymphoma cases were identified in 29,340 child pimecrolimus initiators and 29,887 person-years of follow-up starting 6 months after cohort entry (no results given for tacrolimus).

The nested case-control analysis included a comparison of pimecrolimus versus topical corticosteroids. Compared with a low cumulative amount of topical corticosteroids (≤60g), patients receiving high cumulative amounts of topical corticosteroids (>100g) or pimecrolimus (>100g) showed an increased risk of lymphoma (pimecrolimus >100g: OR=4.17 95% CI 1.06-16.4; CS >100g: OR=3.22 95% CI 1.94-5.36) (Table 4, Appendix 2). Results were similar when including only cutaneous manifestations of lymphoma. These analyses were not performed for tacrolimus. The case-control study did not include any comparisons of pimecrolimus or tacrolimus versus untreated AD.

4.3 ARELLANO (2009) STUDY[6]

4.3.1 Methods

This nested case-control study examined the risk of lymphoma associated with topical immunosuppressants, including pimecrolimus and tacrolimus, using a population-based database in the United Kingdom (The Health Improvement Network (THIN)). The study enrolled patients ≤79 years old with at least 6 months of enrollment in a THIN-registered practice between January 1, 1992 and March 23, 2006. Individuals with a previous diagnosis of lymphoma, cancer, immunosuppression, transplantation, HIV infection/AIDS, psoriasis, rheumatoid arthritis, SLE, Sjorgren syndrome, celiac sprue, or patients with a prescription for immunosuppressive agents and anticancer drugs were excluded. Cases of lymphoma were identified by using READ codes in electronic medical records listed after cohort entry date (codes not given). Cases were only validated when there was not enough information to subdivide cases into Hodgkin's or non-Hodgkin's lymphoma, or when there was suspected skin involvement. Validation included a questionnaire sent to the general practitioner, review of the actual medical records, and review of hospital discharge files. Controls were selected using risk-set sampling and included AD

patients (identified using READ codes M11.00, M11.z, M111-117) and non-AD controls. Exposure to a TCI or TCS was captured using prescription data.

4.3.2 Results

The number of patients exposed to pimecrolimus or tacrolimus was insufficient to study any possible associations; only 3 out of 13,687 study participants were exposed to a TCI.

4.4 ARELLANO (2007) STUDY[5]

4.4.1 Methods

This nested case-control study examined the risk of lymphoma associated with TCI use and topical steroid (TS) treatment in the PharMetrics database. The study cohort included 293,253 participants diagnosed with AD (ICD-9 codes 691.8 and 691, excluding 691.0) between July 1995 and January 2005. All participants had to be enrolled in the database at least 6 months prior to their AD diagnosis. Patients with a diagnosis of lymphoma, cancer, immunosuppression, transplantation, HIV infection and/or AIDS, or those who used immunosuppressive agents, or anticancer drugs before the date of AD diagnosis were excluded. 294 cases, defined as participants with a lymphoma diagnosis occurring after the index date (ICD-9 codes 200, 201, 202 and 204), were identified in the cohort. The type of lymphoma, based on diagnostic coding, could not be determined in 66% of cases. Among the identifiable lymphoma cases, Hodgkin's disease accounted for 11.2% of cases, and non-Hodgkin's lymphoma (NHL) accounted for 22.8% of cases. B-cell NHL accounted for 4.4% and T-cell NHL for 18.4% of all identifiable lymphoma cases. Four controls were selected per case using risk set sampling methods (n=1,176). Exposure was captured using pharmacy claims data. The index date for participants was defined as the day a code for AD was first present in the database.

4.4.2 Results

There were 294 cases of lymphoma identified in 293,253 patients; 81 cases occurred in patients ≤20 years of age. 51.8% of the population was ≤ 20 years old. At the index date, 3% of patients used pimecrolimus and 1.5% of patients used tacrolimus. Use of pimecrolimus or use of tacrolimus at the index date compared to non-use was not associated with a diagnosis of lymphoma (pimecrolimus: crude OR=0.53 95% 0.21, 1.37; tacrolimus: crude OR=0.20 95% CI 0.03-1.49). Cases were more likely to be from the Eastern US than controls. Increasing age was

also associated with lymphoma use, with age categories over 31 years showing increasing risks of lymphoma compared to those 0-2 years old.

In comparison to untreated AD, pimecrolimus monotherapy or combination therapy with TS was not associated with a diagnosis of lymphoma, adjusting for sex, age, region, specialty, presence of infectious mononucleosis, asthma diagnosis, asthma drug use, oral steroid use, and severity of AD (pimecrolimus monotherapy: OR=1.09 95% CI 0.45, 2.64; pimecrolimus with TS: OR= 0.60 95% CI 0.21, 1.69). Similarly, tacrolimus monotherapy or combination therapy with TS was also not associated with a diagnosis of lymphoma when comparing users to untreated AD (tacrolimus monotherapy: OR=0.93 95% CI 0.39, 2.22; tacrolimus with TS OR= 0.50; 95% CI 0.10, 2.53) (Table 5, Appendix 2). Pimecrolimus and tacrolimus use together was limited and did not show an association with lymphoma. The risk of lymphoma excluding T-cell cases also did not show an association with pimecrolimus or tacrolimus, with or without concomitant TS use (Table 5, Appendix 2).

4.5 ARANA (2010) STUDY[4]

4.5.1 Methods

This nested case-control study used the US Pharmetric database to assess the risk of lymphoma among AD patients. Since this study is published only as an abstract at present, we have only summary information regarding its methods and results. The study enrolled AD patients from 1995-2009 (exact time-period not given), and is an extension of the previous US Pharmetrics study, which enrolled patients from July 1995 to January 2005. Cases of lymphoma were identified using ICD-9 codes. Multivariable logistic regression was used to estimate odds ratios of lymphoma overall, and by lymphoma subtype for both TCS and TCI users. Sub-analyses for those <20 years of age were conducted. There is no mention of specific ICD-9 codes used to identify AD or lymphoma, and it is not clear whether a lag period for cancer diagnoses was implemented or whether cases were validated. We are also missing the average duration of TCI use, and a description of variables included in the final regression models.

4.5.2 Results

The abstract reports that 625,915 AD patients were included in the cohort, with 63% of the cohort under 20 years of age. There were 760 cases of lymphoma including the 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 were not classified). The number of controls is

not reported. The adjusted OR (variables adjusted for not specified) for any type of lymphoma associated with any TCI use, topical pimecrolimus use, or topical tacrolimus use versus untreated AD was 0.94 (95% CI 0.79, 0.13), 0.85 (95% CI 0.60, 1.19), and 1.34 (95% CI 0.87–2.07), respectively. There was an increased risk of t-cell lymphoma associated with topical tacrolimus use versus untreated AD (OR=5.38 95% CI 2.04, 14.20). Results for patients <20 years of age are not given; but, the authors state there was no evidence of an increased risk of lymphoma in the pediatric population. It is not clear whether this refers to overall lymphoma risk or risk by lymphoma subtype.

4.6 MARGOLIS (2007) STUDY[7]

4.6.1 Methods

This nested case-control study examined whether pimecrolimus or tacrolimus is associated with an increased risk of non-melanoma skin cancer (NMSC) in adult patients seen by faculty dermatologists at the Department of Dermatology at the University of Pennsylvania between 2002 and 2005. Participants were ≥ 30 years old and were diagnosed as having 'dermatitis' (ICD-9 codes 690.1, 691.8, 692.9, 695.3). Individuals referred to the Department for the treatment or evaluation of skin cancer, and individuals self-reporting a history of organ transplantation or use of systemic immunosuppressive agents were excluded from the study. NMSC cases were randomly selected from this eligible population using ICD-9 CM codes 173.0, 173.1, 173.2, 173.3, 173.4, 173.5, 173.6, 173.7, 173.8. Histologic diagnoses were then used to confirm the NMSC diagnosis and differentiate between basal cell carcinoma and squamous cell carcinoma. Controls were individuals with no ICD-9 code for NMSC, selected from the eligible pool described above. Data on exposure and confounder information was collected using a mailed, self-administered questionnaire. Potential confounders included age, skin type, ethnicity, prior history of skin cancer, history of sunburn, past use of medications, and other unlisted variables. The mailed questionnaire also collected information on skin cancer diagnoses between 2000 to 2005, and whether the patient had a history of AD. 2,394 cases (61.9%) and 2,394 controls (69.6%) completed the survey. Participant who reported that they were exposed to systemic calcineurin inhibitors were excluded, and any control who indicated they had skin cancer during 2000 to 2005 was reassigned to the case group for primary analysis. Logistic regression analyses were used to estimate odds ratios (OR). Confounders were included if they were deemed clinically relevant or changed the effect estimate of NMSC and TCI use by >15%.

4.6.2 Results

Cases were on average older than controls (cases: 66.6 +/- 12.7 years, controls: 59.2 +/-11.9 years, p<.001). A higher percentage of cases versus controls were men, had fair/pale skin, a previous NMSC diagnosis, a history of alcohol use, and a history of cigarette use; fewer cases versus controls had a history of AD. Of NMSC cases, 14.4% and 30.7% of controls reported any TCI exposure (OR=0.54 95% CI 0.41, 0.69). 10.4% of NMSC cases and 20.7% of controls reported pimecrolimus use (OR=0.66 95% CI 0.50, 0.89), while 6.9% of NMSC cases and 19.6% of controls reported tacrolimus use (OR=0.43 95% CI 0.30, 0.60). Although other confounder information was collected, the presented estimates were adjusted only for subject's gender, age, and history of AD. Adjustment for other potential confounders such as tanning history, skin color, eye color, alcohol and cigarette use did not meaningfully change the effect estimates (results not shown). Adjusted estimates including only individuals with a history of AD were similar to estimates for the full cohort, with the exception of pimecrolimus, where the estimate was closer to the null than when including all individuals (OR=0.93 95% CI 0.45,1.93). Adjusted effect estimates were similar when cases were limited to either those with basal cell origin (OR=0.37; 95% CI 0.28, 0.51) and squamous cell origin (OR=0.39; 95% CI 0.25, 0.63). The number of TCI tubes used was similar in the case and control group (results not shown), with 83.2% of TCI exposed individuals reporting using ≤ 2 tubes. For both tacrolimus and pimecrolimus, the risk of NMSC was similar among individuals using < 1 tube, 1-2 tubes, and >= 3 tubes.

4.7 SUMMARY OF NONCOMPARATIVE STUDIES

We reviewed 11 noncomparative studies reporting adverse events among pimecrolimus or tacrolimus users (Table 2, Appendix 1). Most of these studies were of short duration, with only five studies following patients for up to 2 years or more. Of these five longer studies, only one study reported a malignancy in a pediatric patient. The Reitamo (2008) study, a four year open-label non-comparative study conducted in 39 centers in 12 European countries, included 782 patients with a median age of 22 years (range 2-72 years), who were followed for an average of 1422 days. Of the five malignancies reported during the study, only one occurred in a pediatric patient; a five year old girl developed acute lymphoblastic leukemia that was considered unlikely to be related to the applied topical 0.1% tacrolimus ointment. A combined study, which included data from the Hanifan (2005) and Koo (2005) studies, reported 13 cases of NMSC, however none of these cases occurred in pediatric patients.[20]

5 DISCUSSION: MALIGNANCIES

5.1 LYMPHOMA

Four of the reviewed association studies evaluated the risk of lymphoma associated with the use of tacrolimus or pimecrolimus. The Hui (2009), Schneeweiss (2009), and Arana (2010) studies suggest that there is an increased risk of lymphoma among pimecrolimus or tacrolimus users relative to untreated AD patients. The Hui (2009) and Arana (2010) studies both report an increased risk of t-cell lymphoma in tacrolimus users (Hui 2009: HR=3.13 95% CI 1.41, 6.94; Arana 2010: OR=5.38 95% CI 2.04-14.20), and the Hui (2009) study also reports an increased risk of b-cell lymphoma among pimecrolimus users (HR=1.58 95% CI 0.95, 2.63). The Schneeweiss (2009) reports an increased risk of any type of lymphoma, although this increase is not statistically significant (pimecrolimus 1.79 95% CI 0.92, 3.48; tacrolimus 1.97 95% CI 0.87, 4.50). However, in the nested case-control analysis, the Schneeweiss (2009) et al study reports a four-fold increased risk of lymphoma in high cumulative amount use of pimecrolimus users vs. low users of corticosteroids (0R=4.17 95% CI 1.06, 16.4). Cumulative amount of tacrolimus use could not be assessed due to sample size limitations. On the other hand, the nested case-control study by Arellano (2007) notes no association between lymphoma and pimecrolimus or tacrolimus use relative to untreated AD.

All four studies used untreated AD as a comparator, since there is evidence that AD itself may be associated with lymphoma.[21;22] The studies were also similar in that they had rather short follow-up times given the outcome of lymphoma (<2.5 years). However, this timeframe may be adequate to capture short-term risk given that previous Medwatch reports suggest only a median of 150 days (21-790 days) from tacrolimus exposure until cancer diagnoses, and a median of 90 days (7-300 days) from pimecrolimus exposure until cancer diagnoses, though it should be noted that these estimates are not limited to lymphoma.[23] Additionally, all of the studies included pediatric patients (~29% to 63% of study population) but none of the studies provided results for pediatrics only. Thus, the applicability of the results specifically to the pediatric population is questionable. Below is a detailed discussion of each study's findings in light of methodological study issues.

The Hui (2009) study, which noted an increased risk of t-cell lymphoma among tacrolimus users incorporated several measures to reduce protopathic bias. Only cancer diagnosed 6 months after study enrollment (and 24 months in a subsequent sensitivity analysis) in the exposed groups was included. It is not clear from the methods whether person-time in the exposed during these 6 months was also excluded. Medical records of all included cases of t-cell lymphoma were

reviewed for timing and location of the cancer; 4 out of 16 cases of t-cell lymphoma were excluded since the treating clinician suspected the patients had CTCL before exposure to tacrolimus or pimecrolimus. The study also attempted to address confounding by indication. Confounding by indication is a concern given that TCIs are indicated as second-line treatments and therefore may be used in more severe cases. Severe AD cases may be more likely to visit the dermatologist more frequently and therefore be more likely to be diagnosed with certain cancers. Additionally the Arellano (2007) study suggests that AD severity is associated with cancer. In order to address confounding by indication, the study adjusted for disease severity via use of systemic immunosuppressants and psoriasias therapy as covariables. However, there is no description on how well these proxies serve as an indicator for AD severity, and residual confounding could still occur. Furthermore, while other studies excluded individuals with congenital immunodeficiences, transplantion, and HIV infection or AIDs these individuals were not excluded from the Hui (2009) study population. The study instead controlled for exposure to systemic immunosuppressants, which may still allow for confounding by these variables. The study also did not adjust for multiple comparisons, which may be important given the large number of cancer outcomes evaluated. However, the occurrence of t-cell lymphoma is biologically plausible. And although the study did not show a statistically significant dose-response relationship with strength of tacrolimus and cumulative dose, the study did report a higher risk estimate of tacrolimus compared to pimecrolimus, which is supported by an *in vitro* study showing that T cell inhibition by tacrolimus was 8-fold higher than that with pimecrolimus.[24]

The Schneeweiss (2009) study noted an increased risk of lymphoma in pimecrolimus and tacrolimus users however these estimates were not statistically significant. Unlike the Hui (2009) study, these estimates were for all types of lymphoma combined. However if only t-cell lymphoma is truly associated with tacrolimus or pimecrolimus use, including other types of unrelated lymphomas may dilute the effect estimate. Although Schneeweiss (2009) et al did look separately at the risk among HL, NHL, cutaneous, and CLL, these analyses were not informative due to very small sample sizes. The reported dose-response relationship, when comparing pimecrolimus use to low dose CS use, showed pimecrolimus >100g having a four-fold increased risk. However a similar increase was also noted for high dose CS use, which the authors suggest may indicate that uncontrolled factors are leading to increased use of these topical agents in patients at a higher risk of lymphoma. The observed association could also be due to confounding by indication, where more severe cases are taking stronger medications, which would lead to an increased risk if severity of AD was associated with lymphoma. However one

cannot preclude a true association. Exposure misclassification during follow-up is likely since drug status at cohort entry was used for cohort analyses. This misclassification may be biasing the effect estimates toward the null. Additionally, although Schneeweiss (2009) was able to adjust for a large number of covariates using propensity scores, including such a large number of variables likely contributed to the very large variance estimates, as is reflected in the wide confidence intervals seen for many of the point estimates. Schneeweiss (2009) also included anyone using a TCI, regardless of the indication in the exposed group, and only used AD diagnosis codes to select the unexposed group. Although this may make results more generalizable, it may also lead to confounding by indication since the exposure groups differ in indication for use. Lastly, Schneeweiss (2009) adjudicated the cases using medical records, however, 26% of cases could not be validated since a medical record was not available to them.

There is not enough information on the Arana (2010) to comment on the study methodology; further review of this study should be performed when details regarding the entire study are available.

The Arellano (2007) nested case-control study was the smallest of the six studies. The study assessed and adjusted for severity of AD, which was captured based on criteria from Margolis et al. (2001).[25] However there were several major methodological issues which could explain the null study findings. The lack of adjudication of lymphoma cases could result in widespread misclassification. The importance of case adjudication is underscored in the Schneeweiss (2009) study, where only 19.5% of their original claims cases were confirmed. Another limitation is that the study did not use a lag period in the primary analysis, and used only a 60 day lag in their sensitivity analyses. Some of the included cases are thus unlikely to be a result of the exposure. In fact, the authors report a high percentage of lymphoma cases among patients with a short latency period (1-60 days) between the date of AD diagnosis and the date lymphoma diagnosis. Of these cases, 40-50% were t-cell lymphoma (specifically myocisis fungocides) which could potentially be misclassified as severe AD. The study also only looked at lymphoma in two groups: all lymphomas and lymphomas ignoring MF/T cell cases. Therefore, as with the Schneeweiss (2009) study, if only t-cell lymphoma is associated with tacrolimus or pimecrolimus use, including other types of unrelated lymphomas may dilute the effect estimate. Lastly, the wide confidence intervals suggest that the study may not have had enough power to detect a meaningful difference between the two groups, especially in subanalyses (Table 6, Appendix 2).

5.2 MELANOMA AND NON-MELANOMA SKIN CANCER

We reviewed two studies assessing the risk of skin cancer among TCI users. Both studies were of short duration, with little information specific to the pediatric population. Hui (2009) included some pediatric patients whereas Margolis (2007) included only adults. Hui (2009) was the only study to evaluate the risk of melanoma among TCI users, and reported a protective association for tacrolimus versus untreated AD (HR=0.32 95% CI 0.12, 0.84) and no association for pimecrolimus versus untreated AD (HR=0.69 95% CI 0.37, 1.28). Margolis (2007) was the only study to evaluate the risk of NMSC among pimecrolimus and tacrolimus users and found a protective association for NMSC and both pimecrolimus (HR=0.66 95% CI 0.50, 0.89) and tacrolimus (HR=0.43 95% CI 0.30, 0.60). There have been animal photocarcinogensis models showing a decreased association between TCIs and skin cancer,[26] and cell culture studies showing TCIs can inhibit the growth and differentiation of kerantinocytes.[27] Alternatively this could be a spurious association resulting from clinicians not using TCIs on individuals at highest risk for developing NMSC. For example, in the Margolis (2007) study, 60.8% of cases had a previous diagnosis of NMSC versus 9.6% of controls; perhaps physicians are more reluctant to prescribe TCIs to those with a history of NMSC. The results of these studies are unlikely to be due to protopathic bias, as we would then expect an increased risk among the exposed rather than a protective effect. The Hui (2009) study did not do a medical record review of melanoma cases and the Margolis (2007) study used self-reported exposure information, as well as some diagnosis information. Margolis (2007) did not include ICD-9 code 173.9 ("other malignant neoplasm of skin site unspecified") as well as other ICD-9 codes which have been suggested to be useful in identifying NMSC cases.[28;29] Thus, misclassification could in part account for study findings, although misclassification would have to be widespread to reverse a true positive association. There is also the possibility of potential confounding in both studies although Margolis (2007) et al performed a sensitivity analysis suggesting that any unmeasured confounder would have to increase the risk of NMSC 10-fold and be present in 80% of cases and 10% of controls.

5.3 OTHER CANCERS

The Hui (2009) 2009 study evaluated the risk of acute myeloblastic leukemia, adenocarcinoma, breast cancer, bronchus and lung cancer, female reproductive system cancer, kidney cancer, male reproductive system cancer, melanoma, "other cancer", other leukemia, prostate cancer, squamous cell cancer (non-skin location), and thyroid cancer in TCI users. This was the only epidemiologic study to separately evaluate these types of cancers. The only reported association was a decreased risk of bronchus and lung cancers among pimecrolimus users (RR=0.52 95% CI 0.28, 0.94). None of the outcomes were validated in terms of timing and site of drug application,

and the follow-up was short for studying cancer outcomes. Additionally, this study evaluated a large number of outcomes without adjusting for multiple comparisons. Further studies are necessary to substantiate these results.

6 RESULTS: SYSTEMIC INFECTIONS

6.1 METHODS

We did not find any epidemiologic association studies evaluating the risk of infection among pimecrolimus or tacrolimus users. The observational noncomparative studies that we reviewed provided only the frequency of adverse events among pediatric users of pimecrolimus or tacrolimus (Table 2, Appendix 1). Moreover, these studies varied widely in the number of pediatric patients, with studies enrolling 22 to 3959 pediatric patients from <2 years to 17 years of age. The studies also varied in their duration, with follow-up times ranging from 3 weeks to 4 years. The studies were primarily multi-site studies, conducted in the US and abroad, and enrolled AD patients with a range of disease severity.

6.2 RESULTS

Studies reported a broad range of infections including skin infections, flu-like symptoms, fever, cough, shingles, zoster, croup, and pneumonia. Table 2 (Appendix 1) provides a summary of the reviewed studies[9-19] and reported frequencies of fever and flu-like syndrome, irrespective of causality, among pimecrolimus or tacrolimus users. Fever among participants under 2 yrs and from 2-6 yrs occurred with a frequency of ~13 to 25%, with lower frequencies of ~0% to 11.7% reported among children 7-15 yrs of age. The incidence of flu-like symptoms ranged from ~24% to 35% in patients 2-6 yrs of age and ~25% to 44% in patients 7-15 yrs of age. Hannifan (2005) and Koo (2005) reported non-application site infections not otherwise specified with frequencies of 10.5%-16.2% in children 2-6 years old, and 8.6%-10.7% in children 7-15 years old. Hannifan (2005) and Reitamo (2008) reported herpes zoster/varicella zoster in 9.2-12.6% of children 2-6 years old, and in 1.9-2.2% of children 7-15 years old. Data from the 4-year Reitamo (2008) study suggests that the incidence of adverse events such as flu-like syndrome, skin infection, rhinitis/conjunctivitis, and herpes zooster remains uniform throughout follow-up.

There were few details regarding the severity of infections, demographic information on the patients experiencing these infections, or duration of drug use. Some cases of particular interest include a report by the Eichenfeld (2007) study of a 3-month old female patient with two blood concentration measurements of pimecrolimus higher than 1 ng/mL. However the study authors

mention the possibility that these samples were contaminated. Remitz (2007) reports a 6 year old male tacrolimus user with leukopaenia at month 6 (white blood cell count 3.0X109/l), who was withdrawn from the study. Leukopaenia has only rarely been reported in previous clinical trials.

7 DISCUSSION: SYSTEMIC INFECTIONS

The noncomparative studies provided us only with the frequency of infections in the selected pediatric population; there was no comparison group so it is difficult to determine whether the infections occurred at a higher frequency among pimecrolimus or tacrolimus users compared to nonusers. Fever and flu-like syndrome generally occurred with higher frequencies in younger children (2-6 years) compared with older children (7-15 years). We did not attempt to compare incidences with the general US population given that most of these infections are generally very common events. Additionally, it should be noted that some of these studies had high levels of discontinuation, which is not taken into account when reporting only percentage of events in the study population (rather than person-time).

Comparisons of particular events between studies was limited to fever and flu-like syndrome given the differing categorization of events across studies. Examining individual cases of infection more closely for information on duration of treatment, severity of adverse event, and demographic subject information was not possible. Most publications provided no data on individual cases and often categories of adverse events were very broad (i.e., "infections").

8 CONCLUSIONS AND RECOMMENDATIONS

There were a limited number of epidemiologic studies evaluating the risk of malignancies among pimecrolimus and tacrolimus users, with most of these studies following individuals for a short time (<2.5 years). When considered together, the reviewed association studies suggest that there is an increased risk of lymphoma, particularly t-cell lymphoma, among TCI users, with the risk of lymphoma greater among tacrolimus users. These increased risks are supported by results from the Hui (2009) study, Arana (2010) study, and the Schneeweiss (2009) study. Only the Arellano (2007) study, which was a smaller study conducted in the same database as the Arana (2010) study, did not note an increased risk of lymphoma. The Arana (2010) study is published only as an abstract at present and when available, study methodology and results need to be further evaluated. Little statistically meaningful information on duration or intensity of use was provided in any of these studies. The applicability of these results specifically to the pediatric population is questionable, as is the contribution to our understanding of the long-term safety profile of the

drug. Although all of the studies included pediatric patients (~29% to 63% of study population), none of the studies provided results for pediatrics patients only. Furthermore, studies were of short duration (<2.5 years) given the outcome of cancer.

Non-melanoma skin cancer (NMSC), melanoma, and other cancers (e.g., breast, adenocarcinoma, and prostate cancers) were less frequently studied. Although these studies did not report an increased risk of NMSC, melanoma, or other cancer outcomes among TCI users, given the dearth of epidemiologic studies and the limitations of the existing studies (e.g., confounding by indication, lack of case validation, exclusion of pediatric patients, self-reported exposure), we can not draw any conclusions regarding the risk of these other cancers, including melanoma and non-melanoma, in pediatric TCI users.

Whether pimecrolimus or tacrolimus is associated with an increased risk of infection remains difficult to ascertain from the reviewed studies given the broad outcome of systemic infections, lack of comparison group, practice of not confirming the causality of drug exposures to all reported events, and that discontinuation of drugs was not taken into account. Since there are no epidemiologic association studies evaluating this potential association, clinical trials or case reports may provide further information in this area.

9 APPENDICES

Appendix 1: Tables of Reviewed Studies

Table 1. Epidemiologic Studies evaluating the risk of malignancies in Tacrolimus or Pimecrolimus Users[†]

Author, Year	Study Design	N	Database	Population[‡]	Outcome	Results
Hui, 2009	Retrospective Cohort	11,898 TAC; 22,716 PIC; 4,068 both 914,382 unt AD;	Kaiser Permante, Northern and Southern California	Participants diagnosed with AD or eczema between January 2001 to December 2004; all ages	Many types of cancer[§] including lymphoma, and melanoma	<u>T-cell lymphoma:</u> TAC vs. unt AD HR=3.13 95% CI 1.41, 6.94 PIC vs unt AD HR=1.86 95% CI 0.71, 4.87 (n=96 cases) <u>B-cell lymphoma:</u> TAC vs. unt AD HR=1.09 95% CI 0.58, 2.07 PIC vs unt AD HR=1.58 95% CI 0.95, 2.63 (n=473 cases) <u>Melanoma:</u> TAC vs. unt AD HR=0.32 95% CI 0.12, 0.84 PIC vs. unt AD HR=0.69 95% CI 0.37, 1.28 (n=748 cases)
Schneeweiss, 2009	Cohort and Nested Case-control	29,870 TAC; 92,989 PIC; 89,601 unt AD, 88,820 general population	Ingenix Research Data Mart	Participants with TAC or PIC exposure, regardless of diagnosis, unexposed participants with AD or eczema diagnoses, and unexposed general population between January 2002 to June 2006; all ages	Lymphoma	<u>Any lymphoma:</u> Cohort results TAC vs. unt AD RR=1.97 95% CI 0.87, 4.50 PIC vs. unt AD RR=1.72 95% CI 0.92, 3.48 (n=57 cases) Nested case-control results PIC ≤60 g vs. CS ≤100g OR=1.36; 95% CI .68 - 2.70 PIC 61-100g vs.CS ≤100g OR=2.98 95% CI 0.85-10.5 PIC>100g vs. CS≤100g OR=4.17 95% CI 1.06, 16.4 (n=25 cases)

Arellano, 2009	Nested case-control study	2,738 cases 10,949 controls	The Health Improvement Network (THIN), United Kingdom	Cases were patients diagnosed with lymphoma, controls were AD patients not diagnosed with lymphoma; enrollment in a THIN-registered practice between January 1, 1992 and March 23, 2006; age ≤ 79 years	Lymphoma	Results not available, sample size too small for analysis
Arellano, 2007	Nested case-control study	294 cases 1,176 controls	Pharmetrics	Cases were patients diagnosed with lymphoma, controls were AD patients not diagnosed with lymphoma (risk set sampling); July 1995-June 2005; all ages	Lymphoma	<u>Any lymphoma:</u> PIC vs. unt AD: OR=0.82 95% CI 0.42, 0.61 TAC vs. unt AD: OR=0.79 95% CI 0.37, 1.71 <u>Non MF/T cell lymphoma:</u> PIC vs. unt AD: OR=0.65 95% CI 0.31, 1.38 TAC vs. unt AD: OR=0.71 95% CI 0.30, 1.69
Arana, 2010	Nested case-control study	760 cases, number of controls unknown	Pharmetrics	Cases were patients diagnosed with lymphoma, controls were AD patients not diagnosed with lymphoma; 1995-2009; all ages	Lymphoma	<u>Any lymphoma:</u> Any TC vs. unt AD OR=0.94 95% CI 0.79, 0.13* PIC vs unt AD OR=0.85 95% CI 0.60, 1.19 TAC vs unt AD OR=1.34 95% CI 0.87, 2.07 <u>T-cell lymphoma:</u> TAC vs. unt AD OR=5.38 95% CI 2.04, 14.20
Margolis, 2007	Nested case-control study	875 cases, 1,946 controls	UPenn Department of Dermatology	Cases were patients diagnosed with NMSC, controls were AD patients not diagnosed with NMSC; 2002-2005; ≥30 years	NMSC	PIC vs. unt AD: OR=0.66 95% CI 0.50, 0.89 TAC vs. unt AD: OR=0.43 95% CI 0.30, 0.60

†Abbreviations: AD=atopic dermatitis; unt AD=untreated atopic dermatitis; TAC=topical tacrolimus; PIC=pimecrolimus; CS=topical corticosteroids; HR=hazard ratio; RR=relative risk; OR=odds ratio; NMSC=non-melanoma skin cancer

‡Does not include exclusion criteria specific to each study

§Acute myeloblastic leukemia, adenocarinoma, B-cell lymphoma, breast cancer, bronchus and lung cancer, chronic lymphocytic leukemia, chronic myeloblastic leukemia, female reproductive system cancer, kidney cancer, male reproductive system cancer, melanoma, other cancer, other leukemia, prostate cancer, squamous cell cancer (non-skin location), T-cell lymphoma, thyroid cancer

* Typo, as reported in abstract

Table 2. Noncomparative studies of pediatric tacrolimus or pimecrolimus users

Author, Year	Drug	Number of Pediatric patients	Maximum Follow-up Time	Incidence of Fever	Incidence of Flu-like Symptoms
Koo, 2005	TAC 0.03% or 0.1%	3959 (<16 y): 2259 (2-6 y) 1700 (7-15 y)	2 years	2-6 y:17.6% 7-15 y:7.9%	2-6 y: 35.8% 7-15 y: 28.2%
Sundkoetter, 2006	PIC 1%	2,526 (≤17 y)	6 weeks	Not reported	Not reported
Stabb, 2005	PIC 1%	22 (<2 y)	3 weeks	Not reported	0
Lubbe, 2006	PIC 1%	666 (≤17 y): 177 (3 mos-<2 y) 414 (2-12y) 75 (13-17y)	6 months	<2 y:13.6% 2-12 y:8.7% 13-17 y: 0%	<2 y:2.8% 2-12 y:3.1% 13-17 y:1.3%
Papp, 2005	PIC 1%	91 (3-23 mos)	2 years	41.8%	Not reported
Reitamo, 2008	TAC 0.1%	307 (≤15 y): 127 (2-6 y) 180 (7-15 y)	4 years	Not reported	2-6 y: 24.4% 7-15 y:25.6%
Yeung, 2008	TAC 0.03%	37 (3-15 y)	4 weeks	Not reported	Not reported
Hanifan, 2005	TAC 0.1%	391 (2-15 y) 185 (2-6y) 206 (7-15 y)	4 years	2-6 y: 24.9% 7-15y:11.7%	2-6 y: 47.0% 7-15 y: 44.2%
Eichenfeld, 2007	PIC 1%	17 (3.6 mos-11 y)	3 weeks	Not reported	Not reported
Remitz, 2007	TAC 0.03% or 0.1%	466 ≤15 y: 233(7-15 y) 233 (2-6 y)	29.5 months	2-6 y: 13.7% 7-15y: 6.4%	2-6 y: 34.8% 7-15y: 28.3%
Singalavanija S, 2006	TAC 0.03%	61 (2-12 y)	1 month	Not reported	Not reported

†Abbreviations: TAC=topical tacrolimus; PIC=pimecrolimus

Appendix 2: Tables from Reviewed Epidemiologic Studies evaluating the risk of malignancies among Tacrolimus or Pimecrolimus Users

Table 1. Hui (2009): Number of Cancers and Age-and Sex-Adjusted Hazard Ratios by Exposure

Cancer	Unexposed Group (n)	Tacrolimus-Exposed Group (n)	Tacrolimus Hazard Ratio (95% CI)	p Value[a]	Pimecrolimus-Exposed Group (n)	Pimecrolimus Hazard Ratio (95% CI)	p Value[b]
Any cancer	11,573	210	0.93 (0.81 to 1.07)	0.306	226	1.15 (0.99 to 1.31)	0.054
acute myeloblastic leukemia	66	0	NA[c]		2	1.65 (0.41 to 6.75)	0.484
adenocarcinoma	907	17	1.14 (0.70 to 1.85)	0.591	13	0.56 (0.31 to 1.02)	0.059
B-cell lymphoma	447	10	1.09 (0.58 to 2.07)	0.784	16	1.58 (0.95 to 2.63)	0.077
breast cancer	2,449	42	0.92 (0.67 to 1.25)	0.579	51	0.81 (0.61 to 1.07)	0.140
bronchus and lung cancer	1,025	16	0.98 (0.60 to 1.61)	0.943	13	0.52 (0.28 to 0.94)	0.030
chronic lymphocytic leukemia	73	2	1.57 (0.38 to 6.57)	0.535	2	1.26 (0.30 to 5.26)	0.751
chronic myeloblastic leukemia	45	1	1.28 (0.17 to 9.53)	0.810	1	1.05 (0.14 to 7.78)	0.966
female reproductive system cancer	1,005	20	0.98 (0.62 to 1.55)	0.925	22	0.75 (0.48 to 1.16)	0.194
kidney cancer	270	4	0.83 (0.31 to 2.24)	0.711	6	0.87 (0.36 to 2.14)	0.768
male reproductive system cancer	64	2	1.76 (0.42 to 7.33)	0.440	1	0.60 (0.08 to 4.45)	0.617
melanoma	734	4	0.32 (0.12 to 0.84)	0.021	10	0.69 (0.37 to 1.28)	0.237
other cancer	1,912	33	0.90 (0.62 to 1.29)	0.558	36	0.82 (0.58 to 1.16)	0.253
other leukemia	283	8	1.30 (0.58 to 2.94)	0.525	3	0.47 (0.15 to 1.47)	0.192
prostate cancer	1,737	27	0.89 (0.61 to 1.31)	0.552	28	0.82 (0.56 to 1.21)	0.318
squamous cell cancer (non-skin location)	293	8	1.65 (0.81 to 3.35)	0.170	4	0.60 (0.22 to 1.62)	0.312
T-cell lymphoma							
before chart review	82	10	5.04 (2.39 to 10.63)	<0.001	8	3.76 (1.71 to 8.28)	0.010
after chart review	82	9	5.44 (2.51 to 11.79)	<0.001	5	2.32 (0.89 to 6.07)	0.086
after chart review with covariables adjustment[d]	82	9	3.13 (1.41 to 6.94)	0.005	5	1.86 (0.71 to 4.87)	0.204
thyroid cancer	181	5	1.27 (0.51 to 3.15)	0.605	7	1.36 (0.63 to 2.95)	0.430

NA = not applicable.

[a]p Value estimated from parameter estimate of tacrolimus vs unexposed group in Cox proportional hazard models.

[b]p Value estimated from parameter estimate of pimecrolimus vs unexposed group in Cox proportional hazard models.

[c]No cases reported in exposed group.

[d]Covariables: exposure to systemic immunosuppressants (eg, antithymocyte globulin, azathioprine, cyclosporine, daclizumab, corticosteroids, muromonab-CD3, mycophenolate, sirolimus, methotrexate, systemic forms of tacrolimus) or psoriasis-specific therapy (eg, acitretin, alefacept, anthralin, calcipotriene, efalizumab, etretinate, methoxsalen, psoralen, tazarotene, trioxsalen) within 6 months of study entry.

Table 2. Hui (2009): Drug Exposure for Subjects With and Without T-Cell Lymphoma

	With T-Cell Lymphoma	Without T-Cell Lymphoma	p Value[a]
Tacrolimus			
Total subjects exposed, n	9	15,957	
Subjects exposed to 0.1% ointment, n (%)	8 (89)	12,452 (78)	0.764
Median cumulative amount of 0.1% ointment exposed, g (IQR)	75 (60–180)	60 (30–120)	0.809
Median number of 0.1% ointment prescriptions (IQR)	2 (2–4)	2 (2–4)	0.689
Subjects exposed to 0.03% ointment, n (%)	2 (22)	4,413 (28)	0.343
Median cumulative amount of 0.03% ointment exposed, g (IQR)	105 (60–150)	60 (30–120)	0.800
Median number of 0.03% ointment prescriptions (IQR)	4 (3–5)	2 (2–4)	0.294
Pimecrolimus			
Subjects exposed (1% cream only), n	5	26,779	
Median cumulative amount of cream exposed, g (IQR)	60 (30–180)	60 (30–120)	0.947
Median number of prescriptions (IQR)	2 (1–4)	2 (2–4)	0.529

IQR = interquartile range.

[a]p Values were calculated using Wilcoxon rank-sum tests for exposure (cumulative amount of drugs and number of prescriptions) and using χ^2 tests for proportion of subjects exposed to each strength of tacrolimus, comparing exposed subjects with T-cell lymphoma vs exposed subjects without T-cell lymphoma.

Table 3. Schneeweiss (2009): Incidence rate of lymphoma 6 months after cohort entry in topical drug initiators as well as untreated dermatitis patients and a general population sample

	Person-years	Events	Rate/100,000	Person-years	Events	Rate/100,000	RR	95% CI
	Pimecrolimus initiators (n = 92,989)			Untreated dermatitis patients (n = 89,601)				
Any lymphoma	121,793	26	21.35	110,454	13	11.77	1.79	0.92, 3.48
HL	121,814	4	3.28	110,462	1	0.91	3.45	0.38, 31.0
NHL	121,802	18	14.78	110,455	10	9.05	1.63	0.76, 3.51
Cutaneous	121,812	5	4.11	110,462	3	2.72	1.49	0.36, 6.24
CLL	121,817	1	0.82	110,462	2	1.81	0.44	0.04, 4.96
	Pimecrolimus initiators (n = 92,989)			General population (n = 88,820)				
Any lymphoma	121,793	26	21.35	107,902	8	7.41	2.89	1.32, 6.32
HL	121,814	4	3.28	107,911	0	0.00	>1,000	0.00, ∞
NHL	121,802	18	14.78	107,902	7	6.49	2.30	0.95, 5.54
Cutaneous	121,812	5	4.11	107,911	0	0.00	>1,000	0.00, ∞
CLL	121,817	1	0.82	107,911	1	0.93	0.85	0.05, 13.5
	Tacrolimus initiators (n = 29,870)			Untreated dermatitis patients (n = 89,601)				
Any lymphoma	40,548	10	24.66	110,454	13	11.77	1.97	0.87, 4.50
HL	40,557	2	4.93	110,462	1	0.91	5.28	0.47, 58.6
NHL	40,554	5	12.33	110,455	10	9.05	1.35	0.46, 3.97
Cutaneous	40,556	3	7.40	110,462	3	2.72	2.53	0.51, 12.6
CLL	40,558	2	4.93	110,462	2	1.81	2.36	0.32, 17.4
	Tacrolimus initiators (n = 29,870)			General population (n = 88,820)				
Any lymphoma	40,548	10	24.66	107,902	8	7.41	2.82	1.08, 7.39
HL	40,557	2	4.93	107,911	0	0.00	>1,000	0.00, ∞
NHL	40,554	5	12.33	107,902	7	6.49	1.80	0.57, 5.73
Cutaneous	40,556	3	7.40	107,911	0	0.00	>1,000	0.00, ∞
CLL	40,558	2	4.93	107,911	1	0.93	2.80	0.19, 41.9
	Medium/high-potency topical corticosteroids (n = 309,067)			Untreated dermatitis patients (n = 89,601)				
Any lymphoma	397,822	73	18.35	110,454	13	11.77	1.33	0.73, 2.38
HL	397,864	19	4.78	110,462	1	0.91	4.88	0.64, 36.6
NHL	397,845	45	11.31	110,455	10	9.05	1.06	0.53, 2.11
Cutaneous	397,868	16	4.02	110,462	3	2.72	1.27	0.37, 4.37
CLL	397,877	9	2.26	110,462	2	1.81	1.05	0.23, 4.85
	Medium/high-potency topical corticosteroids (n = 309,067)			General population (n = 88,820)				
Any lymphoma	397,822	73	18.35	107,902	8	7.41	2.10	1.01, 4.33
HL	397,864	19	4.78	107,911	0	0.00	>1,000	0.00, ∞
NHL	397,845	45	11.31	107,902	7	6.49	1.46	0.65, 3.27
Cutaneous	397,868	16	4.02	107,911	0	0.00	>1,000	0.00, ∞
CLL	397,877	9	2.26	107,911	1	0.93	2.02	0.26, 15.8

HL = Hodgkin's lymphoma; NHL = non-Hodgkin's lymphoma; cutaneous = cutaneous forms of lymphoma; CLL = chronic lymphocytic leukemia. Categories not mutually exclusive. RR was adjusted for age, sex and calendar year.

Table 4. Schneeweiss (2009): Nested case-control analysis of pimecrolimus versus topical corticosteroids (CS) by different definitions of exposure status

Characteristics	Cases of lymphoma	Controls	Unadjusted analysis		Propensity-score-adjusted analysis[1]	
			odds ratio	95% CI	adjusted odds ratio	95% CI
Ever use						
Pimecrolimus only	21 (15.4)	80 (15.7)	0.95	0.56–1.61	1.27	0.73–2.20
Topical CS only	106 (77.9)	385 (75.5)	ref.	–	–	–
Any combination	9 (6.6)	45 (8.8)	0.73	0.34–1.53	0.94	0.43–2.04
Cumulative amount						
Pimecrolimus ≤60 g	13 (9.6)	61 (12.0)	1.10	0.56–2.14	1.36	0.68–2.70
Pimecrolimus 61–100 g	4 (2.9)	11 (2.2)	1.87	0.58–6.10	2.98	0.85–10.5
Pimecrolimus >100 g	4 (7.0)	8 (1.6)	2.57	0.75–8.85	4.17	1.06–16.4
Topical CS ≤60 g	54 (39.7)	278 (54.5)	ref.	–	ref.	–
Topical CS 61–100 g	12 (8.8)	48 (9.4)	1.29	0.64–2.58	1.40	0.69–2.84
Topical CS >100 g	40 (29.4)	59 (11.6)	3.49	2.13–5.73	3.22	1.94–5.36
Any combination	9 (6.6)	45 (8.8)	1.03	0.48–2.23	1.32	0.60–2.94
Time since initiation						
Pimecrolimus <1 year	9 (6.6)	52 (10.2)	0.58	0.27–1.25	0.74	0.34–1.62
Pimecrolimus 1–2 years	8 (5.9)	19 (3.7)	1.41	0.59–3.38	2.22	0.85–5.79
Pimecrolimus >2 years	4 (2.9)	9 (1.8)	1.49	0.44–5.00	1.68	0.48–5.87
Topical CS <1 year	58 (42.6)	194 (38.0)	ref.	–	ref.	–
Topical CS 1–2 years	34 (25.0)	129 (25.3)	0.88	0.55–1.42	0.89	0.55–1.46
Topical CS >2 years	14 (10.3)	62 (12.2)	0.76	0.39–1.45	0.67	0.35–1.30
Any combination	9 (6.6)	45 (8.8)	0.67	0.31–1.45	0.86	0.39–1.91
Potency						
Pimecrolimus only	21 (15.4)	80 (15.7)	1.07	0.62–1.86	1.34	0.76–2.37
Topical CS high potency	38 (27.9)	107 (21.0)	1.45	0.92–2.29	1.20	0.75–1.90
Topical CS medium potency	68 (50.0)	278 (54.5)	ref.	–	ref.	–
Any combination	9 (6.6)	45 (8.8)	0.82	0.38–1.75	1.00	0.45–2.20

Figures in parentheses are percentages.
[1] Adjusted for propensity scores at cohort entry.

Table 5. Arellano (2007): Exposure to medication and risk of lymphoma

	Cases	Controls	Unadjusted			Adjusted[1]		
Medication	N=294	N=1,176	OR	95% CI		OR	95% CI	
Exposure to medication and risk of lymphoma (all cases)								
Non-use	131	603	1.00			1.00		
Top corticosteroids (high potency)	72	195	1.81	1.27	2.56	1.23	0.83	1.84
Top corticosteroids (low potency)	61	263	1.09	0.78	1.53	1.06	0.72	1.57
Pimecrolimus	14	65	0.99	0.54	1.82	0.82	0.42	1.61
Pimecrolimus with TS	9	27	1.62	0.73	3.57	1.09	0.45	2.64
Pimecrolimus without TS	5	38	0.60	0.23	1.55	0.60	0.21	1.69
Tacrolimus	11	41	1.24	0.62	2.47	0.79	0.37	1.71
Tacrolimus with TS	9	28	1.54	0.71	3.32	0.93	0.39	2.22
Tacrolimus without TS	2	13	0.66	0.14	3.02	0.50	0.10	2.53
Pimecrolimus+Tacrolimus with TS	4	9	2.09	0.64	6.88	1.01	0.25	4.12
Pimecrolimus+Tacrolimus without TS	1	0	INF	0.00	INF	INF	0.00	INF
	Cases	Controls	Unadjusted			Adjusted[1]		
Medication	N=241	N=964	OR	95% CI		OR	95% CI	
Exposure to medication and risk of lymphoma (ignoring MF/T cell cases)								
Non-use	111	481	1.00			1.00		
Top corticosteroids (high potency)	57	161	1.61	1.09	2.37	1.12	0.72	1.74
Top corticosteroids (low potency)	53	220	1.06	0.74	1.53	1.05	0.70	1.59
Pimecrolimus	10	59	0.73	0.36	1.47	0.65	0.31	1.38
Pimecrolimus with TS	5	24	0.94	0.35	2.56	0.77	0.26	2.25
Pimecrolimus without TS	5	35	0.61	0.24	1.59	0.57	0.20	1.60
Tacrolimus	8	36	0.98	0.44	2.15	0.71	0.30	1.69
Tacrolimus with TS	6	24	1.14	0.46	2.85	0.80	0.29	2.18
Tacrolimus without TS	2	12	0.69	0.15	3.20	0.55	0.11	2.79
Pimecrolimus+Tacrolimus with TS	1	7	0.65	0.08	5.33	0.34	0.04	3.26
Pimecrolimus+Tacrolimus without TS	1	0	INF	0.00	INF	INF	0.00	INF

AD, atopic dermatitis; CI, confidence interval; INF, interferon; TS, topical steroids.
[1]Adjusted for sex, age, region, specialty, presence of infectious mononucleosis, asthma diagnosis, asthma drug use, oral steroid use, and severity of AD.

Table 6. Margolis (2007): Odds Ratios as estimated using logistic regression of exposure

Exposure	Unadjusted	Adjusted
TCI for the full case-control study	0.38 (0.31–0.47)	0.54 (0.41–0.69)
Pimecrolimus for the full case-control study	0.44 (0.35–0.57)	0.66 (0.–500.89)
Topical tacrolimus for the full case-control study	0.30 (0.23–0.41)	0.43 (0.30–0.60)
TCI among those with a history of AD	0.42 (0.24–0.72)	0.50 (0.25–0.98)[1]
Pimecrolimus among those with a history of AD	0.62 (0.35–1.11)	0.93 (0.45–1.93)[1]
Topical tacrolimus among those with a history of AD	0.34 (0.17–0.68)	0.31 (0.14–0.72)[1]
TCI only among those originally thought to be controls	0.63 (0.46–0.86)	0.74 (0.51–1.07)
Pimecrolimus only among those originally thought to be controls	0.74 (0.52–1.06)	0.96 (0.64–1.45)
Topical tacrolimus only among those originally thought to be controls	0.39 (0.25–0.62)	0.44 (0.26–0.72)

In most cases the adjusted analysis included the subject's gender, age and history of AD, as determined by the United Kingdom Working Party diagnosis. All estimates are with ORs and 95% confidence intervals in parentheses.

[1] Because only those with a history of ADs were analyzed, adjustment does not include a history of AD.

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