

Risk of Lymphoma Following Exposure to Calcineurin Inhibitors and Topical Steroids in Patients with Atopic Dermatitis

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Systemic use of immunosuppressant agents increases the risk of lymphoma in transplantation. We performed a nested case-control study in the PharMetrics database to evaluate the association between topical immunosuppressants and lymphoma in a cohort of patients with atopic dermatitis. We identified cases of lymphoma and randomly selected four controls for each case, matched by length of follow-up. We used conditional logistic regression to calculate odds ratio (OR) and 95% confidence intervals (CIs) of the association between topical immunosuppressants and lymphoma. Two hundred and ninety-four cases of lymphoma occurred in 293,253 patients, 81 in patients younger than 20 years. The adjusted analysis yielded the following OR (95%CI) for: severity (OR 2.4; 95% CI 1.5–3.8), oral steroids 1.5 (1.0–2.4), “super potent” topical steroids 1.2 (0.8–1.8), “low potency” topical steroids OR 1.1 (0.7–1.6); pimecrolimus 0.8(0.4–1.6), tacrolimus OR 0.8 (0.4–1.7), and concomitant topical steroids, pimecrolimus, and tacrolimus 1.0 (0.3–4.1). We did not find an increased risk of lymphoma in patients treated with topical calcineurin inhibitors. It is difficult to disentangle the effects of severity of disease on outcome *versus* the true effects of drugs. However, in the adjusted analysis, severity of AD was the main factor associated with an increased risk of lymphoma.

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INTRODUCTION

The prevalence of atopic dermatitis (AD) in Western countries has increased over the last 30 years (Fleming *et al.*, 2001). AD affects approximately 20% of children and 1–3% of adults in developed countries (Williams *et al.*, 1999). Patients suffer from itch, loss of sleep, bleeding from the skin and skin infection, and the disease also influences patients' families (Su *et al.*, 1997). AD is primarily a childhood disease but persists through adulthood in up to 50% of cases (Williams, 1997). For many patients with AD, intermittent treatment with topical immunomodulatory drugs, that is, topical corticosteroids or topical calcineurin inhibitors, is necessary for disease control.

In the USA the incidence of lymphoma ranges from around one case per 100,000 persons in children aged 0–19 years to 54 cases per 100,000 in patients over age 50 (Surveillance, Epidemiology, and End Results (SEER) Program. <http://www.seer.cancer.gov>. Last accessed 16 April 2006). Systemic use of immunosuppressive agents increases the risk of lymphoma, especially after transplantation (Opelz and Henderson, 1993). The risk of lymphoma in patients undergoing organ transplantation is closely related to the intensity of immunosuppression (i.e., number and dose of immunosuppressive agents used) and ensuing inability to control Epstein–Barr virus infection by the immune system (Opelz and Döhler, 2003). Cases of immunosuppression-related lymphoma have specific features: they are generally B-cell non-Hodgkin lymphoma (NHL), may present as nodal or extra-nodal tumors and may occur in unusual locations. They are frequently polymorphic and may demonstrate clonal integration of Epstein–Barr virus genome in malignant cells (Liebowitz, 1998). The majority of immunosuppression-related lymphoma develops within the first 2 years after transplantation (Opelz and Döhler, 2003).

Any association between AD and lymphoma irrespective of treatment is unclear. Some authors have found an increased risk of hematological malignancies in patients with eczema (Gibson *et al.*, 1976; Bernard *et al.*, 1984; Linet *et al.*, 1986; Cartwright *et al.*, 1988; Eriksson *et al.*, 1995). On the other hand, at least two studies have observed that eczema decreases the risk of NHL (Bernstein and Ross, 1992; Fabbro-Peray *et al.*, 2001). Recently Söderberg *et al.*

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Abbreviations: AD, atopic dermatitis; CI, confidence interval; MF, mycosis fungoides; NHL, non-Hodgkin lymphoma; OR, odds ratio; OTC, over the counter; RR, relative risk

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(2004) found an association between “eczema” during childhood and NHL in adulthood yielding a relative risk (RR) of 2.3; (95% confidence interval (CI) 1.0–5.3) (Söderberg et al., 2004). Zhang et al. (2004) found an increased odds ratio (OR) of T-cell NHL among women with eczema (OR 2.5; 95% CI 1.1–5.7) (Zhang et al., 2004).

Since December 2000 and December 2001, respectively, two topical calcineurin inhibitors (tacrolimus ointment and pimecrolimus cream) are available for the treatment of AD in the USA; the drugs are also available in other regions of the world. Long-term continuous application of tacrolimus ointment and pimecrolimus in an experimental ethanol solution to the skin of mice was associated with the development of lymphoma. This occurred at 26- and 47-fold higher exposures, measured by the area under the curve, respectively than the maximum individual exposure ever measured in humans after topical treatment (<http://www.pharma.us.novartis.com/product/pi/pdf/elidel.pdf>. Last visited on 16 April 2006). The clinical relevance of the animal findings is uncertain because the skin of mice is more permeable than that of humans and high systemic exposure following topical application in rodents has been documented whereas exposure in humans after topical application of calcineurin inhibitors is minimal (Harper et al., 2005; Paul et al., 2006). During post-marketing surveillance of topical tacrolimus and pimecrolimus, cases of lymphoma have been reported in patients treated with topical calcineurin inhibitors used alone or in combination with topical corticosteroids (Ormerod, 2005). We performed a case-control study to assess the risk of lymphoma associated with the use of topical prescription treatments for AD.

RESULTS

Description of the AD cohort

There were 293,253 patients of whom 171,724 (58.6%) were <20 years old (Table 1). Most patients (75.4%) were enrolled in the database from 2001 onwards. Almost 60% were female

Table 1. Characteristics of the study subjects

Characteristics of the study subjects	N	%
<i>Age (yrs)</i>		
0–2	53,939	18.4
3–5	32,163	11.0
6–10	40,905	13.9
11–20	47,251	16.1
21–30	24,078	8.2
31–40	32,175	11.0
41–50	33,668	11.5
51–60	24,249	8.3
61+	4,825	1.6
	293,253	100.0
<i>Sex</i>		
Males	124,765	42.5
Females	168,488	57.5

Table 1. continued

Characteristics of the study subjects	N	%
<i>Entry period</i>		
<1997	260	0.1
1997–1999	27,554	9.4
2000–2002	151,993	51.8
2003–2004	113,167	38.6
>2004	279	0.1
<i>Region (USA)</i>		
East	87,064	29.7
Midwest	111,014	37.9
South	52,488	17.9
West	42,687	14.6
<i>Physician specialty at index date</i>		
Family/general practice	61,349	20.9
Pediatrics	79,728	27.2
Dermatology	86,285	29.4
Allergy	15,096	5.1
Hematology	28	0.0
Hematology/oncology	131	0.0
Neonatal	1,165	0.4
Other	49,411	16.8
Unknown	2,148	0.7
<i>Presence of infectious mononucleosis</i>		
Anytime in baseline	1,287	0.4
In follow-up period	1,037	0.4
Anytime in baseline or follow-up	2,259	0.8
<i>Presence of asthma as comorbidity</i>		
Anytime in baseline or follow-up	50,794	17.3
<i>Use of medications at index date¹</i>		
Asthma	16,159	5.5
Oral steroids	14,762	5.0
<i>Severity of AD</i>		
Not severe	235,689	80.4
Severe (among pts 0–2 yrs old)	10,804	3.7
Severe (among pts 3+yrs old)	46,760	15.9

pts, patients; yrs, years.

¹Concomitant medications are defined as those having a prescription date+days supplied+a 30-day buffer that includes the index date.

subjects. AD was mainly diagnosed by a family physician, pediatrician, or dermatologist. Twenty percent of patients met the definition of severe.

The OR (95% CI) for each of the covariates on the risk of lymphoma are shown on Table 2. Twenty-five percent of patients used topical steroids at AD index date compared to 3 and 1.5% using pimecrolimus and tacrolimus, respectively.

Table 2. Risk of lymphoma in AD patients (OR; 95% CI)¹

Characteristics of the study subjects	Cases	Controls	OR	95% CI	
<i>Age group at lymphoma date, year</i>					
0–2	24	181	1.00		
3–5	17	142	0.94	0.48	1.82
6–10	10	161	0.48	0.22	1.03
11–20	30	197	1.18	0.66	2.11
21–30	11	85	0.99	0.46	2.13
31–40	31	134	1.67	0.93	2.99
41–50	65	135	3.67	2.17	6.23
51–60	74	118	4.75	2.79	8.10
61+	32	23	9.67	4.74	19.72
<i>Sex</i>					
Males	121	486	0.99	0.76	1.29
Females	173	690	1.00	—	—
<i>Region</i>					
Midwest	92	491	1.00	—	—
East	132	328	2.12	1.56	2.87
South	31	180	0.92	0.59	1.45
West	39	177	1.17	0.77	1.78
<i>Physician specialty at index date</i>					
Family/General practice	49	324	1.72	0.56	5.31
Pediatrics	33	298	0.90	0.29	2.83
Dermatology	140	393	3.00	0.98	9.13
Allergy	16	52	2.53	0.74	8.60
Neonatal	0	5	0.00	0.00	INF
Other	59	197	2.44	0.81	7.35
Unknown	9	22	2.31	0.99	5.35
<i>Disease history</i>					
Presence of infectious mononucleosis	3	3	4.00	0.81	19.82
Presence of asthma	33	122	1.25	0.89	1.76
Use of asthma medication	41	127	1.35	0.92	1.99
Use of oral corticosteroids	56	130	1.92	1.35	2.73
Severe AD (among pts 0–2 years old)	7	34	3.08	2.11	4.49
Severe AD (among pts 3+ years old)	129	353			
<i>Topical steroid use at index date</i>					
Grade 1 (super potent)	20	37	2.24	1.26	4.00
Grade 2	18	72	1.04	0.60	1.79
Grade 3	4	15	1.13	0.37	3.43
Grade 4	15	70	0.89	0.50	1.58
Grade 5	7	40	0.71	0.31	1.59
Grade 6	0	5	0.00	0.00	INF
Grade 7 (least potent)	14	66	0.86	0.47	1.56
None	216	871	1.00	—	—
<i>Use of pimecrolimus at index date</i>					
Yes	5	37	0.53	0.21	1.37
No	289	1,139	1.00	—	—

Table 2 continued on the following page

Table 2. continued

Characteristics of the study subjects	Cases	Controls	OR	95% CI	
<i>Use of tacrolimus at index date</i>					
Yes	1	20	0.20	0.03	1.49
No	293	1,156	1.00	—	—
<i>Exposure category</i>					
Not exposed	123	584	1.00	—	—
Low (among pts 0–2 years old)	10	88	1.27	0.97	1.66
Low (among pts 3+ years old)	137	474			
High (among pts 0–2 years old)	1	0	4.16	2.29	7.56
High (among pts 3+ years old)	23	30			

AD, atopic dermatitis; CI, confidence interval; INF, interferon; OR, odds ratio; pts, patients.

¹Patients were coded as seeing specialists based on their AD claims on their index date. Patients who see more than one specialist will be coded to more than one specialty. Thus the total number cases may be >294.

During follow-up, almost half of the patients used no medication, 40% used topical corticosteroids alone, and 12% were exposed to at least one of the topical calcineurin inhibitors. Of those exposed to the topical calcineurin inhibitors, 7.4% were exposed to pimecrolimus, 3.7% were exposed to tacrolimus, and 0.9% to both agents.

A total of 294 lymphomas occurred after the index date, 81 (27.6%) in patients <20 years old. The incidence rate of lymphoma was 81 per 100,000 person-years. The number of cases exposed to pimecrolimus, tacrolimus and both were 14, 11, and five, respectively. The type of lymphoma could not be specifically determined in 66% of cases. Among those that were identified Hodgkin disease accounted for 11.2%, and a NHL in 22.8%. B-cell NHL accounted for 4.4 and T-cell NHL for 18.4% of all lymphoma cases. All T-cell NHL except one were mycosis fungoides (MF) and the remaining case was Sézary syndrome, which is commonly grouped with MF in the cutaneous T-cell NHL category.

OR for AD patients older than 30 years were elevated, especially for patients older than 60 years (OR 9.7; 95% CI 4.7–19.8). The risk of lymphoma was similar in male and in female subjects. Patients in the East region of the USA were found to have a higher risk of lymphoma (OR 2.1; 95% CI 1.5–2.9) compared to those in the Midwest. Severe AD was associated with an increased risk of lymphoma (OR 3.1; 95% CI 2.1–4.5). Visits to a dermatologist or an allergist in comparison to visits to a family physician at index date yielded elevated OR, as was the use of oral steroids during follow-up OR 1.9 (95% CI 1.4–2.7) or use of grade 1 (“super potent”) topical steroids at index date OR 2.2 (95% CI 1.3–4.0).

Table 3 presents the OR (95% CI) of lymphoma per treatment group with non-use as reference group. The results are presented unadjusted and adjusted for age, sex, region, medical specialty at AD diagnosis, presence of infectious mononucleosis, use of asthma medication, oral steroid use, and severity of AD. In the adjusted analysis, the OR for lymphoma associated with the different treatment modalities were: topical steroids high potency OR 1.2 (95% CI 0.8–1.8);

topical steroids low potency OR 1.1 (95% CI 0.7–1.6); pimecrolimus OR 0.8 (95% CI 0.4–1.6), tacrolimus OR 0.8 (95% CI 0.4–1.7), and the concomitant use of topical steroids, pimecrolimus and tacrolimus OR 1 (95% CI 0.3–4.1) (the concomitant use of tacrolimus and pimecrolimus without steroids had only one case in the exposed group and the OR yielded an ∞ result). Severe AD remained associated with an increased risk of lymphoma (adjusted OR 2.4; 95% CI 1.5–3.8), as did use of oral steroids (adjusted OR 1.5; 95% CI 1.0–2.4). High exposure to topical medications (topical steroids and/or topical calcineurin inhibitors) remained associated with an increased risk of lymphoma (OR 2.30; 95% CI 1.17–4.51).

In order to study the effect of duration of therapy on the relationship between treatment and lymphoma, and to avoid any risk of overmatching we repeated the analyses without matching cases and controls but adjusting for length of follow-up in a logistic regression model. We repeated the stratified analysis using unconditional logistic regression and including length of follow-up as a confounding variable. The results were comparable to the matched results (data not shown). The risk of lymphoma increased with the length of follow-up as may be expected. Therefore we accepted the matched results.

DISCUSSION

The incidence rate of lymphoma was 81 per 100,000 person-years. This figure is compatible with an approximately 2.5-fold increase in risk in AD patients reported by other authors (Söderberg *et al.*, 2004; Zhang *et al.*, 2004). This study did not find an increased risk of lymphoma among users of topical calcineurin inhibitors. However, this finding should be confirmed when longer exposures to these drugs are available. The increase in risk associated with topical steroids disappeared in the adjusted analysis and the OR was slightly greater than one only in patients exposed to “high potency” topical steroids. This finding is difficult to interpret but, together with the higher OR observed for topical calcineurin inhibitors with concomitant use of topical steroids compared

Table 3. Exposure to medication and risk of lymphoma

Medication	Cases N=294	Controls N=1,176	Unadjusted			Adjusted ¹		
			OR	95% CI		OR	95% CI	
<i>Exposure to medication and risk of lymphoma (all cases)</i>								
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
Medication	Cases N=241	Controls N=964	Unadjusted			Adjusted ¹		
<i>Exposure to medication and risk of lymphoma (ignoring MF/T cell cases)</i>								
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.

¹Adjusted for sex, age, region, specialty, presence of infectious mononucleosis, asthma diagnosis, asthma drug use, oral steroid use, and severity of AD.

to topical calcineurin inhibitors alone, as well as the increased risk observed with oral steroids use suggests that further investigation of the relation between topical steroids and the occurrence of lymphoma in patients with AD may also be warranted. The use of systemic corticosteroids has previously been associated with an increased risk of lymphoma (Kato *et al.*, 2002; Sorensen *et al.*, 2004; Zhang *et al.*, 2004), although other studies have not shown an increase (Beiderbeck *et al.*, 2003; Holly and Bracci, 2003; Askling *et al.*, 2005).

Severity of AD was associated with a 3-fold increase in the risk of lymphoma. Although other factors related to severity may play a role in this increased risk, the finding is consistent with the fact that other severe forms of chronic inflammatory diseases, such as rheumatoid arthritis and psoriasis, are associated with an increased risk of lymphoma (Margolis *et al.*, 2001; Mariette *et al.*, 2002; Gelfand *et al.*, 2003). In the univariate analysis, high exposure category had an OR of 4.16 versus the non-exposed (95% CI 2.29–7.56), and severe AD had an OR of 3.08 (95% CI 2.11–4.49). It is virtually impossible to disentangle the effects of severity of disease on

outcome versus the true effects of drugs. However, in the adjusted analysis, that included severity and drug exposure, including topical steroids, in the same model, only severity of AD remained associated with a 3-fold increase in the risk of lymphoma.

It is possible that misclassification of cases or surveillance bias are partially responsible for the increased risk found in patients with severe AD. The high proportion of MF among cases makes misclassification a plausible hypothesis. MF and Sézary syndrome can present with cutaneous manifestations that resemble chronic severe adult AD (Hagstromer *et al.*, 2005) and it is possible that some of the cases diagnosed as AD with ensuing MF were in fact MF cases that had been misdiagnosed as AD. This is suggested by the high prevalence of MF among patients with very short (1–2 days) or short (< 60 days) latency between index date and diagnosis of lymphoma (40–50% of all cases with very short latency were MF). It is also possible that severe cases were under the care of dermatologists and would be biopsied more frequently. The final analysis included any cases of lymphoma developing after the index date. Rather than applying an arbitrary

threshold for making the latency time between exposure and lymphoma development plausible, we included all cases regarding their latency time. We repeated the analysis including only patients with at least 60 days of follow-up and the results were essentially unchanged (data not shown).

If topical immunomodulatory agents were to increase the risk of lymphoma it would be secondary to systemic immunosuppression. The most common presentation of lymphoma associated with systemic immunosuppression is a diffuse large cell B-cell NHL that is Epstein-Barr virus related and occurs relatively early in the first year (often the first 6 months) after solid organ transplantation (Swinnen, 2001; Faye and Vilmer, 2005; Ghobrial *et al.*, 2005). Only one case, a Burkitt's NHL, fitting this pathologic description is reported here and that case occurred 331 days after initiation of topical steroids alone. The remaining cases of B-cell NHL identified in this database are all described as chronic lymphocytic leukemia. Chronic lymphocytic leukemia is essentially unreported as a consequence of systemic immunosuppressive therapy (de Lima *et al.*, 1998; Diehl *et al.*, 1999; Faye and Vilmer, 2005). In contrast among the cases with a definite histopathologic diagnosis, cutaneous T-cell NHL was the most frequent. Although skin T-cell lymphoma has been reported in association with significant immunosuppression (Draoua *et al.*, 2004), it is rare and tends to present late, often after more than a year of intense immunosuppression. The cases of MF observed in this study occurred remarkably early during follow-up.

The main limitation of the study was the inability to validate information obtained by record linkage in PharMetrics. Therefore, we were unable to ascertain the degree of misclassification that may have occurred. The selection of controls was random and the hematologist who classified the cases was blinded to treatment group, so misclassification should be randomly distributed among the different treatment groups. In addition, the misclassification was suspected to mainly consist of false positive cases of MF (cases of severe AD whose eczematoid cutaneous expression would be misclassified as MF). Therefore, reducing misclassification might result in a reduced OR for topical steroids but it would be unlikely to yield higher OR with other treatment groups. We repeated the analysis excluding the MF/T-cell NHL cases and the results did not change (Table 3). The direction of the minimal changes observed was either towards the null value of the OR or a reduced risk associated with the use of topical agents. Likewise, lack of validation did not allow studying the relationship between different subtypes of lymphoma and topical AD treatments.

Another limitation of the study is that information on over the counter (OTC) drug use, including OTC topical steroids, is lacking in PharMetrics. OTC topical steroids are of low potency with no anticipated effect on lymphoma risk, according to the results of this study. The prevalence of severe AD was higher in patients receiving calcineurin inhibitors and there was no increased risk of lymphoma among these patients (with and without steroids). Therefore it seems that the potential bias introduced by OTC topical steroid use would not modify the results substantially, if at all.

The effect of missing OTC drug use in epidemiologic research has been considered negligible in other studies (Drews and Greenland, 1990).

Finally, this study was based on relatively small number of cases and with relatively short follow-up and exposure times. This was, to some extent, unavoidable given that lymphoma is a rare disease, especially among younger patients, AD treatment is typically intermittent and topical calcineurin agents have been recently introduced. The case-control design used can be conceptualized as a follow-up design in which the person time experience of the denominators of the incidence rate is sampled rather than measured outright. It is also important to highlight that the selection of cases and controls was "nested" in a cohort of patients with AD in order to decrease any possible effect that this condition may have in the risk of lymphoma.

The large sample of AD patients used is the main strength of this study. By performing the analysis nested in a cohort of patients with AD we decreased the possibility of confounding by indication, detecting an increased risk of lymphoma owing to AD itself irrespective of treatment. It is possible that some residual confounding remains (e.g., by severity of AD). As some of the AD patients were not being treated at the index date it could be argued that using a more stringent definition of AD might have yielded different results. However, we adjusted for severity in the final model and also repeated the analyses restricting inclusion to those patients with prescription topical treatment of AD and the results did not change (data not shown). The absence of treatment at index date is not surprising. Patients with AD, even severe, are not treated continuously for a variety of reasons, including patients' or parents' fear of steroids (e.g., keeping fluorinated drugs off facial skin of a child), cost of medications, desire to try emollients first, or concerns about compliance.

This study showed no increased risk of lymphoma in patients treated with topical calcineurin inhibitors. It is difficult to disentangle the effects of severity of disease on outcome *versus* the true effects of drugs. However, in the adjusted analysis, severity of AD was the main factor associated with an increased risk of lymphoma. It would be important to confirm this finding allowing longer exposure to these drugs in a population that allows medical validation of cases. Likewise it would be important to evaluate the role of severity of AD, high potency topical steroids, and oral corticosteroids in the development of lymphoma in patients with AD.

MATERIALS AND METHODS

The study population was derived from the PharMetrics database, which includes data from 43 million US patients from 73 health-care plans (http://www.pharmetrics.com/p_overview.html Last visited March 5, 2005). Records in the PharMetrics database are representative of the USA managed care population, based on a variety of patient and health plan demographic measures that include geographic region, age, gender, and plan type.

We obtained all data on patients with International classification of diseases codes 691 and 692 from July 1995 to January 2005. We

then extracted information on all subjects with a history of AD, indicated by the presence of an International classification of diseases-9 CM code consistent with AD: 691.8 (dermatitis other atopic) and 691 (dermatitis atopic) but not 691.0 (rash diaper or napkin). We considered the index date for each patient the day a code for AD was first present in the database.

The population included in PharMetrics consisted of 502,283 with AD. We limited inclusion in the cohort to patients with at least 6 months of enrollment in the database. We then excluded patients with the diagnoses of lymphoma, cancer, immunosuppression, transplantation, HIV infection and/or AIDS, use of immunosuppressive agents, and anticancer drugs before the index date. After applying these inclusion and exclusion criteria the final cohort included 293,253 patients with AD.

Description of the AD cohort

Patients in the cohort were characterized according to the following parameters: age, gender, specialty of the treating physician at index date, year of entry in the cohort based on AD index date, geographic region (East, Midwest, South, West), presence of mononucleosis infection, or asthma during the follow-up period, use of asthma medication and oral corticosteroids at the index date, topical corticosteroid use at the index date, pimecrolimus and tacrolimus use at the index date, and severity of AD. Severity of AD was defined based on criteria from Margolis *et al.* (2001) as: patients who experienced at least four physician visits for AD per year (for patients 3 years and older) or if they had had at least one visit to a dermatologist in the follow-up period (for patients younger than 3 years). Topical corticosteroid potency was classified from grade 1 "superpotent" to grade 7 "least potent" according to a modified version of the USA National Psoriasis Foundation classification of steroid potency. (Potencies of topical steroids. National Psoriasis Foundation. <http://www.psoriasis.org/treatment/psoriasis/steroids/potency.php?PHPSESSID=5cb7cdba9997d740f09bb6534f791e38>. Last visited on 10 January 2006.)

Cases and controls identification and characterization

Cases were identified by the presence of a code for lymphoma (International classification of diseases codes 200, 201, 202, and 204) after the AD index date. The cases of lymphoma were reviewed by a hematologist blinded to exposure. Cases were subdivided based on diagnostic coding as: Hodgkin disease, NHL, and indeterminate (meaning there was insufficient information to make a finer distinction). NHL included B-cell NHL (specific diagnoses provided were Burkitt's lymphoma and chronic lymphocytic leukemia) and T-cell NHL (specific diagnoses provided were MF and Sézary syndrome). Where there were simultaneous diagnoses of indeterminate lymphoma and a more specific descriptor (e.g., Hodgkin disease or MF) on the same day, only the more specific diagnosis was recorded for classification. In one case, two diagnoses were recorded for the same patient several years apart and two different diagnoses were used, acknowledging the finding could be a second malignancy.

Controls were patients from the AD cohort who did not have a code for lymphoma at the time lymphoma was diagnosed in a matched case. Cases and controls were matched for duration of follow-up calculated from the index date until a lymphoma was

diagnosed in the cases according to the risk set sampling method (Navidi and Weinhandl, 2002). For each case, four controls having at least the same duration of follow-up were randomly selected from the cohort of AD patients. Patients who subsequently developed lymphoma were eligible to serve as controls until the date of their lymphoma diagnosis. An individual could serve as a control for more than one case.

Categorization of medication exposure

Exposure to topical AD immunomodulatory treatment was categorized based both on intensity of exposure and type of medication using National Drug Codes.

Intensity of exposure. Patients in the cohort were classified as belonging to "no-use", "low", or "high" exposure categories for topical AD prescription drugs: topical calcineurin inhibitors and topical corticosteroids. Exposure time was estimated from the number of days for which treatment was supplied on relevant pharmacy claims. Patients were considered to be "persistent users" of pimecrolimus, and/or tacrolimus, and/or topical corticosteroids as long as the window between two courses of therapy did not exceed twice the number of days supplied on the previous claim. Upon not fulfilling this persistence definition, the patient was considered discontinued from their index therapy as of the date when the most recent prescription in the course of therapy was "exhausted", this date was deducted from the number of days for which the medication was supplied.

Patients <3 years old were classified as high exposure users if at least a third of their follow-up time was covered by pimecrolimus, tacrolimus, or topical corticosteroids. Patients ≥3 years old were classified as high exposure users if they had at least three prescriptions of pimecrolimus or tacrolimus per year or they had at least three prescriptions of topical corticosteroids classified as potency ≤3 per year.

All patients having at least 1 day of their follow-up time covered by calcineurin inhibitors or topical corticosteroid and who did not meet the criteria for high exposure were classified as low exposure users.

Patients who did not use a calcineurin inhibitor or a topical corticosteroid during their follow-up time were considered "no-use" exposure patients.

Type of medication used: exposure group allocation. Cases and controls were allocated to one of five mutually exclusive exposure groups depending on the type of drug used during the follow-up period: (1) topical steroids if there was a prescription for a topical steroid and not for a calcineurin inhibitor, (2) pimecrolimus if there was a prescription for pimecrolimus regardless of the presence of a prescription for topical steroid, (3) tacrolimus if there was a prescription for tacrolimus regardless of the presence of a prescription for topical corticosteroid, (4) both (tacrolimus and pimecrolimus) if there was a prescription for pimecrolimus and tacrolimus regardless of the presence of a prescription for topical corticosteroid, (5) none, if there was no prescription for a topical corticosteroid or for a topical calcineurin inhibitor. Patients classified under the "pimecrolimus", "tacrolimus", and "both" categories were split into those who received concomitant topical steroids and those who did not.

Analysis

The relationship between exposure to medications and lymphoma occurrence was first described in cross-tabulations. We used logistic regression conditional on case sets with similar duration of follow-up to calculate OR and 95% CI. We described the covariates distribution among controls classified according to the different levels of exposure to medications to analyze differences among treatment groups. The final model was adjusted for all confounders with an effect > 10% on the estimate and confidence limits accrued with all covariates in the initial model (Greenland and Rothman, 1998).

CONFLICT OF INTEREST

This study was sponsored by Novartis, the manufacturer of one of the calcineurin antagonists studied. Risk Management Resources had a contractual agreement giving Risk Management Resources complete control of the content of this paper as well as to the journal of choice for submission. Felix M. Arellano has been a paid consultant for Novartis. Carlos Fernández-Vidaurre is a Novartis employee. Carle Paul was an employee of Novartis at the time the study was performed.

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