The long-term risk of lymphoma and skin cancer did not increase after topical calcineurin inhibitor use and phototherapy in a cohort of 25,694 patients with vitiligo

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Background: Topical calcineurin inhibitors have been used to treat vitiligo, either alone or in combination with phototherapy; however, the long-term safety of these agents remains controversial.

Objective: To investigate the risk of lymphoma and skin cancer in vitiligo patients who received topical calcineurin inhibitors or phototherapy.

Methods: A multicenter retrospective cohort study of 25,694 vitiligo patients who received topical calcineurin inhibitors or phototherapy for 6 weeks or more between 2001 and 2019 was performed. Cumulative doses of topical calcineurin inhibitors and total phototherapy sessions were determined. Outcomes were the development of lymphoma or skin cancer after enrollment, confirmed through chart review and pathology reports.

Results: During 95,203 person-years, 13 cases of lymphoma, 22 of actinic keratosis, 15 of nonmelanoma skin cancer, and 5 of melanoma were observed. The risk of lymphoma and skin cancer was not

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Funding sources: Supported by the Korean Dermatology Foundation in 2019.

IRB approval status: Reviewed and approved by the institutional review board of St. Vincent's Hospital (VC19RESI0121).

Accepted for publication January 21, 2021.

Reprints not available from the authors.

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Published online January 25, 2021.

0190-9622/$36.00

https://doi.org/10.1016/j.jaad.2021.01.067

significantly increased by topical calcineurin inhibitor dose or phototherapy sessions. The interaction between the topical calcineurin inhibitors and phototherapy was not associated with an increased risk of skin cancer.

Limitations: Retrospective study, individual follow-up duration less than 4 years, and no adjustment for comorbidities and medication history. Not generalizable to other races.

Conclusion: The long-term risk of skin cancer or lymphoma was not associated with the use of topical calcineurin inhibitors, phototherapy, and both treatments in combination in patients with vitiligo. (J Am Acad Dermatol 2021;84:1619-27.)

Key words: actinic keratosis; excimer laser; lymphoma; melanoma; narrowband ultraviolet B; skin cancer; tacrolimus; vitiligo.

INTRODUCTION

Since the approval of topical calcineurin inhibitors for atopic dermatitis in 2001, topical calcineurin inhibitors have been used in the treatment of various skin disorders.[1] In 2006, the Food and Drug Administration added a black box warning[2] about the theoretic risk of lymphoma and skin cancer of topical calcineurin inhibitor[3-6] and recommended not using topical calcineurin inhibitor for patients undergoing phototherapy, owing to potential increase in photocarcinogenesis. However, increasing evidence indicates that topical calcineurin inhibitor use may not increase the risk of skin cancer in atopic dermatitis patients. Recently, a registry-based cohort study comprising 93,746 atopic dermatitis patients revealed no increased skin cancer risk in topical calcineurin inhibitor users compared with topical corticosteroid users after a mean period of 7.7 years, but data on phototherapy were insufficient.[7]

In vitiligo, topical calcineurin inhibitors are considered the first-line treatment for localized vitiligo, and topical calcineurin inhibitor in combination with phototherapy is recommended to enhance the response.[8-10] In addition, topical calcineurin inhibitor is effective as a maintenance therapy to prevent the recurrence of vitiligo.[11,12] However, the long-term safety of topical calcineurin inhibitors in vitiligo patients has not been established. In this multicenter cohort study, we assessed the long-term risk of lymphoma and skin cancer in vitiligo patients who underwent topical calcineurin inhibitor treatment and phototherapy since topical calcineurin inhibitors were first introduced in Korea.

CAPSULE SUMMARY

- In this multicenter cohort study, no increased risk of skin cancer or lymphoma was detected after use of topical calcineurin inhibitor and phototherapy in patients with vitiligo.
- Our cohort study could help patients alleviate excessive concerns about topical calcineurin inhibitors use and phototherapy.

METHODS

Study design and population

We conducted a multicenter retrospective cohort study involving 20 hospitals in Korea. All data for vitiligo patients followed for 6 weeks or more were retrieved from the electronic medical record database of each hospital from 2001 through 2019. The following information was collected: name, sex, date of birth, prescribed doses of topical tacrolimus and pimecrolimus, and narrowband ultraviolet B (UVB) and excimer laser treatment received during the study period. If the identifiable information was identical in different hospital records, those records were considered to be of the same person. The index date was defined as the day the patient first received a diagnosis of vitiligo. All patients were followed until the date of the last visit at each hospital, irrespective of the department that they presented to, or until the diagnosis of lymphoma or skin cancer, whichever occurred first. This study was approved by the institutional review board of each participating hospital.

Cumulative dose of topical calcineurin inhibitors

Cumulative dose of topical calcineurin inhibitors was calculated as the number of dispensed prescriptions of topical tacrolimus and pimecrolimus for each patient. Patients were stratified into the following 3 groups according to the cumulative dose: 0 to 60 g (no treatment), 61 to 300 g, or greater than 300 g. Patients who revisited the clinic at least twice for 2 prescriptions were considered to have used the entire previously prescribed amount, and dose less than 60 g was assumed to have minimal

Abbreviations used:

AK: actinic keratosis
CI: confidence interval
HR: hazard ratio
UVB: ultraviolet B

systemic effects thus was defined as no treatment group.

Number of phototherapy sessions

The number of narrowband UVB sessions was calculated for each patient. Psoralen plus ultraviolet A phototherapy was not considered because psoralen was rarely prescribed during the study period. Additionally, we calculated the number of narrowband UVB and excimer laser sessions to assess the risk of skin cancer, assuming excimer laser could influence the likelihood of skin cancer development. Patients were stratified into the following 3 groups according to the number of phototherapy sessions: 0 to 2 sessions (no treatment), 3 to 100 sessions, and greater than 100 sessions. Exposure to fewer than 3 sessions of phototherapy was considered negligible regarding the likelihood of cancer development.

Outcomes of interest

The outcomes of interest were the development of lymphoma, actinic keratosis (AK), nonmelanoma skin cancer, and melanoma after the index date. Medical records, pathologic reports, and clinical photographs were thoroughly reviewed to confirm the diagnosis. The relationship between cancer development and treatment was determined according to the correspondence between the treated area and the site where cancer occurred.

Whether concomitant use of topical calcineurin inhibitors and phototherapy increased the risk of skin cancer or precancer was also assessed.

Statistical analysis

The incidence rate was estimated per 100,000 person-years. Univariable and multivariable Cox proportional hazard models were used to assess the risk of development of each cancer according to topical calcineurin inhibitor use or phototherapy after adjusting for covariables. The interaction between the topical calcineurin inhibitor use (per 30-g tube) and phototherapy (narrowband UVB and excimer laser session) was also analyzed. All statistical analyses were performed with R software (version 3.6.3; R Foundation for Statistical Computing).

Table I. Characteristics of the study population

Characteristics	No.	%
Total	25,694	100.0
Mean age at study entry (range), y	38.7 (0–98)	
Age range, y		
0–9	3808	14.8
10–19	3464	13.5
20–29	2657	10.3
30–39	2513	9.8
40–49	3139	12.2
50–59	4266	16.6
60–69	3655	14.2
70–79	1853	7.2
≥80	339	1.3
Sex		
Male	11,544	44.9
Female	14,150	55.1
Mean follow-up period (range), mo	44.5 (1.5–228.0)	
Follow-up period, y		
<4	16,890	65.7
4–8	5077	19.8
8–12	2358	9.2
>12	1369	5.3
Mean TCI dose (range), g	92.6 (0–15,060)	
TCI dose, g		
≤60* (no treatment)	18,096	70.5
61–300	5973	23.2
>300	1625	6.3
Mean no. of phototherapy (range)	34.3 (0–1067)	
No. of phototherapy		
≤2† (no treatment)	16,827	65.5
3–100	7364	28.7
>100	1503	5.8

TCI, Topical calcineurin inhibitor.
*No treatment topical calcineurin inhibitor group was defined as patients who received less than 60 g (2 tubes).
†No treatment phototherapy group was defined as patients who received fewer than 2 sessions.

RESULTS

Characteristics of the study population

A total of 33,703 vitiligo patients treated with topical calcineurin inhibitors, phototherapy, or both were identified. Among the patients, 25,694 who were followed during 6 weeks were included in the analysis. The mean age of the participants was 38.7 years, and 44.9% were men. The total person-years was 95,203, and the mean follow-up period was 44.5 months (median 38.0 months). The number of patients in each topical calcineurin inhibitor and phototherapy treatment group is described in Table I. There was no baseline difference in age or sex between the groups.

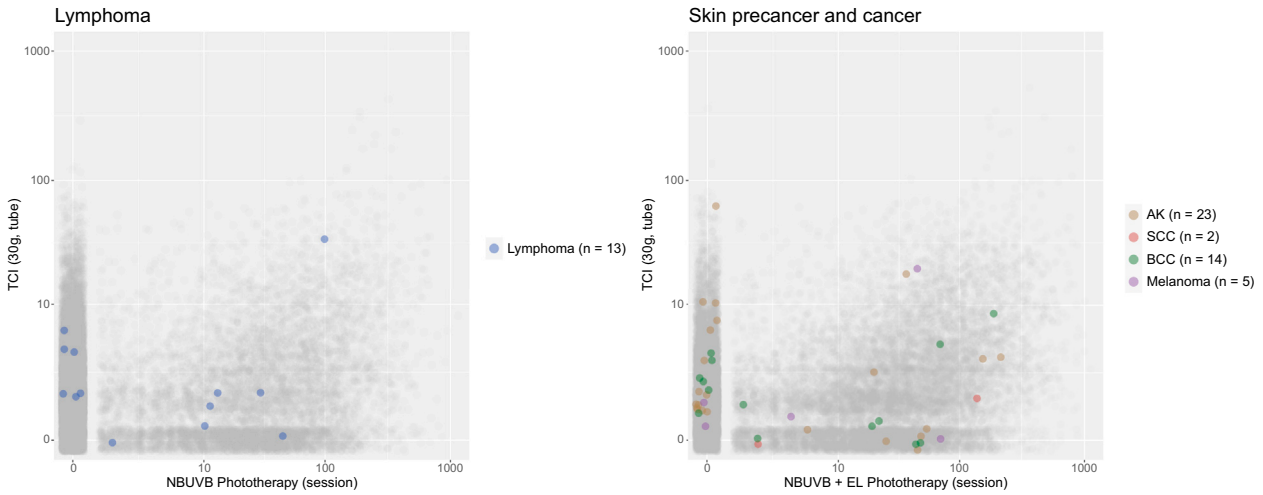

Fig 1. Diagnoses of lymphoma, skin cancer and precancer in patients with vitiligo (N = 25,694) according to topical calcineurin inhibitor use (30-g tube) and phototherapy (sessions). *AK*, Actinic keratosis; *BCC*, basal cell carcinoma; *SCC*, squamous cell carcinoma; *TCI*, topical calcineurin inhibitor.

Incidence of lymphoma in patients with vitiligo

In total, 13 cases of lymphoma (6 women; median age 65 years; range 7-75 years) were identified during the follow-up period, and the overall incidence rate was 13.6 per 100,000 person-years (Fig 1). Among those patients, 7 received a diagnosis of diffuse large B-cell lymphoma, 2 of follicular lymphoma, and 1 each of nasal natural killer/T-cell lymphoma, peripheral T-cell lymphoma, small lymphocytic lymphoma, and T-lymphoblastic lymphoma.

Compared with that of the no treatment group (≤60 g), the risk of lymphoma was not significantly increased in the group receiving 61 to 300 g topical calcineurin inhibitor (hazard ratio [HR] 0.821; 95% confidence interval [CI] 0.222-3.038; P = .77) or greater than 300 g topical calcineurin inhibitor (HR 0.593; 95% CI 0.074-4.726; P = .61) after adjustment for age and sex (Table II).

Incidence of skin cancer and precancer in patients with vitiligo

In total, 44 cases of skin cancer and precancer (27 women; median age 65 years; range 20-89 years) comprising 23 cases of AK, 16 of nonmelanoma skin cancer (14 of basal cell carcinoma and 2 of squamous cell carcinoma), and 5 of melanoma were identified (Fig 1). The incidence rates of AK and nonmelanoma skin cancer were 24.1 and 16.8 per 100,000 person-years, respectively. Compared with that of the no topical calcineurin inhibitor treatment group, the risk of actinic keratosis was not significantly increased in the group receiving 61 to 300 g topical calcineurin inhibitor (HR 1.559; 95% CI 0.642-3.787; P = .33) or greater than 300 g topical calcineurin inhibitor (HR 0.683; 95% CI 0.144-3.234; P = .63) after adjustment for age, sex, and phototherapy. The risk of nonmelanoma skin cancer was also not increased in the group receiving 61 to 300 g topical calcineurin inhibitor (HR 0.708; 95% CI 0.234-2.143; P = .54), and there was no case of nonmelanoma skin cancer in the group receiving greater than 300 g topical calcineurin inhibitor. Regarding phototherapy, the risk of AK was not significantly increased in the 3 to 100 sessions group (HR 0.720; 95% CI 0.288-1.802; P = .48) or greater than 100 sessions group (HR 0.580; 95% CI 0.121-2.773; P = .495) compared with the no treatment group after adjustment for age, sex, and topical calcineurin inhibitor use. The risk of nonmelanoma skin cancer was not significantly increased in the 3 to 100 sessions group (HR 0.708; 95% CI 0.234-2.143; P = .54) or greater than 100 sessions group (HR 0.886; 95% CI 0.179-4.377; P = .88).

Regarding melanoma, the incidence rate was 5.2 per 100,000 person-years. The risk of melanoma was not significantly increased in the group receiving greater than 300 g topical calcineurin inhibitor (HR 1.613; 95% CI 0.176-14.789; P = .67) compared with the no treatment group after adjustment for age, sex, and phototherapy (no case in the 61-300 g topical calcineurin inhibitor group). In terms of phototherapy, the risk of melanoma was not increased in the 3 to 100 sessions group (HR 2.026; 95% CI 0.333-12.311; P = .44) compared with the no phototherapy group after adjustment for age, sex, and topical calcineurin inhibitor use (Table II).

Table II. The risk of lymphoma and skin cancer in patients with vitiligo after use of topical calcineurin inhibitors and phototherapy

					Univariable analysis		Multivariable analysis	
Group	Incidence rate*	Events, n	Population, n	Person-years	Crude HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value
Lymphoma	13.6	13	25,694	95,335				
Age (10 y)					1.376 (1.023−1.852)	.04	1.392 (1.034−1.874)	.03
Sex								
Male	14.3	6	11,544	42,066	Reference		Reference	
Female	13.1	7	14,150	53,269	0.914 (0.307−2.721)	.87	0.831 (0.279−2.478)	.74
TCI, g								
No treatment	14.4	9	18,096	62,610	Reference		Reference	
61−300	12.7	3	5973	23,677	0.878 (0.238−3.244)	.85	0.821 (0.222−3.038)	.77
>300	11.1	1	1625	9048	0.756 (0.096−5.974)	.79	0.593 (0.074−4.726)	.62
NBUVB								
No treatment	12.5	7	16,827	56,111	Reference			
3−100	17.4	5	7364	28,760	1.109 (0.324−3.797)	.87		
>100	9.6	1	1503	10,463	1.526 (0.315−7.404)	.60		
Skin cancer and precancer†	46.2	44	25,694	95,238				
Age (10 y)					2.005 (1.604−2.507)	<.001	1.997 (1.595−2.502)	<.001
Sex								
Male	40.4	17	11,544	42,036	Reference		Reference	
Female	50.7	27	14,150	53,203	1.254 (0.684−2.301)	.46	1.121 (0.610−2.059)	.71
TCI, g								
No treatment	46.4	29	18,096	62,551	Reference		Reference	
61−300	50.7	12	5973	23,646	1.102 (0.562−2.160)	.78	1.043 (0.529−2.057)	.90
>300	33.2	3	1625	9041	0.662 (0.201−2.178)	.50	0.477 (0.140−1.635)	.24
Phototherapy‡								
No treatment	58.5	25	12,090	42,757	Reference		Reference	
3−100	40.8	15	11,093	36,748	0.680 (0.357−1.295)	.24	0.817 (0.427−1.561)	.54
>100	25.4	4	2511	15,733	0.386 (0.133−1.116)	.08	0.610 (0.201−1.849)	.38
Actinic keratosis	24.1	23	25,694	95,323				
Age (10 y)					2.821 (1.938−4.106)	<.001	2.784 (1.900−4.083)	<.001
Sex								
Male	23.8	10	11,544	42,061	Reference		Reference	
Female	24.4	13	14,150	53,262	1.730 (0.601−4.980)	.95	0.938 (0.409−2.150)	.88
TCI, g								
No treatment	20.8	13	18,096	62,608	Reference		Reference	
61−300	33.8	8	5973	23,670	1.641 (0.680−3.962)	.27	1.559 (0.642−3.787)	.33
>300	22.1	2	1625	9045	1.983 (0.221−4.364)	.98	0.683 (0.144−3.234)	.63
Phototherapy‡								
No treatment	32.7	14	12,090	42,809	Reference		Reference	
3−100	19.0	7	11,093	36,776	0.570 (0.229−1.420)	.23	0.720 (0.288−1.802)	.48
>100	12.7	2	2511	15,738	0.346 (0.780−1.534)	.16	0.580 (0.121−2.773)	.50
Nonmelanoma skin cancer	16.8	16	25,694	95,290				
Age (10 y)					1.512 (1.127−2.028)	.01	1.540 (1.139−2.080)	.01
Sex								
Male	11.9	5	11,544	42,055	Reference		Reference	
Female	20.7	11	14,150	53,235	1.730 (0.601−4.980)	.31	1.601 (0.555−4.615)	.38
TCI, g								
No treatment	19.2	12	18,096	62,580	Reference		Reference	
61−300	16.9	4	5973	23,660	0.895 (0.288−2.776)	.85	0.819 (0.258−2.594)	.73
>300	0	0	1625	9049	NA	>.99	NA	>.99
Phototherapy‡								
No treatment	21.0	9	12,090	42,768	Reference		Reference	

Continued

Table II. Cont'd

Group	Incidence rate*	Events, n	Population, n	Person-years	Univariable analysis: Crude HR (95% CI)	Univariable analysis: *P* value	Multivariable analysis: Adjusted HR (95% CI)	Multivariable analysis: *P* value
3–100	13.6	5	11,093	36,788	0.612 (0.203–1.848)	.38	0.708 (0.234–2.143)	.54
>100	12.7	2	2511	15,734	0.509 (0.107–2.406)	.39	0.886 (0.179–4.377)	.88
Melanoma	5.2	5	25,694	95,362				
Age (10 y)					1.771 (0.982–3.195)	.06	1.772 (0.977–3.215)	.06
Sex								
Male	4.8	2	11,544	42,078	Reference		Reference	
Female	5.6	3	14,150	53,285	1.194 (0.200–7.148)	.85	1.062 (0.177–6.380)	.95
TCI, g								
No treatment	6.4	4	18,096	62,633	Reference		Reference	
61–300	0	0	5973	23,683	NA	>.99	NA	>.99
>300	11.1	1	1625	9046	1.731 (0.193–15.530)	.62	1.613 (0.176–14.789)	.67
Phototherapy‡								
No treatment	4.7	2	12,090	42,820	Reference		Reference	
3–100	8.2	3	11,093	36,804	1.800 (0.301–10.780)	.52	2.026 (0.333–12.311)	.44
>100	0	0	2511	15,738	NA	>.99	NA	>.99

CI, Confidence interval; *HR*, hazard ratio; *NA*, not available; *NBUVB*, narrowband ultraviolet B; *TCI*, topical calcineurin inhibitor.
*Per 100,000 person-years.
†Including actinic keratosis, nonmelanoma skin cancer, and melanoma.
‡Including both narrowband ultraviolet B phototherapy and excimer laser therapy.

We further examined the topographic relationship between cancer development and treatment for each patient through a review of medical charts and clinical photographs. Among 23 cases of AK and 16 of nonmelanoma skin cancer, only 7 actinic keratoses and 2 basal cell carcinomas developed at the treatment sites; in all other cases, the cancer developed nearby or far from the treatment sites. All 5 cases of melanoma (2 of acral melanoma and 3 of melanoma of unknown primary origin) showed no association with the treatment site.

Development of lymphoma and skin cancer in pediatric patients with vitiligo

A total of 6919 pediatric patients with vitiligo (≤18 years) were observed for 22,854 person-years (mean follow-up 39.6 months). There was 1 case of lymphoma (14-year-old female adolescent receiving a diagnosis of T-lymphoblastic lymphoma at the anterior mediastinum). The patient had received 40 g of topical pimecrolimus for vitiligo on the scalp lesion 8 years before the development of lymphoma. No skin cancer or precancer was observed.

Assessment of the photocarcinogenic potential of topical calcineurin inhibitor use

Interaction between topical calcineurin inhibitor use and phototherapy was not significantly associated with the risk of skin cancer or precancer (P = .60) (Table III).

DISCUSSION

In this multicenter retrospective cohort study of 25,694 vitiligo patients, we found no evidence of increased risk of lymphoma, AK, nonmelanoma skin cancer, or melanoma according to topical calcineurin inhibitor use and phototherapy. The incidence rate of each type of cancer was in accordance with the rate in the general population. To our knowledge, our study was the first to evaluate the risk of lymphoma and skin cancer after topical calcineurin inhibitor use in a vitiligo cohort since topical calcineurin inhibitors were first introduced in 2001.

Existing studies have reported conflicting results on the risk of lymphoma after topical calcineurin inhibitor use. A retrospective study based on the California Healthcare Delivery System database reported an increased risk of T-cell lymphoma (HR 3.13), primarily cutaneous T-cell lymphoma, in 38,682 patients with atopic dermatitis exposed to topical tacrolimus for a mean of 1.4 years.[13] A US case-control study (N = 293,253) found that severe atopic dermatitis was associated with a 3-fold increase in the risk of lymphoma.[14] A European cohort study (43,788 children and 103,544 adults; follow-up range 2.2-6.5 years) reported that the incidence rate of cutaneous T-cell lymphoma was 2-fold higher in adult patients with atopic dermatitis compared with topical corticosteroids users, but the authors suggested that misdiagnosis of early cutaneous lymphoma as severe atopic dermatitis could be responsible for the increased risk.[15] Meanwhile, a

Table III. The interaction between topical calcineurin inhibitor dose and narrowband ultraviolet B plus excimer laser phototherapy sessions in skin cancer and precancer

Group	Crude HR (95% CI)	*P* value
Skin cancer and precancer		
TCI (30-g tube)	1.009 (0.987–1.031)	.43
Phototherapy* (session)	0.997 (0.991–1.003)	.31
TCI × phototherapy*	1.000 (0.999–1.000)	.60
Actinic keratosis		
TCI (30-g tube)	1.013 (0.996–1.030)	.13
Phototherapy* (session)	0.998 (0.989–1.006)	.56
TCI × phototherapy*	1.000 (0.998–1.001)	.52
Nonmelanoma skin cancer		
TCI (30-g tube)	0.997 (0.990–1.088)	.32
Phototherapy* (session)	0.997 (0.990–1.005)	.48
TCI × phototherapy*	1.000 (1.000–1.000)	.46
Melanoma		
TCI (30-g tube)	1.010 (0.963–1.060)	.69
Phototherapy* (session)	0.994 (0.974–1.014)	.52
TCI × phototherapy*	1.000 (1.000–1.000)	.95

CI, Confidence interval; *HR*, hazard ratio; *TCI*, topical calcineurin inhibitor.
*Including both narrowband ultraviolet B phototherapy and excimer laser therapy.

US cohort study using insurance claims data (38,757 tacrolimus and 118,863 pimecrolimus initiators; mean follow-up 1.5 years) reported no increased risk of lymphoma among topical calcineurin inhibitor users compared with untreated dermatitis patients.[16] According to meta-analyses,[17,18] the relative risk of lymphoma in patients with atopic dermatitis who were exposed to topical calcineurin inhibitors ranged from 0.7 to 1.8. However, the authors pointed out that low-dose, short-term exposure hindered definitive conclusions regarding the association, and study designs based on claims data could result in coding errors and diagnostic misclassification.

In the present study, the risk of lymphoma did not increase with the cumulative dose of topical calcineurin inhibitors in vitiligo patients. The incidence rate of lymphoma in our study was not higher than that in the general Korean population.[19] No dose-response relationship with cumulative dose of topical calcineurin inhibitor was observed; the incidence rate of lymphoma was 14.4 per 100,000 person-years in the no treatment group, 12.7 per 100,000 person-years in the 61 to 300 g topical calcineurin inhibitor group, and 11.1 per 100,000 person-years in the greater than 300 g topical calcineurin inhibitor group. We did not observe any case of cutaneous T-cell lymphoma, which was frequently reported. These findings indicate that atopic dermatitis could have been misdiagnosed as early cutaneous T-cell lymphoma in previous studies.[14,15]

Concerns of skin cancer development after topical calcineurin inhibitor use were raised according to mouse studies,[3,20] but epidemiologic evidence does not support an increased risk of skin cancer. A US cohort study (N = 4761) and a case-control study (N = 3074) reported no increased risk of nonmelanoma skin cancer in atopic dermatitis patients treated with topical tacrolimus compared with a similarly aged normal cohort.[21,22] A European cohort study (N = 147,332) reported that a negative association was observed between melanoma and topical calcineurin inhibitor use.[15] Regarding the phototherapy and skin cancer risk, we previously reported no increased risk of skin cancer or precancer after long-term narrowband UVB or excimer laser treatment in vitiligo patients.[23,24] Overall, we found that the risk of AK, nonmelanoma skin cancer, and melanoma did not vary according to either the dose of topical calcineurin inhibitors or number of sessions of phototherapy in vitiligo patients in the current study.

To our knowledge, the safety of the topical calcineurin inhibitors in combination with phototherapy has not been studied, whereas guidelines for vitiligo have advocated combination treatment rather than monotherapy.[8-10] Moreover, the Food and Drug Administration has warned not to use UV light therapy during treatment with topical calcineurin inhibitors. However, minimal systemic absorption of topical calcineurin inhibitors has been confirmed,[25] and in vitro study showed no direct effect of tacrolimus on UVB-irradiated keratinocytes.[26] A murine study showed that pimecrolimus did not accelerate carcinogenesis in combination with solar radiation.[27] The present study also revealed no evidence of increased photocarcinogenicity of phototherapy in topical calcineurin inhibitor users.

Regarding the pediatric population, only 1 case with T-lymphoblastic lymphoma was observed during 22,854 person-years in our study; in this case, the topical calcineurin inhibitor dose was too low to have had a systemic effect. No cases of skin cancer or precancer were observed in our pediatric population with vitiligo. Topical calcineurin inhibitors were shown not to interfere with normal growth or development of systemic immune responses to vaccinations in infants with atopic dermatitis.[28,29] Previous studies were in accordance with our finding: a European cohort study reported 8 cases of lymphoma and 1 nonmelanoma skin cancer among atopic dermatitis children exposed to topical calcineurin inhibitors (n = 43,788),[15] and an

international prospective cohort study of 7954 atopic dermatitis children reported 6 incident cancers during 44,629 person-years, including 1 case of spitzoid melanoma and no cases of nonmelanoma skin cancer or lymphoma.[30] Overall, increasing evidence indicates no association between use of topical calcineurin inhibitors and skin cancer or lymphoma in children.

The major strength of the present study is in its use of a vitiligo cohort for the first time. Use of a vitiligo cohort does not have the potential problem of misdiagnosis of early cutaneous T-cell lymphoma in atopic dermatitis patients owing to overlapping clinical features. Also, topical calcineurin inhibitor and phototherapy, either alone or in combination, are the mainstay of vitiligo treatments. Oral cyclosporine or methotrexate is not commonly used to treat vitiligo, whereas most atopic dermatitis patients receive medications affecting the systemic immune system. The present study used the medical records data covering prescriptions of off-label drugs for vitiligo, whereas claims databases do not. Medical records provide detailed and accurate information about the time of the diagnosis, location, and pathology reports.

First, our study was limited by its retrospective design and lack of data about underlying comorbidities and medication history between the patient group and control population, which could serve as possible confounding variables. Second, the average duration of individual follow-up was less than 4 years, so skin cancer or lymphoma might not be detected in this period. Third, information about patient transfers to other hospitals was missing. Fourth, our findings are not generalizable to other races. Nevertheless, to our knowledge we provide the first analysis of the long-term safety of topical calcineurin inhibitor use and phototherapy in a vitiligo cohort, and our data should serve as a valuable reference for clinical practice and future studies.

CONCLUSION

In this cohort study, we demonstrated that the long-term risk of lymphoma or skin cancer did not increase with topical calcineurin inhibitors use and phototherapy in vitiligo patients. Also, combined therapies of topical calcineurin inhibitors and phototherapy did not increase the potential risk of photocarcinogenesis. Future prospective studies on other races will be needed.

We thank all the patients included in this study.

Conflicts of interest

None disclosed.

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