Clinical Epidemiology

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Long-Term Risk of Skin Cancer and Lymphoma in Users of Topical Tacrolimus and Pimecrolimus: Final Results from the Extension of the Cohort Study Protopic Joint European Longitudinal Lymphoma and Skin Cancer Evaluation (JOELLE)

Alejandro Arana,[1] Anton Pottegård,[2] Josephina G Kuiper,[3] Helen Booth,[4] Johan Reutfors,[5] Brian Calingaert,[6] Lars Christian Lund,[2] Elizabeth Crellin,[4] Marcus Schmitt-Egenolf,[5,7] James A Kaye,[8] Karin Gembert,[5] Kenneth J Rothman,[8] Helle Kieler,[5] Daniel Dedman,[4] Eline Houben,[3] Lia Gutiérrez,[1] Jesper Hallas,[2] Susana Perez-Gutthann[1]

[1]Department of Epidemiology, RTI Health Solutions, Barcelona, 08028, Spain; [2]Clinical Pharmacology, Pharmacy and Environmental Medicine, Institute of Public Health, University of Southern Denmark, Odense C, 5000, Denmark; [3]The PHARMO Institute, Utrecht, 3528 AE, the Netherlands; [4]Clinical Practice Research Datalink (CPRD), The Medicines and Healthcare Products Regulatory Agency, London, E14 4PU, UK; [5]Centre for Pharmacoepidemiology, Karolinska Institutet, Solna, 171 76, Stockholm, Sweden; [6]Department of Epidemiology, RTI Health Solutions, Research Triangle Park, NC, 27709-2194, USA; [7]Department of Public Health and Clinical Medicine, Umeå University, Umeå, 901 87, Sweden; [8]Department of Epidemiology, RTI Health Solutions, Waltham, MA, 02451-1623, USA

Correspondence: Alejandro Arana
Department of Epidemiology, RTI Health Solutions, Av. Diagonal 605, 9-1, Barcelona, 08028, Spain
Tel +34 93 362 2805
Fax +34 93 414 2610
Email aarana@rti.org

Purpose: Evidence is insufficient to infer whether topical calcineurin inhibitors (TCIs; tacrolimus and pimecrolimus) cause malignancy. The study objective was to estimate the long-term risk of skin cancer and lymphoma associated with topical TCI use in adults and children, separately.

Patients and Methods: A cohort study in Denmark, Sweden, UK, and the Netherlands was conducted. Adjusted incidence rate ratios (IRRs) and 95% confidence intervals (CIs) were calculated for nonmelanoma skin cancer (NMSC), melanoma, cutaneous T-cell lymphoma (CTCL), non-Hodgkin lymphoma (NHL) excluding CTCL, and Hodgkin lymphoma (HL) in new users of TCIs versus users of moderate/high-potency topical corticosteroids.

Results: The study included 126,908/61,841 adults and 32,605/27,961 children initiating treatment with tacrolimus/pimecrolimus, respectively. Follow-up was ≥10 years for 19% of adults and 32% of children. Incidence rate ratios and (95% confidence intervals) for tacrolimus versus corticosteroid users in adults were <1 for melanoma, non-Hodgkin lymphoma, and Hodgkin lymphoma; and 1.80 (1.25–2.58) for cutaneous T-cell lymphoma. For pimecrolimus, IRRs in adults were <1 for non-Hodgkin lymphoma, cutaneous T-cell lymphoma, and Hodgkin's lymphoma; and 1.21 (1.03–1.41) for melanoma; and 1.28 (1.20–1.35) for nonmelanoma skin cancer. In children, results were inconclusive due to few events. In adults, incidence rate ratios ≥5 years after first topical calcineurin inhibitor exposure were not higher than in overall analyses.

Conclusion: Overall, we found little evidence associating use of topical calcineurin inhibitors with skin cancer and lymphoma; confounding by indication, surveillance bias, and reverse causation may have influenced these results. Even if causal, the public health impact of these excess risks would be low and confined to the first years of exposure.

Keywords: tacrolimus, pimecrolimus, cutaneous T-cell lymphoma, malignant melanoma, non-melanoma skin cancer, database study

Introduction

According to approved labeling, topical tacrolimus is indicated for the treatment of moderate to severe atopic dermatitis (AD), and topical pimecrolimus, for the treatment of mild to moderate AD. It is known that they are used off-label, too, but the extent of its use has not been investigated.[1] Safety data from systemic use of

Received: 7 September 2021
Accepted: 6 December 2021
Published: 29 December 2021

immunosuppressants in patients with organ transplants, from animal studies, and from case reports raised initial concerns about a potential increase in the risk of lymphoma and skin cancer associated with the use of topical calcineurin inhibitors (TCIs), especially in children. The epidemiologic literature presents insufficient evidence to infer whether TCIs cause malignancy.[2–5] Differentiating the effects of the medication itself from the risks associated with AD or severe AD is inherently difficult.[6,7] Furthermore, reverse causation is a concern because patients in early stages of certain skin malignancies, particularly cutaneous T-cell lymphoma (CTCL), may present clinical manifestations resembling AD and therefore may be treated with the study medications.

Given the long potential latency for cancer development, postmarketing studies with long follow-up are necessary to determine whether there is an association between TCIs and cancer. The European Medicines Agency requested a European study with sufficient follow-up to evaluate long-term risk of cancer. The objective of the JOELLE extension study was to estimate the long-term risks of melanoma, nonmelanoma skin cancer (NMSC), CTCL, non-Hodgkin lymphoma (NHL) (excluding CTCL), and Hodgkin lymphoma (HL) in adults and children.

Patients and Methods

This cohort study included data from the Clinical Practice Research Datalink (United Kingdom) (UK-CPRD) (2002–2017), the PHARMO Database Network (the Netherlands) (NL-PHARMO) (2002–2017), the Danish health databases (Denmark) (2002–2016), and the Swedish health databases (Sweden) (2006–2015).

Within each data source, eligible patients were required to have ≥12 months of continuous database enrollment before the first recorded prescription (new users) within the study period (except for children 0–12 months of age, who were eligible for inclusion with no required period of prior continuous enrollment). Patients with documented history of skin cancer or lymphoma before cohort entry were excluded. New users of topical tacrolimus and new users of topical pimecrolimus were classified into four groups according to age (children <18 years and adults ≥18 years) and TCI exposure (tacrolimus or pimecrolimus). A comparative cohort of users of moderate- to high-potency corticosteroids was matched to each of the four TCI-exposed cohorts. The corticosteroid comparison cohorts included (i) patients with AD diagnosis with a prescription for topical corticosteroids of moderate to high potency (hereafter, "topical corticosteroids") after the eligibility date and (ii) patients without AD diagnosis with a prescription for topical corticosteroids during the study enrollment period and at least one other prescription within the prior 12 months. The indication for the individual prescriptions was not recorded. A cohort of individuals not treated with any of the study medications ("untreated cohort"), with or without recorded AD diagnosis, was also identified for contextualization.

To control confounding, when selecting the corticosteroid cohort to match to each TCI cohort, we calculated exposure propensity scores (PSs) representing the probability of initiating TCI treatment rather than receiving topical corticosteroids, given a set of baseline covariates. After creating the PSs, trimming was performed to remove non-overlapping and extreme values within the PS distributions. All individuals (both TCI and corticosteroid) above the upper 99th percentile of the corticosteroid PS score distribution were trimmed, as were all individuals below the lowest 1st percentile of the TCI PS score distribution. After trimming, all remaining TCI users were retained as the TCI cohort and PS twentiles within this TCI cohort were identified. Then up to four times as many users of topical corticosteroids, depending on availability, were randomly selected, from all users of topical corticosteroids within each twentile-based stratum, to form the matched corticosteroid cohort.

For contextualization, each user of corticosteroids from the comparator cohort for tacrolimus was matched to four nonusers of any study medication on age, sex, geographic region, and calendar year of start date (untreated cohort).

Follow-up continued from the start date to the earliest of death, database disenrollment, end of the study, or occurrence of one of the study outcomes.

Exposure

Based on records of prescriptions (UK-CPRD) or dispensing (NL-PHARMO, Denmark, and Sweden), exposure to tacrolimus and pimecrolimus was defined as single use (any topical tacrolimus or topical pimecrolimus, but not both) for each of these medications.

Cumulative dose was the total quantity of active substance that a patient received during follow-up (grams) calculated from the strength of the formulation and the package size.

Outcomes

In Denmark and Sweden, outcomes were identified in national cancer registries. For NL-PHARMO, the pathology registry was used, and in the UK-CPRD, outcomes were identified via information from general practices, hospital admissions, and the cancer registry. In NL-PHARMO and UK-CPRD, case validation was performed for all pediatric cases, all CTCL cases, and a random sample of other adult cases. Validation was done in NL-PHARMO by an independent pathologist reviewing pathology excerpts and UK-CPRD by clinical review of electronic medical records.

Covariates

Covariates included immunosuppressive disease and use of immunosuppressive agents; chronic disease; severe skin diseases; AD diagnosis, if available; and measures of healthcare resource utilization. Age, sex, year of start date, and type of prescriber were forced into the PS models. Variables associated with the outcome were also included in the models regardless of whether they were associated with the exposure.[8]

Because information on AD severity was limited or missing in all the data sources, we evaluated the effect of type of prescriber of the first prescription as a proxy for severity of the cutaneous condition. The underlying assumption was that patients with more severe AD would have been seen and treated first by a dermatologist and patients with less severe AD would have been seen and treated first by a GP. The variable was available in Denmark, NL-PHARMO, and Sweden, but not in UK-CPRD.

Statistical Analysis

We evaluated the overall effect as well as the effect of cumulative dose of topical tacrolimus and topical pimecrolimus compared with use of topical corticosteroids. In each data source, cancer events and person-years were stratified between decile boundaries of PSs.[9] We then used Mantel-Haenszel methods[10] to estimate overall adjusted incidence rate ratios (IRRs) and incidence rate differences, stratifying on study database, deciles of PSs, and sex; and, in NL-PHARMO, Denmark, and Sweden, by type of prescriber (dermatologist, non-dermatologist) of the first prescription. For the main analysis, time at risk started after a lag time of 6 months. Additional analyses with 0-month, 12-month, 24-month, and 48-month lag times were conducted to explore reverse causation and surveillance bias. No hypothesis testing was performed, but 95% confidence intervals (CIs) were calculated around IRRs and incidence rate differences to allow interpretation of the strength of observed effects. No imputation was performed for missing values given the observational nature of the data analyzed in this study. If no prescription for a particular medication existed in the patient's record, it was assumed the patient was not taking that medication, and if a medical event was not observed in the patient's medical record, it was assumed they did not have that event.

To further assess whether treatment with the study medications was initiated for signs and symptoms that were compatible with early manifestations of CTCL, we obtained additional information from questionnaires sent to general practitioners in UK-CPRD and reviewed the medical records in Sweden for CTCL cases.[11] We analyzed the occurrence of basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) separately to test the role of immunosuppression in the results.

The study was based on medical records. The individual Institutional Review Boards or the Data Protection and Research committees waived the requirement of informed consent due to appropriate handling of patient data and maintenance of patient data confidentiality. We obtained ethical and scientific reviews from the RTI International institutional review board, the Regional Ethical Review Board of Stockholm, the CPRD Independent Scientific Advisory Committee, and the UK National Cancer Intelligence Network. Ethical approval was not required in PHARMO and Denmark. In PHARMO, the study fulfilled the requirements of the PHARMO Compliance Commission, and permission for the use of data from the Dutch National Pathology Registry was obtained. In Denmark, the study was approved by the Danish Data Protection Agency via Statistics Denmark. The study has received the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Study Seal. The protocol for the JOELLE study extension phase, protocol version 5.0, dated Jun 30, 2017, is posted in the EU PAS Register, EUPAS21769 #21769.

Results

The study included 126,908 adults and 32,605 children initiating treatment with topical tacrolimus. These patients were compared with 452,996 adults and 117,592 children treated with topical corticosteroids. Similarly, 61,841

adults and 27,961 children initiating treatment with topical pimecrolimus were compared with 244,572 adults and 111,024 children treated with topical corticosteroids. The untreated cohort comprised 1,291,042 adults and 361,584 children. Table 2 shows the distribution of patients by study cohort and population. The distributions by age and sex were similar in all study cohorts. The baseline prevalence of comorbidities and use of medications were similar overall between the topical tacrolimus and topical pimecrolimus cohorts but were different across data sources.

Overall follow-up was ≥10 years for 19% of adults and for 32% of children. For users of topical tacrolimus, the median follow-up was 5.7 years in children and 5.0 years in adults. For users of topical pimecrolimus, the median follow-up was 8.9 years in children and 6.5 years in adults.

The median number of prescriptions was 1 for both tacrolimus and pimecrolimus. The median dose of active substance was 0.03 grams for tacrolimus (equivalent to a single 30-gram tube of 0.1% tacrolimus) and 0.3 grams for pimecrolimus (equivalent to a single 30-gram tube of 1% pimecrolimus). Other population characteristics are available in eTable 1 and eTables 4–9 of the Supplementary Materials.

Use of Topical Tacrolimus versus Topical Corticosteroids

In adults, users of topical tacrolimus had an IRR for NMSC of 1.04 (95% CI, 1.00–1.09). The IRR point estimates for melanoma, NHL (excluding CTCL), and HL were <1 (Table 3, Figure 1). The IRR for CTCL with use of topical tacrolimus was 1.80 (95% CI, 1.25–2.58), corresponding to an excess risk of 3 cases per 100,000 person-years (95% CI, 1–6). IRRs for CTCL were 0.81 (95% CI, 0.45–1.47) for a cumulative dose of ≤ 0.05 grams, 2.11 (95% CI, 1.13–3.95) for a cumulative dose from 0.05 to 0.10 grams, and 5.25 (95% CI, 3.21–8.56) for a cumulative dose > 0.10 grams.

For adult users of topical tacrolimus in whom the time since first exposure to treatment was ≥5 years, the IRR for CTCL was 0.25 (95% CI, 0.03–1.87) (Table 4). In the sensitivity analysis to address reverse causation conducted in UK-CPRD and Sweden, there was little change in the estimated effect on CTCL associated with topical tacrolimus when cases with manifestations of a previous skin condition in the same location as the subsequently diagnosed cutaneous lymphoma were omitted (see eTable 2 and eTable 3 in the Supplementary Materials).

In children (Figure 1), the IRR comparing use of topical pimecrolimus with topical corticosteroids was 0.69 (95% CI, 0.20–2.31) for melanoma and 0.63 (95% CI, 0.13–3.13) for NMSC. The IRR comparing use of topical tacrolimus with topical corticosteroids was 2.19 (95% CI, 0.81–5.97) for NHL (excluding CTCL), 2.37 (95% CI, 0.99–5.68) for HL, and 7.77 (95% CI, 0.50–121.45) for CTCL. The IRR for each type of lymphoma was based on few events. For NHL, the IRR was elevated for low cumulative doses, but not for medium or high cumulative doses. For HL, the IRR was elevated for low and high doses, but not for medium doses.

Use of Topical Pimecrolimus versus Topical Corticosteroids

In adults (Table 3, Figure 1), the IRR for melanoma for use of topical pimecrolimus was 1.21 (95% CI, 1.03–1.41), which corresponds to an excess risk of 10 cases per 100,000 person-years (95% CI, 1–18). The adjusted IRR for NMSC with topical pimecrolimus was 1.28 (95% CI, 1.20–1.35), an excess risk of 91 cases per 100,000 person-years (95% CI, 68–114). In adults, the IRR point estimates for NHL (excluding CTCL), HL, and CTCL for users of topical pimecrolimus compared with users of topical corticosteroids were all <1.

In children, the IRR point estimates for each study outcome for topical pimecrolimus compared with topical corticosteroids were based on few events and all were <1 (Figure 1).

Users of Topical Corticosteroids versus Untreated Population

In adults, the IRRs for all outcomes except melanoma were elevated in the cohort of users of topical corticosteroids compared with the untreated population (Figure 2), especially for CTCL (IRR, 5.42; 95% CI, 3.77–7.79). In children, the number of cases was too small for estimating the IRR for the individual outcomes.

Discussion

Adult users of topical tacrolimus had IRRs <1 for melanoma, NHL (excluding CTCL), and HL, which indicates that no increased risk of these outcomes was found in topical tacrolimus users compared with topical corticosteroid users. For topical pimecrolimus users, the IRRs for any

Table 1 STROBE Statement for Cohort Studies with the RECORD Statement Extension—Checklist of Items That Should Be Included in Reports of Observational Studies Using Routinely Collected Health Data

	Item No[a]	Recommendation	Corresponding Page(s)
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	1
	R 1.1	The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included.	1, 2
	R 1.2	If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract.	1, 2
	R 1.3	If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	Not applicable
Introduction			
Background/ rationale	2	Explain the scientific background and rationale for the investigation being reported	1, 2
Objectives	3	State specific objectives, including any prespecified hypotheses	2
Methods			
Study design	4	Present key elements of study design early in the paper	2, 3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	2, 3
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	2, 3
		(b) For matched studies, give matching criteria and number of exposed and unexposed	2, 3, 4
	R 6.1	The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided.	2, 3
	R 6.2	Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided.	2, 3
	R 6.3	If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	Not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Outcomes 3 Exposures 2 Confounders 3, Supplementary Materials
	R 7.1	A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	Provided in study protocol that can be found in EUPAS registry.
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	2, 3

(*Continued*)

Table 1 (Continued).

	Item No[a]	Recommendation	Corresponding Page(s)
Bias	9	Describe any efforts to address potential sources of bias	2, 3, 7–10
Study size	10	Explain how the study size was arrived at	2–4. All available users included
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	2, 3
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	3
		(b) Describe any methods used to examine subgroups and interactions	3
		(c) Explain how missing data were addressed	3. Protocol
		(d) If applicable, explain how loss to follow-up was addressed	Not applicable
		(e) Describe any sensitivity analyses	3, 9, 10
Data access and cleaning methods	R 12.1	Authors should describe the extent to which the investigators had access to the database population used to create the study population.	Full access
	R 12.2	Authors should provide information on the data cleaning methods used in the study.	Not included
Linkage	R 12.3	State whether the study included person level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	Stated in Protocol
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analyzed	Partial description page 3, 4, Supplementary Materials
		(b) Give reasons for non-participation at each stage	Not available
		(c) Consider use of a flow diagram	Not available
	R 13.1	Describe in detail the selection of the persons included in the study (ie, study population selection), including filtering based on data quality, data availability, and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	3, 4
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Page 3, 4, Table 2, Figure 1, Supplementary Materials
		(b) Indicate number of participants with missing data for each variable of interest	Patients with lack of recorded information on specific variables (eg, diagnosis of atopic dermatitis) were considered not to have such diagnoses.
		(c) Summarize follow-up time (eg, average and total amount)	Page 4. Supplementary Materials
Outcome data	15*	Report numbers of outcome events or summary measures over time	Partial Tables 3, 4, E2, E3

(*Continued*)

Table 1 (Continued).

	Item No[a]	Recommendation	Corresponding Page(s)
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Page 4 Adjusted Tables 3, 4, E2, E3
		(b) Report category boundaries when continuous variables were categorized	Tables 3, 4, Supplementary Materials
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Page 4 Tables 3, 4, E2, E3
Discussion			
Key results	18	Summarize key results with reference to study objectives	4, 7–10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	7–10
	R 19.1	Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	7–10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	7–10
Generalizability	21	Discuss the generalizability (external validity) of the study results	7–10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	11
Accessibility of protocol, raw data, and programming code	R 22.1	Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	Provided in study protocol that can be found in EUPAS registry. Supplementary Materials

Notes: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org. [a]Items numbers starting with an "R" correspond to items of the RECORD extension. *Give information separately for exposed and unexposed groups. Adapted from von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol*. 2008;61(4):344–349.[22]

type of lymphoma were likewise <1. In our study, the results were not homogeneous, and topical tacrolimus and pimecrolimus were not found to produce effects on the same outcomes in contrast with findings from a systematic review that suggested an association between TCI use and risk of lymphoma and no other cancers.[4]

For topical tacrolimus users, the IRR for CTCL was elevated, and the incidence of CTCL increased with increasing cumulative dose. This finding may reflect a causal effect or be the result of confounding by indication. AD is associated with increased risk of malignancies, and the strength of the association is related to the

Table 2 Distribution of Users by Study Cohort and Population

Study Database	Topical Tacrolimus, n (%)	Topical Corticosteroids, n (%)	Topical Pimecrolimus, n (%)	Topical Corticosteroids, n (%)	Untreated Cohort, n (%)[a]	Topical Corticosteroids, n (%)
Children aged 0 to < 18 years						
UK-CPRD	3895 (11.9)	15,253 (13.0)	2752 (9.8)	11,008 (9.9)	61,001 (16.9)	15,253 (13.0)
Denmark	11,417 (35.0)	43,673 (37.1)	20,343 (72.8)	81,140 (73.1)	158,089 (43.7)	43,673 (37.1)
NL-PHARMO	5197 (15.9)	14,904 (12.7)	3189 (11.4)	12,168 (11.0)	58,424 (16.2)	14,904 (12.7)
Sweden	12,096 (37.1)	43,762 (37.2)	1677 (6.0)	6708 (6.0)	84,070 (23.3)	43,762 (37.2)
Total	32,605 (100)	117,592 (100)	27,961 (100)	111,024 (100)	361,584 (100)	117,592 (100)
Adults aged ≥ 18 years						
UK-CPRD	12,705 (10.0)	50,822 (11.2)	5124 (8.3)	20,496 (8.4)	202,459 (15.7)	50,822 (11.2)
Denmark	40,710 (32.1)	149,242 (32.9)	43,042 (69.6)	169,559 (69.3)	484,789 (37.6)	149,242 (32.9)
NL-PHARMO	21,037 (16.6)	67,293 (14.9)	8506 (13.8)	33,841 (13.9)	264,378 (20.5)	67,293 (14.9)
Sweden	52,456 (41.4)	185,639 (41.4)	5169 (8.4)	20,676 (8.5)	339,416 (26.3)	185,639 (41.4)
Total	126,908 (100)	452,996 (100)	61,841 (100)	244,572 (100)	1,291,042 (100)	452,996 (100)

Notes: [a]Untreated cohort members were matched 4:1 to corticosteroid users on year of birth, sex, and general practice/geographic region. In Sweden, the matching ratio was of approximately 2:1; however, in UK-CPRD and Denmark, age at cohort entry date (defined as date of first qualifying corticosteroid prescription) was estimated from the year and month of birth, where possible). This resulted in a small number of matches being split across age bands.
Abbreviations: NL-PHARMO, PHARMO Database Network (the Netherlands); UK-CPRD, Clinical Practice Research Database (United Kingdom).

severity of the AD.[6,7] According to the European Medicines Agency–approved labeling, TCIs are indicated only for AD, while topical corticosteroids are also indicated for the treatment of other skin diseases, so a higher proportion of patients without AD are likely included in the topical corticosteroid than in the TCI cohorts. In databases capturing diagnosis from hospital data only, AD diagnoses are often missing, which could hamper the control of confounding and result in overestimation of the risks associated with use of TCIs. Type of prescriber of the first prescription was used as a proxy measure for severity of the underlying cutaneous condition, except in UK-CPRD, where this information was not available. Still, residual confounding is possible and would result in an overestimation of the effect of the study medications, especially for topical tacrolimus, which is indicated for more severe forms of AD.

The IRRs for all outcomes except melanoma were elevated in the analysis of topical corticosteroid users compared

Table 3 Pooled Adjusted Incidence Rate Ratios in Users of Topical Tacrolimus and Topical Pimecrolimus Compared with Users of Topical Corticosteroids—Adults

Exposure	Adjusted[a] Incidence Rate Ratios (95% CI)				
	Malignant Melanoma	Nonmelanoma Skin Cancer	Non-Hodgkin Lymphoma	Hodgkin Lymphoma	Cutaneous T-cell Lymphoma
Topical tacrolimus					
Single use	1.00 (0.88–1.14)	1.04 (1.00–1.09)	0.96 (0.80–1.14)	0.89 (0.58–1.35)	1.80 (1.25–2.58)
Cumulative dose (grams)[b]					
≤ 0.05	1.01 (0.87–1.18)	1.03 (0.98–1.09)	0.93 (0.75–1.15)	0.85 (0.52–1.41)	0.81 (0.45–1.47)
> 0.05 to 0.1	0.92 (0.71–1.20)	1.00 (0.91–1.09)	0.86 (0.60–1.25)	0.66 (0.25–1.79)	2.11 (1.13–3.95)
> 0.1	1.09 (0.82–1.45)	1.12 (1.02–1.24)	1.18 (0.82–1.69)	1.48 (0.65–3.38)	5.25 (3.21–8.56)
Topical pimecrolimus					
Single use	1.21 (1.03–1.41)	1.28 (1.20–1.35)	1.01 (0.79–1.28)	0.81 (0.47–1.38)	0.57 (0.25–1.33)
Cumulative dose (grams)[b]					
≤ 0.5	1.15 (0.95–1.38)	1.23 (1.15–1.32)	0.85 (0.63–1.15)	0.56 (0.27–1.16)	0.40 (0.12–1.29)
> 0.5 to 1.0	1.04 (0.68–1.60)	1.32 (1.15–1.52)	1.41 (0.85–2.33)	2.42 (1.04–5.64)	0.00 (0.00-N/E)
> 1.0	1.59 (1.14–2.22)	1.43 (1.26–1.62)	1.39 (0.83–2.32)	0.72 (0.18–2.78)	2.11 (0.66–6.71)

Notes: [a]Adjusted by study database, deciles of propensity scores, and sex; and, in Denmark, NL-PHARMO, and Sweden, by type of prescriber (dermatologist, non-dermatologist) of the first prescription. [b]Grams of active substance.
Abbreviations: CI, confidence interval; N/E, not estimable.

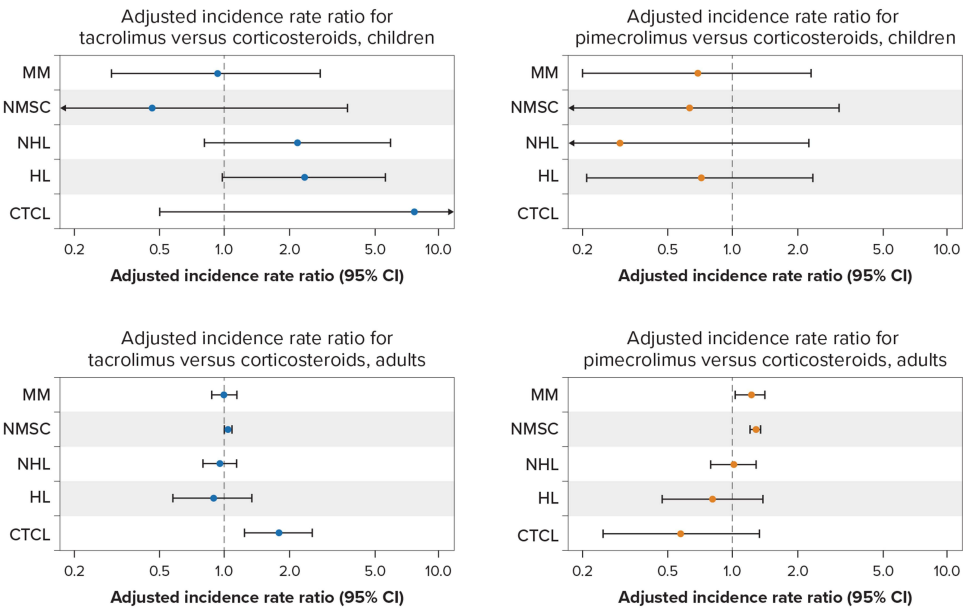

Figure 1 Summary results for tacrolimus and pimecrolimus in children and adults combined.
Abbreviations: CI, confidence interval; CTCL, cutaneous T-cell lymphoma; HL, Hodgkin lymphoma; M, Melanoma; NHL, non-Hodgkin lymphoma; NMSC, nonmelanoma skin cancer.

with nonusers of any study medication, indicating that either the topical corticosteroids or their indication confers an increased risk of the outcomes studied.

Reverse causation is a concern because patients in early stages of certain skin malignancies, particularly CTCL, may present clinical manifestations resembling AD and therefore may be treated with the study medications. Our efforts to address this produced conflicting results. Although the cumulative dose-response analysis shows the highest risk with the highest cumulative dose, in one sensitivity analysis, the elevated relative risk of CTCL associated with topical tacrolimus was confined to the first years after starting the medication, a pattern that seems more consistent with reverse causation than with a causal effect of topical tacrolimus. However, the other sensitivity analysis for reverse causation indicated little change in the estimated effect of topical tacrolimus on the risk of CTCL when cases with manifestations of a previous skin condition in the same location as the subsequently diagnosed cutaneous lymphoma were omitted.[11]

In adults, IRRs for melanoma and NMSC in users of topical pimecrolimus were elevated. This may reflect surveillance bias, although that does not explain the greater IRR with greater cumulative doses. In a sensitivity analysis, among NMSC, the overall BCC-to-SCC ratio was >3 in the pimecrolimus and the corticosteroids cohorts. Because SCCs predominate over BCCs in clinical settings where strong immunosuppression is associated with an increased risk of NMSC, these results suggest that systemic immunosuppression is unlikely to be an important cause of the observed associations between exposure to the study drugs and the risk of NMSC in this study.[12–16]

Results from this study are consistent with those from other published studies[7,17–19] summarized in a 2011 briefing document to the US Food and Drug Administration:

> causality is difficult to determine in light of the potential study biases. (eg, misclassification of lymphoma, protopathic bias, and confounding by indication)[20]

Moreover, this study shows that any excess risk would be low and confined to a few years after first exposure.

The pediatric population in the JOELLE study was larger than all previous study populations in this area; however, few events occurred among children treated with TCIs. The IRR for each type of lymphoma was elevated for topical tacrolimus at low cumulative doses. Associations that are strongest among those with a low cumulative dose typically are the result of reverse causation or surveillance bias rather than a causal effect because low cumulative dose is correlated with short duration of use and an outcome may already have been present, although clinically undetected, when exposure began. It is also notable that no lymphomas occurred in a recently presented cohort study of 7954 children treated with topical tacrolimus in 2005–2012 (mean follow-up, 6.4 years; 15% were followed for ≥10 years).[21]

Table 4 Sensitivity Analysis by Time Since Start of Exposure, by Each Type of Malignancy: Adjusted Incidence Rate Ratios in Users of Topical Tacrolimus Compared with Users of Topical Corticosteroids—Adults

Exposure Category by Outcome	Topical Tacrolimus (Single Use) Adjusted IRR[a] (95% CI)	Topical Pimecrolimus (Single Use) Adjusted IRR[a] (95% CI)
Malignant melanoma		
Main analysis	1.00 (0.88–1.14)	1.21 (1.03–1.41)
Time since exposure		
< 6 months	0.90 (0.64–1.27)	1.38 (0.84–2.25)
6–24 months	1.07 (0.83–1.38)	0.70 (0.47–1.04)
2–5 years	1.03 (0.84–1.25)	1.60 (1.24–2.07)
≥ 5 years	0.91 (0.73–1.14)	1.18 (0.94–1.49)
Nonmelanoma skin cancer		
Main analysis	1.04 (1.00–1.09)	1.28 (1.20–1.35)
Time since exposure		
< 6 months	0.99 (0.88–1.11)	1.29 (1.08–1.54)
6–24 months	1.09 (1.00–1.19)	1.31 (1.15–1.48)
2–5 years	1.05 (0.98–1.13)	1.28 (1.16–1.42)
≥ 5 years	1.00 (0.92–1.08)	1.25 (1.15–1.36)
Cutaneous T-cell lymphoma		
Main analysis	1.80 (1.25–2.58)	0.57 (0.25–1.33)
Time since exposure		
< 6 months	1.34 (0.64–2.80)	0.28 (0.03–2.33)
6–24 months	2.07 (1.18–3.61)	0.96 (0.28–3.35)
2–5 years	2.09 (1.25–3.48)	0.21 (0.03–1.56)
≥ 5 years	0.25 (0.03–1.87)	1.33 (0.43–4.07)

Notes: [a]Adjusted by study database, deciles of propensity scores, and sex; and, in Denmark, NL-PHARMO, and Sweden, by type of prescriber (dermatologist, non-dermatologist) of the first prescription.
Abbreviations: CI, confidence interval; IRR, incidence rate ratio.

This study is the largest to date to evaluate the association of TCIs with skin cancer and lymphomas and includes the longest duration of follow-up of patients in population-based data sources. When analyzing the risk of malignancies associated with long-term follow-up, the data were not consistent with an increased risk of skin cancer or lymphoma as the duration of follow-up increased. However, despite being the largest study of these agents with the longest follow-up, the rarity of the outcomes in children limits the conclusions.

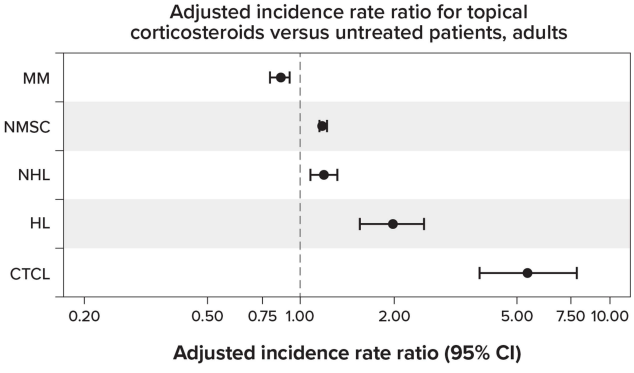

Figure 2 Summary results: untreated adults.
Abbreviations: CI, confidence interval; CTCL, cutaneous T-cell lymphoma; HL, Hodgkin lymphoma; M, Melanoma; NHL, non-Hodgkin lymphoma; NMSC, nonmelanoma skin cancer.

Conclusion

We found little evidence of an association between the use of either topical tacrolimus or topical pimecrolimus and the occurrence of skin cancer and lymphoma. The elevated IRR for CTCL among adult users of topical tacrolimus and the elevated IRRs for melanoma and NMSC among adult users of topical pimecrolimus could represent causal effects or might result from the underlying disease. The IRRs for skin cancer or lymphoma in adults in the fifth and subsequent years since first exposure to the study medications were not increased as might be expected if these were causal effects. Even if causal, the public health impact of these excess risks would be low. Also, the prognosis of these outcomes might be improved through early diagnosis by doctors being alert to the potential development or unmasking of a cutaneous malignancy in patients with a dermatological condition treated with topical immunomodulators.

Abbreviations

AD, atopic dermatitis; BCC, basal cell carcinoma; CI, confidence interval; CTCL, cutaneous T-cell lymphoma; EMA, European Medicines Agency; HL, Hodgkin lymphoma; IRR, incidence rate ratio; JOELLE study, Protopic Joint European Longitudinal Lymphoma and Skin Cancer Evaluation; NHL, non-Hodgkin lymphoma; NL-PHARMO, PHARMO Database Network in the Netherlands; NMSC, nonmelanoma skin cancer; PS, propensity score; RTI, RTI International, of which RTI Health Solutions is a business unit; SCC, squamous cell carcinoma; TCI, topical calcineurin inhibitor; UK, United Kingdom; UK-CPRD, Clinical Practice Research Datalink in the UK; US, United States.

STROBE Statement

This manuscript complies with the STROBE Statement for the reporting of epidemiological studies (https://www.strobe-statement.org/index.php?id=strobe-home). The STROBE checklist is on Table 1.

Data Sharing Statement

Data in the study were aggregated. Individual patient-level data from each database were analyzed and remain in the home institutions because of data protection rules.

Ethics Approval and Informed Consent

The RTI study team received approval for exemption from review by the RTI International institutional review board on November 22, 2017.

Ethics approval is not required for anonymized database research in the Netherlands. However, this study fulfilled the requirements, as checked by the PHARMO Compliance Commission on October 7, 2011, to use data from the PHARMO Database Network (NL-PHARMO) for this specific study. Permission for the use of data from the Dutch National Pathology Registry (PALGA) was received on April 23, 2013. Approval for access to the Netherlands Cancer Registry staging data for melanoma cases was received on August 9, 2018.

The study extension was approved by the Danish Data Protection Agency via Statistics Denmark on March 13, 2018. According to Danish law, studies based solely on register data do not require approval from an ethics review board.

The Centre for Pharmacoepidemiology at Karolinska Institutet received ethics approval for the JOELLE study extension phase and for the medical record review of cutaneous lymphoma cases on July 12, 2017, and approval to use data from the Swedish registers from the National Board of Health and Welfare on November 24, 2017.

Approval of the Clinical Practice Research Datalink (CPRD) Independent Scientific Advisory Committee was received on March 26, 2018 (protocol number, 13_121RAR).

Acknowledgments

The contract between RTI Health Solutions and LEO Pharma to conduct this study provides independent publication rights to the research team. The sponsor provided input on the study design but had no role in data collection or analysis. In line with the Guidance on Good Pharmacovigilance Practices (GVP): Module VIII, of the European Medicines Agency, the sponsor reviewed the manuscript and provided comments, but the authors made final decisions regarding its content and submission. All authors had full access to all of the data (including statistical reports and tables) and take responsibility for the integrity and accuracy of the data analysis and results.

The investigators would like to thank Henny Bang Jakobsen, Malene Nielsen, Thomas Delvin, and Mette Stagaard Janas, for the continuous support and coordination within LEO Pharma.

At RTI Health Solutions: Joan Fortuny, MD, PhD, and Xabier García de Albéniz, MD, MS, PhD, for clinical case review; Carla Franzoni, BS, for project management and administration; Joan Forns, PhD, David Martinez, BS, MSc, and Nuria Riera, PhD, for epidemiology support; and Paul Hobson, John Forbes, and Adele Monroe, DVM, MSPH, ELS, for editorial review.

At the UK-CPRD: the Independent Scientific Advisory Committee; the Interventional Research team for their work on the questionnaire study; and all contributing general practitioners.

At PHARMO: Willeke Blokx, MD, for clinical case review; Huub Straatman, data analyst, for programming and analysis; and all contributing health care providers for providing their data to the PHARMO Database Network and the Dutch National Pathology Registry (PALGA).

At the University of Southern Denmark: Morten Olesen and Martin T. Ernst for valuable help with data management.

At the Centre for Pharmacoepidemiology, Karolinska Institutet: Camilla Byström for medical record reviews.

The authors would like to thank the general practitioners contributing information to the Clinical Practice Research Datalink (CPRD) in the United Kingdom and the health care providers contributing information to the PHARMO Database Network and the Dutch National Pathology Registry (PALGA).

The research team chose the acronym JOELLE to honor Dr Joelle Erkens, pharmacoepidemiologist at Astellas and formerly at PHARMO Institute, who was lost to the research team in June 2011 upon her untimely death.

Funding

The study was funded by LEO Pharma.

Disclosure

Alejandro Arana, Lia Gutiérrez, Brian Calingaert, Kenneth J Rothman, James A Kaye, and Susana Perez-Gutthann are full-time employees of RTI International, an independent nonprofit research organization that does work for government agencies and pharmaceutical companies including LEO Pharma and Astellas Pharma. As employees of RTI International, Susana Perez-Gutthann, Kenneth J Rothman, and James A Kaye also participate in scientific advisory boards (for studies and medications) that are funded by pharmaceutical companies.

Josephina Kuiper and Eline Houben are employees of the PHARMO Institute for Drug Outcomes Research. This

independent research institute performs financially supported studies for government and related health care authorities and several pharmaceutical companies.

Jesper Hallas, Anton Pottegård, and Lars Christian Lund are employees of the University of Southern Denmark, Clinical Pharmacology and Pharmacy. They have participated in studies funded by pharmaceutical companies including LEO Pharma and Menarini Pharmaceuticals; funds are paid to their employer.

Daniel Dedman, Elizabeth Crellin, and Helen Booth are employees of the Clinical Practice Research Datalink (CPRD), which provides contract research services for government and related health care authorities and pharmaceutical companies including LEO Pharma.

Helle Kieler, Karin Gembert, and Johan Reutfors are employees of the Centre for Pharmacoepidemiology of the Karolinska Institutet in Sweden, which receives grants from regulatory authorities, pharmaceutical companies including LEO Pharma and Astellas Pharma, and contract research organizations for performance of drug safety and drug utilization studies.

Professor Marcus Schmitt-Egenolf MD, PhD, is an employee of the Department of Public Health & Clinical Medicine, Umeå University, Sweden. The authors report no other conflicts of interest in this work.

References

1. Örtqvist A, Lundholm C, Wettermark B, Ludvigsson J, Ye W, Almqvist C. Validation of asthma and eczema in population-based Swedish drug and patient registers. *Pharmacoepidemiol Drug Saf*. 2013;22(8):850–860. doi:10.1002/pds.3465
2. Asgari MM, Tsai AL, Avalos L, Sokil M, Quesenberry CP Jr. Association between topical calcineurin inhibitor use and keratinocyte carcinoma risk among adults with atopic dermatitis. *JAMA Dermatol*. 2020;156(10):1066–1073. doi:10.1001/jamadermatol.2020.2240
3. Castellsague J, Kuiper JG, Pottegard A, et al. A cohort study on the risk of lymphoma and skin cancer in users of topical tacrolimus, pimecrolimus, and corticosteroids (Joint European Longitudinal Lymphoma and Skin Cancer Evaluation - JOELLE study). *Clin Epidemiol*. 2018;10:299–310. doi:10.2147/CLEP.S146442
4. Lam M, Zhu JW, Tadrous M, Drucker AM. Association between topical calcineurin inhibitor use and risk of cancer, including lymphoma, keratinocyte carcinoma, and melanoma: a systematic review and meta-analysis. *JAMA Dermatol*. 2021;157(5):549–558. doi:10.1001/jamadermatol.2021.0345
5. Tennis P, Gelfand JM, Rothman KJ. Evaluation of cancer risk related to atopic dermatitis and use of topical calcineurin inhibitors. *Br J Dermatol*. 2011;165(3):465–473. doi:10.1111/j.1365-2133.2011.10363.x
6. Arana A, Wentworth CE, Fernandez-Vidaurre C, Schlienger RG, Conde E, Arellano FM. Incidence of cancer in the general population and in patients with or without atopic dermatitis in the U.K. *Br J Dermatol*. 2010;163(5):1036–1043. doi:10.1111/j.1365-2133.2010.09887.x
7. Arellano FM, Wentworth CE, Arana A, Fernandez C, Paul CF. Risk of lymphoma following exposure to calcineurin inhibitors and topical steroids in patients with atopic dermatitis. *J Invest Dermatol*. 2007;127(4):808–816. doi:10.1038/sj.jid.5700622
8. Brookhart Ma, Schneeweiss S, Rothman KJ, Glynn RJ, Avorn J, Sturmer T. Variable selection for propensity score models. *Am J Epidemiol*. 2006;163(12):1149–1156. doi:10.1093/aje/kwj149
9. Sturmer T, Wyss R, Glynn RJ, Brookhart MA. Propensity scores for confounder adjustment when assessing the effects of medical interventions using nonexperimental study designs. *J Intern Med*. 2014;275(6):570–580. doi:10.1111/joim.12197
10. Rothman KJ, Greenland S, Lash TL, eds. *Modern Epidemiology*. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2008.
11. Gutierrez L, Booth H, Dedman D, et al. Case validation of cutaneous lymphoma to minimize protopathic bias. Poster presented at the 35th Annual ICPE Conference; August 27, 2019; Philadelphia, Pennsylvania.
12. Berg D, Otley CC. Skin cancer in organ transplant recipients: epidemiology, pathogenesis, and management. *J Am Acad Dermatol*. 2002;47(1):1–17;quiz 18-20. doi:10.1067/mjd.2002.125579
13. Hartevelt MM, Bavinck JN, Kootte AM, Vermeer BJ, Vandenbroucke JP. Incidence of skin cancer after renal transplantation in The Netherlands. *Transplantation*. 1990;49(3):506–509. doi:10.1097/00007890-199003000-00006
14. Jensen P, Hansen S, Moller B, et al. Skin cancer in kidney and heart transplant recipients and different long-term immunosuppressive therapy regimens. *J Am Acad Dermatol*. 1999;40(2 Pt 1):177–186. doi:10.1016/S0190-9622(99)70185-4
15. Mittal A, Colegio OR. Skin cancers in organ transplant recipients. *Am J Transplant*. 2017;17(10):2509–2530. doi:10.1111/ajt.14382
16. Zwald FO, Brown M. Skin cancer in solid organ transplant recipients: advances in therapy and management: part I. Epidemiology of skin cancer in solid organ transplant recipients. *J Am Acad Dermatol*. 2011;65(2):253–261; quiz 262. doi:10.1016/j.jaad.2010.11.062
17. Hui RL, Lide W, Chan J, Schottinger J, Yoshinaga M, Millares M. Association between exposure to topical tacrolimus or pimecrolimus and cancers. *Ann Pharmacother*. 2009;43(12):1956–1963. doi:10.1345/aph.1M278
18. Schneeweiss S, Doherty M, Zhu S, et al. Topical treatments with pimecrolimus, tacrolimus and medium- to high-potency corticosteroids, and risk of lymphoma. *Dermatology*. 2009;219(1):7–21. doi:10.1159/000209289
19. Margolis DJ, Abuabara K, Hoffstad OJ, Wan J, Raimondo D, Bilker WB. Association between malignancy and topical use of pimecrolimus. *JAMA Dermatol*. 2015;151(6):594–599. doi:10.1001/jamadermatol.2014.4305
20. Manthripragada A. Addendum: update on calcineurin inhibitor pediatric literature review (FDA briefing document). Office of Surveillance and Epidemiology, FDA Center for Drug Evaluation and Research, Food and Drug Administration; May 10, 2011. Available from: https://wayback.archive-it.org/7993/20170114054651/http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/UCM255140.pdf. Accessed September 19, 2019.
21. Paller AS, Folster-Holst R, Chen SC, et al. No evidence of increased cancer incidence in children using topical tacrolimus for atopic dermatitis. *J Am Acad Dermatol*. 2020;83(2):375–381. doi:10.1016/j.jaad.2020.03.075
22. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol*. 2008;61(4):344–349.