# To What Extent Are Topical Tacrolimus or Pimecrolimus Associated With Increased Risk of Skin Cancer and Lymphoma? Long-Term Results From the JOELLE Study


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## DISCLOSURES

- This study was funded by LEO Pharma under a contract granting the research team independent publication rights.
- AA, AP, JGK, EC, JR, LCL, EH, HB, BC, JAK, KG, KJR, DD, HK, LG, JH, and SPG work for entities that perform independent research work for government and related health care authorities, private organizations, and pharmaceutical companies. MSE is an employee of the Department of Public Health and Clinical Medicine, Umeå University, Sweden.


## OBJECTIVE

- To estimate the long-term risk of skin cancer and lymphoma associated with use of topical tacrolimus or pimecrolimus in adults and children

## BACKGROUND

- Topical tacrolimus is indicated for the treatment of moderate to severe atopic dermatitis (AD), and topical pimecrolimus is indicated for the treatment of mild to moderate AD.
- There are concerns about a potential increase in the risk of lymphoma and skin cancer associated with the use of these topical calcineurin inhibitors (TCIs), especially in children. The epidemiologic literature presents insufficient evidence to infer whether TCIs cause malignancy. In particular, it is difficult to differentiate the effects of these medications themselves from the effects of the conditions they treat or the severity of the AD.
- Reverse causation (protopathic bias) is a concern because patients with early stages of certain skin malignancies, particularly cutaneous T-cell lymphoma (CTCL), may present clinical manifestations resembling AD, which could lead to a mistreatment with the study medications.
- The JOELLE study was requested by the European Medicines Agency to (1) provide sufficient observation time to identify long-term risk of cancer, (2) include validation of outcomes, and (3) conduct sensitivity analyses that address potential biases.
- The study obtained the ENCePP Study Seal (posted in the EU PAS Register, EUPAS21769).

## METHODS

### Data Sources

- Clinical Practice Research Datalink in the United Kingdom (UK CPRD)
- PHARMO Database Network in the Netherlands (NL PHARMO)
- Danish health databases (Denmark)
- Swedish health databases (Sweden)

### Study Period

- UK CPRD and NL PHARMO: January 2002 through December 2017
- Denmark: January 2002 through December 2016
- Sweden: January 2006 through December 2015

### Study Design

- Comparative cohort study with up to 17 years follow-up.
- Except for children aged 0 to 12 months, patients were required to have at least 12 months of continuous enrolment in the study databases and no documented history of skin cancer or lymphoma before cohort entry.
- Within each data source, new users of topical tacrolimus and new users of topical pimecrolimus were identified and classified into four groups according to age (children aged < 18 years and adults aged ≥ 18 years) and exposure to TCI (topical tacrolimus or topical pimecrolimus).
- Corticosteroid user cohorts included patients with a recorded diagnosis of AD who received a prescription for topical corticosteroids of moderate to high potency during the study period or patients without a recorded diagnosis of AD who received a prescription for topical corticosteroids during the study period and at least one other prescription within the previous 12 months.
- We calculated propensity scores for patients in each of the four TCI cohorts and their corresponding corticosteroid cohorts. Propensity scores were estimated as the probability of initiating TCI treatment given a set of baseline covariates. The covariates included age, sex, immunosuppressive disease, chronic disease, severe skin diseases, AD, severity of AD, use of immunosuppressive agents, use of other medications, and measures of health care resource utilization.
- Within each data source and for each of the four TCI cohorts and the corresponding corticosteroid cohorts: individuals below the first percentile of the TCI cohort and individuals above the 99th percentile of the corticosteroid cohort were excluded.
- The remaining users were stratified by twentile of propensity score of the TCI cohort. All users of TCIs were retained, and a maximum of four times as many users of topical corticosteroids within each twentile-based stratum were randomly selected and retained.
- For the comparison of topical corticosteroid users with the untreated population, we employed individual matching; each user of corticosteroids from the comparator cohort for tacrolimus was matched to 4 patients taken from the general population and treated with any study medication. Cohorts were matched on age, sex, geographic region, and calendar year of start date.

### Analysis

- We evaluated the overall and the cumulative dose effects of topical tacrolimus and topical pimecrolimus compared with use of topical corticosteroids.
- Malignancies included Hodgkin's lymphoma, CTCL, non-Hodgkin's lymphoma other than CTCL, and skin cancer (melanoma and nonmelanoma).
- In each data source, cancer events and person-years were stratified between decile boundaries of propensity score to control potential confounding. We then used Mantel-Haenszel methods to estimate overall adjusted incidence rate ratios (IRRs) and incidence rate differences for children and adults across the study data sources.
- For the main analysis, time at risk started after a lag time of 6 months.
- Sensitivity analyses with lag times of 0 months, 12 months, 24 months, and 48 months were conducted to explore reverse causation and surveillance bias.
- To further assess reverse causation, we obtained additional information on CTCL cases from questionnaires sent to general practitioners in the UK CPRD and medical record review in Sweden.

## RESULTS

- After propensity score trimming and matching, the study included 32,605 children (aged < 18 years) and 126,908 adults (aged ≥ 18 years) initiating treatment with topical tacrolimus, and 27,961 children and 61,841 adults initiating treatment with topical pimecrolimus. Denmark and Sweden together contributed the largest number of users of topical tacrolimus: 72.1% of all children and 73.5% of all adults. Denmark contributed the largest number of users of topical pimecrolimus: 72.8% of children and 69.6% of adults.
- Users of moderate- to high-potency topical corticosteroids included 117,592 children and 452,996 adults matched to users of tacrolimus and 111,024 children and 244,572 adults to users of pimecrolimus.
- Across all patients, follow-up was 10 years or more for 19% of adults and for 32% of children. Figure 1 shows the distribution of minimum follow-up in each population.
- 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).
- Table 1 and Figure 2 show cancer outcome results for the use of topical tacrolimus or use of topical pimecrolimus vs. topical corticosteroids in adults. The IRR for CTCL with tacrolimus corresponds to an excess risk of 3 cases per 100,000 person-years (95% confidence interval [CI], 1-6). In the UK CPRD and Sweden, there was little change in the estimated effect of topical tacrolimus on CTCL when cases with manifestations of a previous skin condition in the same location as the subsequently diagnosed cutaneous lymphoma were omitted.[1]
- 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 2).
- In adults (Table 1 and Figure 2), the adjusted 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). For cumulative doses greater than 1 gram, the IRR was 1.59 (95% CI, 1.14-2.22). The excess risk for nonmelanoma skin cancer with use topical pimecrolimus was 91 cases per 100,000 person-years (95% CI, 68-114).
- In the sensitivity analyses examining time since exposure to the study medications, the IRRs for cutaneous outcomes in adults for periods of 5 years or longer after first exposure to topical pimecrolimus were not increased compared with estimated IRRs in the main analyses (Table 2).
- In children (Figure 2), the pooled adjusted IRRs comparing use of topical tacrolimus or topical pimecrolimus with use of topical corticosteroids were based on few events (Figure 2). The IRR comparing use of topical tacrolimus with use of topical corticosteroids was 2.19 (95% CI, 0.81-5.97) for non-Hodgkin's lymphoma (excluding CTCL), 2.37 (95% CI, 0.99-5.68) for Hodgkin's lymphoma, and 7.77 (95% CI, 0.50-121.45) for CTCL. The IRR was elevated for low cumulative doses but not for medium or high cumulative doses. For Hodgkin's lymphoma, the IRR was elevated for low and high doses but not for medium doses.

### Users of Topical Corticosteroids vs. Untreated Population

- In adults, the IRRs for all outcomes except melanoma were elevated in the cohort of users of topical corticosteroids compared with those in the untreated population (Figure 3).
- The IRR for CTCL was 5.42 (95% CI, 3.77-7.79) for topical corticosteroid users compared with the untreated population. In children, the number of cases was too small to estimate the IRR for the individual outcomes for patients exposed to topical corticosteroids compared with the untreated population.

**Figure 1. Distribution of Topical Calcineurin Users by Minimum Years of Follow-up**

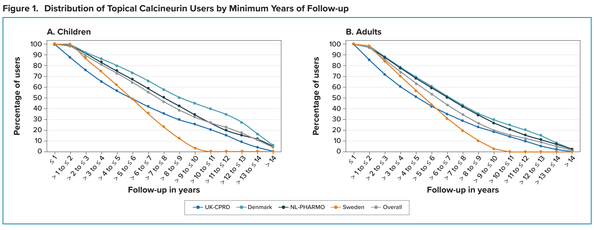
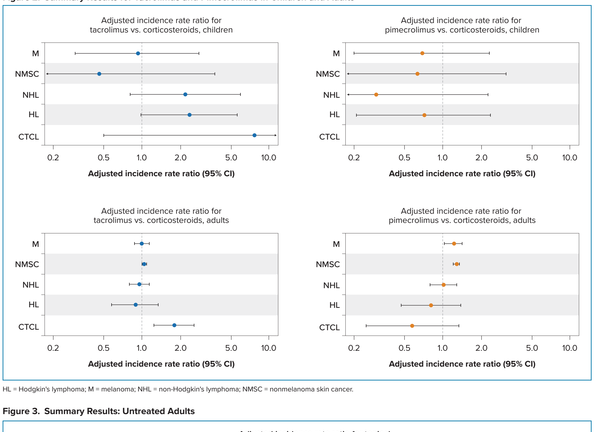



**Figure 2. Summary Results for Tacrolimus and Pimecrolimus in Children and Adults**




HL = Hodgkin's lymphoma; M = melanoma; NHL = non-Hodgkin's lymphoma; NMSC = nonmelanoma skin cancer.

**Figure 3. Summary Results: Untreated Adults**

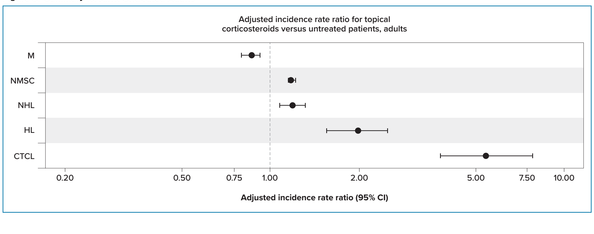



**Table 1. Overview of Pooled Adjusted IRRs in Users of Topical Tacrolimus and Topical Pimecrolimus Compared With Users of Topical Corticosteroids, Adults**

| Exposure | Adjusted[a] IRRs (95% CI) | | | | |
|---|---|---|---|---|---|
| | Malignant Melanoma | Nonmelanoma Skin Cancer | Non-Hodgkin's Lymphoma Other Than CTCL | Hodgkin's Lymphoma | CTCL |
| **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]** | | | | | |
| ≤ 0.5 | 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) |
| > 0.5 to 1.0 | 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) |
| > 1.0 | 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-NE) |
| > 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) |

NE = not estimable.
[a] Adjusted by study database, deciles of propensity scores, and sex; in Denmark, NL PHARMO, and Sweden, also adjusted by type of prescriber (dermatologist, nondermatologist) of the first prescription.
[b] Grams of active substance.

**Table 2. Sensitivity Analysis by Time Since Start of Exposure by Each Type of Malignancy: Adjusted IRRs 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) |
| **CTCL** | | |
| 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) |

[a] Adjusted by study database, deciles of propensity scores, and sex; in Denmark, NL PHARMO, and Sweden, also adjusted by type of prescriber (dermatologist, nondermatologist) of the first prescription.

## CONCLUSIONS

- The elevated IRR for CTCL among adult users of topical tacrolimus and the elevated IRR for melanoma and nonmelanoma skin cancer among adult users of topical pimecrolimus could be the results of the underlying disease or reverse causation or could represent causal effects.
- 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.
- In children, IRRs comparing use of topical tacrolimus or topical pimecrolimus with use of topical corticosteroids were based on few events
- Even if causal, the public health impact of these excess risks would be low.

## REFERENCE


1. Gutierrez L, Booth H, Dedman D, Crellin E, Kaye JA, Franzoni C, et al. Case validation of cutaneous lymphoma to minimize protopathic bias. Poster presented at the 35th Annual ICPE Conference; August 27, 2019. Philadelphia, PA. [abstract] Pharmacoepidemiol Drug Saf. 2019 Aug 20;28(S2):645.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