Risk of Skin Cancer in Users of Topical Tacrolimus, Pimecrolimus, and Corticosteroids: JOint European Longitudinal Lymphoma and skin cancer Evaluation (JOELLE) study

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CONFLICT OF INTEREST

J. Castellsague, B. Calingaert, K. Rothman, L. Gutierrez, J. Kaye, and S. Perez-Gutthann are full-time employees of RTI Health Solutions, an independent non-profit research organization that does work for government agencies and pharmaceutical companies. RTI Health Solutions received funding from Astellas Pharma to conduct this study. The contract provides the research team independent publication rights.

M. van Herk-Sukel and J. Kuiper 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.

C. Pardo is an employee of Astellas Pharma Europe.

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BACKGROUND

- Topical tacrolimus (TAC) is indicated for the treatment of moderate to severe atopic dermatitis (AD), and topical pimecrolimus (PIM) is indicated for mild to moderate AD.
- Concerns about a potential increase in risk of cancer with the use of these medications emerged from the increased risk of lymphomas, non-melanoma skin cancer, and melanomas observed with the systemic use of tacrolimus in organ transplant, in animal studies, and in a small number of case reports.[1-4] Therefore, evaluation of the long-term safety profile of TAC related to a potential increased risk of skin cancers is of relevance to patients and public health.
- We conducted a post-authorization safety study to evaluate the risk of skin cancer and lymphoma associated with the use of TAC (EU PAS Register ID 4357).

OBJECTIVE

- The main objectives of this study were to estimate the incidence rate of malignant melanoma (MM) of skin and non-melanoma skin cancer (NMSC) in the pediatric (aged < 18 years) and adult (aged ≥ 18 years) populations comparing cohorts of new users of TAC and new users of PIM with current users of moderate- to high-potency topical corticosteroids (TCS) and users of TCS with general population untreated subjects.

METHODS

- A cohort study was conducted using health and prescription data from populations covered in the PHARMO Database Network (The Netherlands), the Danish and Swedish national registers, and the Clinical Practice Research Datalink (CPRD) (United Kingdom) from the date of first availability of TAC and PIM in each country (from 2002) through 2011. In Sweden, prescription data were available from 2006, and new users of TAC and PIM were selected from that point.
- New users of TAC and new users of PIM were frequency matched to users of TCS on twentiles of propensity scores.
- Estimation of crude and adjusted incidence rate ratios (IRRs) and 95% confidence intervals (CIs) for each outcome, separately for children and adults, were made by comparing the incidence rates for each exposure category with the rates in the corresponding TCS cohort, using Mantel-Haenszel methods.
- IRRs were adjusted by deciles of propensity scores and sex in each data source; in addition, in the PHARMO and Swedish data, IRRs were also adjusted by type of prescriber of the first prescription, as a proxy for severity of AD.
- To account for the effect of type of prescriber of first prescription, we corrected the partially adjusted IRRs in the Danish and CPRD data, using probabilistic bias analysis for unmeasured confounders.
- Several sensitivity analyses were performed, as results of analyses of time since start of exposure are relevant when assessing cancer risk.

DISCUSSION AND CONCLUSIONS

- These results suggest a small association or no association of TAC and PIM with the rate of skin cancer, with low absolute excess rate estimates. Rate ratios were close to the null, although the CIs did not reflect additional uncertainty stemming from possible residual confounding by severity of AD. Bias related to increased surveillance of patients receiving these medications is suggested by the results of time since first exposure analyses.

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ABSTRACTS FROM THIS STUDY ALSO PRESENTED IN THIS CONFERENCE

Castellsague J, et al. **Probabilistic bias analysis for unmeasured confounders in a study of users of topical tacrolimus, pimecrolimus, and corticosteroids (JOELLE).** Abstract #238. Poster Session A: Confounding/Bias, Friday 26 August 2016, 8:00 AM-6:00 PM

Castellsague J, et al. Risk of lymphoma in users of topical tacrolimus, pimecrolimus, and corticosteroids (JOELLE study). Abstract #854. Session: Adverse Outcomes of Glucocorticoid and Immunomodulator Use, Sunday, 28 August 2016, 3:15 PM-4:45 PM, Presentation time: 4:00 PM-4:15 PM.

Kuiper JG, et al. Utilization of tacrolimus and pimecrolimus in Europe: results from the JOint European Longitudinal Lymphoma and skin cancer Evaluation (JOELLE) study. Abstract #1087. Poster Session C: DUR – Trends, Sunday, 28 August 2016, 8:00 AM-1:45 PM.

RESULTS

- We included 19,948 children and 66,127 adults who were new users of TAC and 23,840 children and 37,417 adults who were new users of PIM in each group matched with current users of moderate- to high-potency TCS. Denmark and Sweden contributed approximately 70% of the users of TAC. Figure 1 presents specific numbers for the TAC and PIM cohorts.
- In children, there were no events of MM or NMSC in the TAC cohort; there were two events of MM and one event of NMSC in the TCS cohort. For PIM, there were no events of MM and one event of NMSC in the PIM cohort; there was one event of MM and one event of NMSC in the TCS cohort. The IRR for NMSC comparing PIM with TCS was 1.24 (0.21-7.41).
- Summary results on the incidence rates and 95% CIs for MM and NMSC among adults for the TAC and PIM cohorts are displayed in Figure 2 and Figure 3.
- In adults, the pooled corrected IRR (95% CI) for current single use of TAC versus TCS was 0.90 (0.66-1.22) for MM and 1.08 (0.98-1.19) for NMSC. The pooled corrected IRR for current single use of PIM versus TCS was 1.16 (0.87-1.56) for MM and 1.20 (1.07-1.35) for NMSC (Figure 4 and Figure 5). There was heterogeneity of results across databases for PIM.
- The analysis of time since start of exposure showed higher adjusted IRRs for MM and NMSC in the first 6 months following the start of treatment than in later periods (Figure 6).
- In children, IRRs for TCS versus untreated were 1.93 (0.16-23.03) for MM and 0.94 (0.06-15.66) for NMSC. In adults, IRRs were 0.87 (0.74-1.03) for MM and 1.19 (1.11-1.27) for NMSC.

Figure 1. Number of TAC and PIM Users by Data Source: Children and Adults

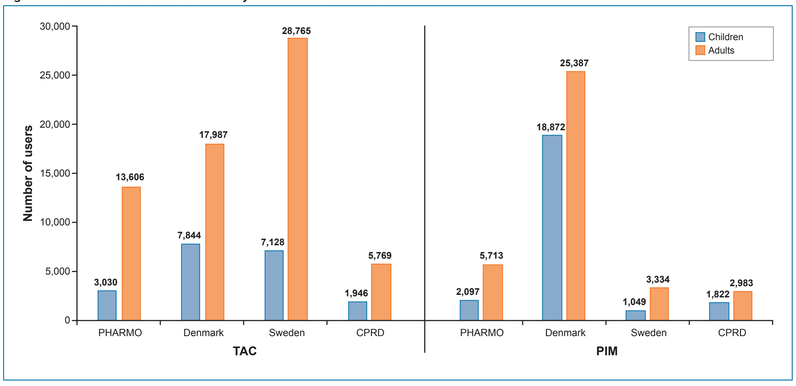

Figure 2. Incidence Rates and 95% CIs of MM and NMSC Among Adults in TAC Cohort Compared With TCS Cohort

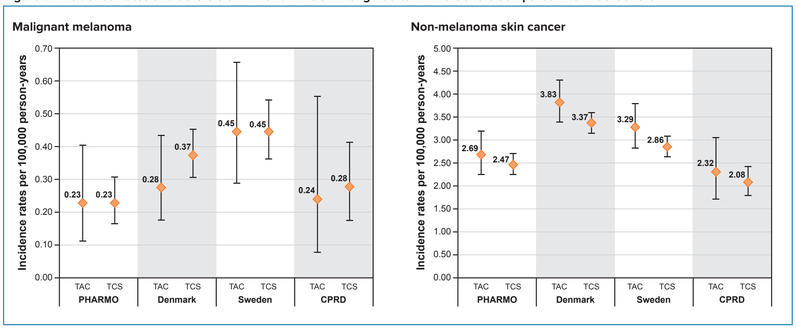

Figure 3. Incidence Rates and 95% CIs of MM and NMSC Among Adults in PIM Cohort Compared With TCS Cohort

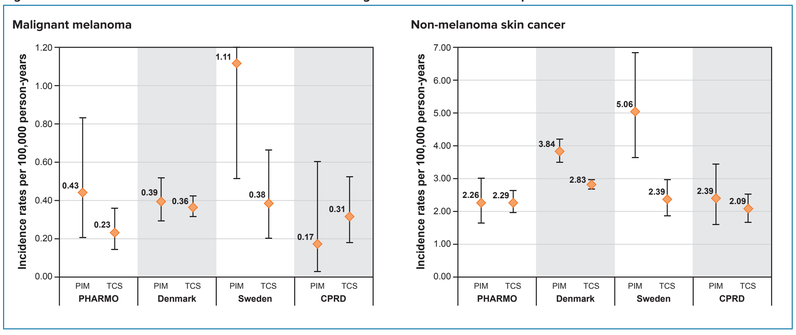

Figure 4. Corrected IRRs and 95% CIs of MM and NMSC Among Adults for TAC

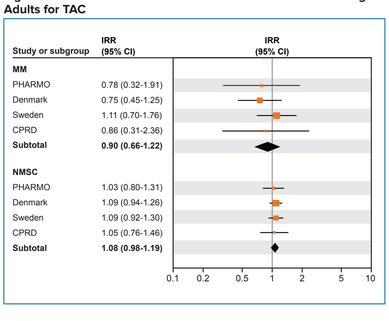

Figure 5. Corrected IRRs and 95% CIs of MM and NMSC Among Adults for PIM

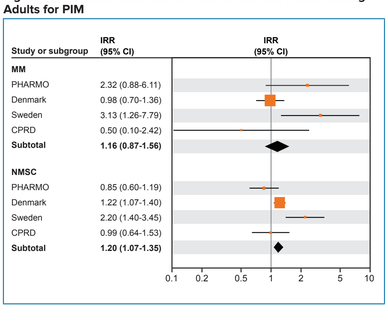

Figure 6. Adjusted IRRs and 95% CIs of MM and NMSC Among Adults in TAC and PIM Cohorts Compared With TCS by Time Since Start of Exposure