Probabilistic Bias Analysis for Unmeasured Confounders in a Study of Users of Topical Tacrolimus, Pimecrolimus, and Corticosteroids (JOELLE)

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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.

University of Southern Denmark, Karolinska Institutet, and CPRD coauthors do not have conflicts to disclose.

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.
- We conducted a post-approval cohort study in four European databases to estimate the risk of lymphoma and skin cancer in new users of these medications (EU PAS Registry ID 4357). Severity of AD could confound the association between the risk of lymphoma and skin cancer and the use of TAC and PIM.
- Because information on severity of AD was partially or not recorded in the study databases, we used type of prescriber of first prescription (TPFP) (dermatologist vs. non-dermatologist) as a proxy for AD severity. As TPFP was only available in two of the four databases, we used probabilistic bias analysis for unmeasured confounders to correct partially adjusted pooled incidence rate ratios (IRRs).

OBJECTIVE

- To use probabilistic bias analysis for unmeasured confounders to correct partially adjusted pooled IRRs of lymphoma and skin cancer comparing new users of TAC and new users of PIM with users of moderate- to high-potency topical corticosteroids (TCS).

METHODS

- A cohort study was conducted in the PHARMO Database Network (The Netherlands), the Danish and Swedish national registers, and the Clinical Practice Research Datalink (CPRD) (United Kingdom), with RTI Health Solutions as the coordinating/pooled analysis center.
- Each cohort of new users of TAC and new users of PIM was frequency matched to users of TCS by twentiles of propensity scores.
- Study outcomes were malignant melanoma (MM), non-melanoma skin cancer (NMSC), any lymphoma (LYM), non-Hodgkin lymphoma (NHL), Hodgkin lymphoma (HL), and cutaneous T-cell lymphoma (CTCL).
- We estimated pooled IRRs adjusted by TPFP in PHARMO and Sweden where information on this variable was available. We corrected these partially adjusted pooled IRRs using probabilistic bias analysis for unmeasured confounders,[1] applying bias parameters from PHARMO and Sweden to the crude IRRs estimated in Denmark and CPRD.
- Bias parameters were as follows:
  - Prevalence of dermatologist as TPFP in the exposed groups (TAC, PIM)
  - Prevalence of dermatologist as TPFP in the unexposed groups (cohort of TCS matched to TAC, cohort of TCS matched to PIM)
  - Strength of association between dermatologist as TPFP and each study outcome
- In probabilistic bias analysis, probability distributions, instead of fixed values, are specified for each bias parameter. Monte Carlo sampling techniques are used to generate frequency distributions of corrected effect estimates.
- We assumed a trapezoidal distribution of each bias parameter. The trapezoidal distribution allows bias parameters within a range to be characterized as more likely than others according to the following parameters:
  - Two modes: upper mode and lower mode. Each value between the two modes has an equal probability density.
  - Minimum and maximum values: probability decreases linearly to zero as one moves away from the mode to the minimum and maximum values.
- For each bias parameter, we obtained upper and lower mode and minimum and maximum values from data from PHARMO and Sweden (Table 1).

RESULTS

- A total of 19,948 children and 66,127 adults treated with TAC were matched with 79,700 children and 264,482 adults treated with TCS. A total of 23,840 children and 37,417 adults treated with PIM were matched with 90,268 children and 149,671 adults treated with TCS.
- Table 1 and Table 2 present the probabilistic bias analysis for unmeasured TPFP used to estimate the corrected IRR of CTCL for TAC versus TCS in adults. We applied this method to all study outcomes and exposures.
- Figure 1 and Figure 2 present the partially adjusted and corrected IRRs in children and adults for all the study outcomes.
- For TAC compared with TCS, the corrected IRR (95% confidence interval [CI]) was as follows:
  - Lymphoma in children decreased by 35.7% from 5.26 (1.14-24.29) to 3.74 (1.00-14.06).
  - CTCL in adults decreased by 55.6% from 2.71 (1.35-5.44) to 1.76 (0.81-3.79).
- For PIM compared with TCS, the corrected IRR (95% CI) was as follows:
  - Lymphoma in children decreased by 91.4% from 1.81 (0.41-8.02) to 1.07 (0.25-4.60).
  - CTCL in adults increased by 181.80% from 1.11 (0.28-4.32) to 1.31 (0.33-5.14).
- Smaller IRR reductions were observed for skin cancer in both TAC and PIM.

Table 1. Values of Bias Parameters for CTCL, Comparing TAC and TCS in Adults

Bias Parameter	Minimum Value	Lower Mode	Upper Mode	Maximum Value
Prevalence of dermatologist as TPFP in users of TAC	0.43	0.63	0.74	0.94
Prevalence of dermatologist as TPFP in users of TCS	0.00	0.11	0.18	0.38
IRR of CTCL for TPFP	1.47	1.63	7.38	8.16

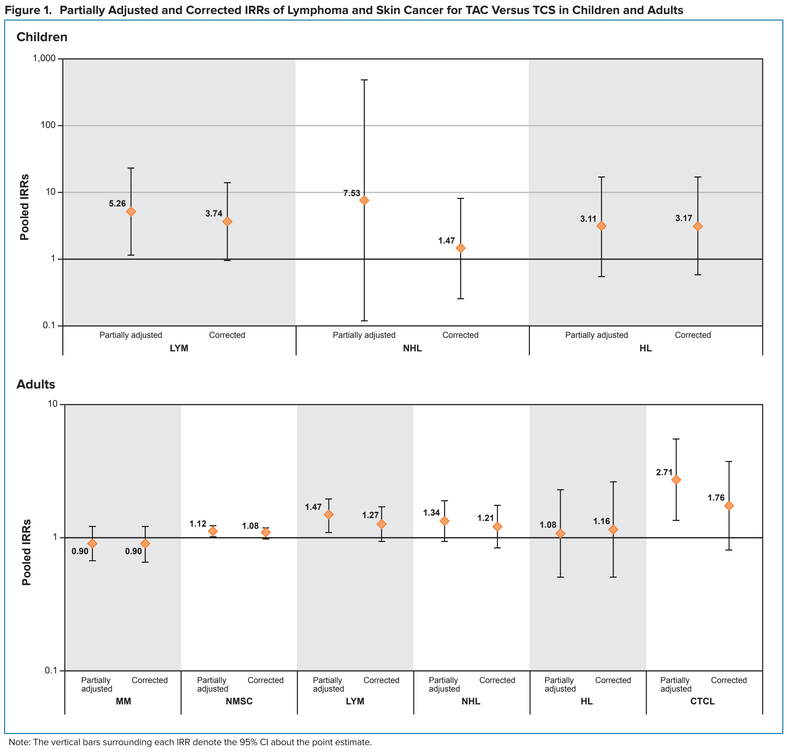
Note: Distribution of bias parameters values was chosen based on information from PHARMO and Sweden. For the prevalence parameter, the proportions of dermatologists as TPFP seen in PHARMO and Sweden were used as the two modes. The minimum value was calculated as the maximum of (lower mode −0.2, 0). The maximum value was calculated as the minimum of (upper mode +0.2, 1). The IRRs seen in PHARMO and Sweden were used as the two modes. If the lower mode was > 0, then the minimum value was calculated as exp(log(lower mode) – 0.1); otherwise, the lower mode was used as the minimum value. The maximum value was calculated as exp(log(upper mode) + 0.1).

Table 2. Results of Bias Analysis for CTCL, Comparing TAC and TCS in Adults

Database	Crude IRR (95% CI)	IRR Adjusted by TPFP[a] (95% CI)	Corrected[b] IRR (95% CI)
PHARMO	2.09 (0.45-9.74)	3.06 (0.07-126.18)	3.06 (0.07-126.18)
Denmark	1.46 (0.49-4.35)	1.46 (0.46-4.64)[c]	0.71 (0.19-2.64)
Sweden	7.09 (2.22-22.67)	3.79 (0.96-14.99)	3.79 (0.96-14.99)
CPRD	4.14 (1.28-13.36)	4.18 (1.20-14.54)[c]	2.04 (0.50-8.33)
Pooled[d]	**3.13 (1.71-5.73)**	**2.71 (1.35-5.44)**	**1.76 (0.81-3.79)**

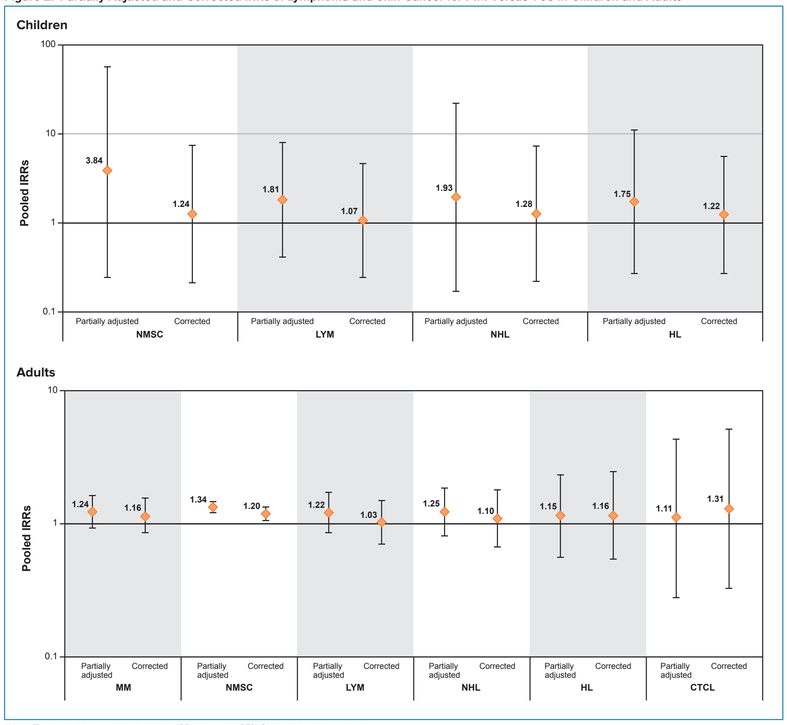
[a] IRR additionally adjusted by deciles of propensity scores and sex.
[b] Corrected IRR using probabilistic bias analysis for unmeasured confounders.
[c] IRR is adjusted by deciles of propensity scores and sex but not for TPFP.
[d] Estimated using inverse variance meta-analysis.

Figure 1. Partially Adjusted and Corrected IRRs of Lymphoma and Skin Cancer for TAC Versus TCS in Children and Adults



Note: The vertical bars surrounding each IRR denote the 95% CI about the point estimate.

Figure 2. Partially Adjusted and Corrected IRRs of Lymphoma and Skin Cancer for PIM Versus TCS in Children and Adults



Note: The vertical bars surrounding each IRR denote the 95% CI about the point estimate.

DISCUSSION/CONCLUSIONS

- Probabilistic bias analysis for unmeasured confounders led to noticeable corrections of the association of TAC and PIM with lymphoma and skin cancer.
- Results from this bias analysis are based on bias parameters estimated from PHARMO and Sweden, which might not apply to Denmark and the CPRD.
- Probabilistic bias analysis for unmeasured confounders can be a useful tool to explore the impact of unmeasured confounders and correct effect estimates in multidatabase studies where information on relevant confounders is partially recorded or not available in all databases.

ABSTRACTS FROM THIS STUDY ALSO PRESENTED IN THIS CONFERENCE

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.

Castellsague J, et al. **Risk of skin cancer in users of topical tacrolimus, pimecrolimus, and corticosteroids. JOint European Longitudinal Lymphoma and skin cancer Evaluation (JOELLE) study.** Abstract #908. Poster Session C: Safety & Effectiveness – Cancer, Sunday, 28 August 2016, 8:00 AM-1:45 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.

REFERENCE

1. Lash TL, Fox MP, Fink AK. Applying quantitative bias analysis to epidemiologic data. Springer Science+Business Media, LLC; 2009.

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