1 Abstract

Title: Risk of Skin Cancer and Lymphoma in Users of Topical Tacrolimus, Pimecrolimus, and Corticosteroids. Protopic® JOint European Longitudinal Lymphoma and skin cancer Evaluation (JOELLE) Study: Extension Phase

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Rationale and background: Topical tacrolimus is indicated for the treatment of moderate to severe atopic dermatitis, and topical pimecrolimus for the treatment of mild to moderate atopic dermatitis. Safety data from animal studies, systemic use in patients with organ transplants, and case reports have raised concerns about a potential increase in the risk of lymphoma and skin cancer associated with the use of these agents, especially in children. The conduct of this study was requested by the European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) to further evaluate the incidence of skin cancer and lymphoma in children treated with topical tacrolimus. The JOELLE Phase I study analysed observed data from 2002 through 31-Dec-2011, and the study report dated 30-Nov-2015, was endorsed by the EMA on 21-Jul-2016. In the JOELLE study extension phase, the additional study period started 1-Jan-2012 in all databases and was prolonged for 4-6 years. The JOELLE study extension phase analysed observed data from 2002 through 31-Dec-2017 in the Clinical Practice Research Datalink in the United Kingdom (UK-CPRD) and the PHARMO Database Network in the Netherlands (NL-PHARMO), through 31-Dec-2016 in the Danish nationwide health registers (Denmark), and through 31-Dec-2015 in the Swedish health care registers (Sweden). This report summarises the results of the JOELLE study, including the extension phase, with re-created cohorts covering up to an additional 6 years of data, allowing for evaluation of longer latency period for the development of skin cancers and lymphomas.

Research question and objectives: The primary objective was to estimate the incidence rate ratios (IRRs) of malignant melanoma, non-melanoma skin cancer (NMSC), non-Hodgkin lymphoma [except cutaneous T-cell lymphoma (CTCL)], Hodgkin lymphoma, CTCL, and any type of lymphoma in the paediatric and adult populations, comparing new users of topical tacrolimus and topical pimecrolimus with users of moderate- to high-potency topical corticosteroids. The secondary objective was to estimate the IRRs of these malignancies

comparing users of moderate- to high-potency topical corticosteroids with the untreated population.

Study design: JOELLE is a multinational cohort study of new users of topical tacrolimus and new users of topical pimecrolimus, frequency matched to users of moderate- to high-potency topical corticosteroids[*] on twentiles of propensity scores, and of users of moderate- to high-potency topical corticosteroids individually matched at a ratio of 1 study medication user to 4 untreated patients from the general population on age, sex, geographic region, and calendar year of start date.

Setting: Information recorded in health databases in four European countries on prescriptions dispensed in community pharmacies or prescribed in the primary care setting and diagnoses from hospitalisations, primary health care, and cancer registries. Researchers with access to such databases in Denmark, the Netherlands, Sweden, and the United Kingdom collaborated with RTI Health Solutions (Spain and the United States) as the coordinating centre.

Subjects and study size, including dropouts: The study cohort sizes before propensity score matching were 40,786 children (aged less than 18 years) and 153,257 adults (age 18 years or older) initiating treatment with topical tacrolimus, and 38,168 children and 76,549 adults initiating treatment with topical pimecrolimus. After trimming, the study included 32,605 children and 126,908 adults initiating treatment with topical tacrolimus matched to 117,592 children and 452,996 adults treated with topical corticosteroids; 27,961 children and 61,841 adults initiating treatment with topical pimecrolimus matched to 111,024 children and 244,572 adults treated with topical corticosteroids. Compared with JOELLE Phase I, the final cohort numbers represent a 39% and 48% increase for new users of tacrolimus and 15% and 39% for new users of pimecrolimus, for children and adults, respectively. The untreated cohort comprised 361,585 children and 1,291,042 adults.

Variables and data sources: Data sources were UK-CPRD, NL-PHARMO, and the Danish and Swedish national registers (Denmark and Sweden, respectively). The coordinating centre was RTI Health Solutions in Spain and the United States. In Denmark, NL-PHARMO, and Sweden, outcomes were identified in cancer or pathology registries. In UK-CPRD, outcomes were identified through general practice, hospital, and cancer register data. In NL-PHARMO and UK-CPRD, case validation was performed. Exposure to topical tacrolimus and topical pimecrolimus was defined as ever use (topical tacrolimus or topical pimecrolimus) and single use (topical tacrolimus or topical pimecrolimus but not both) of each of these medications. The effect of cumulative dose and duration of use of each medication was also evaluated. In

[*] Use of the term “topical corticosteroids” refers to moderate- to high-potency topical corticosteroids unless otherwise specified.

each data source, data were collapsed and stratified by deciles of propensity scores. The coordinating centre conducted a central stratified analysis, using Mantel-Haenszel methods to estimate overall IRRs and incidence rate differences for children and adults across the study data sources. Incidence rate ratios were adjusted by the type of prescriber of the first prescription, as a proxy for severity of the underlying cutaneous condition, in Denmark, NL-PHARMO, and Sweden. A sensitivity analyses were conducted to evaluate the potential for a protopathic bias (reverse causation) for CTCL cases in UK-CPRD by obtaining additional information from questionnaires sent to general practitioners of individual cases and in Sweden by reviewing medical records of the cases.

Results: Denmark and Sweden contributed the largest number of users of topical tacrolimus: together, they contributed 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.

Among users of topical tacrolimus, the median follow-up period ranged from 4.0 years in UK-CPRD to 6.8 years in NL-PHARMO in children and from 3.7 years in UK-CPRD to 6.1 years in NL-PHARMO in adults. Among users of topical pimecrolimus, the median follow-up ranged from 5.5 years in the UK-CPRD and Sweden to 8.1 years in Denmark in children and from 4.6 years in UK-CPRD to 7.0 years in Denmark in adults.

JOELLE study extension phase follow-up was longer than the follow-up in any other study of topical calcineurin inhibitors and malignancies. Among children, the proportion of topical tacrolimus users with a duration of follow-up of at least 10 years was 45.1% in Denmark, 34.1% in NL-PHARMO, and 25.3% in UK-CPRD. Among adults, the proportion of users with a duration of follow-up of at least 10 years was 29.6% in Denmark, 26.5% in NL-PHARMO, and 18.4% in UK-CPRD. In Sweden, the study period started on 1-Jan-2006, and the proportion of users with at least 10 years of follow-up was minimal.

Among children treated with topical tacrolimus, the median number of prescriptions was one prescription in Denmark and Sweden, and two prescriptions in UK-CPRD and NL-PHARMO. The mean number of grams of active substance (1 tube of 30 grams at 0.03% contains 0.09 grams of tacrolimus), was 0.11 grams in UK-CPRD, 0.10 grams in Denmark, 0.09 grams in NL-PHARMO, and 0.05 grams in Sweden.

Among adults treated with topical tacrolimus, the median number of prescriptions was one prescription in all the study databases. The mean number of grams of active substance was 0.12 grams in UK-CPRD, 0.10 grams in Demark, 0.11 grams in NL-PHARMO, and 0.07 grams in Sweden.

In children, there were few cases of lymphoma. The pooled adjusted IRRs comparing single use of topical tacrolimus versus topical corticosteroids for malignant melanoma and NMSC were lower than 1. The IRR comparing single use of topical tacrolimus versus topical corticosteroids was 2.19 (95% confidence interval [CI], 0.81-5.97) for non-Hodgkin lymphoma (excluding CTCL), 2.37 (95% CI, 0.99-5.68) for Hodgkin lymphoma, and 7.77 (95% CI, 0.50-121.45) for CTCL. The IRR for each type of lymphoma was based on a low number of events and was elevated for low cumulative doses, but not for medium and high cumulative doses, in the case of non-Hodgkin lymphoma, and not for medium doses in Hodgkin lymphoma. In children, the relative risk for each study outcome, skin cancers and lymphomas, for topical pimecrolimus compared with topical corticosteroids was also based on a low number of events and did not suggest an increased risk.

In adults, compared with topical corticosteroids, users of topical tacrolimus had an IRR for NMSC of 1.04 (95% CI, 1.00-1.09), and the IRRs for non-Hodgkin lymphoma and Hodgkin lymphoma (excluding CTCL) were lower than 1. For adults, the adjusted IRR of CTCL for single use of topical tacrolimus was 1.80 (95% CI, 1.25-2.58); there was a dose-response relationship of increased incidence with increasing dose. Adjusted IRRs of CTCL for single use of topical tacrolimus were 0.81 (95% CI, 0.45-1.47) for a cumulative dose of 0.05 gram or less, 2.11 (95% CI, 1.13-3.95) for a cumulative dose from 0.05 to 0.10 gram, and 5.25 (95% CI, 3.21-8.56) for a cumulative dose greater than 0.10 gram.

In the sensitivity analysis, the possibility of protopathic bias present in the estimation of the association of topical tacrolimus or pimecrolimus with cutaneous lymphoma (compared with topical corticosteroids) was investigated by calculating the IRR in different time windows after first exposure. For tacrolimus, the IRR of CTCL for time since exposure > 5 years was 0.25 (95% CI, 0.03-1.87), suggesting that the risk is confined to the first years after the start of the medication. For the same purpose, the analyses were restricted to cases with unknown or no evidence of protopathic bias. In other words, these analyses included cases without documented evidence of symptoms or signs of a previous skin condition in the same location as the subsequently diagnosed cutaneous lymphoma. The result of this sensitivity analysis did not provide evidence for protopathic bias contributing to the observed association between topical tacrolimus and CTCL.

The adjusted IRR of malignant melanoma for single use of topical pimecrolimus in adults was 1.21 (95% CI, 1.03-1.41). Adjusted IRRs were higher in the highest category of cumulative dose. The adjusted IRR for single use with a cumulative dose greater than 1 gram was 1.59 (95% CI, 1.14-2.22).

The adjusted IRR of NMSC for single use of topical pimecrolimus in adults was 1.28 (95% CI, 1.20-1.35). Crude and adjusted IRRs were higher in the highest category of cumulative dose. The adjusted IRR for single use with a cumulative dose greater than 1 gram was 1.43 (95% CI, 1.26-1.62). In adults, the IRRs for non-Hodgkin lymphoma (excluding CTCL), Hodgkin lymphoma, and CTCL for users of topical pimecrolimus compared with users of topical corticosteroids were lower than 1.

Except for malignant melanoma, the IRRs for all other outcomes were elevated in the cohort of users of topical corticosteroids compared with non-users of any study medication. In adults, the IRR for CTCL was 5.42 (95% CI, 3.77-7.79). In the sensitivity analyses performed by time since exposure to the study medications, IRRs for periods of 5 years or longer after first exposure to topical tacrolimus or topical pimecrolimus were not increased compared to the main analyses.

Discussion: Results from the JOELLE study extension phase are similar to those from Phase I of JOELLE and add a longer follow-up to the existing knowledge on the matter. JOELLE study extension phase follow-up was longer than follow-up in any other study of topical calcineurin inhibitors and malignancies, with more than 20% of the study population followed for more than 10 years. When analysing the risk of malignancies associated with long-term follow-up in the sensitivity analyses performed by time since exposure to the study medications, no evidence for the relative risk of skin cancer or lymphoma increasing with increasing duration of follow-up was observed.

Severity of atopic dermatitis is associated with increased risk of malignancies; to control for severity, we used a variable based on the type of prescriber of the first prescription. Nevertheless, type of prescriber is not equivalent to severity of atopic dermatitis, and the lack of more accurate measures of the severity of atopic dermatitis (e.g., clinical assessment) could have resulted in residual confounding and overestimation of the effect of the study medications, especially for topical tacrolimus, which is indicated for more severe forms of atopic dermatitis.

In one sensitivity analysis for protopathic bias, the elevated relative risk of CTCL associated with topical tacrolimus was confined to the first years after starting the medication, which suggests the presence of protopathic bias. However, in the other sensitivity analysis, there was no effect on the elevated relative risk of 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, which implies there was no substantial protopathic bias. In summary, the results of different analyses addressing protopathic bias are inconclusive.

Conclusions: To date, this is the largest study and the one with the longest follow-up evaluating the risk of skin cancer and lymphoma in users of topical tacrolimus and topical pimecrolimus, although half of them received only one prescription/dispensing.

The results of this study are in line with prior studies and could be consistent with an increased risk with topical tacrolimus of CTCL in adults or any lymphoma in children and an increased risk with topical pimecrolimus of skin cancer in adults. However, the interpretation of these findings is complicated by alternative explanations, mainly confounding by indication, protopathic bias, and surveillance bias, which cannot be ruled out. The excess risk of CTCL associated with the use of topical tacrolimus versus the use of moderate- to high-potency topical corticosteroids in adults was 3 cases of CTCL per 100,000 person-years of follow-up (95% CI, 1 to 6). The public health impact associated with such excess risk, if causal, would be low.

In the JOELLE study extension phase, follow-up was longer than in any other study of its kind. The evaluation of a longer latency period for the development of skin cancers and lymphomas in the sensitivity analyses performed by time since exposure to the study medications did not show evidence of malignancies associated with new use of topical tacrolimus or pimecrolimus with long-term follow-up.

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