NON-INTERVENTIONAL STUDY REPORT ABSTRACT

Title:A Population-Based Cohort Study Using an Existing Database to Evaluate the Association Between Latanoprost Use and Primary Malignant Ocular Melanoma And Facial Cutaneous Melanoma

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Rationale and background: Xalatan® (latanoprost ophthalmic solution 0.005%), a topical prostaglandin $F_{2\alpha}$ analogue, was approved for the reduction of elevated intraocular pressure (IOP) in adult patients with glaucoma and ocular hypertension (OH) in the European Union (EU) in 1996. A potential signal of an increased risk of melanoma with latanoprost treatment was raised at the June 2009 Pharmacovigilance Working Party (PhVWP) of the Committee for Medicinal Products for Human Use (CHMP) meeting. This study was designated as a Post-Authorization Safety Study (PASS) committed to the Medicines and Healthcare products Regulatory Agency (MHRA).

Research question and objectives: The primary aim was to examine the potential risk of primary ocular melanoma (OM) and primary facial cutaneous melanoma (CM) associated with latanoprost exposure, among patients with glaucoma or OH. The secondary aim was to examine the potential risk of OM and facial CM for topical prostaglandin analogues (PGAs) exposure among patients with glaucoma or OH.

Study design: A retrospective cohort study using data from the National Health Registers in Sweden.

Setting: Data were used from the Swedish National Health Registers to identify users of topical drugs for glaucoma and OH, co-morbidity, and outcomes of the study. The National Health Registers comprise data on the entire population of Sweden.

Subjects and study size, including dropouts: All Swedish patients with at least one filled prescription of topical drugs for glaucoma or OH between 01 July 2006 and 31 December 2012, without a record of any melanoma at the time of their first dispensing, were included in the study. A patient could contribute exposure time to more than one individual glaucoma and OH medication. In total 227,863 individuals were included in the study, of which 123,235 were exposed to latanoprost. The corresponding figures for other PGAs and non-PGAs were 73,974 and 169,873, respectively. For each subject, follow-up started on the date of the first filled prescription for a topical drug for glaucoma or OH, and ended at the earliest

of the following events: end of the study period (31 December 2012), death, emigration, or occurrence of OM and facial CM.

Variables and data sources: The exposure groups (Latanoprost, other topical PGAs , PGAs and topical non-PGAs), the outcome events (OM and facial CM) and important covariates (socio-demographic factors, clinical characteristics, comorbidities, and concomitant drug use) were ascertained through the following data sources linked by a unique identifier: The National Patient Register, , Prescribed Drug Register, The Population Registers of Statistics Sweden, Sweden Cancer Register and the Causes of Death Register. Cox regression model with time-fixed and time-varying covariates was used for all analyses. The main analyses were conducted on two exposure definitions: ever exposure with 6 months lag time and real-time exposure using no lag time. The ever exposure definition maintained the first drug of exposure until censoring while, the real-time definition considered the drug exposure as a time-varying exposure.

Results

Primary Objectives: In the ever exposure analyses, the observed adjusted hazard ratio (HR) showed no associated risk for OM and facial CM among those exposed to latanoprost compared to non-PGAs (HR: 0.82; 95% CI: 0.27-2.49 and HR: 0.71; 95% CI: 0.48-1.03, respectively). When latanoprost use was compared to other PGA use in the ever exposure analyses, no associated risk for OM (HR: 0.52; 95% CI: 0.19-1.48) or facial CM (HR: 0.71; 95% CI: 0.46-1.10) were identified. The corresponding the real-time exposure analyses also did not show an associated risk.

Secondary Objectives: In the ever exposure analyses, the observed adjusted HR showed no associated risk for OM (HR: 1.58; 95% CI: 0.47-5.32) or facial CM (HR: 1.03; 95% CI: 0.64-1.64) among those exposed to other PGAs compared to non-PGAs. When PGA use was compared to non-PGA use in the ever exposure analyses, no associated risk for OM (HR:1.02; 95% CI: 0.36-2.84) or facial CM (HR:0.79; 95% CI: 0.55 1.13) were identified. The corresponding real-time exposure analyses also did not show an associated risk.

Discussion: The study data showed that latanoprost exposure was not associated with an increased risk of OM or facial CM compared to other PGAs or non-PGAs. The results were consistent across analyses of different exposure definitions, incident use, and across different lag times. The study attempted to control for confounding by utilizing both time-varying and time-fixed covariates of importance in the multivariable model. Even though the study included almost all users of topical PGAs and topical non-PGAs in Sweden, the outcomes of interest, especially OM were uncommon.

Protopathic bias may occur since glaucoma/OH could be the first sign of OM, and the drug exposure may incorrectly be associated with an increased risk of OM. Surveillance bias, may also occur since latanoprost is the first line treatment among PGAs and an ophthalmoscopy is more likely to be performed when initiating glaucoma/OH treatment, than later during treatment, which could increase the probability to detect an OM. However, utilization of lag time seemed to have no substantial impact on the risks, since the results of the cox

regressions were consistent regardless of applied lag time. Residual confounding due to sun exposure is possible since only region of residency was used as proxy of sun exposure; data on occupational sun exposure was not available.

In conclusion, among patients with glaucoma or OH, this study did not find an association between the risk of primary OM and facial CM and lantanoprost utilization compared to utilization of topical non-PGAs or other topical PGAs. Furthermore, no associations were observed between the risk of primary OM and facial CM and PGAs compared to non-PGAs.

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