MAPPING THE GLOBAL SAFETY PROFILE OF SODIUM-GLUCOSE CO-TRANSPORTER-2 INHIBITORS: ANALYSIS OF INTERNATIONAL SPONTANEOUS REPORTING SYSTEMS (FAERS, WHO-VIGIBASE, EUDRAVIGILANCE)

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Background: Sodium-glucose co-transporter-2 inhibitors (SGLT2-Is) are novel antidiabetic drugs, with a possible class effect in reducing cardiovascular mortality, so far shown only for empagliflozin in a dedicated post-marketing trial. Their safety profile is still partly characterized in the post-marketing phase, especially for rare and unpredictable adverse drug reactions (ADRs), which may escape detection in clinical trials.

Aim: To analyze spontaneous reports submitted to major international pharmacovigilance databases, to inform clinicians on their current safety profile in clinical practice.

Method: Eudravigilance, WHO-Vigibase and the FDA Adverse Event Reporting System (FAERS) were queried to extract cases recording SGLT2-Is as suspect. Disproportionality analyses (case/non case method) were performed on FAERS data (2004 first quarter - 2016 second quarter) comparing SGLT2-Is with other antidiabetics. The reporting odds ratio (ROR) with 95% confidence interval (CI) was calculated according to the Medical Dictionary for Regulatory Activities (MedDRA) terminology, from the System Organ Class (SOC) level to Preferred Term (PT) level. Potential signals were defined by statistically significant ROR (i.e., lower limit – LL – of the 95%CI>1) undetected by literature analysis (as of December 2016).

Results: SGLT2-Is were recorded in 7.972, 19.775, 11.148 reports (Eudravigilance, WHO-Vigibase and FAERS, respectively); “infections and infestations” and “metabolism and nutrition disorders” were the most frequently reported SOCs for all SGLT2-Is in the three databases. In FAERS, statistically significant ROR emerged for: “infections and infestations” (N=2.162; LL95%CI=3.25), “metabolism and nutrition disorders” (2.278; 1.36), “renal and urinary disorders” (1.665; 2.31), “reproductive system and breast disorders” (471; 4.85), “skin and subcutaneous tissue disorders” (1.136; 1.52), which emerged as potential signals. Significant RORs were found for all SGLT2-Is for the following PTs: rash, photosensitivity and urticaria. However, no disproportionality emerged when analyzing 81 cases of severe cutaneous ADRs (i.e., Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis, Drug reaction with eosinophilia and systemic syndrome, and acute generalized exanthematous pustolosis).

Discussion and conclusion: As compared to other antidiabetics, SGLT2-Is are associated with higher reporting of infections, metabolism, renal and reproductive ADRs, corroborating evidence from clinical trials. Their reporting pattern and the unexpected signal of skin toxicity justify the need of 1) maintaining active vigilance by clinicians and regulators; 2) performing a periodic “real-time” monitoring of reporting pattern by pharmacovigilance experts. In the meantime, diabetologists, dermatologists and pharmacologists should cooperate to fully characterize clinical data of patients experiencing skin toxicity in order to assess the actual drug-related risk.