Model-based meta-analysis of glucosuria-related adverse events in SGLT2 inhibitors

Authors: Lulu Chu1, Robert C. Penland1, Gabriel Helminger1, David Boulton2

Quantitative Clinical Pharmacology, AstraZeneca, 1Waltham, USA; 2Gaithersburg, USA

Objectives: Dapagliflozin and canagliflozin are two sodium-glucose cotransporter 2 (SGLT2) inhibitors, approved for the treatment of Type 2 diabetes mellitus (T2DM) through promotion of glucose excretion into urine. Inhibition specificities, however, differ between drugs: dapagliflozin has a greater specificity for SGLT2, while canagliflozin demonstrates dual reabsorption inhibitory effects on both SGLT1/2, resulting in greater glucose excretion. We hypothesized that higher urinary glucose excretion, based on dual SGLT1/2 inhibition, may also be associated with higher incidence of adverse events (AE); such potential differences have not been thoroughly explored and remain controversial. We quantified glucosuria-related AEs, including urinary tract infection (UTI), genital mycotic infections, and volume depletion, using a model-based meta-analysis (MBMA) approach.

Methods: We performed a systematic collection of clinical data from PubMed, Google Scholar, ClinicalTrials.gov, and internal study reports, up to 2015, to identify randomized Phase II/III trials reporting the occurrence of UTIs, genital mycotic infections and volume depletion in T2DM patients. Logistic regression models were developed to assess the relationship between dose and AE rates. UTI was described using a linear logistic model; genital mycotic infections and volume depletion were modeled at individual dose levels.

Results: The MBMA included 29 trials of dapagliflozin and canagliflozin, reflecting 15,790 patients. Modeling results show that a significantly higher percentage (> 3-fold) of canagliflozin patients experienced a greater rate of genital mycotic infections at both approved doses (100 and 300 mg QD) vs. dapagliflozin (5 and 10 mg QD) (Figure 1). Canagliflozin had statistically non-significant incidences of urinary tract infection (UTI) and in volume depletion AEs compared to dapagliflozin, but UTIs were numerically higher for canagliflozin (≤6.8%) than dapagliflozin (≤4.8%).

Conclusions: Our study showed that patients with T2DM treated with canagliflozin experienced a significantly higher (>3-fold) incidence of genital mycotic infections compared to dapagliflozin at approved doses presumably due to canagliflozin’s greater extent of glucosuria.