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Analysis and projection of SGLT2-inhibitor-related urinary tract infections throughout the decade

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Background

In the search for an anti-diabetic medication that avoids the effect of hypoglycemia, a new diabetes class of medication known as the sodium glucose co transporter 2 inhibitor (SGLT2) was discovered. Invokana® (Canagliflozin) is the first FDA approved medication of its class in 2013. In conjunction with diet and exercise, it aims to improve glycemic control in patients with type 2diabetes.[1] The protein SGLT2 works by facilitating glucose reabsorption into the kidney. Inhibition of this protein leads to an increased amount of glucose excreted in the urine while simultaneously lowering blood glucose levels.[2] However, post marketing data and phase 3 trials indicated a potential for increased urinary tract infections (UTI) as collateral damage from large glucose amounts in the normally sterile urine.[3] There is even a FDA safety communication that was issued in 2015 explaining the increased risk of urinary tract infections with these agents.[4]

The FDA's adverse event reporting system (FAERS) is a publicly available database that contains thousands of adverse events pertaining to medications and is a tool that can be utilized to track adverse reactions. The database consists of safetyreport_id (a number correlating each drug listed along with its reported reactions) and reactionmedrapt (a word or phrase detailing the reaction), and other variables in order to track specific medications and adverse events by location, indication, etc. Using the database to generate a case control study with these two variables will allow researchers to generate the number of urinary tract infections reported since 2013 in canagliflozin and project forwards.

With the advent of machine learning software prevalent throughout the scientific community, it has now become a common luxury to utilize such statistical learning methods in an effort to elucidate trends over time and create an ever adaptable predictive model generating projected incidence rates based on tamed data. Google has created free ML software known as Smart ML which utilizes a mathematical statistical model known as a root mean square error.[5] The model works by taking into account all of the categorical data fed into it and then predicts the following year. The process is repeated as many times as possible to predict any number of years desired. Combining the FAERS database and statistical execution has a myriad of applications in the clinical and pharmacovigilance fields as a powerful evaluative benchmark for adverse event reporting.

Methods

The FAERS database will be cultivated for all safety report id, medicinal product, report year, and adverse reaction for canagliflozin from 2013 - 2015. A subgroup of all of the patients taking canagliflozin who developed a urinary tract infection will be data mined into a separate excel sheet. Subsequently, the accrued data will be fed into the Google machine learning model known as Smart Autofill in order to predict the amount of UTI occurrence in 2016. Then accounting for the new data, it will be fed into Smart Autofill to predict 2017-2020. Ideally, this computation will estimate the number of pertinent adverse reports filed for the coming years and then, upon instruction from the researchers, evaluate how the expected amount of urinary tract infections will vary from 2016 to 2020. After final projections were tallied using the ML Autofill, the amount of reactions in the upcoming 5years were graphed in an effort to detail the trends of reported urinary tract infection.

Results

As shown in the charts below, the lowest incidence of reported urinary tract infections was in 2013 because it was a recently approved medication. As the years went on, more adverse events were being reported and thus the amount of urinary tract infections that was being reported increased tremendously. The reports reached a peak in 2015 when the FDA safety communication was released early that year. When all of the data was fed into the Google drive software it predicted that the amount of reported urinary tract infections over a 5year span. It showed a decrease in reports in 2016 followed by an increase over the next 4years. Overall by the year 2020, the prevalence of urinary tract infections will be at an all time high (Figure 1).

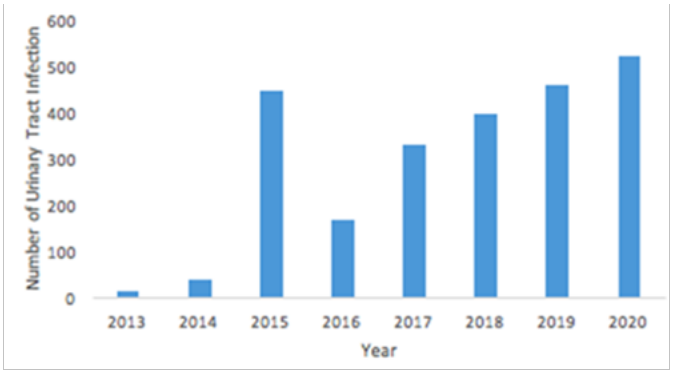

Figure 1 Invokana urinary tract infection reports

Discussion

While the fundamental limitation of a retrospective case control may be problematic in reversing or reinforcing current prescribing

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information, certain conclusions from the data can be drawn at this particular cross section in time. Firstly, projected SGLT2 caused UTIs seem to be a growing report in the near future, as opposed to a shrinking dataset. Ideally, the recent FDA warning would temper use of the drug and therefore show less reaction in 2017 and beyond than calculated. The increase in reports from 2013 - 2015 is expected since the sheer amounts of UTI being reported warranted a FDA warning. On the other hand our model predicts a growing trend from 2016 - 2020 since the data that was fed into the statistical model showed an increase from 2013 - 2015. One possibility of the decreased reports in 2016 is due to the FDA warning that was issued in 2015. Since the warning will be fairly new, health care professionals may take into account more patient factors before prescribing Invokana. Secondly, this model may not be perfect for predicting occurrence of UTI since there is only a small amount of data since the SGLT2 inhibitors have only been on the market since 2013. If more data could be accumulated and fed into Smart Autofill, then a more accurate picture can be presented in a 5year span. Lastly, although this model does not account for extraneous factors such as drug shortages and general catastrophes, extrapolation of pharmacovigilance data is now a real-time capability for healthcare providers.

This tool fundamentally allows clinicians to assess safety data over time and into the future as needed, perhaps even in ad-hoc patient care. Configuring the historical dataset to each patient's electronic health profile could allow instantaneous predictive analysis and generate faster, statistically-reinforced clinical decisions, combining breakthrough technological applications with expert opinion and guidance. This predictive model of patient reported UTIs caused by canagliflozin, serves as a quick glance into future if patient's and health care providers do not heed the FDA communication warning in May of 2015.

Acknowledgements

None.

Conflict of interest

The author declares no conflict of interest.

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