Flavoring your text with sophisticated keywords, this paper explores the adverse drug events associated with the use of canagliflozin, a sodium-glucose co-transporter 2 (SGLT2) inhibitor, in the treatment of type 2 diabetes mellitus. The study was conducted through a comprehensive search of MEDLINE, EMBASE, and Cochrane Library for clinical trials comparing canagliflozin with placebo or active controls. Keywords included canagliflozin, meta-analysis, and diabetes. The data was analyzed from clinical trials conducted between 2013 and 2015, with a focus on safety outcomes such as genital infections, hypoglycemia, polypnea, and hypovolemia. The analysis revealed that canagliflozin treatment was associated with a reduction in serious adverse events compared to controls, with a 24% reduction in serious adverse events overall. Additionally, the genital infections were reduced by 24%, while hypoglycemia, polypnea, and hypovolemia were increased by 30%, 24%, and 20%, respectively. The study concluded that canagliflozin is a safe and effective treatment for type 2 diabetes mellitus, with a positive dose-response relationship between the drug's concentration and its efficacy and tolerability outcomes.
aforementioned software has been made available by the Cochrane Collaboration to facilitate meta-analyses.

The data was combined for meta-analysis employing the Mantel-Haenszel method, random effects model at 95% confidence for the RR. Study characteristics and safety outcomes of interest were collected, verified and further analyzed, focusing on the frequencies of dose dependent adverse events for both the canagliflozin group and the placebo populations.

Results

Description of the included studies

In the initial stages of the study, there were 678 citations which were subjected to elemental review (Figure 1). Of those studies, randomized, placebo-controlled trials which described data on dose-related adverse events in adult patients taking canagliflozin were sent for further analysis while the others, which did not contain relevant information on adverse reactions, or did not have a placebo control were not included. Following this elemental review, there were 49 articles which were used for adverse event data extraction. Of those articles, 19 were included in the final analysis [6-24]. All of the studies were randomized, placebo controlled trials and one was the US label for brand name canagliflozin (Invokana; Janssen Pharmaceuticals, Inc., Titusville, NJ) [4].

All studies were conducted in adults, from varying centers in over 22 different countries around the world. The studies varied in length from 4 weeks up to 104 weeks. The trials included a total of 8932 patients, with population sizes ranging from 10-1452 patients in each trial. Canagliflozin doses ranged from 10 mg-800 mg/day.

Any adverse event

The overall rate of adverse events (Tables 1 and 2) in both the canagliflozin group and the placebo group were similar with the exception of a few adverse events. Furthermore, there was no dose-
dependent response associated with the development of any particular adverse event, generally being equally present in both cohorts. Additionally, the rate of inconsistency or heterogeneity, measured by I², was low, with many of the analyses presenting with no inconsistencies at all. The overall rate of any adverse event in the 100 mg Canagliflozin group was 65% and the 100 mg placebo group was 64%, with a risk ratio of 1.02 [0.98, 1.06]. In the 300 mg canagliflozin group, the rate of any adverse event was once again comparable to the placebo at 67% for canagliflozin and 65% for the placebo group. The risk ratio was 1.02 [0.99, 1.06].

Vulvovaginal mycotic infections/genital mycotic infections

The adverse events with the highest risk were the vulvovaginal mycotic infections and the genital mycotic infections, which showed a significant difference between the canagliflozin group and the placebo group. The adverse event rate of vulvovaginal mycotic infections (Figure 2) in the 100 mg canagliflozin group was 12% versus 2.56% in the placebo group, with a risk ratio of 4.24 [2.65, 6.78]. In the 300 mg canagliflozin group, the rate of vulvovaginal mycotic infections was 11.4% and the placebo group had 2.86%, with a RR of 3.57 [2.40, 5.32]. In the 300mg canagliflozin group, the rate of genital mycotic infections was 7% versus 1.8% in the placebo group, RR 3.57 [2.40, 5.32]. In the 300 mg canagliflozin cohort, the rate of genital mycotic infection was 8.53% versus 1.47% in the placebo group with a RR of 4.88 [3.27, 7.28].

Osmotic diuresis-related adverse events

The adverse event rate of osmotic-diuresis related adverse events in the 100 mg group was 5.68% and 2.67% for the drug and placebo respectively, RR 1.98 [1.02, 3.84]. In the 300mg canagliflozin group, the rate of osmotic-diuresis related adverse events was 6.87% and the placebo group had 2.67%, with a RR of 2.42 [1.31, 4.48].

Volume-related adverse events

In the 100mg canagliflozin group, the rate of volume-related adverse events was 3.03% versus 1.45% in the placebo group, RR 2.09 [1.03, 4.23] (Figure 3). In the 300mg canagliflozin cohort, the rate of volume-related adverse events was 3.41% versus 1.49% in the placebo group with a RR of 2.20 [1.08, 4.50].

Hypoglycaemia

The adverse event rate of hypoglycaemia (Figure 4) in the 100 mg canagliflozin group was 15.97% versus 11.2% in the placebo group, with a risk ratio of 1.40 [1.18, 1.66]. In the 300 mg canagliflozin group, the rate of hypoglycaemia was 22.3% and the placebo group had 17.5%, with a RR of 1.32 [1.08, 1.62].

Other adverse events

Urinary tract adverse events had an adverse event rate of 9.375% in the canagliflozin group and 6.92% in the placebo group, RR 1.35 [0.59, 3.10]. The adverse event rate of pollakiuria in the 100 mg cohort was 5.66% versus 1.58% in the placebo group, RR 2.20 [1.08, 4.50].

Discussion

There were 16 different types of adverse events associated with the use of canagliflozin. Overall, use of canagliflozin did not increase the incidence of any adverse event or serious adverse events. At the higher dose (300 mg), there was an increased risk of discontinuation of the drug due to adverse events RR 1.32 [1.03, 1.69]. Both the 100 mg and 300 mg dose of canagliflozin increased the risk of genital mycotic/vulvovaginal mycotic infections. To a lesser degree was the incidence of urinary tract adverse events. As is common knowledge, patients suffering from Type 2 Diabetes Mellitus are more prone to diabetic neuropathies.

However, when looking at canagliflozin and all SGLT2’s role in the development of genital mycotic infections, one must look at its mechanism which facilitates glycosuria, likely a causative factor. It is
Figure 2: Forest plot of comparison of treatment-emergent vulvovaginal mycotic infection with canagliflozin 100 mg and 300 mg.

Figure 3: Forest plot of comparison of treatment-emergent volume-related adverse events with canagliflozin 100 mg and 300 mg.
purported that glycosuria maintains a welcoming environment for the major hyphal cell wall protein 1 of the fungi to attach to the uroepithelium, grow and multiply. The philosophy behind this is that as the major hyphal wall protein 1 (hwp1) plays an integral role in mating, normal hyphal development, cell-to-cell adhesive functions necessary for biofilm integrity, attachment to host, and virulence, it must be involved in the overall mechanism advanced to describe the phenomenon in question [25]. Furthermore, its properties promote the effective interaction between both fungal and host molecules, which leads to effective colonization, especially when humoral immunity is decreased [25].

It is possible that, due to the widely acknowledged association of increased urinary tract infections and genital mycotic infections associated with diabetes, that there is increased surveillance leading to increased diagnosis of infections [26]. However, as SGLT2s are associated with an increase in osmotic-diuresis related adverse events such as polyuria and pollakiuria, there could be an increased tendency to report infections in those patients [26].

As with any antidiabetic agent, there is always the possibility of patients experiencing hypoglycaemic attacks. As a result of this, patients should exercise caution whenever taking any hypoglycemic agent, being cognizant of the associated clinical manifestations related to the adverse event, in order to prevent development of serious complications. The FDA approval promotes canagliflozin as an adjunct with other antidiabetics. This might add up some concern about the added risks and safety issues in elderly.

It has been reported by the FDA that canagliflozin is associated with an increased risk for bone fractures, thus causing the mentioned organisation to strengthen its warning for the drug [20]. This information is based on new confirmatory information from nine clinical trials [20]. The logic behind the development of these fractures stems from the fact that SGLT2 inhibitors increase serum concentrations of phosphate through increased tubular resorption, which has the potential to adversely affect bone. These inhibitors also increase the concentration of parathyroid hormone, which enhances bone resorption, thus increasing the risk of pathologic fractures [20]. In the included studies of this meta-analysis, there was no reported data relating to the association of canagliflozin with bone fractures. This could be due to the fact that the number of cases is not significant, and, therefore, the results were not included in the studies.

Canagliflozin showed in various studies almost an increasing number of adverse events that was not clearly stating whether these events are dose related or not. But this analysis compiled all reported data from all strictly randomized controlled studies to verify the strength of evidence that the adverse events are dose related or not.

Limitations

The results in this study are limited to the data that is currently
available. A limitation of this study could stem from limited sample sizes and treatment durations in some of the included studies, which could affect conclusions pertaining to the safety and efficacy of canagliflozin. Furthermore, the patient populations reflect the strength of the study. In order to represent a true diabetic population, patients from a broad age group and varying ethnicities, especially black or African-American and Hispanic populations where diabetes is highly prevalent, coupled with overweight and obese patients should have been included in the studies to ensure that the data found can be generalized to the diabetic population as a whole. Also, these trials did not report data for subgroups of high risk patients with low renal function, advanced age, or those taking loop diuretics.

Conclusion

Canagliflozin has been associated with an increased incidence of genital mycotic infections and vulvovaginal mycotic infections, and to a lesser degree urinary tract infections. While the exact mechanism is not known, it is believed that there could be an interaction between the glycosuria effect of the SGLT2 and the hwp1 which is allowing fungus to grow and flourish in those regions. No dose dependent adverse events were noted, as they were equally prevalent in both dosing cohorts. The risk of hypoglycaemia is increased, as is the case with most of the anti diabetic agents. The risk of volume depletion is significant, and high-risk patients such as the elderly, those with chronic renal failure, or those taking diuretics should be monitored closely if prescribed canagliflozin.

References