SUMMARY

Diabetes mellitus impacts a substantial number of people worldwide and despite numerous antidiabetic medications available, approximately half of the drugs do not attain their recommended target, glycated hemoglobin (HbA1c). Recently, the kidney and its role in glucose reabsorption through the sodium/glucose cotransporter 2 (SGLT2) has been the target for novel antidiabetic treatments. Pharmacologic inhibition of SGLT2 in patients with diabetes results in increased urinary glucose excretion and decreased blood glucose levels, decreasing HbA1c levels. Tofogliflozin is the most selective SGLT2 inhibitor, with HbA1c reductions ranging from -0.44% to -0.99% throughout clinical studies, and it is well tolerated with a low rate of drug-related adverse events. Tofogliflozin has demonstrated efficacy and safety as monotherapy or as add-on to various antidiabetic agents, and it is currently undergoing phase IV clinical studies in Japanese patients with diabetes on background insulin therapy. Tofogliflozin is currently approved in Japan for use in patients with type...
2 diabetes at a dose of 20 mg orally once daily in the morning, either before or after breakfast.

Key words: Tofogliflozin – Sodium/glucose cotransporter 2 – Diabetes

BACKGROUND

Diabetes mellitus (DM) impacts over 347 million persons worldwide and these numbers continue to rapidly grow due to rises in overweight, obesity and physical inactivity (1). Total deaths from DM are projected to climb by more than 50% in the next 10 years and DM is predicted to become the seventh leading cause of death in the world by the year 2030 (1). In the United States, DM impacts more than 25 million persons and despite numerous antidiabetic medications being available, approximately half do not attain the American Diabetes Association (ADA) recommended target HbA1c of < 7.0% (2). In many cases, currently available antidiabetic medications are not sufficient in controlling DM and their undesirable adverse events (AEs), such as hypoglycemia, weight gain, edema or gastrointestinal symptoms, to name just a few, further limit the ability to maximize their use.

Historically, scientists understood DM to be caused by a triad of pathophysiological defects affecting beta cells, the liver and muscle. However, researchers now appreciate that DM includes eight pathogenic mechanisms, termed the “ominous octet” (Fig. 1) (3). One of the most recent areas of interest being studied within the “ominous octet” is the kidney and its predilection for enhanced glucose reabsorption in DM (3). In healthy individuals without DM, glucose is filtered in the glomerulus of the kidney and almost completely reabsorbed in the proximal tubule by sodium/glucose cotransporters (SGLTs), mainly by low-affinity/high-capacity SGLT2 and slightly by high-affinity/low-capacity SGLT1 (4). In these healthy individuals with complete reabsorption of glucose, there is minimal urinary glucose excretion (UGE), unless the transporter capacity is exceeded (5). DM patients have an upregulation of SGLT2 expression with an increased threshold for UGE, resulting in increased renal glucose reabsorption, decreased UGE and hyperglycemia (5). Inhibition of SGLT2 lowers the glucose excretion threshold in DM patients, ultimately decreasing renal glucose reabsorption, increasing UGE and decreasing hyperglycemia (5).

Genetic mutations of SGLT2 in humans, also known as familial renal glucosuria, result in increased UGE with minimal sequelae; these patients are generally asymptomatic with increased UGE (6, 7). Such observations increased the enthusiasm for SGLT2 inhibition as a treatment for DM. On the other hand, mutations of the SGLT1 gene, also known as glucose-galactose malabsorption, result in severe diarrhea and dehydration due to the presence of SGLT1 in the small intestine, with only mild UGE (4, 7, 8). Therefore, an ideal pharmacological treatment for DM would be a medication highly selective for SGLT2 inhibition resulting in increased UGE and decreased blood glucose levels in an insulin-independent manner, which would allow its use in combination with other antidiabetic agents for both type 1 and type 2 diabetes (T1DM, T2DM) patients (4, 7, 8).

SGLT2 inhibitors are the most recent medication class approved for the treatment of T2DM. These drugs have a promising future due to their distinct mechanism of action and positive AE profile. Several medications in this drug class have already been approved worldwide for the treatment of T2DM, including canagliflozin (Invokana®; Janssen; US), dapagliflozin (FarxigaTM; Bristol-Myers Squibb, AstraZeneca; US), empagliflozin (Jardiance®; Boehringer Ingelheim, Eli Lilly; US), and ipragliflozin (Suglat®, Astellas Pharma; Japan), and many more are currently undergoing different phases of clinical studies.

The objective of this review is to discuss the role of the kidney in glucose homeostasis and evaluate the efficacy and safety of tofogliflozin, a novel drug within the drug class SGLT2 inhibitors.

Figure 1. Ominous octet (3).
LITERATURE SEARCH

A comprehensive literature search of the MEDLINE database was conducted to identify all relevant studies and articles published in English up until September 2014. The search terms utilized were tofogliflozin, CSG452, RG7201, RO4998452, Apleway(R), Deberza(R), SGLT2 inhibitor, antidiabetic agents and renal glucose reabsorption. All pertinent studies and articles were evaluated for use, including preclinical, animal and human studies. Because of the limited information available, abstracts and scientific presentations of clinical studies not published were incorporated for completeness.

DRUG DISCOVERY

Phlorizin, a natural nonselective SGLT inhibitor, was the first compound identified that supported the idea of inhibiting SGLT to reduce blood glucose in rodents, but could not be developed into a pharmacological treatment due to poor stability to β-glucosidases (9). Since the discovery of phlorizin, many different SGLT2 inhibitors have been developed and are categorized as O-glucosides (T-1095, sergliflozin, remogliflozin) and C-aryl glucosides (canagliflozin, empagliflozin, dapagliflozin) (10). To date, not a single O-glucoside SGLT2 inhibitor has successfully passed phase II studies, likely due to their instability to β-glucosidases, similarly to phlorizin, and only C-aryl glucosides have been Food and Drug Administration (FDA) approved (10, 11).

Tofogliflozin (CSG-452, RG-7201, RO-4998452; Fig. 2) was discovered through a structural database search using a 3D pharmacophore model derived from known inhibitors, and specific substitutions on the aromatic rings were chosen based on favorable properties (10). In the para-substitution position on the distal benzene ring, a small alkyl was advantageous to achieve both SGLT2 inhibition and SGLT2 selectivity (10). In the 4-substitution position on the central benzene ring, a small group, such as chloro, slightly increased the SGLT2 inhibition potency, but lowered the SGLT2 selectivity (10). The compound with the most balanced profile for selectivity and potency was selected to create tofogliflozin, O-spiroketal C-aryl glucoside, which is the most selective SGLT2 inhibitor currently developed (7, 10, 12).

Tofogliflozin was originally developed by Chugai Pharmaceutical, which entered a licensing agreement with F. Hoffmann-La Roche in January, 2007, granting the overseas development and marketing rights for tofogliflozin to Roche (13). The two companies conducted a global phase II study as a co-development program, but on July 5, 2011, Roche returned the development and marketing rights to Chugai Pharmaceutical (13). Chugai Pharmaceutical then entered a licensing agreement with Kowa Company, Ltd. and Sanofi K.K. on October 26, 2012 (14). This arrangement stated that all three companies would co-develop the compound, but Kowa and Sanofi would file the application for marketing authorization under their own brand names (14). Tofogliflozin (Apleway, Sanofi K.K., Japan; Deberza, Kowa Company, Ltd., Japan) received its first global approval in Japan on March 24, 2014, for the treatment of T2DM in adults at a dose of 20 mg orally once daily in the morning either before or after breakfast.

PHARMACOKINETICS AND PHARMACODYNAMICS

A phase I, open-label, nonrandomized study investigated the excretion, pharmacokinetics and metabolism of a single oral dose of $^{14}$C-labeled tofogliflozin 20 mg and an intravenous microdose of $^{13}$C-labeled tofogliflozin 0.1 mg 45 minutes after the oral dose in six healthy male subjects (15, 16). Tofogliflozin has a rapid and high oral bioavailability of 97.5%, achieving a maximum plasma concentration ($C_{\text{max}}$) of 489 ng/mL at 0.75 hours post-administration (16, 17). The volume of distribution at steady-state was low at 50.6 and tofogliflozin had a low clearance of approximately 10 L/h, which allowed for high exposures to the medication (17). Renal clearance of tofogliflozin accounted for 15.5% of total clearance, implying that patients with renal impairment likely will not require dose adjustments (16-18). In addition, the active tubular secretion of tofogliflozin ensured a high exposure of the medication to the target region of the kidney (i.e., proximal tubule) despite the low contribu-
tion of renal clearance to the total clearance (16). After oral administration of tofogliflozin, approximately 76% was excreted in the urine within 48 hours and approximately 20% was excreted in the feces within 72 hours, increasing to 77 and 22% within 168 hours, respectively, indicating complete excretion (> 99%) of tofogliflozin occurs within 7 days (15). According to in vitro data, tofogliflozin is mainly metabolized by cytochrome P450 (CYP) enzymes (2C18, 4A11, 4F3B, 3A) and only one transporter, P-glycoprotein, is potentially relevant (17). Tofogliflozin has not been found to inhibit any major CYP enzymes or transporters, reducing its risk of drug–drug interactions (17).

A phase I open-label study investigated the effects of renal impairment on pharmacodynamics and pharmacokinetics of tofogliflozin following a single dose of tofogliflozin in T2DM patients with varying degrees of renal impairment (e.g., mild, moderate, severe or no renal impairment) (17, 18). A single oral dose of tofogliflozin 20 mg was administered to 36 T2DM patients with an estimated glomerular filtration rate (eGFR) ranging from 8 to 142 mL/min (17, 18). Renal clearance had a slight contribution (19%) to total systemic clearance, thus impaired renal function has no effect on systemic exposure to tofogliflozin (17, 18). Results of the study indicated that although there was stable inhibition of glucose reabsorption across all renal function groups, a decrease in UGE correlated with worsening eGFR (17, 18).

**CLINICAL STUDIES**

Table I summarizes the clinical efficacy studies completed or ongoing with tofogliflozin. A phase II, 12-week, placebo-controlled, dose-ranging study evaluated the safety, tolerability and efficacy of tofogliflozin in 398 patients with T2DM on diet and exercise alone (40%) or on a stable dose of metformin (60%) (19, 20). Patients were randomized in a 1:1:1:1:1 fashion to tofogliflozin 2.5 mg (n = 64), 5 mg (n = 65), 10 mg (n = 66), 20 mg (n = 64), 40 mg (n = 66) or placebo (n = 65), administered orally once daily in the morning 15 minutes before breakfast (20). At baseline, the mean HbA1c ranged from 7.87 to 8.01% and the mean body weight ranged from 81.6 to 85.5 kg (20). The mean change in HbA1c from baseline to week 12 was significantly greater (P < 0.001) in all tofogliflozin arms (except 2.5 mg) compared with the placebo arm, with placebo-adjusted mean changes of −0.44, −0.62, −0.69, −0.77 and −0.83% in the tofogliflozin 2.5, 5, 10, 20 and 40 mg arms, respectively (20). There were significant reductions in body weight in the tofogliflozin arms, with placebo-adjusted differences of −1.6, −1.9, −2.2, −2.6 and −2.8 kg for tofogliflozin 2.5, 5, 10, 20 and 40 mg, respectively (20).

A combined phase II/phase III study evaluated the efficacy and safety of tofogliflozin in 235 Japanese patients with T2DM treated exclusively with diet and exercise for at least 8 weeks (21, 22). Patients were randomized in a 1:1:1:1 fashion to tofogliflozin 10 mg (n = 59), 20 mg (n = 60), 40 mg (n = 59) or placebo (n = 57), administered orally once daily in the morning before breakfast (21, 22). At baseline, the mean age for all four arms ranged from 56.6 to 58.6 years, the mean HbA1c ranged from 8.34 to 8.45%, the mean fasting blood glucose ranged from 167.9 to 170.2 mg/dL, the mean BMI ranged from 25.0 to 26.0 kg/m², the mean duration of T2DM ranged from 6.0 to 6.7 years, and 26.3 to 39.7% of patients had previously received anti-diabetic treatments (6, 22). The least squares mean change in HbA1c from baseline to week 24 was significantly greater (P < 0.0001) in all three tofogliflozin arms compared with the placebo arm, with placebo-adjusted mean changes of −0.769, −0.990 and −0.842% in the tofogliflozin 10, 20 and 40 mg groups, respectively (6, 22). There were significant reductions in body weight in the tofogliflozin arms, with placebo-adjusted differences of −1.87, −2.50 and −2.61 kg for tofogliflozin 10, 20 and 40 mg, respectively (6, 22). Significant reductions in systolic blood pressure (SBP) of −6.8, −7.6, and −9.4 mmHg and significant reductions in diastolic blood pressure (DBP) of −5.6, −4.1 and −4.1 occurred with tofogliflozin 10, 20 and 40 mg, versus placebo (SBP = −3.2 mmHg; DBP = −1.4 mmHg) (21, 22).

A phase III study examined the efficacy and safety of tofogliflozin administered for 52 weeks as monotherapy in addition to diet and exercise in 194 Japanese patients with T2DM (12). Patients were randomized to tofogliflozin 20 mg (n = 65) and 40 mg (n = 129) administered orally once daily before or after breakfast (12). At baseline, the mean age was 58.7 and 57.8 years, the mean BMI was 25.88 and 25.39 kg/m², the mean HbA1c was 7.83 and 7.86% and the mean duration of DM was 5.63 and 5.36 years, in the tofogliflozin 20- and 40-mg groups, respectively (12). The mean change in HbA1c was significantly different from baseline to week 52 with a reduction of −0.67 and −0.66% (P < 0.0001) in the tof ogliflozin 20- and 40-mg groups, respectively (12). At 52 weeks, 34.9 and 40.9% of patients on tofogliflozin 20 and 40 mg, respectively, reached an HbA1c goal of < 7% (12). There were significant reductions in body weight in
both groups, with mean reductions in body weight compared to baseline of –3.06 and –3.44 kg, respectively (12). Significant reductions in SBP of –6.00 and –3.3 mm Hg, and significant reductions in DBP of –3.9 and –1.0 mm Hg occurred on tofogliflozin 20 and 40 mg, respectively (12).

A phase III study examined the efficacy and safety of tofogliflozin administered for 52 weeks combined with one other oral hypoglycemic agent (e.g., biguanides, sulfonylureas, thiazolidinediones, meglitinides, α-glucosidase inhibitors and dipeptidyl peptidase 4 inhibitors) in addition to diet and exercise in 602 Japanese patients with T2DM (12, 23). Patients were randomized to tofogliflozin 20 mg (n = 178) and 40 mg (n = 424) administered orally once daily before breakfast (12). For tofogliflozin 20- and 40-mg, the mean age was 58.2 and 58.7 years, the mean BMI was 25.53 and 25.68 kg/m², the mean HbA₁c was 8.13 and 8.12% and the mean duration of DM was 7.62 and 7.71 years, respectively (12, 23). The mean change in HbA₁c was significantly different from baseline to week 52 with a reduction of –0.77 and –0.87% (P < 0.0001) in the tofogliflozin 20 and 40 mg arms, respectively (12). After 52 weeks, 32.0 and 34.4% of patients on tofogliflozin 20 and 40 mg, respectively, reached an HbA₁c goal of < 7% (12). There were significant reductions in body weight in both study groups, with mean reductions in body weight compared to baseline of –2.51 kg in patients treated with 20 mg of the drug and –2.98 kg in the 40-mg group (12). Significant reductions in SBP of –3.1 and –5.2 mmHg, and significant reductions in DBP of –2.1 and –2.2 mmHg occurred in the 20- and 40-mg groups, respectively (12).

There is one phase IV study currently enrolling T2DM patients aged 20-75 years with an HbA₁c ≥ 7.5 - ≤ 10.5% and fasting plasma glucose ≤ 220 mg/dL on insulin for ≥12 weeks. The study has a 16-week placebo-controlled portion to assess the 16-week efficacy and safety of treatment with tofogliflozin in addition to a 36-week open-label extension study to assess the 52-week long-term safety of tofogliflozin with insulin treatment in T2DM patients (24).

**SAFETY AND TOLERABILITY**

In a phase II dose-ranging study adding tofogliflozin from 2.5 to 40 mg to diet and exercise or metformin for 12 weeks, tofogliflozin was well tolerated and did not
increase the incidence of hypoglycemia, urinary or genital tract infection, or cardiovascular events compared to placebo (20). In a phase II/III study adding 10, 20 or 40 mg of tofogliflozin to diet and exercise, approximately 44.6-60.3% of patients experienced at least one AE, but only 3.4% experienced AEs leading to discontinuation of study medication (6, 22). AEs occurring in ≥ 5% of patients and likely due to tofogliflozin were hyperketonemia, ketonuria, polyuria and headache (6, 22). Hyperglycemia occurred at a very low rate of 1.7%, were all mild or moderate, and all resolved on their own (6, 22). Urinary tract and genital infections occurred in two patients in the tofogliflozin 40-mg group (1.7%), were both mild and both resolved on their own without treatment (6, 22).

In a phase III study adding tofogliflozin 20 or 40 mg to diet and exercise in T2DM patients, 76.6% (20 mg) and 86.6% (40 mg) of patients experienced at least one AE (12). AEs likely due to treatment occurring at an incidence of ≥ 5% were polyuria (12.5% and 14.2%), thirst (10.9 and 12.6%), increased blood ketone bodies (6.3 and 20.5%) and hypoglycemia (6.3 and 3.9%) (12, 17). Genital infections occurred in 1.6% (vulvitis and vulvovaginal candidiasis) of patients in the tofogliflozin 40-mg arm, but none occurred in the tofogliflozin 20-mg arm (12). Urinary tract infections occurred in 1.6 and 0.8% of the patients in the tofogliflozin 20- and 40-mg groups, respectively (12).

In a phase III study adding tofogliflozin 20 or 40 mg to one other oral hypoglycemic agent (e.g., biguanides, sulfonylureas, thiazolidinediones, meglitinides, α-glucosidase inhibitors and dipeptidyl peptidase 4 inhibitors) in addition to diet and exercise, 86.3 and 84.7% of patients experienced at least one AE, respectively (12). AEs likely due to tofogliflozin 20 and 40 mg occurring at an incidence of ≥ 5% were polyuria (6.3 and 6.7%), thirst (8.0 and 10.0%), increased blood ketone bodies (13.1 and 11.2%) and hypoglycemia (4.0 and 4.8%) (12). Investigating the hypoglycemia further, 63% of the hypoglycemias occurred when tofogliflozin was used in combination with sulfonylureas or meglitinides (12, 23).

CONCLUSIONS

Tofogliflozin is a highly selective SGLT2 inhibitor currently approved in Japan for use in T2DM patients at a dose of 20 mg orally once daily in the morning either before or after breakfast. The strong selectivity of tofogliflozin for SGLT2 may be the reason for reduced AEs, specifically a lower hypoglycemia rate since glucose reabsorption is not inhibited via SGLT1. Tofogliflozin has demonstrated efficacy and safety as monotherapy and as add-on to various antidiabetic agents, but further large-scale studies are vital to determine the effects of tofogliflozin on cardiovascular events and to investigate any further safety concerns.

DISCLOSURES

The authors state no conflicts of interest.


REFERENCES


