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REVIEW

Ertugliflozin: a sodium-glucose cotransporter-2 (SGLT-2) inhibitor for glycemic control in type 2 diabetes

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Abstract: Recently, a new class of anti-diabetic drugs has found its way into the market: sodium-glucose cotransporters (SGLT) inhibitors. Two major SGLT isoforms have been identified: SGLT-2, mainly expressed in proximal renal tubules, and SGLT-1, mainly expressed in the small intestine, the proximal renal tubule, and the myocardium. SGLT-2 inhibitors increase urinary glucose excretion, lowering glycemia without inducing excessive insulin secretion. Marketed SGLT-2 inhibitors actually include dapagliflozin, canagliflozin, and empagliflozin; a new SGLT-2 inhibitor is being studied: ertugliflozin. Ertugliflozin is a potent inhibitor of SGLT-2 and possesses a high selectivity over glucose transport via SGLT-1 and several other glucose transporters GLUT-1–4. Ertugliflozin inhibits renal glucose reabsorption resulting in urinary glucose excretion and thereby reduces plasma glucose and glycated hemoglobin in subjects with type 2 diabetes mellitus. Ertugliflozin is being developed as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus. The aim of this review is to evaluate the preliminary published data about this new molecule.

Keywords: ertugliflozin, glycol-metabolic control, SGLT-2 inhibitors

Introduction

The latest American Diabetes Association guidelines assert that lowering glycated hemoglobin (HbA_{1c}) to 7% reduces microvascular and neuropathic complications of diabetes[1]; this is related also to a decrease in long-term macrovascular complications. For this reason, in the latest years, several drugs have been marketed for the cure of type 2 diabetes mellitus (T2DM). The latest class to be marketed is the class of sodium-glucose cotransporters-2 (SGLT-2) inhibitors. Physiologically, the kidney transfers all plasma glucose into urine within the nephron, but subsequently, completely reabsorbs the filtered glucose through 2 types of SGLTs,[2] unless plasma glucose reaches a threshold of about 180 mg/dL. According to this mechanism in non-diabetic patients, no glucose is found in urine. SGLTs belong to sodium-glucose cotransporters,[3] among them, 2 major SGLT isoforms have been isolated: SGLT-2, mainly expressed in the brush border of epithelial cells in S1 and S2 segments of proximal renal tubules, and SGLT-1, expressed in the small intestine, the S3 segment of the proximal renal tubule, and in the myocardium.[4] Under physiological conditions, SGLT-2 controls 80%–90% of renal glucose reabsorption and SGLT-1 the remaining 10%–20%. Blocking SGLT-2 via selective inhibitors, SGLT-2 inhibitors increase glucose excretion from the body, reducing hyperglycemia. To increase urinary glucose excretion, SGLT-2 inhibitors lower glycemia without inducing excessive insulin

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secretion. SGLT-2 inhibitors-induced glycosuria provides relief from glucose toxicity,[5] improves β-cell insulin secretion and insulin sensitivity in peripheral tissues.[6]

In Europe, marketed SGLT-2 inhibitors include dapagliflozin, canagliflozin, and empagliflozin; in particular canagliflozin was studied in the CANVAS Program,[7] while empagliflozin was studied in the EMPA-REG OUCOME Trial.[8] In Japan, also ipragliflozin, tofogliflozin, and luseogliflozin are already available.

The CANVAS Program enrolled about 10,142 type 2 diabetic patients with high cardiovascular risk. Participants were randomized to placebo or canagliflozin and followed for a mean of 47 months. The primary outcome was a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.[7]

The EMPA-REG OUCOME Trial enrolled about 7,020 type 2 diabetics with a median observation time of 37 months. Patients randomly received placebo or 10 or 25 mg of empagliflozin once daily. The primary composite outcome was death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. Empagliflozin proved to be associated not only with a better decrease in HbA_{1c} and lipid profile, but also with a slower progression in kidney disease and a decreased rate of renal events than was placebo when added to standard care.[8] Recently, a new SGLT-2 inhibitor is being studied: ertugliflozin. Ertugliflozin is a potent inhibitor of SGLT-2 and possesses a high selectivity over glucose transport via SGLT-1 and several other glucose transporters GLUT-1–4. Ertugliflozin inhibits renal glucose reabsorption, resulting in urinary glucose excretion and thereby reducing plasma glucose and HbA_{1c} in subjects with T2DM. Ertugliflozin is being developed as an adjunct to diet and exercise to improve glycemic control in patients with T2DM.

The aim of this review is to evaluate the preliminary published data about this new molecule.

VERTIS program

Ertugliflozin is being evaluated in several international multicenter clinical trials, belonging to the VERTIS program Studies (eValuation of ERTugliflozin effIcacy and Safety). In these studies, ertugliflozin has been evaluated in monotherapy and as add-on/combination therapy with other anti-diabetic drugs in diabetic patients (Table 1).

Previously conducted open-label Phase I study reported that ertugliflozin is well absorbed and metabolized via glucuronidation for the main extent, and to a lesser extent by oxidative metabolism. Recovery of administered radioactivity

Table 1 Ertugliflozin Phase III clinical trials

Trial name	Patients (n)	Time (weeks)	Previous therapy (total dose/day)	Treatments
VERTIS MONO[10]	461	26+26	Lifestyle	Ertugliflozin 5 mg Ertugliflozin 15 mg Placebo in Phase A Metformin in Phase B
VERTIS MET[11]	621	26+26	Metformin ≥1,500 mg	Ertugliflozin 5 mg Ertugliflozin 15 mg Placebo
VERTIS FACTORIAL[13]	1,233	26+26	Metformin ≥1,500 mg	Ertugliflozin 5 mg Ertugliflozin 15 mg Sitagliptin 100 mg Ertugliflozin 5 mg+ sitagliptin 100 mg Ertugliflozin 15 mg+ sitagliptin 100 mg
VERTIS SITA[14]	291	26	Lifestyle	Ertugliflozin 5 mg+ sitagliptin 100 mg Ertugliflozin 15 mg+ sitagliptin 100 mg Placebo
VERTIS SITA2[12]	463	26+26	Metformin ≥1,500 mg+ sitagliptin 100 mg	Ertugliflozin 5 mg Ertugliflozin 15 mg Placebo
VERTIS SU[15]	1,326	52	Metformin ≥1,500 mg	Ertugliflozin 5 mg Ertugliflozin 15 mg Titrated glimepiride
VERTIS CV (study still ongoing)	Estimated 8,000	316	On stable allowable anti-hyperglycemic agents or life style	Ertugliflozin 5 mg Ertugliflozin 15 mg Placebo

was >90% with radiolabeled material eliminated via the fecal and urinary route.[9]

The VERTIS MONO study is a Phase III, 52-week, multicenter, randomized, parallel-group study, with a 26-week, double-blind, placebo-controlled period, followed by a 26-week active-controlled treatment period.[10] A total of 461 participants were randomized and received at least 1 dose of study medication, ertugliflozin 5 or 15 mg, or placebo. The mean age of the study participants was 56.4 years, 83.7% were white, and 56.6% were men. Mean baseline HbA_{1c} was 8.21% and the mean duration of T2DM was ~5 years. At screening, ~52% of the randomized population was receiving treatment with a single anti-diabetic agent, which was discontinued during screening. At Week 26, the placebo-adjusted least squares (LS) mean HbA_{1c} changes from baseline were –0.99% and –1.16% for the ertugliflozin 5 and 15 mg doses, respectively ($P<0.001$ for both doses). Percentage of patients reaching HbA_{1c} <7.0% were significantly greater in the ertugliflozin 5 and 15 mg groups compared with the placebo group. Both doses of ertugliflozin significantly lowered fasting plasma glucose (FPG) and 2-hour postprandial glucose levels and body weight (BW). The placebo adjusted LS mean BW changes from baseline were –1.76, and –2.16 kg for ertugliflozin 5 and 15 mg, respectively. No statistically significant reduction in systolic blood pressure (SBP) was observed for the ertugliflozin 15 mg group vs placebo. Ertugliflozin tolerability was good throughout the 26-week duration of phase A, even if genital mycotic infections occurred more frequently in men and women treated with ertugliflozin compared with placebo. The proportions of participants discontinuing study medication in phase A were 22.2%, 14.1%, and 13.8% for placebo, ertugliflozin 5 mg, and ertugliflozin 15 mg, respectively. The 2 treatments did not differ in the proportion of participants with symptomatic hypoglycemia or adverse events (AEs) associated with urinary tract infection or hypovolemia.

In the VERTIS MET trial, instead, ertugliflozin was studied in addition to metformin monotherapy (≥1,500 mg/d for ≥8 weeks) in T2DM patients inadequately controlled (HbA_{1c}, 7.0%–10.5%).[11] A total of 621 participants were randomized 1:1 to placebo, or ertugliflozin 5 or 15 mg/d. Authors evaluated the change of HbA_{1c} from baseline to the end of the study (at Week 26). Authors also evaluated differences from baseline in FPG, BW, SBP/diastolic blood pressure (DBP) and the percentage of patients reaching HbA_{1c} <7.0%. AEs were also evaluated, such as percent change from baseline in bone mineral density (BMD).

At Week 26, the placebo-adjusted LS mean change from baseline HbA_{1c} (8.1%) was –0.7% and –0.9% for ertugliflozin 5 and 15 mg, respectively (both $P<0.001$), to final means of 7.3% and 7.2%, respectively. Percentage of patients reaching HbA_{1c} <7.0% was significantly higher in both ertugliflozin groups vs placebo. Ertugliflozin significantly reduced FPG, BW, SBP, and DBP vs placebo. A higher incidence of genital mycotic infections was reported in the groups treated with ertugliflozin (female subjects: placebo, 0.9%; ertugliflozin 5 mg, 5.5%; and ertugliflozin 15 mg, 6.3% [$P=0.032$]; male subjects: 0%; 3.1%; and 3.2%, respectively). Also the incidence of urinary tract infections and symptomatic hypoglycemia was higher with ertugliflozin. The incidence of hypovolemia AEs was similar across groups. Ertugliflozin had no adverse impact on BMD at Week 26.

In the VERTIS SITA 2 trial, authors enrolled patients with HbA_{1c} between 7.0% and 10.5%, in therapy with metformin ≥1,500 mg/day and sitagliptin 100 mg/day, and estimated glomerular filtration rate [eGFR] ≥60 mL/min/1.73 m^2. Patients were randomized to ertugliflozin 5 mg, 15 mg once daily or placebo.[12] Authors evaluated HbA_{1c} at baseline and after 26 weeks; treatment was continued until Week 52, 464 patients were randomized, mean baseline HbA_{1c} was 8.0%, and eGFR was 87.9 mL/min/1.73 m^2. After 26 weeks, HbA_{1c} was reduced by –0.7%, and –0.8% with ertugliflozin 5 and 15 mg, respectively (both $P<0.001$) compared with placebo. Moreover, 17.0% of patients receiving placebo, 32.1% receiving ertugliflozin 5 mg, and 39.9% receiving ertugliflozin 15 mg reached an HbA_{1c} <7.0%. Ertugliflozin also induced significant reductions in FPG, BW, and SBP compared with placebo. The positive effects of ertugliflozin on glycemic control, BW, and SBP were observed through Week 52. More genital mycotic infections were recorded in subjects receiving ertugliflozin (3.7%–14.1%) vs placebo (0%–1.9%) through week 52. Urinary tract infections, symptomatic hypoglycemia, and hypovolemia incidence did not differ among groups.

The VERTIS FACTORIAL, a double-blind Phase III trial, confirmed that the incidence of AEs was identical across groups, with the exception of more genital mycotic infections in groups treated with ertugliflozin vs sitagliptin in monotherapy (females, 4.9%–7.6% vs 1.1%; males, 2.4%–4.7% vs 0%, respectively).[13] There was a higher rate of urinary tract infection with ertugliflozin alone (but not ertugliflozin+ sitagliptin) vs sitagliptin in monotherapy (range: 3.2% [sitagliptin] to 5.6% [ertugliflozin 15 mg]). Symptomatic hypoglycemia was 2.4% with ertugliflozin 5 mg and 4.9% with ertugliflozin 15 mg+ sitagliptin. Hypovolemia AE rates were 1.6% and 0.8% in ertugliflozin 5 and 15 mg groups, respectively, and 0% in all other groups.

Other studies are still ongoing; in particular, the VERTIS CV trial (cardiovascular outcomes following ertugliflozin treatment in T2DM participants with vascular) will evaluate the cardiovascular outcomes following treatment with ertugliflozin in participants with T2DM, and established vascular disease. The results of this trial will be important to establish if the positive results obtained with empagliflozin in the EMPA-REG trial are a class effects or a molecule effect. Other interesting results will be obtained from the MK-8835–001 trial, "A Study of the Efficacy and Safety of Ertugliflozin in Participants With Type 2 Diabetes Mellitus With Stage 3 Chronic Kidney Disease Who Have Inadequate Glycemic Control on Antihyperglycemic Therapy", where the primary aim will be to evaluate the HbA_{1c}-lowering efficacy of the addition of ertugliflozin compared with the addition of placebo; the primary aim will be tested for both 5- and 15-mg doses of ertugliflozin.

Based on the approved labeling (US Package Insert and European Union Summary of Product Characteristics) for SGLT-2 inhibitors, including canagliflozin, dapagliflozin, and empagliflozin, and on data for ertugliflozin, the following are considered identified risks of ertugliflozin treatment: 1) genital mycotic infection; 2) osmotic diuresis and volume depletion; 3) hypoglycemia in combination with insulin and/or insulin secretagogues; 4) ketoacidosis; and 5) increased LDL-C. The following are considered potential risks of ertugliflozin treatment: 1) urinary tract infection, including urosepsis and pyelonephritis; 2) renal impairment; 3) lower limb amputation 4) fracture; and 5) hypoglycemia in the absence of insulin and/or insulin secretagogues. The incidence of side effects is in line with what has been reported with other SGLT-2 inhibitors.

Conclusion

The results reported with ertugliflozin, are in line with the ones reported with the other SGLT-2 inhibitors, such as the incidence of side effects.

Disclosure

The authors report no conflicts of interest in this work.

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