EMERGING TYPE 2 DIABETES TREATMENT: NOVEL THERAPY SGLT-2 INHIBITORS
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Existing therapies for type 2 diabetes mellitus (T2DM) target beta cell dysfunction in the pancreas, hepatic glucose overproduction by the liver, glucose absorption in the gut, or insulin resistance in muscle and fat tissue. A new class of therapy for T2DM, sodium glucose cotransporter 2 (SGLT-2) inhibitors, is the first to target glucose reabsorption by the kidney. Emerging data on these novel agents suggest that this is a safe and effective strategy for reducing hyperglycemia, with a mechanism that is potentially complementary to that of existing therapies.

Normal Glomerular Filtration and Renal Glucose Transport
The kidney plays a key role in maintaining stable plasma glucose levels. In healthy individuals, about 162 g of glucose is filtered by the kidney every 24 hours, but virtually all glucose is reabsorbed from the glomerular filtrate back into the bloodstream; none is excreted in the urine.

Glucose reabsorption takes place primarily in the S1 and S2 segments of the proximal convoluted tubule. Two types of glucose transporters are involved in this process. SGLT-2 receptors couple glucose with sodium, allowing glucose to be moved across the luminal membrane by active transport due to a sodium gradient created by sodium/potassium adenosine triphosphate (ATPase) pumps. SGLT-2 is responsible for 90% of tubular reabsorption of glucose. The remaining 10% is absorbed by SGLT-1 receptors in the S3 segment of the proximal convoluted tubule. Once glucose has entered the proximal tubule cells, glucose transporter (GLUT) receptors then facilitate passive transport across the basolateral membrane into the interstitium, where glucose re-enters the bloodstream.

When plasma glucose levels are normal, all glucose is reabsorbed by the kidney. However, when plasma glucose levels rise to more than about 200 to 300 mg/dL, there is a saturation of glucose transporters such that the transport maximum is exceeded and excess glucose spills over into the urine.

Rationale for SGLT-2 Inhibition in T2DM
In patients with T2DM and hyperglycemia, the kidney compensates for the increased demand for glucose reabsorption by increasing expression of SGLT-2. Compared with persons who have normal glucose tolerance, those with T2DM have three-fold higher levels of SGLT-2 and renal glucose uptake.

Proof-of-concept preclinical studies conducted with phlorizin, a nonselective SGLT-2 inhibitor that also inhibits SGLT-1 and GLUT1, confirmed that SGLT is a valid therapeutic target in diabetes. However, these studies also showed that
inhibition of SGLT-1, which is responsible for glucose absorption in the gut as well as the kidney, would result in diarrhea and other gastrointestinal side effects.

Selective inhibition of SGLT-2 became the therapeutic target. This was further supported by the fact that familial renal glucosuria, a rare kidney disorder associated with SGLT-2 gene mutations, prevents glucose reabsorption but is considered a benign condition with no corresponding kidney complications.

**SGLT-2 Inhibitors in Development**

Four SGLT-2 inhibitors are now in phase III trials: dapagliflozin, canagliflozin, BI10773, and ASP1941. Numerous other SGLT-2 inhibitors are currently in clinical trials (see slide 15 in this webcast for more information).

*Dapagliflozin*

Several phase III trials of dapagliflozin have now been completed.

In one 24-week double-blind trial, 485 patients with treatment-naive T2DM and HbA1c of 7% to 10% were randomized to placebo or dapagliflozin monotherapy at doses of 2.5, 5, or 10 mg/day given in the morning, or the same doses given in the evening. An additional 74 patients whose baseline HbA1c was 10.1% to 12% were randomized to dapagliflozin 5 or 10 mg daily in the morning. Open-label metformin was allowed for patients with fasting plasma glucose >270 mg/dL at week 4, >240 mg/dL at week 8, or >200 mg/dL at weeks 12 to 24. With the morning doses, there were dose-related reductions in HbA1c (0.6%–0.9%), whereas with evening administration, all three doses showed consistent reductions in HbA1c on the order of about 0.8% to 0.9%. The subgroup of patients with baseline HbA1c levels of 10.1% to 12% had the most dramatic HbA1c reductions on treatment, averaging about 2.7% to 2.9%. Similar patterns were seen with regard to reductions in fasting plasma glucose levels. Glucose excretion results in a net caloric loss, which promotes weight loss. In this study, dapagliflozin-treated patients lost 3.1 to 3.8 kg, compared with a loss of 2.2 kg in the placebo group; the subgroup of patients with high baseline HbA1c levels lost 1.9 to 2.1 kg.

Two other randomized, double-blind, placebo-controlled phase III trials have reported on dapagliflozin as add-on therapy to metformin or glimepiride. In both trials, dapagliflozin again produced significant reductions in HbA1c and fasting and/or postprandial glucose levels compared with placebo. Patients in these trials also lost about 2 to 3 kg of bodyweight while taking the SGLT-2 inhibitor.

Dapagliflozin was generally well tolerated. Urinary tract and genital infections were the most noteworthy side effects, occurring in 4% to 15% and 3% to 18% of patients, respectively. Other common side effects included nasopharyngitis, diarrhea, headache, and hypotensive events. Hypoglycemia was rare, occurring in less than 3% of patients in the monotherapy study, in 2% to 4% of those also taking metformin, and in 7% to 8% of those also taking glimepiride.
Additional phase III trials are evaluating dapagliflozin as add-on therapy to thiazolidinediones, dipeptidylpeptidase 4 (DPP-4) inhibitors, and insulin. Other phase III trials are assessing this therapy in special populations that include patients with T2DM and cardiovascular disease, hypertension, or moderate renal impairment.

**Canagliflozin**

To date, only data from phase II studies are available for canagliflozin. In a 12-week phase IIb study, 451 patients with T2DM inadequately controlled on metformin were randomized to canagliflozin 50 mg QD, 100 mg QD, 200 mg QD, 300 mg QD, or 300 mg BID, or to sitagliptin 100 mg QD or placebo. There was a dose-response reduction in placebo-adjusted HbA1c ranging from 0.45% to 0.73% compared with 0.56% for sitagliptin. A dose response was also seen with regard to effect on placebo-adjusted fasting plasma glucose levels, which were reduced by 16.2 to 32.4 mg/dL with canagliflozin versus 18 mg/dL with sitagliptin. Patients in the canagliflozin arms lost an average of 1.3 to 2.3 kg of body weight after placebo adjustments, whereas patients treated with sitagliptin lost an average of 0.4 kg after placebo adjustments. Adverse effects of canagliflozin included genital infections (3%–8%), urinary tract infections (3%–9%), and hypoglycemia (0%–6%).

Phase III trials are now being conducted with canagliflozin monotherapy or canagliflozin as add-on therapy to metformin, metformin plus a sulphonylurea, and metformin plus pioglitazone. Canagliflozin is also being studied in phase III trials in special populations including elderly patients, patients with cardiovascular risk factors, and patients with renal impairment.

**BI10773**

In a 4-week phase II study, 80 patients with T2DM were randomized to BI10773 10, 25, or 100 mg QD or placebo. BI10773 increased urinary glucose excretion, consistent with the mechanism of SGLT-2 inhibitors. Fasting plasma glucose levels decreased by 44, 34, and 29 mg/dL for the three doses, respectively, compared with only 4 mg/dL in the control arm. The most common adverse effects included frequent urination, nasopharyngitis, constipation, headache, and mild hypoglycemia.

BI10773 is currently being assessed in phase III trials of monotherapy in treatment-naive and metformin-pretreated T2DM, as well as add-on therapy to metformin, metformin/sulphonylurea, pioglitazone, or pioglitazone/metformin. It is also being evaluated as add-on to usual therapy in patients at high cardiovascular risk and those with renal impairment.

**ASP1941**

In a phase IIa study, 61 patients with T2DM (some treatment naive and others taking monotherapy or low-dose combination therapy) underwent a 2-week
washout period and were then randomized to 28 days of treatment with ASP1941 50, 100, 200, or 300 mg QD or placebo. Again, urinary glucose excretion was increased with all doses, and fasting plasma glucose declined by 49 to 71 mg/dL compared with 10 mg/dL in the control arm. The ASP1941 group had weight loss averaging 3.2 to 4.2 kg compared with 1.8 kg in the placebo group. The most common adverse effects included constipation, nausea, xerosis, and headache. Phase III trials of ASP1941 are evaluating it as monotherapy and as add-on treatment to metformin, thiazolidinediones, sulfonylureas, DPP-4 inhibitors, and alpha-glucosidase inhibitors.

Conclusions
SGLT-2 is a low-affinity high-capacity glucose transporter located in the proximal tubule and is responsible for 90% of glucose reabsorption. Oral selective SGLT-2 inhibitors in development reduce blood glucose levels by increasing renal excretion of glucose. Thus, SGLT-2 inhibitors represent a promising class of T2DM therapy with a novel mechanism of action complementary to those of available agents. Once available, they may be considered for monotherapy as second-line treatment or even in the first-line setting for patients intolerant of metformin. They may also be used in combination with available therapies. These agents are generally well tolerated, although they may be associated with increased rates of genitourinary infections.

Suggested Readings


