New and Emerging Therapies for Type 2 Diabetes

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Curtis L. Triplitt, PharmD, CDE, University of Texas, San Antonio, Texas, USA, and Joshua J. Neumiller, PharmD, CDE, Washington State University, Spokane, Washington, USA, provided an update on new and emerging therapies for type 2 diabetes mellitus (T2DM).

According to Dr. Neumiller, a better understanding of the pathophysiology of T2DM has expanded the armamentarium of drugs to treat hypoglycemia. The glycemic control algorithm established by the American Association of Clinical Endocrinologists in 2013 favors lifestyle modifications. If the baseline HbA_{1c} level is <7.5%, monotherapy with metformin is the preferred treatment strategy [Garber AJ et al. *AACE Comprehensive Diabetes Management Algorithm* 2013]. Although there are many options for add-on therapy, the final choice of agent(s) should take into consideration factors such as hypoglycemia risk, weight-gain potential, side effect profile, and cost. Patients with higher entry HbA_{1c} levels of ≥7.5% and >9.0% will require dual and triple therapy, respectively. In addition, patients who do not meet their initial HbA_{1c} goals within 3 months of therapy should have their treatment uptitrated.

Dr. Triplitt reviewed new insulin therapies, some of which are still being developed. Insulin degludec is an ultra-long-acting basal insulin approved for once-daily dosing in adults with type 1 diabetes mellitus and T2DM in the European Union, Japan, and Mexico. It is not currently approved for use in the United States. The agent is associated with less nocturnal hypoglycemia when given daily compared with insulin glargine. Phase 2 trials had suggested that injection of insulin degludec 3 times a week provided similar control to once-daily insulin glargine. However, data from 2 Phase 3 trials suggested that insulin degludec provided inferior glycemic control and an increased risk for hypoglycemia [Zinman B et al. *Lancet Diabetes Endocrinol* 2013]. The cardiovascular (CV) safety of insulin degludec is still under investigation, since initial clinical trials raised the possibility that this agent may increase cardiovascular risk.

U300 insulin glargine is a new, longer lasting formulation of insulin glargine that is also under development. Blood glucose control is similar between U300 and the older insulin glargine, but rates of hypoglycemia and nocturnal hypoglycemia have been lower with U300 [Riddle MC et al. American Diabetes Association Scientific Sessions 2014; (abstract 81-LB)].

PEGylated insulin Lispro (LY2605541) is a novel, long-acting basal insulin designed to be dosed once daily in patients with T2DM. In a randomized Phase 2 trial, LY2605541 was compared with glargine in 288 adults with T2DM who had blood glucose levels not at target despite treatment with metformin. In this trial, the daily mean blood glucose level was significantly lower with LY2605541 (Table 1) [Bergenstal RM et al. *Diabetes Care* 2012]. There were no significant differences in fasting blood glucose ($p = .388$), fasting serum glucose ($p = .8812$), or change in HbA_{1c} level ($p = .197$). At Week 12, mean body weight was .8 kg lower ($p = .001$) in patients who received LY2605541.

Technosphere insulin (insulin human inhalation powder) is a powdered insulin that is inhaled and delivered deep into the lungs. The drug has properties that are similar to those of intravenous insulin, and it rapidly achieves a maximum concentration in the blood (half-life of 45 minutes). The fast onset of action means that patients will inhale the powder at the time of meals. Insulin levels return to baseline about 3 hours after inhalation. The inhaled insulin reduces HbA_{1c} by .5 to .7 mg/dL [Neumiller JJ et al. *Ann Pharmacother* 2010; Rosenstock J et al. *Diabetes Care* 2008; Tack CJ et al. *J Diabetes Sci Technol* 2008]. Adverse events unique to insulin human inhalation powder are cough and small reductions in pulmonary function. As such, acute bronchospasm is possible if used in patients with asthma or chronic obstructive pulmonary disease. Assessment of pulmonary function is recommended at initiation, 6 months, 1 year, and then annually. Technosphere insulin is not recommended for use for smokers or for patients with active lung cancer.

Dr. Neumiller also provided an update on oral medications for the treatment of T2DM, focusing first on sodium-glucose linked transporter-2 (SGLT2) inhibitors. Glucose reabsorption is increased in

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Table 1. LY2605541 Versus Insulin Glargine at Week 12

Variable	Combined LY2605541	GL	LS Mean Difference (90% CI)	p Value
n	195	93		
FBG (SMBG) (mg/dL)				
Baseline	146.6 ± 2.9	140.3 ± 4.1	—	.131
Week 12	118.2 ± 2.0	116.9 ± 2.7	—	.433
Change from baseline	−25.9 ± 2.5	−24.5 ± 3.8	−3.6 (−10.6 to 3.4)	.388
FSG (laboratory) (mg/dL)				
Baseline	146.5 ± 3.2	151.3 ± 4.9	—	.404
Week 12	122.9 ± 2.7	128.6 ± 4.1	—	.347
Change from baseline	−23.2 ± 3.4	−22.2 ± 4.7	−0.9 (−9.9 to 8.3)	.882
Daily mean BG (mg/dL)				
Baseline	170.1 ± 3.1	164.7 ± 3.8	—	.073
Week 12	138.9 ± 2.2	144.7 ± 3.4	—	.741
Change from baseline	−27.4 ± 2.5	−19.6 ± 3.1	−8.8 (−15.0 to −2.7)	.017
HbA_{1c} (%)				
Baseline	7.7 ± 0.1	7.8 ± 0.1	—	.766
Week 12	7.0 ± 0.1	7.2 ± 0.1	—	.279
Change from baseline	−0.7 ± 0.1	−0.7 ± 0.1	−0.1 (−0.2 to 0.0)	.197
Body weight (kg)				
Baseline	90.7 ± 1.39	89.7 ± 2.1	—	.845
Week 12	90.4 ± 1.4	89.6 ± 2.1	—	.001
Change from baseline	−0.6 ± 0.2	0.3 ± 0.2	−0.8 (−1.3 to −0.4)	.001
Triglycerides (mg/dL)				
Baseline	163.0 ± 8.0	160.4 ± 13.3	—	.910
Week 12	171.9 ± 7.1	147.1 ± 8.9	—	.005
Change from baseline	10.6 ± 7.1	−15.1 ± 8.9	26.6 (11.5 to 42.5)	.005
AST (U/L)				
Baseline	22.9 ± 0.7	23.8 ± 1.0	—	.330
Week 12	26.5 ± 1.0	23.6 ± 1.0	—	.001
Change from baseline	3.1 ± 0.7	−0.4 ± 0.9	3.6 (1.7 to 5.4)*	.001
ALT (U/L)				
Baseline	26.0 ± 1.0	27.3 ± 1.4	—	.243
Week 12	32.7 ± 1.6	25.6 ± 1.2	—	< .001
Change from baseline	6.0 ± 1.1	−1.9 ± 1.2	8.5 (5.8 to 11.3)	< .001

ALT=alanine aminotransferase; AST=aspartate aminotransferase; BG=blood glucose; FBG=fasting blood glucose; FSG=fasting serum glucose; GL=insulin glargine; LS=least squares; SMBG=self-monitored blood glucose.

Bergenstal RM et al. A randomized, controlled study of once-daily LY2605541, a novel long-acting basal insulin, versus insulin glargine in basal insulin-treated patients with type 2 diabetes. *Diabetes Care.* 2012;11:2140-2147. With permission from American Diabetes Association.

*On November 12, 2014, this was changed from 3.6 (0.7 to 5.4) to 3.6 (1.7 to 5.4).

Table 2. Renal Dosing of SGLT2 Inhibitors

Agent	Dosing in CKD Stages 3, 4, and 5 (Nondialysis)
Canagliflozin	▪ eGFR > 60 mL/min/1.73 m² No dosage adjustment needed ▪ eGFR 45–59 mL/min/1.73 m² Do not exceed 100 mg/d orally ▪ eGFR < 45 mL/min/1.73 m² Do not initiate and discontinue in patients currently receiving drug
Dapagliflozin	**Do not initiate and discontinue with eGFR < 60 mL/min/1.73 m²**
Empagliflozin	▪ eGFR > 45 mL/min/1.73 m² No dosage adjustment needed ▪ eGFR < 45 mL/min/1.73 m² Do not initiate and discontinue in patients currently receiving drug

CKD=chronic kidney disease; eGFR=estimated glomerular filtration rate; SGLT2=sodium-glucose linked transporter-2.

Source: Dapagliflozin Prescribing Information 2014; Empagliflozin Prescribing Information 2014; Canagliflozin Prescribing Information 2013.

T2DM primarily through increased expression and activity of SGLT2 [Bakris GL et al. *Kidney Int* 2009; Marsenic O et al. *Am J Kidney Dis* 2009; Rahmoune H et al. *Diabetes* 2005]. Inhibition of SGLT2 transporters blocks the reabsorption of filtered glucose, serving to increase glucose excretion in the urine [Idris I, Donnelly R. *Diabetes Obes Metab* 2009]. When used as monotherapy, the risk for hypoglycemia with the SGLT2 inhibitors is low. Caution must be exercised when these agents are used with insulin secretagogues or insulin. Potential benefits of the agents include weight loss and a modest decrease in blood pressure.

The newest SGLT2 inhibitor to be approved in the United States for adults with T2DM is empagliflozin. In a placebo-controlled Phase 3 trial of treatment-naive adults with T2DM, both doses of empagliflozin (10 and 25 mg) reduced levels of HbA_{1c} more than did placebo ($p < .001$ for both). The reductions in HbA_{1c} at 24 weeks were similar in magnitude to those attained with sitagliptin. Patients randomly assigned to sitagliptin had a mean increase in body weight, whereas those randomly assigned to empagliflozin experienced considerable body weight reductions [Roden M et al. *Lancet Diabetes Endocrinol* 2013]. When studied as an add-on to metformin plus a sulfonylurea, empagliflozin was associated with an additional reduction in HbA_{1c} of approximately .8% in patients [Häring HU et al. *Diabetes Care* 2013].

The risk for urinary tract infections and genital fungal infections occurs more often in both women and men (mostly uncircumcised men) taking SGLT2 inhibitors compared with placebo [Stenlöf K et al. *Diabet Obes Metab* 2013]. Adverse events related to osmotic diuresis-related (eg, hypovolumia) are also observed more frequently with SGLT2 inhibitors.

Estimated glomerular filtration rate (eGFR) will decline in the first 3 to 6 weeks of therapy with an SGLT2 inhibitor. According to Dr. Neumiller, this is a hemodynamic effect of therapy rather than a toxic effect. Volume status and eGFR should be assessed before starting an SGLT2 inhibitor and periodically during treatment to ensure that patients are good candidates for this therapy. Patients with reduced eGFR may not benefit from SGLT2 inhibitors, because the drug uses renal excretion for the removal of glucose. Renal dosing is summarized in Table 2.

SGLT2 inhibitors currently being studied in Phase 2 studies include ertugliflozin, LX4211, EGT1474, and ISIS388626, while ipragliflozin, luseogliflozin, and tofogliflozin are being studied in Phase 3 trials.

Albiglutide is a weekly injectable glucagon-like peptide-1 (GLP1) receptor agonist that received approval in the United States for the treatment of T2DM in April 2014. It was developed through fusion of 2 copies of a modified GLP-1 to recombinant human albumin. A single amino acid substitution renders albiglutide resistant to dipeptidyl peptidase-4 metabolism. The structure prolongs the half-life of the drug for up to 6.8 days, and steady state is reached in 3 to 4 weeks. Dosing is 30 mg weekly, which can be increased to 50 mg weekly. In a 32-week study of adults with T2DM poorly controlled on oral agents ($n = 422$), albiglutide 50 mg/week did not meet a noninferiority end point on change in HbA_{1c} level compared with liraglutide 1.8 mg/day [Pratley RE et al. *Lancet Diabetes Endocrinol* 2014]. Thus far, treatment with albiglutide has not been shown to either increase or decrease the risk for CV events.

Dr. Triplitt concluded his presentation by noting that dulaglutide and semaglutide are GLP-1 agonists that can be administered weekly and are currently in development. An implantable GLP-1 agonist that delivers exenatide continually for 6 months is also under development.