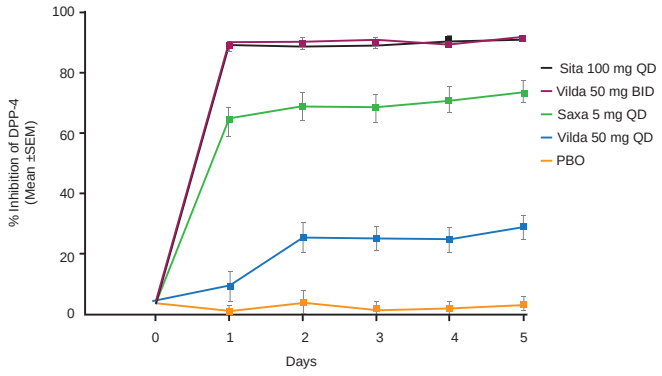
assess trough DPP-4 inhibition after the final dose following 5 days of administration of saxagliptin 5 mg QD, sitagliptin 100 mg QD, and vildagliptin 50 mg QD and BID regimens in a cohort of patients with T2DM (n=22). Trough DPP-4 inhibition for each of the four regimens and placebo control could be directly compared at 24 hours following the final morning dose. Eligible patients were required to have HbA1C levels of 6.5% to 10.0% (inclusive) either while treatment-naïve or after being washed off of prior antihyperglycemic medication.

In separate treatment periods, each participant received 5 days of either saxagliptin 5 mg QD, sitagliptin 100 mg QD, vildagliptin 50 mg QD, vildagliptin 50 mg BID, or placebo. Each participant was assigned to a randomized treatment sequence according to a computer-generated allocation schedule. Treatment periods were separated by at least 10 days. The randomized cohort included 12 women and 10 men with a mean HbA1C of 7.4% and mean age of 55 years.

The percent DPP-4 inhibition was calculated for each treatment relative to the predose DPP-4 activity in each period. Sitagliptin QD and vildagliptin BID achieved >90% trough DPP-4 inhibition, reaching steady state within 1 day. In contrast, trough DPP-4 inhibition was 73.5% after saxagliptin QD and 28.8% after vildagliptin QD. The trough DPP-4 inhibition following placebo treatment was within 3.9% of the baseline measure (Figure 1). "DPP-4 inhibition ≥80% is believed to be necessary to achieve maximal efficacy of DPP-4 inhibitors", said Dr. Katzeff.

Figure 1. Trough % Inhibition of DPP-4 Activity Over 5 Days



DPP-4=dipeptidyl peptidase-4; PBO=placebo.
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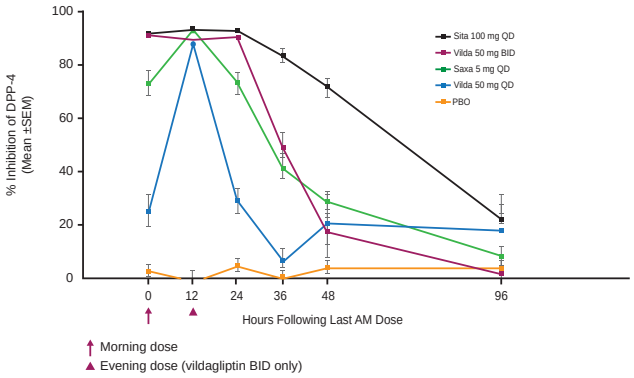
The time course of DPP-4 inhibition over 96 hours and following 5 days of administration favored sitagliptin 100 mg QD (Figure 2), which maintained DPP-4 inhibition of ~92% over 24 hours that declined slowly over the following 24 to 96 hours. Vildagliptin 50 mg BID maintained >90% DPP-4 inhibition over 24 hours but inhibition declined rapidly over the following 12 to 24 hours. Saxagliptin 5 mg QD maintained ~72% DPP-4 inhibition at 24 hours but inhibition also declined rapidly over the following 12 to 24 hours. Vildagliptin 50 mg QD achieved rapid DPP-4 inhibition but inhibition declined rapidly starting at 12 hours.

Figure 2. Percent Inhibition of DPP-4 Activity at 0-96 Hours



DPP-4=dipeptidyl peptidase-4; PBO=placebo.
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Ten adverse events were reported in 7 of the 22 patients, with headache the most commonly reported adverse event (6 events reported in 3 patients). All adverse events were mild or moderate in intensity and were transient in nature. There were no adverse events that led to patient withdrawal from the study.

Dr. Katzeff concluded that the three DPP-4 inhibitors studied provided significantly different trough levels of DPP-4 inhibition. Trough inhibition was submaximal in patients treated with saxagliptin 5 mg QD and vildagliptin 50 mg QD, whereas >90% DPP-4 inhibition was sustained throughout 24 hours in patients treated with sitagliptin 100 mg QD and vildagliptin 50 mg BID.

Fixed-Ratio Combination of Insulin Degludec and Liraglutide Improves Glycemic Control in Type 2 Diabetes

Written by **Wayne Kuznar**

A fixed-ratio combination of insulin degludec and liraglutide significantly improves glycemic control in patients with type 2 diabetes mellitus (T2DM) compared with either drug as monotherapy, with a low risk of hypoglycemia. Data from a Phase 3 randomized, 3-arm, open-label study were discussed by Stephen C. L. Gough, Oxford Centre for Diabetes, Endocrinology and Metabolism, University of Oxford, Oxford, United Kingdom.

The fixed-ratio combination is delivered in a once-daily single-injection device, consisting of insulin degludec 1 U and liraglutide 0.036 mg. It was compared with its individual components, liraglutide or insulin degludec alone, in a 26-week study of insulin-naïve patients with T2DM (n=1663) who were inadequately controlled on metformin plus/minus pioglitazone. Patients were randomized to the fixed-dose combination insulin degludec/liraglutide once daily (n=834), insulin degludec (n=414), or liraglutide 1.8 mg (n=415). The dosages of the fixed-dose combination and insulin degludec were titrated to achieve a mean fasting plasma glucose (FPG) of 72 to 90 mg/dL.

The primary endpoint was the change in HbA1C level over 26 weeks. HbA1C decreased by a mean of 1.91% (from 8.3% to 6.4%) in the patients randomized to fixed-dose insulin degludec/liraglutide, which was superior to liraglutide (1.28% reduction in HbA1C) and noninferior to insulin degludec (1.44% reduction in HbA1C).

Some 80.6% of patients treated with the fixed-dose combination reached the HbA1C goal of <7%, and 69.7% reached <6.5%, compared with 60.4% and 41.4%, respectively, with liraglutide alone, and 65.1% and 47.5%, respectively, with insulin degludec alone.

The fixed-dose insulin degludec/liraglutide combination also resulted in a mean weight reduction of 0.5 kg compared with a 2.2-kg increase with insulin degludec alone. The rate of confirmed hypoglycemia was 32% lower with fixed-dose insulin degludec/liraglutide than with insulin degludec. As expected, liraglutide was associated with less hypoglycemia and greater weight reduction than either basal insulin formulation.

At 26 weeks, change in FPG was similar for fixed-dose insulin degludec/liraglutide (5.6 mmol/L) and insulin degludec (5.8 mmol/L), compared with 7.3 mmol/L with liraglutide ($p<0.0001$ vs fixed-dose insulin degludec/liraglutide). An identical reduction in FPG level from baseline (65 mg/dL) in each insulin group occurred even though the final mean daily dose of insulin degludec in the group randomized to the fixed-dose combination was 15 U/day lower than in the group randomized to insulin degludec alone, said Prof. Gough.

Nine-point glucose profiles showed significantly lower mean prandial increments with fixed-dose insulin degludec/liraglutide and liraglutide compared with insulin degludec following all three main meals.

Gastrointestinal side effects with fixed-dose insulin degludec/liraglutide occurred less frequently than with liraglutide.

Fixed-dose insulin degludec/liraglutide combines the effects of insulin degludec and liraglutide in one injection, resulting in a substantial overall improvement in glycemic control with a low risk of hypoglycemia and weight gain, concluded Prof. Gough.

Glycemic Improvement With Canagliflozin Is Durable in T2DM Patients on Metformin

Written by **Wayne Kuznar**

The sodium glucose cotransporter 2 inhibitor canagliflozin is associated with durable glycemic improvement over 104 weeks compared with glimepiride in patients with type 2 diabetes mellitus (T2DM) on background metformin therapy. Such was the primary finding of a Phase 3 randomized, double-blind efficacy and safety study presented by Gisle Langslet, MD, Lipid Clinic, Oslo University Hospital, Oslo, Norway.

A previous Phase 3 study had demonstrated that canagliflozin 100 mg/day was noninferior to glimepiride (mean maximum dose 5.6 mg) and canagliflozin 300 mg/day was superior to glimepiride in lowering levels of HbA1C in patients with T2DM on background metformin over 52 weeks; both doses of canagliflozin were associated with reductions in body weight compared with glimepiride [Cefalu WT et al. *Lancet* 2013].

The 104-week study represents the longest follow-up of canagliflozin treatment to date, said Prof. Langslet. It compared canagliflozin with glimepiride in patients with T2DM inadequately controlled on metformin monotherapy. Patients with HbA1C ≥7.0% and ≤9.5% were randomized after a 2-week placebo run-in to canagliflozin 100 or 300 mg/day, or glimepiride up to 8 mg/day during the 52-week core period (n=1450), followed by a 52-week extension (n=1050). The mean duration of diabetes was 6.6 years. At baseline, patients' mean age was 56.2 years, their mean HbA1C was 7.8%, their mean fasting plasma glucose (FPG) was 9.2 mmol/L, and their mean body mass index was 31.0 kg/m^2.

The rate of rise per year in HbA1C from Week 26 to Week 104 was lower with canagliflozin 100 and 300 mg than with glimepiride (0.16%, 0.16%, and 0.37%, respectively). The mean change in FPG from baseline to Week 104 was –0.6 mmol/L with glimepiride compared with –1.1 mmol/L with canagliflozin 100 mg, and –1.3 mmol/L with canagliflozin 300 mg. Body weight increased from baseline to Week 104 by 0.9% in the glimepiride group and decreased by 4.1% and 4.2% in the groups randomized to canagliflozin 100 mg and 300 mg, respectively. The weight changes were maintained over the 52-week extension period.

Systolic blood pressure increased by 1.7 mm Hg from baseline to Week 104 in the glimepiride group but declined by 2.0 and 3.1 mm Hg with canagliflozin 100 and 300 mg, respectively. Both canagliflozin doses were associated with increases in high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) that were