DIA-AID 1 was a 2-year double-blind study conducted in 42 medical centers in 11 countries in Europe, South Africa, and Israel. It included 457 patients aged 16 to 45 years with newly diagnosed T1D (<3 months) and residual β-cell function fasting C-peptide ≥0.22 nmol/L.

The peptide DiaPep227 is an immunodominant epitope of heat shock protein 60 that is found in insulin secretory granules of β cells. It is thought to be an autoantigen and induces T regulatory cells via toll-like receptors [Gupta S. *Med Clin N Am* 2012].

Patients were randomized 1:1 to receive a total of 9 injections of either 1 mg DiaPep277 or placebo administered quarterly at a medical center. The primary outcome was the change in stimulated C-peptide area under the curve (AUC) from baseline to Month 24 as measured by a 20-minute glucagon-stimulated test. Secondary outcomes included the change in stimulated C-peptide AUC from baseline to Month 24 as measured by the mixed-meal tolerance test (MMTT), the proportion of patients who maintained HbA1C levels ≤7% at the end of the study, and the change in fasting C-peptide from baseline to Month 24.

The primary efficacy endpoint in the modified intention-to-treat population (mITT) showed a trend that became significant (p=0.037) at 24 months, with a 23.4% decline in progression in the DiaPep277 group versus placebo. The difference was even more pronounced in the per-protocol (PP) population, with a relative treatment effect of 29.2% (p=0.011).

Among the secondary endpoints, there was no significant difference between the placebo and treatment groups in change in stimulated C-peptide AUC from baseline to Month 24 as measured by the MMTT. Although there was a trend toward a treatment effect in the change from baseline in fasting C-peptide, the difference between the treatment and placebo groups was not significant.

A significantly greater number of treated patients in the mITT population maintained HbA1C levels ≤7% at the end of the study versus those who received placebo (p=0.03), with an even greater difference between the 2 groups in the PP population (p=0.0082). The number of patients with at least 1 treatment emergent adverse advent (TEAE) was 173 (76.9%) in the DiaPep277 group and 164 (71%) in the placebo group. The number of patients with at least 1 life-threatening TEAE was the same for both groups (2; 0.9%). The most common TEAEs were nasopharyngitis, influenza, upper respiratory tract infection, gastroenteritis, headache, pyrexia, and back pain.

Outcomes from a continuous glucose monitoring substudy conducted on 78 patients at 17 sites showed a significantly lower number of hyperglycemic excursions per patient (defined by glucose levels >140 mg/dL) in the DiaPep277-treated group compared with those who received the placebo (11.5 vs 14.4; p=0.032). In the treated group, the duration of hypoglycemia was shorter and the magnitude of the events showed a strong trend of less severity.

Linagliptin Proves Safe and Effective as Add-on Therapy to Basal Insulin

Written by ***Rita Buckley***

Linagliptin may be a treatment option in patients with type 2 diabetes mellitus (T2DM) taking basal insulin, especially in those prone to hypoglycemia and/or declining renal function, according to Hannele Yki-Järvinen, MD, PhD, University of Helsinki, Helsinki, Finland, who presented results from a 52-week, multicenter, randomized, placebo-controlled, Phase 3 clinical trial.

The objective of the Efficacy and Safety of Linagliptin in Combination with Insulin in Patients with Type 2 Diabetes study was to determine the efficacy of the dipeptidyl peptidase-4 inhibitor linagliptin after 24 weeks, and long-term safety after 52 weeks as add-on therapy to basal insulin alone or in combination with metformin and/or pioglitazone in patients with T2DM [NCT00996658]. The primary endpoint was change in HbA1C from baseline to Week 24. Secondary endpoints were changes from baseline in fasting plasma glucose, basal insulin dose, and body weight after 24 and 52 weeks, ie, sustained glucose control and long-term safety data with an emphasis on hypoglycemia.

A total of 1261 patients inadequately controlled on insulin glargine, insulin detemir, or neutral protamine Hagedorn insulin were randomized 1:1 to receive either linagliptin 5 mg QD or placebo QD for at least 52 weeks. The background dose of basal insulin was kept stable up to 24 weeks but could then be freely adjusted. Inclusion criteria were male and female subjects at least 18 years of age with T2DM, body mass index (BMI) ≤45 kg/m^2, detectable C-peptide, pretreatment with basal insulin and/or metformin and/or pioglitazone, and HbA1C of 7% to 10% [Yki-Järvinen H et al. EASD 2012 Abstract 6].

Mean ± standard deviation (SD) baseline characteristics were similar in the linagliptin versus placebo groups: age, 59.7±9.9 versus 60.4±10.0 years; BMI, 30.8±5.4 versus 31.2±4.9 kg/m^2; HbA1C, 8.3%±0.9% in both groups; and basal insulin dose, 41.5±31.9 versus 40.1±27.3 IU/day. Mean exposure to study medication was comparable in both groups: 435 days for linagliptin versus 422 days for placebo.

Overall safety and tolerability of linagliptin was similar to placebo. The proportion of patients with ≥1 adverse event (AE) was slightly lower with linagliptin (78.4%) compared with placebo (81.4%); most AEs were of mild or moderate intensity. Despite better glycemic control with linagliptin, the incidence of hypoglycemia was similar in both groups (linagliptin 31.4%; placebo 32.9%), and the number of severe hypoglycemic events was low (linagliptin 1.7%; placebo 1.1%; Table 1). Mean ± SD change in body weight was minimal and comparable between the treatment groups (linagliptin –0.30±3.70 kg; placebo –0.04±3.10 kg).

Table 1. Incidence of Hypoglycemia in Linagliptin and Placebo Groups.

	Week 24		End of Treatment	
	Linagliptin 5 mg QD	Placebo	Linagliptin 5 mg QD	Placebo
Number of patients[a]	631	630	631	630
Hypoglycema (%)	22.0	23.2	31.4	32.9
Any confirmed symptomatic hypoglycemia[1] **with plasma glucose ≤3.9 mmol/L (70 mg/dL)**	17.0	18.7	23.9	25.1
Any confirmed symptomatic hypoglycemia[2] **with plasma glucose ≤3 mmol/L (54 mg/dL)**	8.6	8.7	14.3	14.1
Any severe hypoglycemic episode[3]	0.3	0.6	1.7	1.1

a Treated set: all patients who were treated with at least one dose of the study medication.

1 Accompanied by typical symptoms of hypoglycemia.

2 Accompanied by typical symptoms of hypoglycemia, but no need for external assistance.

3 Requiring the assistance of another person to actively administer carbohydrate, glucagon, or other actions.

The placebo-adjusted mean ± standard error (SE) change in HbA1C from baseline to Week 52 was –0.53%±0.05% ($p<0.0001$). This was accompanied by a mean ± SE change in basal insulin dose up to Week 52 of +2.6±0.8 IU/day for linagliptin versus +4.2±0.8 IU/day for placebo ($p<0.003$).

This trial demonstrated that linagliptin as add-on therapy to basal insulin significantly improved glycemic control after 24 weeks and did so independently of renal function and type of basal insulin. It was not associated with an increased risk of hypoglycemia or weight gain. Adding a DPP-4 inhibitor instead of a sulfonylurea to further improve glucose control might avoid hypoglycemia and weight gain.

12-Week Treatment with LY2409021 Significantly Lowers HbA1C and Is Well Tolerated in Patients with Type 2 Diabetes Mellitus

Written by ***Maria Vinall***

The glucagon receptor antagonist LY2409021 (LY) substantially lowers HbA1C without severe hypoglycemia or weight gain in type 2 diabetes mellitus (T2DM) patients. In a double-blind, randomized, placebo-controlled, Phase 2 study presented by Christof M. Kazda, MD, Eli Lilly and Company, Suresnes, France, researchers examined the margin between LY efficacy and safety by comparing mean changes in HbA1C and liver aminotransferases at 3 dose levels.

T2DM pathophysiology is characterized by greater postprandial glucose release, impaired insulin secretion, and abnormal glucagon plasma levels [Woerle HJ et al. *Am J Physiol Endocrinol Metab* 2006]. LY is a potent, selective glucagon receptor antagonist that inhibits hepatic glucose output and has significant glucose-lowering effects [Kelly RP et al. ADA 2011 Abstract 1004-P; Tham LS et al. ADA 2011 Abstract 416-PP]. In a Phase 1 study [NCT01606397], LY improved glycemic parameters and showed reversible dose-dependent increases in serum aminotransferase levels. The incidence of hypoglycemia was infrequent and was considered to be of mild to moderate intensity [Kelly RP et al. ADA 2011 Abstract 305-OR].

The primary endpoint of the current Phase 2a study [NCT00871572] was mean change in HbA1C and liver aminotransferases. Secondary objectives included the evaluation of LY effects on blood glucose, insulin, glucagon, glucagon-like peptide-1 (GLP-1), and blood lipids, as well as safety and tolerability.

Patients aged 18 to 70 years with T2DM (HbA1C 6.5% to 10%) and a body mass index of 25 to 40 kg/m^2 who were