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A novel combination of basal insulin and GLP-1 analog

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The progressive nature of type 2 diabetes necessitates that treatment is intensified as the disease advances. Several studies have shown that basal insulin and glucagon-like peptide-1 receptoragonists (GLP-1RAs) can be used in combination to successfully improve glycemic control and this combination is increasingly being considered as an alternative to intensification with prandial insulin.

Insulin degludec/liraglutide (IDegLira) is the first fixed-ratio combination of a basal insulin and a GLP-1RA in a single formulation. IDegLira offers an efficacious combination therapy (mean end-of-trial HbA1c was 6.4%-6.9% across the five completed Phase 3 trials), which was well-tolerated in clinical trials. The complementary modes of action resulted in a low rate of hypoglycemia and no weight gain ininsulin-treated patients. As a once-daily injection with effects on both fasting and post prandial hyperglycemia, IDegLira has the potential to help many patients reach glycemic target (60%-81% of patients achieved HbA1c <7% in clinical trials).

The complex pathophysiology of type 2 diabetes is characterized by declining β-cell function resulting in reduced insulin secretion in response to glucose, hyper secretion of glucagon from pancreatic α-cells and insulin resistance in the muscle and liver. This favors a strategic approach involving combinationtherapy that can address the full spectrum of underlying abnormalities and maximize the chance of treatment success. Metformin is recommendedas first-line therapy in most patients with type 2 diabetes, and it is recommended that an additional therapy be added if a patient is not at target after 3-6 months treatment. Incretin and insulin therapies are both efficacious blood glucose lowering therapies, but with different mechanisms of action. GLP-1RAs increase insulin secretion by β-cells and decrease glucagon secretion by α-cells, both in a glucose-dependent manner.

Depending on their duration of action, they can decrease both fasting plasma glucose (FPG) and postprandial glucose (PPG), with longeracting GLP-1RAs having a greater effect on FPG and shorter acting products having a greater effect on PPG. GLP-1RAs also reduce satiety, delay gastric emptying, can reduce body weight and areassociated with a low risk of hypoglycemia. However, GLP-1RAsmay not lead to sufficient insulin secretion from β-cells to achieve

the desired glycemic control. Basal insulin therapy increases circulating insulin in a non-glucose-dependent manner and has been associated with improved β-cell function. Basal insulin has a role in glucose regulation in the liver and peripheral tissues, and modulates hepatic glucose production. Basal insulin is very effective at lowering HbA1c and FPG, but has less of an effect on PPG.

Insulin is associated with an increase in body weight (due in part to increased appetite and food intake) and a risk of hypoglycemia. Therefore, the two mechanisms of action may complement each other, with the glucose-dependent effect of GLP-1RAs on pancreatic islet function counterbalancing the risk of hypoglycemia observed with increasing doses of insulin. By reducing hunger and food intake, GLP-1RAs can decrease the weight gain associated with insulin. The individual effects of basal insulin and GLP-1RAs suggest a theoretical rationale for combination therapy with clinical benefits to be expected.

As described above, the beneficial effects of combining incretin and insulin therapies have now been well documented. When titrated as per the clinical trials and guidelines, IDegLira offers a treatment that is likely to be less complex than adding-multiple prandial insulin injections to basal insulin plus OADs, perhaps making therapy adherence less difficult for patients.The end-of-trial HbA1c was particularly impressive in the IDegLira arms of DUAL I–V, with high numbers of patients reaching glycemic target after 26 weeks of treatment, and many patients not requiring the maximum dose in order to do so. In the context of existing therapies, IDegLira provides a novel treatment option that could enable more patients to reach glycemic target, thereby avoiding or delaying future diabetic complications.

It is important to consider where this therapy will fit in the pathway of diabetes care. When patients remain above target on OADs, treatment algorithms recommend therapy intensification. However, the initiation of injectable therapy after oral agents can be problematic and therefore delayed, as is often observed for insulin and therefore potentially IDegLira, too. The combination of an effective basal insulin and an effective GLP-1RA in a single co-formulation for once-daily injection,without compromising the properties of either, provides a simple, user-friendly approach to therapy intensification for a broad spectrum of patients. In our study we investigated the clinical outcomes in a real-world population with long standing, poorly controlled type 2 diabetes mellitus (T2DM) after switching from oral antidiabetic drugs(OADs), GLP-1 RAs or/and insulin to IDegLira [a combination of insulin degludec (IDeg) and liraglutide (Lira)].We observed that mean HbA_{1c} reduced with IDegLira versus previous regimens significantly (8.9%±1.6% vs 7.3%±0.7%, $p < 0.001$). There was a mean decrease in weight of 3 kg with IDegLira (97.4%±18.4 kg vs 94.4%±18.4 Kg, $p < 0.001$) during the three months follow up. There was a decline in mean systolic (135.6±19.4 mmHg vs 130.7±16.4 mmHg, $p < 0.05$), also. Mean dose of IDegLira was 35.9±13.8 dose steps/24h. There were no episodes of severe hypoglycemia during treatment with IDegLira. In conclusion from our study, switching to IDegLira, mostly from regimens using insulin together with oral antidiabetic drugs (OADs) in a real-world population of patients with type 2 diabetes, resulted in improved glycemic control along with weight loss and lower systolic blood pressure. The safety profile with IDegLira was consistent with previous findings.

Furthermore, IDegLira was well tolerated: the rate of hypoglycemia with IDegLira was lower than that with insulin degludec alone and the rate of gastrointestinal side effects was lower than with liraglutide alone in all studies mentioned above.

To summarize, Insulin degludec/liraglutide (IDegLira) is the first fixed-ratio combination of a basal insulin (insulin degludec) and a glucagon-like peptide-1 receptor agonists (liraglutide) available in a single once-daily injection. It is an attractive and effective combination for patients and there are clear benefits associated with use of a fixed ratio single injection in terms of glycemic control, body weight and hypoglycemia. IDegLira associated with a low incidence of side effects for many of our patients with type 2 diabetes, also.