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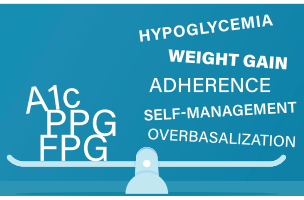
EXPERT perspectives

THE WHY AND HOW FOR COMBINATION BASAL INSULIN + GLP-1RA THERAPY IN TYPE 2 DIABETES



Dear Colleague:

There have been numerous advances in the treatment of patients with type 2 diabetes mellitus (T2DM), yet numerous unmet needs remain. These include increased cardiovascular risk, frequent hypoglycemia, poor adherence, and psychosocial distress. For many, glycemic control remains suboptimal despite the use of basal insulin. While prandial insulin has typically been used as add-on therapy to basal insulin, the glucagon-like peptide-1 receptor agonists (GLP-1RAs) are recommended as an alternative in current guidelines. Please consider some key points from our certified, case-based ExpertPerspectives activity, The Why and How for Combination Basal Insulin + GLP-1RA Therapy in Type 2 Diabetes in which we discuss the rationale and evidence for this combination. We also discuss how the combination of basal insulin and GLP-1RA, including as fixed-ratio products, addresses many unmet needs in patients with type 2 diabetes.

- Patients with T2DM are at increased cardiovascular risk–reducing this risk is a key treatment goal. However, only approximately half of patients with T2DM achieve glycemic targets; few achieve glycemic, blood pressure, and low-density lipoprotein-cholesterol targets. Poor patient adherence to treatment likely contributes to suboptimal disease control.
- Depression and diabetes distress are common in patients with T2DM. Identifying and addressing patient concerns may help to relieve patient distress. This can be achieved through active listening, use of motivational interviewing, asking open-ended questions, and involving the patient in decision-making.
- There are numerous imbalances in glucose homeostasis in T2DM that make it difficult to achieve and maintain glycemic control. Basal insulin and GLP-1RAs may be used across the spectrum of T2DM. The basal insulin analogs glargine and degludec, and the GLP-1RAs liraglutide and semaglutide (as well as the sodium glucose cotransporter-2 inhibitors canagliflozin and empagliflozin), have been shown to reduce cardiovascular risk.
- Basal insulin effectively lowers fasting plasma glucose, but has little effect on postprandial glucose. Consequently, up-titrating basal insulin may not achieve the glycated hemoglobin (A1c) target, but is likely to increase the risk of hypoglycemia. GLP-1RAs are associated with a low risk of hypoglycemia and generally promote modest weight loss.
- Combining basal insulin with a GLP-1RA has a scientific basis. They have complementary actions in addressing key alterations in glucose homeostasis in T2DM that, when combined, result in improvement of both fasting and postprandial glucose.
- In patients with inadequate glycemic control with basal insulin, adding a GLP-1RA vs prandial insulin results in significantly greater improvements in A1c and body weight and a lower risk of hypoglycemia. Moreover, the addition of a GLP-1RA vs prandial insulin requires fewer injections and less glucose monitoring. Limitations with the addition of a GLP-1RA vs prandial insulin include gastrointestinal side effects and higher medication cost.
- The combination of basal insulin and GLP-1RA is available as 2 fixed-ratio products, one consisting of degludec/liraglutide (IDegLira) and the other glargine/lixisenatide (IGlarLixi). These products target both fasting and postprandial glucose, simplify administration and dose titration, and may minimize the delay in achieving glycemic control.
- The DUAL clinical trial program investigated the use of fixed-ratio IDegLira in patients with and without treatment with basal insulin. In insulin-naïve patients, compared to treatment with degludec or liraglutide alone, the A1c reduction was significantly greater with IDegLira and was independent of baseline body mass index; significantly more patients treated with IDegLira achieved A1c targets. Also, the change in body weight was intermediate between treatment with basal insulin or liraglutide. In patients not controlled on insulin glargine in combination with oral medications, treatment with IDegLira resulted in significantly greater reduction in A1c across all baseline A1c, fasting plasma glucose, and body mass index categories, compared with glargine.

- Additional findings from the DUAL program showed the glycemic and weight effects with IDegLira to be durable over 52 weeks. In addition, IDegLira was found to be insulin-sparing, reduce glycemic excursions, result in a lower rate of confirmed hypoglycemia vs glargine, and cause nausea at a rate intermediate between basal insulin and liraglutide. Significantly more patients treated with IDegLira achieved several composite endpoints that included glycemic control, no weight gain, and/or no hypoglycemia. One major adverse cardiovascular event occurred each with IDegLira and glargine. There were no cases of treatment-related, positively adjudicated cases of metastatic pancreatic cancer, pancreatitis, or thyroid disease. Finally, IDegLira was associated with greater improvement than comparators in patient-reported outcomes and treatment satisfaction.
- The LixiLan clinical trial program investigated the use of fixed-ratio IGlarLixi in patients with and without treatment with basal insulin. In insulin-naïve patients, compared to treatment with glargine or lixisenatide alone, the A1c reduction was significantly greater with IGlarLixi, and was independent of baseline body mass index. The change in body weight was intermediate between treatment with glargine or lixisenatide in insulin-naïve patients. The rate of confirmed hypoglycemia with IGlarLixi was similar to glargine in insulin-naïve and insulin-treated patients. Significantly more patients treated with IGlarLixi achieved several composite endpoints that included glycemic control, no weight gain, and/or no hypoglycemia. Adjudicated major cardiovascular events occurred in a low percentage of patients treated with IGlarLixi. There were no cases of adjudicated pancreatitis, pancreatic cancer, or medullary thyroid cancer with IGlarLixi.
- A key finding of the DUAL and LixiLan programs is that the incidence of nausea was significantly less with IDegLira or IGlarLixi than with either liraglutide or lixisenatide alone, respectively. This was likely due to the fact that the titration of IDegLira and IGlarLixi is based on the basal insulin component, resulting in slow up-titration of the GLP-1RA.
- The recommended initial dose of IDegLira is 16 units/day, while the initial dose of IGlarLixi is 15 or 30 units/day depending on previous treatment with basal insulin or lixisenatide. Both fixed-ratio products are given once daily; IDegLira can be given anytime of the day at the same time each day without regard to food, while IGlarLixi is given within the hour prior to the first meal of the day. The maximum dose of IDegLira is 50 units of degludec and 1.8 mg of liraglutide. The maximum dose of IGlarLixi is 60 units of glargine and 20 mcg of lixisenatide.
- The efficacy and safety of basal insulin and GLP-1RA combination therapy have been established in clinical trials of patients with T2DM. The fixed-ratio basal insulin/GLP-1RA combination products offer many glycemic and nonglycemic benefits compared with the individual components, and address many unmet needs encountered in managing patients with T2DM.

With the continued evolution in our care of patients with type 2 diabetes, including the optimal use of combination therapy, we can help our patients achieve glycemic control and address key unmet needs.

Yours sincerely,

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