

Advances in Type 2 Diabetes: Focus on Basal Insulin/Glucagon-Like Peptide-1 Receptor Agonist Combination Therapy

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INTRODUCTION

Despite a greater understanding of pathophysiologic processes of type 2 diabetes mellitus (T2DM) and new classes of medications targeting these processes, the treatment of persons with T2DM remains a formidable challenge. Recent evidence suggests that one-third to one-half of patients with T2DM have not achieved target glycemic control, that is, a glycosylated hemoglobin (A1c) <7%.^{1,2} A key reason appears to be a low rate of timely treatment intensification. Among patients with A1c >7% on metformin monotherapy, recent data indicate that only 38% had evidence of addition of a second glucose-lowering medication during the subsequent 12 months.³

Patients treated with basal insulin fare no better. Blonde et al found that 19% achieved A1c control 6 months after initiating basal insulin therapy and 31% after 12 months.⁴ Other investigators showed that after initiation of basal insulin, an A1c level \leq 7% was achieved in 21% to 27% of patients at 3 months and 28% at 24 months.^{5,6} Individuals who do not have early treatment intensification are less likely to have any treatment intensification at all. For example, failure to achieve A1c \leq 7% at 3 months was found to be associated with an increased risk of failing to achieve the A1c target at 24 months (odds ratio [OR] 3.7; 95% confidence interval [CI], 3.41-4).⁶ Recent evidence indicates that in patients with inadequate glycemic control taking basal insulin, treatment intensification with prandial or premix insulin or a glucagon-

like peptide-1 receptor agonist (GLP-1RA) took an average 4.3 years and happened in 31% of eligible patients.⁷

In patients treated with basal insulin, markers indicating the need to consider additional therapy include (1) an elevated A1c and persistent postprandial hyperglycemia despite a normal or near-normal fasting plasma glucose (FPG) concentration; (2) a total daily dose of basal insulin >0.5 units/kg; (3) severe, nocturnal, or frequent symptomatic hypoglycemia; and (4) persistent difference between bedtime and before-breakfast blood glucose >55 mg/dL.^{8,9} An even lower total daily dose of basal insulin as a marker for dose intensification has been suggested by a post hoc analysis of 3 insulin glargine titration studies of at least 24 weeks' duration (N=458).¹⁰ The analysis found that reduction in the FPG begins to slow at \sim 0.3 units/kg, leveling at \sim 0.5 units/kg.

These findings are a concern and emphasize the importance of staying ahead of this progressive disease through timely, individualized treatment intensification. Recommendations for intensifying glycemic control over time vary between the American Diabetes Association/European Association for the Study of Diabetes (ADA/EASD) and the American Association of Clinical Endocrinologists/American College of Endocrinology (AAACE/ACE), although both recommend using a patient-centric approach to treatment and intensifying every 2 to 3 months.^{8,11} The 2018 ADA/EASD guideline recommends a sequential approach to treatment, generally beginning with metformin monotherapy.⁸ If the A1c target is not achieved after 3 months of metformin monotherapy, and adherence is assured, treatment should be intensified based on patient factors, including cardiovascular risk. Options include sodium-glucose cotransporter-2 inhibitors (SGLT-2is), GLP-1RAs, dipeptidyl peptidase-4 inhibitors (DPP-4is), thiazolidinediones (TZDs), sulfonylureas, and basal insulin. For patients with A1c \geq 10%, blood glucose \geq 300 mg/dL, or markedly symptomatic, combination injectable therapy (basal insulin in combination with a GLP-1RA or prandial insulin) should be considered.

In contrast, the 2018 AAACE/ACE guideline stratifies therapy based on A1c (<7.5%, 7.5%-9%, >9%).¹¹ The AAACE/ACE guideline recommends the following hierarchy of usage

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for addition to metformin monotherapy: GLP-1RA, SGLT-2i, DPP-4i, TZD, basal insulin, and others. Each of these classes of agents has benefits and limitations to be considered when individualizing treatment. For patients with A1c >9%, basal insulin alone or in combination with other agents should be used if the patient is symptomatic; if not, metformin-based dual or triple therapy should be considered. No matter the treatment chosen, the treatment plan should be assessed every 2 to 3 months and treatment intensified if target glucose goals are not achieved. The remainder of this article will discuss the use of basal insulin and GLP-1RAs, focusing on their combined use.

EFFECTS OF BASAL INSULIN AND GLP-1RAS ON THE GLYCEMIC PROFILE

Long-acting basal insulins are intended to reduce the FPG level by mimicking the nonmeal secretion of insulin over the 24-hour day, which in turn suppresses hepatic glucose production. This mechanism of action is in contrast to bolus or prandial insulins, which are intended to lower the postprandial rise in glucose level after nutrient ingestion. People who are using insulin alone for the treatment of their diabetes will often need both insulin components for target glucose control. However, the use of basal insulin is much more common than meal-time insulin in primary care for the treatment of patients with T2DM. If basal insulin at a daily dose ≥ 0.5 units/kg is needed to normalize the FPG, close blood glucose monitoring is advised because of an increasing risk of hypoglycemia, especially if a meal is missed or a person is more active on a given day.

A key feature of the GLP-1RAs is their ability to stimulate insulin secretion and suppress glucagon secretion, both in a glucose-dependent manner, thus exerting greater effect when the blood glucose level is elevated and minimal effect as the blood glucose level approaches normal, thereby reducing the risk of hypoglycemia. The long-acting GLP-1RAs (albiglutide, dulaglutide, exenatide once-weekly, liraglutide, and semaglutide), which have a greater effect on stimulating insulin secretion and inhibiting glucagon secretion, produce strong reduction of FPG and modest reduction of postprandial glucose (PPG).¹²⁻¹⁸ The short-acting GLP-1RAs (exenatide twice-daily and lixisenatide), which slow gastric emptying, produce strong reduction of PPG and modest reduction of FPG.^{12,13,19} The GLP-1RAs also suppress appetite, producing modest weight loss of 1 to 2 kg in most patients with T2DM.^{20,21}

EARLY USE OF BASAL INSULIN AND GLP-1RAS

Among the attributes of an ideal medication for T2DM is the ability to achieve and maintain long-term glycemic-lowering effectiveness. The early addition of basal insulin to metformin improves glycemic control and lowers the risk of hypoglycemia compared with later addition of a sulfonylurea

to metformin.²² Moreover, as a natural hormone, insulin is effective long-term, with the magnitude of glycemic lowering dependent on dose and limited by the risk of hypoglycemia.

The GLP-1RAs serve to normalize the impaired incretin effect observed in patients with T2DM, providing an additional 0.5% to 1.3% A1c lowering when added to metformin.²³ Clinical investigation shows that GLP-1RAs improve various markers of beta-cell function, including homeostatic model assessment of β -cell function (HOMA-B), thus suggesting long-term effectiveness.²⁴ Further support for long-term glycemic effectiveness for GLP-1RAs stems from a network meta-analysis of 301 clinical trials (118,000 patient-years of treatment). The analysis yielded an intermediate OR for treatment failure for a GLP-1RA in combination with metformin. Treatment failure was defined as lack of efficacy or need for additional glucose-lowering therapy. Using the sulfonylureas as the reference class (treatment failure OR = 1), the order of treatment failure (ORs least to greatest) was estimated to be basal insulin (0.1); SGLT-2i (0.68); GLP-1RA (0.84); sulfonylurea (1); TZD (1.18); and DPP-4i (1.37).²⁵

COMBINATION OF BASAL INSULIN WITH A GLP-1RA

As suggested above, patients who do not achieve adequate A1c control despite basal insulin therapy often have postprandial hyperglycemia.^{26,27} Historically, to normalize the PPG, rapid- or short-acting prandial insulin has been added to basal insulin.^{28,29} Although generally effective in improving postprandial hyperglycemia and achieving A1c <7%, the addition of prandial insulin to basal insulin is often limited by weight gain and more frequent symptomatic hypoglycemia.⁸ Further, prandial insulin is a dosing challenge unless the person is willing to be carbohydrate consistent. Otherwise, matching the dose with food intake is difficult. In addition, the general need for multiple injections per day usually requires people to carry their “diabetes supplies” with them to work, school, or eating out. This can be a substantial burden that adversely affects patient adherence.

In contrast, the complementary glycemic effects of a GLP-1RA with basal insulin, coupled with their low incidence of hypoglycemia and their weight-loss effects, provide a strong rationale for using a GLP-1RA in place of prandial insulin for use in combination with basal insulin. They can be taken less often (twice daily to once weekly) and often do not need to be taken outside the home.

Comparison of GLP-1RA vs prandial insulin

Diamant et al compared a GLP-1RA vs prandial insulin, both in combination with basal insulin and metformin.³⁰ After a 12-week period to optimize the dose of insulin glargine

(mean dose 61 units/d), patients with A1c >7.0% (N=627) were randomized to exenatide 5 to 10 mcg twice daily or insulin lispro 3 times per day titrated to achieve a premeal glucose concentration of 100 to 108 mg/dL. After 30 weeks, the A1c was reduced to 7.2% and 7.1% in the exenatide and lispro groups, respectively, down from randomization A1c values of 8.3% and 8.2% (end of treatment difference -0.04%; 95% CI, -0.18-0.11). From a randomized FPG of 128 mg/dL for both groups, the FPG was 117 and 130 mg/dL at study end in the exenatide and lispro groups, respectively ($P=0.002$). Reductions in PPG were similar in both groups except after lunch, in which the reduction with lispro was greater than with exenatide (-56 vs -39 mg/dL; $P<0.001$).

Other randomized controlled trials investigating the addition of albiglutide or lixisenatide to basal insulin have shown similar results when compared with the addition of prandial insulin.^{31,32}

Combination of insulin with a GLP-1RA

The complementary glycemic and nonglycemic effects of basal insulin and GLP-1RAs provide a strong rationale for their combined use. The benefits of the combination were demonstrated by a systematic review of 14 observational/real-world studies and 5 clinical trials involving approximately 5000 patients with T2DM for 7 to 15 years and treated with the combination of GLP-1RA and basal insulin with or without prandial insulin.³³ Across the 19 studies, the combination of a GLP-1RA with insulin improved glycemic control without weight gain or an increased risk of hypoglycemia. Weight loss was commonly observed. The addition of a GLP-1RA to basal insulin therapy allowed for a reduction of the total daily insulin dose without a loss of glucose control. The most commonly reported adverse events were gastrointestinal, but were generally mild or moderate in severity and decreased in occurrence with continued dosing.

Similar results were reported in a more recent meta-analysis of 26 randomized clinical trials involving 11,425 patients treated for 12 to 52 weeks.³⁴ Compared with patients treated with a variety of regimens consisting of basal insulin with or without prandial insulin, patients treated with the combination of basal insulin and GLP-1RA had significantly greater reductions in A1c (weighted mean difference [WMD], -0.47%; 95% CI, -0.59 to -0.35) and body weight (WMD, -2.5 kg; 95% CI, -3.3 to -1.7 kg), were more likely to achieve the A1c target (relative risk [RR], 1.65; 95% CI, 1.44-1.88), and had similar rates of hypoglycemia (RR, 1.14; 95% CI, 0.93-1.39).

Fixed-ratio combination products of basal insulin and GLP-1RA

The glycemic and nonglycemic benefits observed with the

combination of basal insulin and a GLP-1RA as individual medications led to the development of fixed-ratio combination products. An advantage of these combination products for patients is that they avoid the need for 2 separate injections and 2 copays.

One fixed-ratio product combines insulin glargine U-100 with lixisenatide (IGlarLixi) and the other combines insulin degludec U-100 with liraglutide (IDegLira).^{35,36} Both products are indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2DM inadequately controlled on basal insulin or GLP-1RA therapy. Both are titrated based on the basal insulin component, allowing for a slow increase in the GLP-1RA dose, thereby minimizing the frequency and severity of nausea and vomiting. IGlarLixi can be titrated over the range of 15 to 60 units, in which 1 unit of IGlarLixi equals 1 unit of glargine and 0.33 mcg of lixisenatide. The maximum dose of lixisenatide is 20 mcg. IDegLira can be titrated over the range of 10 to 50 units, in which 1 unit of IDegLira equals 1 unit of degludec and 0.036 mg of liraglutide. The maximum dose of liraglutide is 1.8 mg. Both are available only in pen devices.

INSULIN GLARGINE/LIXISENATIDE

LixiLan-O trial

The LixiLan-O trial compared the individual components of glargine U-100 and lixisenatide with the fixed-ratio product IGlarLixi in patients with T2DM inadequately controlled with metformin with or without a second oral medication (N=1170).³⁷ At the end of 30 weeks, from a baseline of 8.1%, the A1c was reduced -1.6% with IGlarLixi compared with -1.3% for glargine and -0.9% for lixisenatide 20 mcg/d ($P<0.0001$ IGlarLixi vs comparators). The reduction in FPG was similar with IGlarLixi (-63 mg/dL) and glargine (-59 mg/dL) and smaller with lixisenatide 20 mcg/d (-27 mg/dL; $P<0.0001$ vs IGlarLixi). The reduction in PPG was greater with IGlarLixi (-103 mg/dL) than glargine (-59 mg/dL; 95% CI, -2.8 to -2.0) or lixisenatide (-83 mg/dL; 95% CI, -1.6 to -0.6). The total daily dose of insulin at study end was 39.8 units with IGlarLixi and 40.3 units with glargine.

Changes in body weight were as expected, with a -0.3 kg loss with IGlarLixi. The rate of symptomatic hypoglycemia (≤ 70 mg/dL) was highest with IGlarLixi at 1.4 events/patient-year, compared with glargine at 1.2 events/patient-year and lixisenatide at 0.3 events/patient-year. Nausea (9.6% vs 24.0%) and vomiting (3.2% vs 6.4%) occurred less frequently with IGlarLixi than lixisenatide, respectively, likely due to the slow increase in lixisenatide dose due to titration of the insulin dose. A positively adjudicated major adverse cardiovascular event occurred in 2 patients in the IGlarLixi group, 7 patients in the glargine group, and 2

patients in the lixisenatide group. No cases of pancreatitis occurred.³⁷

LixiLan-L trial

The LixiLan-L trial compared IGLarLixi with up-titrated glargine U-100 in patients who had inadequate glycemic control while using glargine 15 to 40 units/d plus oral agents (N=736).³⁸ After a 6-week run-in during which oral agents other than metformin were stopped, patients were treated for 30 weeks with doses of IGLarLixi and up-titrated glargine capped at 60 units/d. From a baseline A1c of 8.1%, the A1c was reduced -1.1% in the IGLarLixi group and -0.6% in the glargine group ($P<.0001$). A post hoc analysis demonstrated that the reductions in A1c were greater for IGLarLixi than glargine for each of 3 groups of patients based on screening A1c level (A1c \leq 8%, 8%-9%, and $>$ 9%) (all $P<.0001$).³⁹

Although the reduction in FPG was small (-7 mg/dL with IGLarLixi and -9 mg/dL with glargine), the PPG reduction was significantly greater with IGLarLixi than glargine (-85 vs -25 mg/dL, respectively; 95% CI, -3.9 to -2.8). The mean final total daily dose of insulin was 47 units in both groups.

More patients in the IGLarLixi group than the glargine group achieved several composite endpoints that consisted of glycemic control, no weight gain, and/or no hypoglycemia. These benefits were independent of baseline A1c, body mass index, and duration of T2DM.^{40,41} For example, 20% of patients treated with IGLarLixi achieved A1c $<$ 7% without weight gain and documented symptomatic hypoglycemia, compared with 9% of glargine patients ($P<.0001$).³⁸

Post hoc analyses

Further analyses of LixiLan-O, LixiLan-L, and other trials demonstrated additional benefits of IGLarLixi compared with glargine. In LixiLan-L, an A1c $<$ 7% was achieved by 50% of IGLarLixi patients at a median of 153 days, but was never reached by 50% of patients with glargine.⁴² In patients treated with IGLarLixi in LixiLan-O, the change from baseline in PPG excursion was -29, -36, and -52 mg/dL for the lixisenatide dose groups of 5 to 10, 10 to 15, and 15 to 20 mcg, respectively.⁴³ Glycemic and nonglycemic outcomes with IGLarLixi have been found to be generally similar in patients \geq 65 years of age compared with patients $<$ 65 years, with no increased risk of hypoglycemia.⁴⁴ Modest weight loss was observed in patients \geq 65 years of age.

INSULIN DEGLUDEEC/LIRAGLUTIDE

DUAL-I trial

The DUAL-I trial compared the individual components of degludec U-100 and liraglutide 1.8 mg/d with the fixed-ratio product IDegLira in patients with T2DM inadequately

controlled with metformin with or without pioglitazone (N=1660).⁴⁵ Patients were treated for 26 weeks, after which approximately three-quarters of patients continued treatment for an additional 26 weeks. After 52 weeks, from a baseline A1c of 8.3%, the A1c reduction was greatest with IDegLira than degludec or liraglutide (1.8% vs 1.4% vs 1.3%; both $P<.0001$ vs IDegLira). The reduction in FPG was similar with IDegLira (-62 mg/dL) and degludec (-61 mg/dL), and smaller with liraglutide (-30 mg/dL; $P<.0001$ vs IDegLira). The total daily dose of insulin at study end was 39 units with IDegLira and 62 units with degludec. Substudy analysis showed the decrease in the PPG increment was similar with IDegLira and liraglutide, both of which were greater than with degludec.⁴⁶

Changes in body weight were as expected, with a -0.4 kg loss with IDegLira. The rate of confirmed hypoglycemia (requiring assistance or $<$ 56 mg/dL with or without symptoms) was highest with degludec (2.6 events/patient-year) and least with liraglutide (0.2 events/patient-year). Nausea occurred less frequently with IDegLira than liraglutide (9% vs 20%), likely because of the slow increase in liraglutide dose due to titration of the insulin dose. A positively adjudicated major adverse cardiovascular event occurred in 4 patients in the IDegLira group and 1 in each of the degludec and liraglutide groups. Two cases of treatment-emergent pancreatitis occurred in the liraglutide group, but were judged as unlikely to be treatment-related.

DUAL-II trial

The DUAL-II trial compared IDegLira with degludec, both once daily with the maximum degludec dose capped at 50 units.⁴⁷ Patients (N=413) had inadequate glycemic control despite basal insulin 20 to 40 units/d in combination with metformin with or without a sulfonylurea or meglitinide. At randomization to IDegLira or degludec, patients were continued on metformin alone. Insulin doses were titrated to achieve a FPG of 72 to 90 mg/dL. After 26 weeks, from a baseline A1c of 8.7% to 8.8%, the A1c was reduced -1.9% in the IDegLira group and -0.9% in the degludec group ($P<.0001$). Similarly, the FPG reduction was greater with IDegLira than with degludec (-62 vs -46 mg/dL, respectively; $P=.0019$). The 2-hour PPG excursion was similar (40 vs 43 mg/dL, respectively). The mean total daily degludec dose was 45 units in each group.

More patients in the IDegLira group than the degludec group achieved several composite endpoints that consisted of glycemic control, no weight gain, and/or no hypoglycemia. The rates of confirmed and nocturnal hypoglycemia were similar in both groups. Similar to DUAL-I, nausea occurred more frequently with IDegLira than with degludec (6.5% vs 3.5%). One positively adjudicated major adverse cardiovas-

cular event occurred with IDegLira and 2 with degludec. No cases of pancreatitis were observed.

Post hoc analyses

Further analyses of DUAL-I and DUAL-II and other DUAL trials have provided additional insight regarding the benefits of IDegLira compared with degludec. As expected, the magnitude of A1c lowering increased with increasing A1c at baseline.⁴⁸ However, A1c reductions with IDegLira were significantly greater than with degludec or liraglutide in all baseline A1c categories ($P < .01$) ($\leq 7.5\%$, $> 7.5\% - 8.5\%$, $> 8.5\% - 9\%$, $> 9\%$), except for no difference in the lowest A1c category in DUAL-II. The DUAL-V trial, which compared IDegLira with glargine, also showed IDegLira to be significantly more effective than glargine for reducing A1c across all baseline A1c categories ($P < .0001$) ($\leq 7.5\%$, $> 7.5\% - 8.5\%$, $> 8.5\%$).⁴⁹ Similarly, IDegLira was significantly more effective than glargine for reducing A1c irrespective of baseline FPG ($P < .0001$) (< 130 and ≥ 130 mg/dL) or body mass index ($P < .0001$) (< 30 , 30 to < 35 , and ≥ 35 kg/m²).

Additional analysis of DUAL-I and DUAL-II showed the mean A1c to be significantly lower and the proportion of patients achieving A1c $< 7\%$ significantly greater at weeks 8 and 12 with IDegLira (all $P < .0001$).⁵⁰ Reductions in A1c also have been shown to be significantly greater with IDegLira vs comparators (basal insulin, GLP-1RA, placebo) in patients with mildly or moderately impaired renal function (estimated glomerular filtration rate ≥ 90 , ≥ 60 to < 90 , ≥ 30 to < 60 mL/min/1.73 m²).⁵¹

In DUAL-I, a subset of patients underwent continuous glucose monitoring after meal tests.⁴⁶ Results showed a reduction in the PPG increment after all 3 main meals. The reduction was similar for IDegLira and liraglutide, both significantly greater than for degludec. Additional data suggested that the improvement was partially explained by higher endogenous insulin secretion and improved β -cell function due to liraglutide.

The data from DUAL-I, as well as 9-point self-monitored blood glucose (SMBG) profiles from DUAL-I and DUAL-II, showed that IDegLira resulted in a higher proportion of patients with SMBG values within the target range (70-162 mg/dL) for all pre- and postprandial values, as well as for the full 9-point profile ($P < .01$ for all).⁵² Moreover, reduction in the fluctuation of interstitial glucose was significantly greater with IDegLira than liraglutide ($P = .0072$).

DOSING AND TITRATION

Before initiating IGLarLixi or IDegLira, basal insulin and GLP-1RA therapy must be discontinued.³⁵ IGLarLixi is initiated at a dose of 15 units (15 units glargine and 5 mcg lixisenatide) for

patients taking basal insulin < 30 units/d or taking lixisenatide, or at a dose of 30 units (30 units glargine and 10 mcg lixisenatide) for patients taking basal insulin 30 to 60 units/d.³⁵ The dose of IGLarLixi is administered once daily prior to the first meal of the day and should be titrated up or down by 2 to 4 units between 15 and 60 units every week.

IDegLira is initiated at a dose of 16 units (16 units degludec and 0.58 mg liraglutide).³⁶ The dose of IDegLira is administered at the same time each day and should be titrated up or down by 2 units between 10 and 50 units every 3 to 4 days.

The pen devices for IGLarLixi and IDegLira are similar to the pen devices for their respective insulin products, which should simplify transitioning patients from the insulin product to the fixed-ratio combination product.

CLINICAL IMPLICATIONS OF FIXED-RATIO BASAL INSULIN/GLP-1RAS

The fixed-ratio basal insulin/GLP-1RA combination products combine 2 important patient-centered features: high levels of efficacy as represented by most patients achieving target treatment goals and superior glucose control compared with insulin. Furthermore, a single daily injection with no substantial dosing preparation should seem simple for patients. However, the use of these agents as the first injectable treatment may be limited by insurance coverage and cost, likely because this use is outside the currently approved indication. If these agents are added after basal insulin or GLP-1 RA, the provider should be mindful of the starting dose and discuss the expected glucose changes and common adverse reactions during titration. ●

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