Basal Insulin Use With GLP-1 Receptor Agonists

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■ IN BRIEF The combination of basal insulin and a glucagon-like peptide 1 receptor agonist is becoming increasingly common and offers several potential benefits to patients with type 2 diabetes. Clinical studies have demonstrated improved glycemic control and low risks of hypoglycemia and weight gain with the combination, which provides a safe and effective alternative to basal-bolus insulin with less treatment burden. Fixed-ratio combination products that administer both agents in a single injection are in the pipeline and will offer additional options for clinicians and patients. This review focuses on the rationale for, clinical evidence on, and implications of using this combination of therapies in the treatment of type 2 diabetes.

Type 2 diabetes is a chronic, progressive disease that remains difficult to control despite a growing armamentarium of treatment options. National data show that only 52.5% of people with diabetes achieved a goal A1C <7% in the 2007–2010 period, indicating the continued need for effective and durable treatment approaches (1).

The typical clinical course of type 2 diabetes involves periods

TABLE 1. Complementary Characteristics of Basal Insulin and GLP-1 Receptor Agonists

	Basal Insulin	GLP-1 Receptor Agonists
Mechanism of action	• Augments basal insulin • Increases glucose disposal • Decreases hepatic glucose production	• Increases glucose-dependent insulin secretion from the pancreas • Decreases glucose-dependent secretion of glucagon • Slows gastric emptying • Increased satiety
Glucose profile effects	• Primarily lowers FPG	• Short-acting agents primarily lower PPG excursions • Longer-acting agents lower PPG and FPG
Effect on weight	• Increases weight	• Decreases weight
Main adverse effect	• Hypoglycemia	• GI issues (nausea, vomiting, diarrhea) • Low risk of hypoglycemia
Administration requirements	• Subcutaneous injection once or twice daily	• Subcutaneous injection once or twice daily or once weekly

of adequate glycemic control followed by glycemic deterioration and the need for additional treatment. Ideally, add-on therapies should provide significant glucose reduction with a complementary mechanism of action, without adding significant side effects. Basal insulin (e.g., detemir, glargine, or degludec) is a recommended option at many stages of type 2 diabetes and is often added to oral antidiabetic agents (OADs) to achieve target fasting plasma glucose (FPG) levels. However, it increases the risk of hypoglycemia and weight gain, and its dosage must be titrated effectively to achieve glycemic targets (2,3). Glucagon-like peptide 1 (GLP-1) receptor agonists are also reasonable options at many stages of type 2 diabetes. These agents effectively lower A1C, show favorable effects on weight, and have a low risk of hypoglycemia (4). Their use may be limited by gastrointestinal (GI) adverse effects (AEs), administration requirements, and cost. The combination of basal insulin and a GLP-1 receptor agonist offers several potential benefits to patients with type 2 diabetes. This review focuses on the rationale for, clinical evidence on, and implications of the combination of basal insulin and GLP-1 receptor agonists in the treatment of type 2 diabetes.

Rationale for Combining Basal Insulin with GLP-1 Receptor Agonists

Several considerations make the combination of basal insulin and a GLP-1 receptor agonist appealing (Table 1). First, the combination provides complementary effects on the glucose profile. Basal insulin delivers sustained insulin throughout the day, and therapy can be individualized by titrating the dose to the patient's target FPG levels. However, barriers such as fear of hypoglycemia and weight gain may limit the initiation and adequate titration of basal insulin (5,6). In addition, basal insulin does not target postprandial glucose (PPG); thus, more than half of patients treated with basal insulin do not achieve A1C targets (7–9). GLP-1 receptor agonists stimulate glucose-dependent insulin secretion, inhibit glucose-dependent glucagon secretion, slow gastric emptying, and increase satiety. Some evidence also suggests that GLP-1 receptor agonists may preserve β-cell function (10,11). Through these mechanisms, GLP-1 receptor agonists provide improvements in both PPG and FPG levels, complementing the effects of basal insulin.

There are currently six GLP-1 receptor agonists approved for use in either the United States or Europe

(Table 2). The pharmacokinetics, pharmacodynamics, dosing, and clinical effects differ among these agents. The shorter-acting agents (exenatide and lixisenatide) are associated with more significant delays in gastric emptying and more targeted reductions in PPG. Compared to short-acting GLP-1 receptor agonists, the longer-acting agents (albiglutide, dulaglutide, exenatide XR, and liraglutide) have less of an effect on gastric emptying and rely more on the insulin secretion mechanism, which leads to reductions in both FPG and PPG (4,12). Of note, although liraglutide and lixisenatide are both dosed once daily, lixisenatide has a shorter half-life and primarily lowers PPG, whereas liraglutide has a longer half-life, thus lowering both PPG and FPG (13). These distinctions should be considered when selecting a specific GLP-1 receptor agonist to use in combination with basal insulin.

Combining therapy may also potentially lower the risk of AEs. Basal insulin may cause weight gain and hypoglycemia. GLP-1 receptor agonists usually cause weight loss and have a low risk of hypoglycemia but do cause GI AEs. Combining the two classes may allow patients to achieve glycemic control with lower doses, which could potentially result in

TABLE 2. GLP-1 Receptor Agonists Approved for Use in the United States or Europe

	Short-Acting			Long-Acting		
Generic name (trade name)	Exenatide (Byetta)	Lixisenatide (Lyxumia)	Liraglutide (Victoza)	Exenatide XR (Bydureon)	Albiglutide (Tanzeum, Eperzan)	Dulaglutide (Trulicity)
Year of FDA approval	2005	Pending	2010	2012	2014	2014
Year of EMA approval	2006	2013	2009	2011	2014	2014
Dose	5–10 µg	10–20 µg	0.6–1.8 mg	2 mg	30–50 mg	0.75–1.5 mg
Administration*	Twice daily	Once daily	Once daily	Once weekly	Once weekly	Once weekly
Delivery	Multi-use pen	Multi-use pen	Multi-use pen	Single-use pen#	Single-use pen#	Single-use pen
Renal dosing	Not recommended if CrCl is <30 mL/min; use caution if CrCl is 30–50 mL/min	None	None	Not recommended if CrCl is <30 mL/min; use caution if CrCl is 30–50 mL/min	None	None

*Delivered via subcutaneous injection.
#Requires reconstitution.
CrCl, creatinine clearance; EMA, European Medicines Agency; FDA, U.S. Food and Drug Administration.

fewer AEs than when the individual drugs are used independently.

Finally, adding a GLP-1 receptor agonist to basal insulin offers a potentially safer and easier approach to achieving glycemic control compared to prandial insulin. Initiation of prandial insulin increases treatment burden for patients and management burden for providers. It requires one to three injections per day in addition to the basal insulin injection, significant patient education, dose titration, and increased monitoring and increases the risk of hypoglycemia and weight gain. Alternatively, adding a GLP-1 receptor agonist involves fewer injections, simplified dose titration, less education, reduced weight, and a lower risk of hypoglycemia.

Clinical Evidence
Evidence supporting the use of GLP-1 receptor agonists in combination with basal insulin is growing. A meta-analysis from 2014 described 15 studies (*n* = 4,348) in which GLP-1 receptor agonists were added to basal insulin therapy or vice versa in type 2 diabetes patients (14). The authors determined that combination therapy yielded a mean reduction in A1C of 0.44% (95% CI –0.60 to –0.29, *P* <0.0001) and weight of 3.22 kg (95% CI –4.90 to –1.54, *P* <0.0001). Combination therapy did not increase the relative risk of hypoglycemia (relative risk 0.99, 95% CI 0.76–1.29, *P* <0.0001). Although these findings were favorable, only 4 of the 15 studies in the meta-analysis used an active comparator.

The four active comparator studies, plus a fifth study published after the meta-analysis was completed, compared the addition of a GLP-1 receptor agonist or prandial insulin to basal insulin therapy (15–19). Of these, two evaluated twice-daily exenatide (15,16); two evaluated once-daily liraglutide and lixisenatide, respectively (17,18); and one evaluated once-weekly albiglutide (19). Overall, these studies demonstrated efficacy with regard to A1C and body weight reductions of basal insulin plus a GLP-1 receptor agonist compared to basal insulin plus prandial insulin (Table 3). There was minimal hypoglycemia in the GLP-1 receptor agonist–treated patients; the most common AEs were predictably GI related.

Diamant et al. randomized 627 patients with insufficient glycemic control despite 12 weeks of intensive protocol-driven glargine titration to add twice-daily exenatide or thrice-daily lispro to their regimen (15). Patients receiving exenatide reduced their glargine dose by 10% (or more if their A1C was ≤8%), and patients receiving lispro reduced their glargine dose by 33–50%. Exenatide was initiated at 5 µg twice daily for 4 weeks and then up-titrated to 10 µg initiated at a dose to replace the reduced dose of glargine, divided across three meals. After exenatide or lispro initiation, glargine was titrated as in the 12-week optimization phase, and lispro was titrated based on premeal glucose values. After 30 weeks of therapy after the optimization phase, patients in each treatment arm experienced similar reductions in A1C based on the initial A1C at the end of the optimization phase (exenatide –1.13%, 95% CI –1.24 to –1.03; lispro –1.10%, 95% CI –1.20 to –1.0).

TABLE 3. Clinical Trials Comparing Basal Insulin Plus a GLP-1 Receptor Agonist to Basal Plus Prandial Insulin

Clinical Trial (Duration)	Background Therapy	n	Mean Duration of Type 2 Diabetes (years)	Comparator Arms	Baseline A1C (%)	Baseline FPG (mg/dL)	Baseline Basal Insulin Dose (units/day)	Δ A1C (%)	Final Basal Insulin Dose (units/day)	Δ Weight (kg)	Hypoglycemia* (%)	Nausea (%)	Vomiting (%)	Diarrhea (%)
Diamant (15) (30 weeks)	Glargine + metformin	627	11.5	Exenatide	8.3	129.6	61.5	−1.13‡	56.8	−2.5†	30	2.9	0.6	0.3
				Lispro (each meal)	8.2	126.0	61.1	−1.10	51.5†	+2.1	41	0	0	0
Shao et al. (16) (12 weeks)	None	60	Newly diagnosed	Exenatide + glargine	7.68	168.3	NA	−1.42#	NR	−7.77#†	20	6.7	3.3	3.3
				Aspart (each meal) + glargine	7.59	165.4	NA	−1.31#	NR	+3.27#	0	0	0	0
Mathieu et al. (17) (28 weeks)	Degludec + metformin	177	11.8	Liraglutide	7.7	115.2	0.70&	−0.74†	0.65&	−2.8†	1.00**	20.7	5.7	10.3
				Aspart (largest meal)	7.7	109.8	0.66&	−0.39	0.64&	+0.9	8.15**	0	0	0
Roy-Duval et al. (18)§ (26 weeks)	Glargine ± metformin	890	Unknown	Lixisenatide	7.76	118.4	67	−1.34‡	67	−0.7†	31.5	25	9	7
				Aspart (one meal)	7.72	123.3	65	−1.28	64	+0.9	37.5	2	2	3
Rosenstock et al. (19) (26 weeks)	Glargine ± metformin, pioglitazone, or both	566	11	Albiglutide	8.5	153.0	47.0	−0.82‡	53.2	−0.73#‡	15.8	11.2	6.7	13
				Lispro (each meal)	8.4	153.0	43.4	−0.66	50.6	+0.81	29.9	1.4	1.4	4.3

#P <0.05 versus baseline. †P <0.05 versus comparator group. ‡Met noninferiority criteria. &Units/kg/day. §Abstract only. *Definition of hypoglycemia was unique to each study: Diamant et al., blood glucose <54 mg/dL; Shao et al., blood glucose <70 mg/dL; Mathieu et al., blood glucose <56 mg/dL; Roy-Duval et al., blood glucose <60 mg/dL, and Rosenstock et al., blood glucose <70 mg/dL. **Episodes per patient-year of exposure. NA, not applicable; NR, not reported.

The difference in A1C between exenatide and lispro was −0.04% (95% CI −0.18 to 0.11) in the per-protocol population and −0.03% (95% CI −0.16 to 0.11) in the intent-to-treat population, which met noninferiority criteria. The glargine dose decreased from a mean of 61.5 to 56.8 units in the exenatide group and from 61.1 to 51.5 units in the lispro group (*P* <0.001 for between-group difference). Patients receiving exenatide lost weight, whereas those receiving lispro gained weight. The incidences of minor and non-nocturnal hypoglycemia were lower in the exenatide group compared to the lispro group (30 vs. 41%, *P* = 0.004, and 15 vs. 34%, *P* <0.001, respectively). However, the incidence of nocturnal hypoglycemia was similar between groups (25 vs. 27%, *P* not reported). GI AEs were more prevalent in the exenatide group, but no cases of pancreatitis were observed in either group. The authors concluded that twice-daily exenatide was a reasonable alternative to prandial insulin for type 2 diabetes patients with suboptimal glycemic control despite glargine therapy (15).

Shao et al. also studied the addition of twice-daily exenatide or prandial insulin to glargine (16). This study enrolled 60 patients with newly diagnosed type 2 diabetes, obesity (BMI ≥28 kg/m^2), and non-alcoholic fatty liver disease (NAFLD) with elevated liver enzymes. Thirty patients were randomized to twice-daily exenatide plus glargine, and 30 patients were randomized to thrice-daily aspart plus glargine. Exenatide was initiated at 5 μg twice daily for 4 weeks and up-titrated to 10 μg twice daily for 8 weeks. Insulin dosing algorithms and mean daily doses of insulin were not reported. At the end of 12 weeks, A1C had decreased by 1.42% in the exenatide group and 1.31% in the aspart group (both *P* <0.001 vs. baseline A1C at diagnosis). Patients in the exenatide group lost weight (−7.77 kg, *P* <0.001), whereas those in the

aspart group gained weight (+3.27 kg, *P* <0.001). Patients in the exenatide group experienced decreases in liver enzymes compared to the aspart group (*P* <0.001). One-third of patients in the exenatide group reported a mild to moderate GI AE, and 10% of patients in the aspart group reported an episode of symptomatic hypoglycemia. The authors concluded that exenatide was effective at decreasing A1C, weight, and elevated liver enzymes in newly diagnosed type 2 diabetes patients with obesity and NAFLD (16).

BEGIN: VICTOZA ADD-ON was a 26-week study by Mathieu et al. that evaluated the addition of once-daily liraglutide or aspart with the largest meal in 177 patients with type 2 diabetes receiving degludec with or without metformin who had completed the 52-week BEGIN ONCE-LONG trial plus a 52-week extension and had an A1C ≥7% (17). These 177 patients had a mean A1C of 7.7% at the end of the 104 total weeks from previous study enrollment. Patients receiving liraglutide had their degludec dose decreased by 20% at study initiation, and the dose could not be increased until week 6. Liraglutide was initiated at 0.6 mg daily for 1 week and increased to 1.2 mg daily for 5 weeks. At week 5, if the mean prebreakfast FPG value was ≥90 mg/dL, liraglutide was increased to 1.8 mg daily. From week 6 onward, if the mean prebreakfast FPG value was ≥90 mg/dL, liraglutide was increased to 1.8 mg daily, or the degludec dose could be increased per the study-specified titration schedule. Patients receiving aspart started on a dose of 4 units before their largest meal of the day. Aspart was titrated weekly based on the mean of three premeal or bedtime blood glucose values. At 26 weeks, A1C decreased more in the liraglutide group than in the aspart group (−0.74 vs. −0.39%, *P* = 0.0024). The mean degludec dose in the liraglutide group was 0.70 units/kg/day at study initiation and 0.65 units/kg/day at 26 weeks,

and the mean degludec dose in the aspart group was 0.66 units/kg/day at study initiation and 0.64 units/kg/day at week 26 (*P* not reported). The mean aspart dose at week 26 was 0.21 units/kg/day. Patients receiving liraglutide lost weight, whereas patients receiving aspart gained weight (−2.8 vs. +0.9 kg, *P* <0.0001 for the comparison). Patients randomized to liraglutide were less likely to experience hypoglycemia than those in the aspart group (estimated rate ratio 0.13, 95% CI 0.08–0.21, *P* <0.0001). The most common AEs in the liraglutide group were GI-related. The authors concluded that the addition of liraglutide was more effective at reducing A1C than aspart; however, aspart was only given once daily. Liraglutide had positive effects on weight and was associated with a low risk of hypoglycemia (17).

Roy-Duval et al. evaluated the addition of the GLP-1 receptor agonist lixisenatide 20 μg daily versus daily glulisine or thrice-daily glulisine in 890 patients with type 2 diabetes poorly controlled on glargine ± metformin after a 12-week optimization phase (18). Data are currently published only in abstract form. At the end of a 12-week run-in period, the mean daily doses of glargine were similar between the lixisenatide, daily glulisine, and thrice-daily glulisine groups (67 ± 32 units, 65 ± 32 units, and 65 ± 27 units, respectively). Lixisenatide was deemed noninferior to either once- or thrice-daily glulisine with respect to A1C change from the end of the 12-week optimization phase to the end of the 26-week study period (−0.59 vs. −0.52 vs. −0.83%) and was superior in terms of weight loss, as patients lost weight with lixisenatide and gained with glulisine (*P* <0.0001 for lixisenatide vs. each glulisine arm). The mean daily dose of glargine in the lixisenatide, daily glulisine, and thrice-daily glulisine groups remained the same or decreased (67 ± 36 units, 64 ± 36 units, and 61 ± 29 units, respectively; the treatment difference

between the lixisenatide and thrice-daily glulisine groups was statistically significant). The patients receiving lixisenatide experienced significantly less hypoglycemia than those receiving thrice-daily glulisine ($P <0.0001$); however, patients in the lixisenatide group experienced more GI AEs compared to either glulisine group. The authors concluded that once-daily lixisenatide may be a preferred add-on therapy to glargine for improving glycemic control while minimizing hypoglycemia and promoting weight loss (18).

Finally, the Harmony 6 study by Rosenstock et al. evaluated once-weekly albiglutide versus thrice-daily lispro as add-on therapy in 566 patients with uncontrolled type 2 diabetes despite therapy with glargine ± OADs (19). Patients receiving albiglutide initiated at 30 mg weekly and up-titrated to 50 mg weekly if their A1C was >8% between weeks 8 and 12. Patients receiving thrice-daily lispro had their dose initiated based on self-monitoring of blood glucose data and were titrated to a preprandial goal of 80–130 mg/dL. Patients in each group had their glargine titrated in increments of 2–8 units to a FBG goal of 100 mg/dL. The mean daily glargine dose increase was similar between groups over the 26-week study period (albiglutide 47.0–53.2 units vs. lispro 43.4–50.6 units, P not reported). At the end of 26 weeks, albiglutide and lispro decreased A1C by 0.82 and 0.66%, respectively ($P = 0.053$). The treatment difference of –0.16% between the two groups met prespecified noninferiority criteria (19). After 52 weeks, patients in both arms experienced further decreases in A1C (–1.01 vs. –0.84%, respectively, $P = 0.086$), but albiglutide no longer met noninferiority criteria versus lispro. Patients receiving albiglutide lost weight (–0.96 kg), whereas those receiving lispro gained weight (+1.66 kg, $P <0.001$). Hypoglycemia occurred more frequently in lispro-treated patients (39 vs. 23%), but overall, AEs were more common in the patients receiving albiglutide. The authors concluded that once-weekly albiglutide was comparably efficacious to thrice-daily lispro as add-on therapy for type 2 diabetes patients not optimized on glargine ± OADs. Albiglutide was associated with weight loss, less hypoglycemia, and fewer injections per week compared to lispro (20).

Fixed-Ratio Combinations

Two fixed-ratio combinations (FRCs) containing a GLP-1 receptor agonist and a basal insulin in a single injection are in the development pipeline. Novo Nordisk has submitted materials for U.S. Food and Drug Administration (FDA) approval of an FRC containing degludec and liraglutide (IDegLira) (21). The combination product has been approved in Europe under the trade name Xultophy and is supplied as a 3-mL pen device containing 100 units/mL degludec and 3.6 mg/mL liraglutide (22). Sanofi submitted materials for FDA approval of an FRC containing glargine and lixisenatide (LixiLan or iGlarLixi) in December 2015 and redeemed a priority review voucher to shorten the review time to 6 months (23).

The DUAL I study evaluated IDegLira versus each of its individual components in insulin-naive patients taking metformin with or without pioglitazone with a baseline A1C of 7–10% (24). At the end of 26 weeks, patients receiving IDegLira experienced an A1C reduction of 1.9% compared to a 1.4% reduction with degludec (IDegLira noninferior; treatment difference –0.47%, 95% CI –0.58 to –0.36, $P <0.0001$) and a 1.3% reduction with liraglutide (IDegLira superior; treatment difference –0.64%, 95% CI –0.75 to –0.53, $P <0.0001$) (24). A 26-week extension to this study confirmed sustained efficacy and safety in 78% ($n = 1,311/1,663$) of the patients enrolled in the original DUAL I study (25). At the end of 52 weeks, mean A1C had decreased by 1.84% in the IDegLira group, 1.4% in the degludec group, and 1.21% in the liraglutide group ($P <0.0001$ for IDegLira vs. either degludec or liraglutide). The daily degludec dose was 37% lower in the IDegLira group (39 units) versus the degludec group (62 units; estimated treatment difference –23.4 units, 95% CI –26.4 to –20.3, $P <0.0001$). The rate of confirmed hypoglycemia was significantly lower in the IDegLira group compared to the degludec group (rate ratio 0.63, 95% CI 0.50–0.79, $P <0.0001$) (25).

The DUAL II study evaluated the safety and efficacy of degludec versus IDegLira, each in combination with metformin in 413 patients with a mean baseline A1C of 8.7–8.8 ± 0.7% already receiving basal insulin and OADs (26). Patients were randomized to receive IDegLira plus metformin or degludec plus metformin for 26 weeks, with titration aimed to achieve an FPG of 72–90 mg/dL. The maximum doses allowed were 50 units for degludec and 50 units for degludec plus 1.8 mg of liraglutide for IDegLira. At equivalent degludec doses (mean dose of 45 units in each group), IDegLira decreased A1C by more than twice that of degludec (–1.9 vs. –0.9%; estimated treatment difference –1.1%, 95% CI –1.3 to –0.8%, $P <0.0001$). Patients randomized to IDegLira lost weight (–2.7 kg), whereas patients on degludec maintained their weight ($P <0.0001$), and the incidence of hypoglycemia between groups was similar (24 vs. 25%). The most common AEs of IDegLira were GI-related, but the incidence was much less than that observed in other liraglutide studies; incremental titration allowed for improved GI tolerability. The authors concluded that the FRC IDegLira was superior to degludec for optimizing glycemic control in patients inadequately controlled on OADs and basal insulin (26).

Post-hoc analyses of the DUAL I extension and DUAL II studies determined that IDegLira is efficacious irrespective of baseline A1C, duration of diabetes, and diabetes treatment

at screening. In the DUAL I study, IDegLira significantly reduced A1C irrespective of baseline A1C; this trend held true for the DUAL II study in all baseline A1C categories except for those with an A1C <7.5%. The dose of insulin and rates of hypoglycemia were lower for the IDegLira versus the degludec group, and as expected, the rate of hypoglycemia was higher in the IDegLira versus the liraglutide group in DUAL I. In DUAL II, insulin doses and rates of hypoglycemia were similar between groups. In both studies, reduction in A1C with IDegLira was independent of type 2 diabetes duration and baseline insulin dose but varied based on baseline OAD use (27).

The DUAL V study evaluated the safety and efficacy of IDegLira compared to continued titration of insulin glargine in type 2 diabetes patients not controlled on metformin and insulin glargine (28). A1C reduction was greater in patients taking IDegLira compared to patients continuing with glargine (–1.81 vs. –1.13%; estimated treatment difference –0.59%, 95% CI –0.74 to –0.45%, meeting criteria for noninferiority and superiority, P <0.001). Treatment with IDegLira was associated with weight loss compared to weight gain with glargine (–1.4 vs. +1.8 kg, P <0.001). IDegLira had lower rates of hypoglycemia but higher rates of GI AEs compared to insulin glargine (28).

The completed but not yet published LixiLan-O (n = 1,170) and LixiLan-L (n = 736) phase III 30-week clinical studies evaluated the efficacy and safety of LixiLan. LixiLan-O evaluated LixiLan verses each of its individual components in insulin-naive type 2 diabetes patients not controlled on metformin (29). LixiLan-L evaluated LixiLan compared to glargine in type 2 diabetes patients not controlled on basal insulin plus one or two OADs (30). Patients in each study continued on metformin throughout. Both studies have been reported to have met

their primary endpoints showing superior A1C reduction by LixiLan versus the comparator arms (29,30). A phase IIB study evaluated LixiLan versus glargine (each in combination with metformin) in 323 type 2 diabetes patients with a mean baseline A1C of 8%. The results of this study, currently reported in abstract form, demonstrated superior glycemic efficacy with LixiLan versus glargine without increased risk of hypoglycemia. Patients receiving LixiLan experienced a decrease in A1C from a mean of 8.1 to 6.3% after 24 weeks. Nearly two-thirds of patients achieved an A1C <7% with no documented hypoglycemia (31).

Clinical Implications

Treatment guidelines from the American Diabetes Association indicate that either basal insulin or GLP-1 receptor agonists are reasonable agents to add on as second- or third-line options (2). In 2015, these recommendations were updated to include GLP-1 receptor agonists as alternatives to prandial insulin to treat PPG excursions in patients with uncontrolled A1C despite reaching FPG goals with basal insulin (3). These recommendations are well supported by clinical evidence and offer several advantages, making the use of this combination in clinical practice increasingly more common. There likely will be several clinical scenarios in which the combination may be used. Each scenario requires unique considerations to ensure safe and effective use. In most of these situations, patients likely also would be taking one or more additional OADs such as metformin.

Adding a GLP-1 Receptor Agonist to Basal Insulin

This scenario is well supported by clinical evidence showing decreased A1C and weight compared to placebo and similar efficacy with less hypoglycemia compared to prandial insulin. This option would be a reasonable treatment option in patients with controlled FPG levels but ele-

vated PPG and A1C levels. This may also be a reasonable option for patients on a large dose of basal insulin or those who are not willing or able to optimize their basal insulin dose. A GLP-1 receptor agonist would be a more straightforward approach to glycemic control with less treatment burden and less training, monitoring, and dose titration necessary than with prandial insulin. In most case scenarios, it would increase the injection burden only modestly.

Clinicians should consider patients' primary glucose profile defect to determine whether a short- or long-acting GLP-1 receptor agonist would be preferred. Adherence to administration requirements, patients' preferences, and insurance coverage also will help to determine which GLP-1 receptor agonist would be most appropriate.

When initiating a GLP-1 receptor agonist, the basal insulin dose may need to be decreased as the GLP-1 receptor agonist starts to take effect. Across clinical studies, there were varying approaches to adjusting basal insulin doses, with some empirically decreasing the dose by 10–20% when the GLP-1 receptor agonist was initiated. This basal dose adjustment should depend on baseline glucose and A1C levels, as well as the onset of action, dose titration schedule, and expected impact on glucose profile of the specific GLP-1 receptor agonist. Patients should be educated about the potential for GI AEs, which likely will be transient in nature, and close follow-up is warranted.

Adding Basal Insulin to a GLP-1 Receptor Agonist

The addition of basal insulin to a GLP-1 receptor agonist is also well supported by clinical evidence. This is a reasonable option to consider for patients with uncontrolled FPG and A1C levels despite treatment with one or more OADs and a GLP-1 receptor agonist. Clinicians should educate patients about how to titrate their dose to a target FPG range and, for pa-

tients taking a sulfonylurea, should evaluate the additive risk of hypoglycemia and consider discontinuation of the sulfonylurea.

Adding Basal Insulin Plus a GLP-1 Receptor Agonist Simultaneously

Adding basal insulin plus a GLP-1 receptor agonist simultaneously has been shown to be safe and effective in insulin-naive patients (16,24,25,29). In DUAL-1, adding both simultaneously (IDegLira) allowed patients to use lower doses of each component to achieve the same glycemic control as with the basal insulin degludec and glycemic control superior to that with liraglutide (24,25). Adding the combination also negated some of the side effects of each component, particularly the GI AEs of the GLP-1 receptor agonist, likely because of the slower titration. This may be a reasonable option for a wide range of patients; post-hoc analysis of the DUAL studies demonstrated efficacy independent of duration of disease, background therapies, and baseline A1C levels (except for patients with A1C levels <7.5%) (27).

FRCs offer the advantage of fewer injections and possibly improved adherence and less transient GI AEs resulting from the slower titration of the GLP-1 receptor agonist component. Challenges are similar to those with many combination products. Patients' AEs related to one component may limit their ability to titrate the dose or their persistence with both components. Patients also may reach the maximum dose of the combination but still require more basal insulin to reach FPG goals. Prescribing information for IDegLira indicates that the FRC pen is recommended for patients with basal insulin needs of 20–50 units (22). The recommended starting dose of IDegLira is 10 dose steps (10 units insulin degludec and 0.36 mg liraglutide). The dose can be titrated by 2 dose steps every 3 days until an FPG target of <90 mg/dL is reached. The

maximum dose is 50 units of insulin degludec and 1.8 mg of liraglutide (22). When added to a sulfonylurea, a reduction of the dose of the sulfonylurea should be considered.

Switching to an FRC Product

It may be appropriate for patients to switch from basal insulin alone or a GLP-1 receptor agonist alone to an FRC product. In either scenario, the prescribing information for IDegLira recommends a starting dose of 16 units of insulin degludec and 0.6 units of liraglutide (22). This regimen could lead to challenges in short-term glycemic control for patients who were already taking higher doses of either component individually. To date, transitioning from patients taking <20 units or >50 units of basal insulin per day has not been studied. For patients who are switching from a long-acting GLP-1 receptor agonist, there may be overlapping effects during the transition because of its longer duration of action. Either scenario necessitates close follow-up and education during the transition.

Conclusion

Clinical studies have demonstrated improved glycemic control and low risk of hypoglycemia and weight gain with the combination of basal insulin and a GLP-1 receptor agonist. This approach provides a safe and effective alternative to basal-bolus insulin with less treatment burden. FRC products are in the pipeline and will offer additional options for clinicians and patients.

Duality of Interest

Dr. Trujillo is an advisory board consultant for Sanofi. No other potential conflicts of interest relevant to this article were reported.

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