Initiating Titratable Fixed-Ratio Combinations of Basal Insulin Analogs and Glucagon-Like Peptide-1 Receptor Agonists: What You Need to Know

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IN BRIEF Titratable fixed-ratio combinations (FRCs) of a basal insulin and a glucagon-like peptide-1 (GLP-1) receptor agonist are new therapeutic options for people with type 2 diabetes. Two FRCs—insulin degludec/liraglutide and insulin glargine/lixisenatide—have been approved for use in the United States. The two components in these FRCs target different aspects of diabetes pathophysiology, working in a complementary manner to decrease blood glucose while mitigating the side effects associated with each component (hypoglycemia and weight gain with insulin and gastrointestinal side effects with GLP-1 receptor agonists). This article reviews these products and key considerations for their use.

The burden of diabetes on individuals and society continues to grow. The worldwide prevalence of diabetes was estimated to be 422 million in 2014 (1), with ~30 million people (>9% of the total population) having the disease. In the United States, 1.5 million adults received a new diagnosis of diabetes in 2015 (2).

The U.K. Prospective Diabetes Study in type 2 diabetes and the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study in type 1 diabetes showed that early achievement of target glucose levels reduces the long-term risk of microvascular and macrovascular complications, even when A1C increases over time (3,4). Guidelines recommend lowering A1C to <7.0% or ≤6.5% for most patients, although less stringent goals may be advised based on individual patient factors (5,6).

Improvements in the clinical management of type 2 diabetes and diabetes-associated complications have substantially reduced rates of cardiovascular disease, stroke, kidney failure, and amputations (7). However, despite the availability of detailed guidelines and an expanding range of therapeutic options to reduce hyperglycemia, between 2007 and 2010, almost half (47.5%) of patients with diabetes in the United States failed to attain an A1C <7.0% (8).

The reasons behind this failure are multifactorial; however, clinical inertia on the part of both clinicians and patients, resulting in delay in treatment intensification at every stage of disease progression, is an important contributing factor (9,10). Once patients are no longer achieving their target A1C on basal insulin, options for intensifying therapy add to the complexity of day-to-day management. The need for additional injections (up to three per day plus the single basal insulin injection if prandial insulin is added) contributes to poor adherence (11) and may also deter patients and physicians from intensifying therapy.

Fixed-ratio combinations (FRCs) of a basal insulin and a glucagon-like peptide-1 (GLP-1) receptor agonist

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may help to address gaps in care for basal insulin treatment intensification by targeting both fasting plasma glucose (FPG) and postprandial plasma glucose (PPG), simplifying treatment regimens, and mitigating gastrointestinal side effects and weight gain associated with insulin, with no increased risk of hypoglycemia, both of which affect patients' willingness to intensify and adhere to treatment. Early use of multiple agents targeting the various pathophysiologic abnormalities of the disease may also have a beneficial effect in the early management of type 2 diabetes (12).

Basal Insulin Plus GLP-1 Receptor Agonist: A Rational Approach to Combination Therapy

Multiple clinical trials support the benefit of combining basal insulin and a GLP-1 receptor agonist for the treatment of type 2 diabetes (13–15). A proof-of-concept study showed that twice-daily administration of exenatide plus basal insulin resulted in A1C improvement comparable to that observed with basal-bolus insulin, but yielded a greater reduction in some measures of glycemic variability, weight, and some cardiometabolic risk markers (16).

Several clinical trials investigated the addition of lixisenatide in patients with type 2 diabetes inadequately controlled on basal insulin therapy with or without metformin and/or other oral antidiabetes drugs (OADs) (17–19). Patient populations included those newly initiated on insulin glargine 100 units/mL (U100), patients on established basal insulin therapy with or without metformin, and patients on established basal insulin therapy with or without OADs who required additional control. The addition of lixisenatide consistently improved A1C and PPG excursions, with body weight benefits and without an increase in hypoglycemia risk compared to basal insulin therapy alone (17,18). Compared to insulin glulisine once or three times daily, administration of lixisenatide resulted in similar A1C reductions with a greater reduction in PPG excursions, weight loss, and less hypoglycemia (19).

Another study compared once-daily insulin aspart to liraglutide added to insulin degludec and metformin in patients with type 2 diabetes inadequately controlled after 1 year of treatment. Liraglutide improved glycemic control, with body weight reduction and less hypoglycemia and with more patients achieving a composite endpoint of A1C <7.0% without weight gain or confirmed hypoglycemia compared to insulin aspart (20). Further evidence for the potential benefits of basal insulin and GLP-1 receptor agonist combination therapy showed that albiglutide added to insulin glargine U100 with or without OADs resulted in noninferior A1C control associated with weight loss and lower hypoglycemia risk compared to the addition of insulin lispro three times daily to insulin glargine U100 with or without OADs (21).

Titratable FRCs of a Basal Insulin and a GLP-1 Receptor Agonist

In November 2016, two titratable FRCs of a long-acting basal insulin and a once-daily GLP-1 receptor agonist were approved by the U.S. Food and Drug Administration (FDA). These products offer a once-daily alternative for intensifying type 2 diabetes therapy (as an adjunct to diet and exercise) when glycemia is inadequately controlled with basal insulin or the GLP-1 receptor agonist component used alone (22,23).

iGlarLixi is a combination of insulin glargine U100 with lixisenatide. Insulin glargine U100 is a mainstay of long-acting basal insulin therapy and was first approved for clinical use in 2000. Its pharmacologic effects are well characterized; once-daily insulin glargine U100 results in glucose-lowering activity for up to 24 hours, with blood glucose values of 130 mg/dL maintained until 15 hours and then slightly increasing to ~140 mg/dL between 16 and 24 hours (24). Lixisenatide is a once-daily, shorter-acting GLP-1 receptor agonist recently approved in the United States for the treatment of patients with type 2 diabetes as an adjunct to diet and exercise to improve glycemic control. It has a half-life of 2–3 hours and acts mainly by delaying gastric emptying, exerting a pronounced PPG-lowering effect with a lesser effect on FPG at doses as low as 2.5 μg (25–27). Although lixisenatide has a shorter half-life, it retains the ability to reduce PPG with once-daily dosing through reduction of PPG exposure after meals. Unlike longer-acting GLP-1 receptor agonists, its effects on gastric emptying or PPG levels do not disappear because they do not seem to be subjected to tachyphylaxis (28).

IDegLira combines insulin degludec 100 units/mL (U100) with liraglutide. Insulin degludec, a longer-acting, once-daily basal insulin analog that received approval for the treatment of diabetes in the United States in 2015, shows glucose-lowering activity for >42 hours, no pronounced peak, and even exposure over a 24-hour period once at steady state (29,30). The long-acting, once-daily GLP-1 receptor agonist liraglutide was approved in the United States in 2010 for the treatment of patients with type 2 diabetes as an adjunct to diet and exercise to improve glycemic control. It shows activity over a range of concentrations and has a longer half-life (11–15 hours) (31), as well as a smaller effect on gastric emptying and reduction in PPG excursions, but a greater effect on FPG, than lixisenatide (27,32).

Clinical Studies With FRCs

Both iGlarLixi and IDegLira have been studied in several phase 3 clinical trials (Table 1). It is important to point out that these trials are not directly comparable because of differences in design, titration schemes, and glycemic targets and that current-

TABLE 1. Phase 3 Clinical Trials With IDegLira and iGlarLixi in Patients With Type 2 Diabetes

	Patient Population	*n*	Mean A1C at Baseline (%)	A1C Change From Baseline (%)	Patients Achieving an A1C <7.0% (%)	Body Weight Change From Baseline (kg)	Hypoglycemia (%)*
iGlarLixi studies							
LixiLan-O (33)	Insulin-naive; metformin ± another OAD	iGlarLixi: 469 iGlar: 467 Lixi: 234	iGlarLixi: 8.1 iGlar: 8.1 Lixi: 8.1	Run-in: –0.1 iGlarLixi: –1.6§ iGlar: –1.3§ Lixi: –0.9§	iGlarLixi: 73.7 iGlar: 59.4 Lixi: 33.0	iGlarLixi: –0.3§ iGlar: +1.1§ Lixi: –2.3§	iGlarLixi: 25.6 iGlar: 23.6 Lixi: 6.4
LixiLan-L (34)	Basal insulin ± up to 2 OADs	iGlarLixi: 367 iGlar: 369	iGlarLixi: 8.1 iGlar: 8.1	Run-in: –0.4 iGlarLixi: –1.1§ iGlar: –0.6§	iGlarLixi: 54.9 iGlar: 29.6	iGlarLixi: –0.7§ iGlar: +0.7§	iGlarLixi: 40.0 iGlar: 42.5
IDegLira studies							
DUAL I (35)	Insulin-naive; Metformin ± pioglitazone	IDegLira: 833 IDeg: 413 Lira: 414	IDegLira: 8.3 IDeg: 8.3 Lira: 8.3	IDegLira: –1.9 IDeg: –1.4 Lira: –1.3	IDegLira: 81 IDeg: 65 Lira: 60	IDegLira: –0.5 IDeg: +1.6 Lira: –3.0	IDegLira: 32 IDeg: 39 Lira: 7
DUAL II (39)	Previous insulin + metformin ± another OAD	IDegLira: 199 IDeg: 199	IDegLira: 8.7 IDeg: 8.8	IDegLira: –1.9 IDeg: –0.9	IDegLira: 60 IDeg: 23	IDegLira: –2.7 IDeg: 0	IDegLira: 24 IDeg: 25
DUAL III (36)	Previous GLP-1 RA + metformin ± another OAD	IDegLira: 292 GLP-1 RA: 146	IDegLira: 7.8 GLP-1 RA: 7.7	IDegLira: –1.3 GLP-1 RA: –0.3	IDegLira: 75 GLP-1 RA: 36	IDegLira: +2.0 GLP-1 RA: –0.8	IDegLira: 2.82 episodes/PYE† GLP-1 RA: 0.12 episodes/PYE†
DUAL IV (38)	Insulin-naive; sulfonylurea ± metformin	IDegLira: 289 Placebo: 146	IDegLira: 7.9 Placebo: 7.9	IDegLira: –1.5 Placebo: –0.5	IDegLira: 79.2 Placebo: 28.8	IDegLira: +0.5 Placebo: –1.0	IDegLira: 41.7 Placebo: 17.1
DUAL V (37)	iGlar + metformin	IDegLira: 278 iGlar: 279	IDegLira: 8.4 iGlar: 8.2	IDegLira: –1.81 iGlar: –1.13	IDegLira: 71.6 iGlar: 47.0	IDegLira: –1.4 iGlar: +1.8	IDegLira: 28.4 iGlar: 49.1
DUAL VII (40)	iGlar + metformin	IDegLira: 252 iGlar + insulin aspart: 254	IDegLira: 8.2 iGlar + insulin aspart: 8.2	IDegLira: –1.49 iGlar + insulin aspart: –1.48	IDegLira: 66.0 iGlar + insulin aspart: 67.0	IDegLira: –0.92 iGlar + insulin aspart: +2.64	IDegLira: 1.07 episodes/PYE† iGlar + insulin aspart: 8.17 episodes/PYE†

**DUAL studies, confirmed or severe hypoglycemia (<56 mg/dL); LixiLan studies, documented symptomatic hypoglycemia (≤70 mg/dL). †Incidence of hypoglycemia events (%) was not reported for this trial. §Least squares. GLP-1 RA, glucagon-like peptide-1 receptor agonist; IDeg, insulin degludec U100; iGlar, insulin glargine U100; Lira, liraglutide; Lixi, lixisenatide; PYE, patient-years of exposure.*

ly there are no head-to-head comparisons of FRCs.

iGlarLixi was studied in two phase 3 clinical trials for the intensification of treatment in insulin-naive (LixiLan-O) and insulin-experienced (LixiLan-L) populations (33,34). LixiLan-O evaluated patients with type 2 diabetes inadequately controlled with metformin alone or combined with another OAD, whereas LixiLan-L enrolled patients with diabetes inadequately controlled with basal insulin (with or without up to two OADs).

Both trials included an initial run-in phase, during which all OADs except for metformin were discontinued. In LixiLan-O, the metformin dose was optimized during the 4-week run-in phase, and patients were then randomized to receive lixisenatide (maintenance dose of 20 µg/day), insulin glargine U100 (up to 60 units/day), or iGlarLixi (up to 60 units insulin glargine U100/20 µg lixisenatide per day) for 30 weeks. In LixiLan-L, patients continuing on or switching to insulin glargine U100 had their daily dose optimized during a 6-week run-in period and were then randomized to receive insulin glargine U100 (up to 60 units/day) or iGlarLixi (up to 60 units insulin glargine U100/20 µg lixisenatide per day) with or without metformin for 30 weeks. At the end of the run-in phase, A1C levels were reduced by 0.1% in LixiLan-O and 0.4% in LixiLan-L.

iGlarLixi consistently led to significantly greater A1C reductions than the comparators. In LixiLan-O, A1C reductions were –1.6, –1.3, and –0.9% in patients treated with iGlarLixi, insulin glargine U100, and lixisenatide, respectively; in LixiLan-L, reductions were –1.1 and –0.6% for patients treated with iGlarLixi and insulin glargine U100, respectively. A larger proportion of patients treated with iGlarLixi achieved a target A1C of <7.0% across studies (LixiLan-O: 73.7% for iGlarLixi vs. 59.4% for insulin glargine U100 and 33.0% for lixisenatide; LixiLan-L: 54.9% for iGlarLixi vs. 29.6% for insulin glargine U100; $P < 0.0001$ vs. insulin glargine U100 in both trials and vs. lixisenatide in LixiLan-O). The incidence of symptomatic hypoglycemia (≤70 mg/dL) with iGlarLixi was similar to that of basal insulin (25.6 and 40.0% vs. 23.6 and 42.5% in LixiLan-O and LixiLan-L, respectively), although it was higher than with lixisenatide alone (6.4% in LixiLan-O). iGlarLixi also mitigated the weight gain seen with insulin glargine U100 in both trials (LixiLan-O: –0.3 and +1.1 kg for iGlarLixi and insulin glargine U100, respectively; LixiLan-L: –0.7 and +0.7 kg for iGlarLixi and insulin glargine U100, respectively) (Table 1). The incidence of gastrointestinal adverse events (AEs) was lower with iGlarLixi than with lixisenatide alone (nausea: 9.6 vs. 24.0%, respectively, in LixiLan-O) (33), but higher than with insulin alone (nausea: 9.6 vs. 3.6%, respectively, in LixiLan-O; 10.4 vs. 0.5%, respectively, in LixiLan-L), and resulted in very low treatment discontinuation rates (0.4% due to nausea or vomiting and 0.2% due to diarrhea in LixiLan-O; 1.1% due to nausea in LixiLan-L) (33,34).

The DUAL series of phase 3 clinical trials looked at the use of IDegLira for intensifying treatment in a range of patient populations: insulin-naive (DUAL I and IV), insulin experienced (DUAL II, V, and VII), and those already on a GLP-1 receptor agonist (DUAL III). Treatment with IDegLira reduced A1C across the studies (ranging from –1.3 to –1.9%), and these reductions were consistently greater than those seen with the comparators (–0.9 to –1.4% with insulin degludec in DUAL I and II, –1.3% with liraglutide in DUAL I, –1.13% with insulin glargine U100 in DUAL V, and –0.5% with placebo in DUAL IV). In addition, a larger proportion of patients treated with IDegLira achieved a target A1C <7.0% than with the comparators (60–81% for IDegLira, 23–65% for insulin degludec, 60% for liraglutide, 47% for insulin glargine U100, and 28.8% for placebo). In DUAL VII, IDegLira was noninferior to insulin glargine U100 plus insulin aspart (up to 4 times a day) in controlling A1C, and a similar proportion of patients achieved glycemic targets (Table 1) (35–40).

The reported incidence of hypoglycemia (severe hypoglycemia events and episodes of hypoglycemia with plasma glucose ≤56 mg/dL regardless of symptoms) was lower with IDegLira (24–41.7%) than with basal insulin comparators (25–49.1%), but higher than with placebo (17.1%) or liraglutide (7%) (35,37–39). However, a re-analysis of hypoglycemia rates conducted by the FDA, using the American Diabetes Association definition of documented symptomatic hypoglycemia (typical symptoms accompanied by plasma glucose concentration ≤70 mg/dL) showed comparable hypoglycemia rates for IDegLira and insulin degludec (41).

IDegLira also led to less weight loss or to weight gain (–2.7 to +2.0 kg) compared to the insulin comparator (0 to +1.8 kg) in many of the trials. Compared to treatment with a sulfonylurea alone in DUAL IV, IDegLira resulted in a slight weight gain (+0.5 kg), whereas sulfonylurea therapy resulted in weight loss (–1.0 kg) (Table 1). The incidence of gastrointestinal AEs was higher with IDegLira than with basal insulin and placebo comparators, but lower than with GLP-1 receptor agonist comparators (incidence of nausea: IDegLira, 6.5–9.4%; basal insulin, 1.1–4.0%; GLP-1 receptor agonist, 20%) and did not lead to any patients discontinuing treatment in DUAL II (35,37,39).

Rare cases of allergic reactions to both iGlarLixi and IDegLira or their GLP-1 receptor agonist components have been reported in clinical trials and after commercialization (42,43).

Advantages and Disadvantages of FRCs

Combination products such as FRCs have the potential to improve blood glucose control and adherence while simplifying patients' treatment regimens compared to the use of multiple agents. In addition, they present less potential for clinical inertia and have decreased side effects compared to insulin or a GLP-1 receptor agonist alone.

Basal insulin therapy aims to provide consistent, flat, long-acting insulin levels to mimic the constant physiological release of hormone that regulates endogenous glucose levels. Basal insulin acts in a nonglucose-dependent manner predominantly on FPG levels and has less of an effect on PPG.

Long-acting GLP-1 receptor agonists also primarily affect FPG, whereas short-acting agents in this class have a greater effect on PPG (44,45). The lesser effect on PPG exerted by longer-acting GLP-1 receptor agonists may be the result of continuous stimulation of the GLP-1 receptor, which attenuates the effect on gastric emptying via tachyphylaxis at the level of the vagal nerve (44) and is supported by clinical studies showing greater reductions in PPG and PPG excursions for shorter-acting compared to longer-acting agents (46,47). Shorter-acting GLP-1 receptor agonists are therefore used in FRCs to complement the mechanism of action of basal insulin. GLP-1 receptor agonists have also been shown to reduce PPG increments in a dose-dependent manner, stimulate glucose-dependent insulin secretion, suppress glucagon secretion, inhibit gastric acid secretion and emptying, and increase satiety, with potential reductions in caloric intake (48).

Treatment with insulin is generally associated with an increase in body weight (an A1C decrease of 2.5% from baseline was associated with an increase in body weight of 5 kg during 1 year in one study) and risk of hypoglycemia (5,6,49,50), but the use of an insulin/GLP-1 receptor agonist combination product appears to mitigate the side effects of its individual components. In clinical trials, both weight gain and the incidence of hypoglycemia with FRCs were found to be comparable to or lower than with basal insulin (average weight loss of 0.5 kg with iGlarLixi vs. weight gain of 0.9 kg with insulin glargine U100 in the LixiLan trials and average weight loss of 1.5 kg with IDegLira vs. weight gain of 1.1 kg with insulin degludec in DUAL I, II, and V) (Table 1). In addition, the incidence of gastrointestinal AEs was lower with FRCs compared to a GLP-1 receptor agonist alone (33–39), which constitutes an additional advantage because reductions in AEs and tolerability issues may also help to increase medication adherence (51).

Experience with fixed-dose oral combination drugs in other therapeutic areas (e.g., combinations of antihypertensive agents or bronchodilators/corticosteroids) shows positive impacts on efficacy and adherence compared to their free-drug components (52–55). In addition, the use of complex type 2 diabetes treatment regimens, involving multiple combinations of several oral and/or injectable agents, has been shown to be associated with intentional and accidental nonadherence to treatment (11,56). In a real-world study of patients treated with basal insulin and a GLP-1 receptor agonist, only 17% were persistent with treatment (defined as the absence of a prescription gap of at least 90 days for either agent) during a 12-month period (57). Simple, once-daily regimens thus have the potential to improve adherence and outcomes and may also encourage more timely treatment intensification for patients and clinicians who are deterred by more complicated regimens.

Disadvantages of combination therapy include the potential increase in direct costs of medications. The total direct and indirect costs of diabetes in the United States were $245 billion in 2012, with average medical expenditures for people with diabetes of $13,700 annually (2). Thus, the burden of treatment costs for patients is an important factor to consider in treatment decision-making (5,6). However, if current fixed-dose oral combinations are a guide, the cost of FRCs may be lower than the cost of the components taken separately (58); iGlarLixi is currently sold for a price comparable to that of its GLP-1 receptor agonist component lixisenatide (59). Indirect costs must also be considered, including lost productivity and quality-of-life issues related to hypoglycemia and weight gain or worsening diabetes associated with delay of insulin therapy (6,60), which may be mitigated by earlier intensive treatment and offset by the use of FRCs.

Finally, injectable therapy is often perceived as a hurdle for patients on oral therapies. However, results from the Perspectives in Diabetes Care surveys show that there is a disconnect between patient and physician perceptions, with many patients in fact willing to do more to achieve their target A1C (57%) and a smaller proportion of clinicians believing the same (19%) (61). Based on their experience with oral fixed-dose combinations, clinicians and patients may have the impression that injectable FRCs are inflexible for dose adjustments and will limit their ability to titrate to target. Therefore, it is important to note that these are fixed-ratio, but not fixed-dose, combinations: both components are titratable based on patients' insulin needs, with the GLP-1 receptor agonist component increasing in ratio to the insulin dose and so still providing flexibility in dosing.

Initiating Therapy With FRCs

FRCs are administered using modified insulin pens that contain a premixed fixed-ratio supply of the basal insulin and GLP-1 receptor agonist components, such that as the insulin dose is adjusted, the GLP-1 receptor

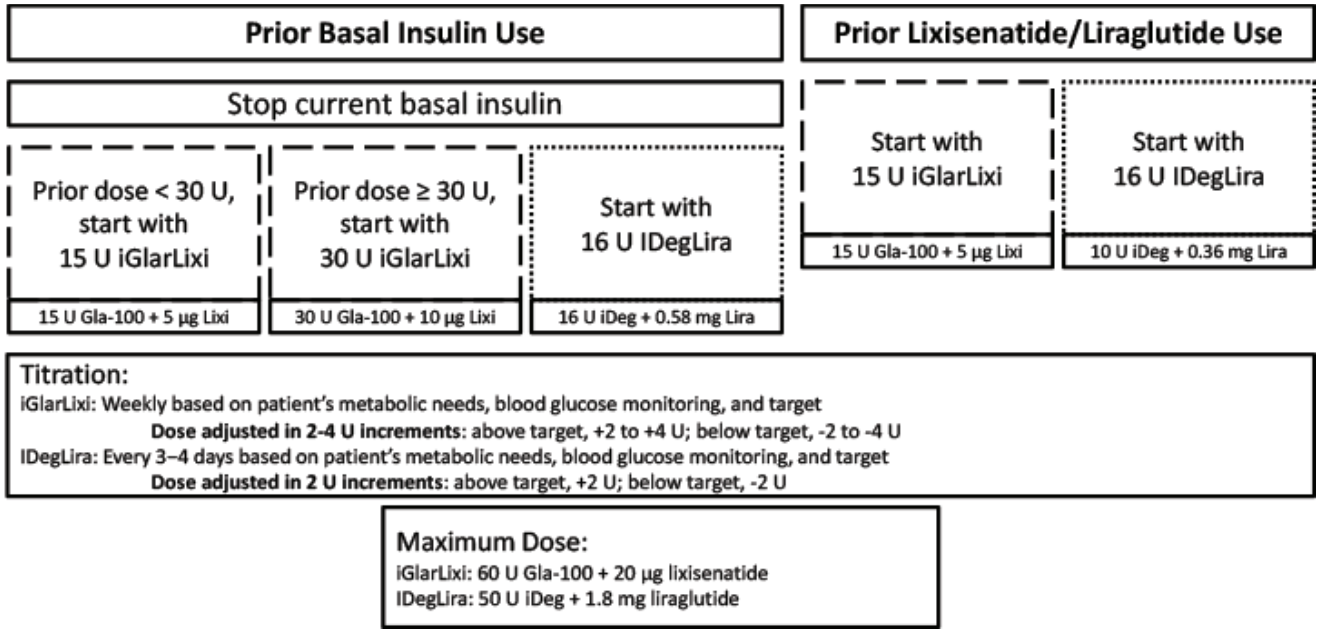

FIGURE 1. Guidance for initiating, switching, and titrating FRCs. Gla-100, insulin glargine U100; Lira, liraglutide; Lixi, lixisenatide; U, units.

agonist dose also changes according to the fixed ratio. FRC doses are guided by the insulin dose component, following titration schedules similar to those used for titrating insulin (42,43). When initiating therapy, it is important for clinicians to inform their patients that, as with basal insulin, they will be starting at a low dose and titrating upward or downward to achieve their individual FPG goal, and it may be helpful to inform them about their anticipated final dose. This enables patients to know that they are not failing when they move away from the starting dose and that this is part of the normal treatment pattern (62).

When switching to either FRC from basal insulin, back-titration from the previous insulin dose is required for most patients; this may lead to transient increases in FPG that do not affect A1C reduction. Patients should also be alerted to this possibility so that they are prepared for any changes after switching.

iGlarLixi

iGlarLixi (Soliqua 100/33, Sanofi) has been approved for use in the United States in a modified Sanofi SoloStar pen, which delivers 3 units of insulin glargine U100 to 1 µg of lixisenatide and ranges from 15 units/5 µg to 60 units/20 µg (43). It is indicated to improve glycemic control in adults with type 2 diabetes inadequately controlled on basal insulin (<60 units) or lixisenatide. iGlarLixi should be administered within 1 hour before the first meal of the day. In patients who are on lixisenatide, iGlarLixi is initiated at a starting dose of 15 units. For those switching from basal insulin, the starting dose of iGlarLixi is based on the previous dose of basal insulin; in patients receiving doses <30 units, the starting iGlarLixi dose will be 15 units, and in those receiving doses of 30–60 units, the starting iGlarLixi dose will be 30 units. Upward or downward titration is done according to the insulin glargine U100 dose, with dose changes of 2–4 units weekly. Initiation and titration dosing is described in Figure 1.

In the LixiLan clinical trials, the mean daily dose of basal insulin after 30 weeks of treatment in the FRC arm was 40 units (0.45 units/kg) in insulin-naive and 47 units (0.54 units/kg) for insulin-experienced patients (33,34). Furthermore, in both trials the final mean basal insulin daily dose was similar for patients in the iGlarLixi group and the insulin glargine U100 group (LixiLan-O: 39.8 vs. 40.3 units; LixiLan-L: 46.67 vs. 46.71 units for the FRC vs. the basal insulin arms, respectively; data on file). There was an insulin dose limit of 60 units in both arms of the two LixiLan trials (33,34).

Although iGlarLixi has been approved in a 3:1 ratio of insulin glargine U100 to lixisenatide in the United States, the LixiLan trials were conducted using pens delivering 3:1 and 2:1 ratios (33,34), and these two pen options may be available in other regions of the world. Regardless of presentation, iGlarLixi pens should be stored in the refrigerator at a temperature between 2 and 8°C before opening. Once opened, they should be kept at room temperature (<25°C) and disposed of after 28 days (43).

IDegLira

IDegLira (Xultophy 100/3.6, Novo Nordisk) is available in one prefilled pen at a ratio of 1 unit insulin degludec to 0.036 mg liraglutide and is indicated as an adjunct to diet and

exercise to improve glycemic control in patients with type 2 diabetes inadequately controlled on basal insulin (<50 units/day) or liraglutide (≤1.8 mg/day). IDegLira can be administered daily at the same time each day and does not need to be taken with a meal. The recommended starting dose is 16 units, which can be titrated upward or downward by 2 units every 3–4 days. The maximum dose of IDegLira is 50 units insulin degludec/1.8 mg liraglutide (42). Initiation and titration dosing is described in Figure 1.

In the DUAL clinical trials, the dose of IDegLira was 38 dose steps (one dose step was equivalent to 1 unit of insulin degludec plus 0.036 mg liraglutide) for insulin-naive patients (35) and 41–45 dose steps for insulin-experienced patients (37,39). The mean insulin dose was 28% lower at week 26 with IDegLira than with insulin degludec (38 vs. 53 units) in insulin-naive patients in DUAL I, where there was no maximum dose limit for insulin degludec (35) and similar for both drugs (45 units) in insulin-experienced patients in DUAL II, where the insulin degludec dose was capped at 50 units in both arms (39). The predominant effect of liraglutide on FPG versus PPG is likely responsible for the insulin-sparing effect observed with IDegLira. In addition, the design of the DUAL studies, which, unlike the LixiLan program, did not include a run-in phase in which basal insulin was titrated or stabilized, may also explain the lower insulin dose observed in the IDegLira arm.

Unopened IDegLira pens should be stored in the refrigerator at a temperature of 2–8°C. After opening, the pens should be kept at room temperature between 15 and 30°C or in the refrigerator at 2–8°C and disposed of after 21 days (42).

Minimizing AEs Associated With FRCs

Clinicians should provide information to manage patients' expectations regarding the scope and duration of expected AEs. AEs seen in the clinical trials for FRCs were predominantly gastrointestinal in nature; nausea, vomiting, and diarrhea were experienced by 6.5–10.4%, 2.5–4%, and 3.1–9% patients, respectively. Across the studies, these AEs were generally transient, with a greater incidence during the first 8–12 weeks, and resulted in treatment discontinuation rates of ~0–1% (33–39). The slow dose increase of the GLP-1 receptor agonist component is believed to lead to a reduction in gastrointestinal AEs compared to GLP-1 receptor agonist therapy alone (33,35).

Strategies used for minimizing gastrointestinal side effects when initiating a GLP-1 receptor agonist are also appropriate for FRCs. These include advising patients to stop eating when they feel full and suggesting that they eat slowly and avoid administering their dose before a large or high-fat meal (63,64). The risk of hypoglycemia is comparable to that associated with basal insulin, so it is important to provide patients with appropriate strategies to avoid and treat hypoglycemia.

Conclusion

Two FRC products, iGlarLixi and IDegLira, have recently been approved in the United States. FRCs are currently indicated for patients with type 2 diabetes inadequately controlled on basal insulin or lixisenatide (for iGlarLixi) or liraglutide (for IDegLira). Some patients may particularly benefit from FRC therapy, such as those for whom the weight gain seen with insulin alone would be a problem and who would benefit from the weight neutrality/weight loss seen with FRCs. For patients in whom increased treatment complexity is an issue, the use of a single co-formulation with once-daily injection provides a simple, user-friendly method of treatment intensification, which may help improve adherence. The potential to achieve greater A1C-lowering efficacy with less weight gain than seen with insulin, fewer gastrointestinal AEs than with GLP-1 receptor agonists, and no increase in risk of hypoglycemia are key attributes of FRCs.

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Duality of Interest

N.S. has participated in advisory boards for AstraZeneca, Boehringer Ingelheim, Eli Lilly and Company, Intarcia, Novartis, Sanofi, and Teva and has acted as a speaker for AstraZeneca and Boehringer Ingelheim. D.H. has participated in advisory boards for Eli Lilly and Company, Novo Nordisk, and Sanofi, and has acted as a speaker for Eli Lilly and Company/Boehringer Ingelheim, Janssen, Novo Nordisk, and Sanofi. M.L.M. has participated in advisory boards and/or has acted as a speaker for Janssen, Novo Nordisk, and Sanofi. J.R.W. has participated in advisory boards for Novo Nordisk and Sanofi and has acted as a consultant to Becton-Dickenson. No other potential conflicts of interest relevant to this article were reported.

Author Contributions

All authors contributed to the discussion and reviewed/edited the manuscript originally drafted by a professional editorial service. N.S. is the guarantor of this work and, as such, had full access to all the data in the study and takes full responsibility for the integrity of the data and the accuracy of the data analysis.

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