Fixed-Ratio Combinations

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Introduction

Combination treatment with basal insulin and a glucagon-like peptide-1 (GLP-1) receptor agonist targets different aspects of the pathophysiology of type 2 diabetes to achieve glycemic control. In November 2016, the U.S. Food and Drug Administration approved two titratable fixed-ratio combinations (FRCs) of basal insulin and a GLP-1 receptor agonist: insulin glargine/lixisenatide 3:1 ratio (iGlarLixi [Soliqua]) and insulin degludec/liraglutide 1:0.036 ratio (IDegLira [Xultophy]) (1,2).

Indications

Both agents are indicated to improve glycemic control in adults with type 2 diabetes inadequately controlled on basal insulin or the respective GLP-1 receptor agonist along with diet and exercise (1,2). Use of these agents is not recommended for patients with type 1 diabetes, diabetic ketoacidosis, gastroparesis, or a history of pancreatitis. Additionally, these agents should be avoided in patients using another GLP-1 receptor agonist or prandial insulin (1,2).

Mechanisms of Action

Insulin glargine and insulin degludec improve glycemic control through stimulation of glucose uptake in the body and inhibition of glucose production in the liver (1,2). Lixisenatide and liraglutide mimic the action of GLP-1 through stimulation of glucose-dependent insulin release, suppression of glucagon production, and slowing of gastric emptying (1,2).

Potential Advantages

A main advantage of FRCs, as single daily injections of two glycemic control medications, is regimen simplification to promote treatment adherence with less potential for clinical inertia. Greater efficacy in glycemic control is achieved with FRCs compared to each of their component agents alone (Table 1) (3–9). Furthermore, the principal side effects of each component agent when used alone are mitigated when used in combination. Less weight gain and hypoglycemia occurred in patients on FRCs compared to those taking basal insulin alone, and fewer gastrointestinal (GI) adverse effects were observed in patients on FRCs compared to those taking a GLP-1 receptor agonist alone (Table 1) (3–9).

Potential Disadvantages

FRCs are injectable products. Although these agents are titratable based on the basal insulin component, patients requiring less than the minimum starting doses (iGlarLixi, 15 units; IDegLira, 16 units) or more than the maximum doses (iGlarLixi, 60 units; IDegLira, 50 units) may not be good candidates for these agents (1,2). At the end of the study periods, mean daily doses of iGlarLixi were ~40–50 units (3,4) and mean daily doses of IDegLira were ~30–45 units (5–9). For patients who struggle with compliance, reinitiating at the starting dose is recommended for IDegLira after missing 3 days, whereas no guidance has been pro-

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TABLE 1. Summary of Clinical Trials of FRCs in Patients With Type 2 Diabetes (3–9)

	Population Characteristics	A1C Change From Baseline (%)	Patients Achieving A1C <7.0% (%)	Body Weight Change From Baseline (kg)	Patients With Hypoglycemia* (%)	Patients With GI Side Effects† (%)
iGlarLixi						
LixiLan-O *n* = 1,170 Duration: 30 weeks	Inadequately controlled on metformin ± a second oral antidiabetic agent Mean age: 58.4 years Mean BMI: 31.7 kg/m^2 Mean duration of diabetes: 8.8 years Mean A1C at baseline: 8.1%	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§	iGlarLixi: 21.7 iGlar: 12.6§ Lixi: 36.9§
LixiLan-L *n* = 736 Duration: 30 weeks	Inadequately controlled on basal insulin ± 1–2 OADs Median age: 60.0 years Mean BMI: 31.2 kg/m^2 Mean duration of diabetes: 12.1 years Mean A1C at baseline: 8.1%	iGlarLixi: –1.1 iGlar: –0.6‡	iGlarLixi: 54.9 iGlar: 29.6‡	iGlarLixi: –0.7 iGlar: +0.7‡	iGlarLixi: 40.0 iGlar: 42.5§	iGlarLixi: 17.0 iGlar: 7.9§
IDegLira						
DUAL I *n* = 1,663 Duration: 26 weeks	Previously treated with metformin ± pioglitazone Mean age: 55.0 years Mean BMI: 31.2 kg/m^2 Mean duration of diabetes: 6.9 years Mean A1C at baseline: 8.3%	IDegLira: –1.9 IDeg: –1.4‖ Lira: –1.3‡	IDegLira: 80.6 IDeg: 65.1‡ Lira: 60.4‡	IDegLira: –0.5 IDeg: +1.6‡ Lira: –3.0‡	IDegLira: 31.9 IDeg: 38.6§ Lira: 6.8§	IDegLira: 3.9–8.8 IDeg: 1.5–4.6§ Lira: 8.5–19.7§
DUAL II *n* = 413 Duration: 26 weeks	Inadequately controlled on basal insulin + metformin ± sulfonylurea or glinides Mean age: 57.5 years Mean BMI: 33.7 kg/m^2 Mean duration of diabetes: 10.5 years Mean A1C at baseline: 8.8%	IDegLira: –1.9 IDeg: –0.9‡	IDegLira: 60.3 IDeg: 23.1‡	IDegLira: –2.7 IDeg: 0‡	IDegLira: 24.1 IDeg: 24.6	IDegLira: <2–6.5 IDeg: 0–3.5§

TABLE CONTINUED ON P. 244 →

TABLE 1. Summary of Clinical Trials of FRCs in Patients With Type 2 Diabetes (3–9), *continued from p. 243*

	Population Characteristics	A1C Change From Baseline (%)	Patients Achieving A1C <7.0% (%)	Body Weight Change From Baseline (kg)	Patients With Hypoglycemia* (%)	Patients With GI Side Effects† (%)
DUAL III *n* = 438 Duration: 26 weeks	Inadequately controlled with a GLP-1RA and OADs (metformin ± pioglitazone ± sulfonylurea) Mean age: 58.4 years Mean BMI: 33.0 kg/m^2 Mean duration of diabetes: 10.4 years Mean A1C at baseline: 7.8%	IDegLira: –1.3 U GLP-1RA: –0.3‡	IDegLira: 75 U GLP-1RA: 36‡	IDegLira: +2.0 U GLP-1RA: –0.8‡	IDegLira: 32.0 U GLP-1RA: 2.8‡	IDegLira: 3.1 U GLP-1RA: 4.1§
DUAL IV *n* = 435 Duration: 26 weeks	Inadequately controlled on metformin ± sulfonylureas Mean age: 59.7 years Mean BMI: 31.6 kg/m^2 Mean duration of diabetes: 9.2 years Mean A1C at baseline: 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‡	Not reported as one of the most frequently occurring adverse events
DUAL V *n* = 557 Duration: 26 weeks	Inadequately controlled on insulin glargine and metformin Mean age: 58.8 years Mean BMI: 31.7 kg/m^2 Mean duration of diabetes: 11.5 years Mean A1C at baseline: 8.3%	IDegLira: –1.8 iGlar: –1.1‡	IDegLira: 71.6 iGlar: 47.0‡	IDegLira: –1.4 iGlar: +1.8‡	IDegLira: 28.4 iGlar: 49.1‡	IDegLira: 9.4 iGlar: 1.1§

**LixiLan trials, symptomatic and blood glucose ≤70 mg/dL; DUAL trials, requiring assistance or blood glucose <56 mg/dL.*
†GI side effects include nausea, vomiting, and/or diarrhea; not defined or reported similarly in each study.
‡Statistically significant with comparator(s).
§Did not report or unknown whether statistical significant was determined.
||Met noninferiority.
GLP-1RA, GLP-1 receptor agonist; IDeg, insulin degludec; iGlar, insulin glargine; Lira, liraglutide; Lixi, lixisenatide; U, unchanged.

vided for iGlarLixi (1,2). Antibody development has been noted for the individual components in both FRCs; clinical significance is unknown at this time (1,2). Attenuated glycemic response and a higher incidence of allergic reactions were seen in patients on lixisenatide with elevated antibody concentrations (1). Cost may also be a hindrance (10).

TABLE 2. Cost Comparison of FRCs Compared to Their Individual Component Agents Using a Mid-Range Dose (10)

	Daily Dose	Approximate Cost for 30-Day Supply
iGlarLixi	35 units/11.7 µg	$445
Insulin glargine	35 units	$261
Lixisenatide	10 µg	$279
IDegLira	35 units/1.26 mg	$667
Insulin degludec	35 units	$311
Liraglutide	1.2 mg	$498

Cost

Both FRCs are supplied as 3-mL prefilled pens. The wholesale acquisition cost for five pens of iGlarLixi is $635 and for IDegLira is $953 (10). Using a mid-dose range of 35 units for a 30-day supply, the FRCs cost less than the combined costs of their component agents at the corresponding available doses (Table 2) (10). However, it is difficult to make direct comparisons because the individual GLP-1 receptor agonist products are supplied as fixed amounts per dose.

Commentary

LixiLan-O and LixiLan-L examined the effects of iGlarLixi over 30 weeks (Table 1) (3,4). Patients were insulin-naive in LixiLan-O and insulin-experienced in LixiLan-L. A run-in period was conducted in both trials, during which all oral antidiabetic agents (OADs) except metformin were discontinued. Patients receiving iGlarLixi achieved a statistically significant greater reduction in mean A1C from baseline compared to each individual agent. Additionally, a larger proportion of patients achieved an A1C <7.0%. Similar proportions of serious adverse effects were observed between comparison groups (~4–5%). Weight loss was achieved in patients on iGlarLixi. Conversely, weight gain was seen in patients on insulin glargine. Rates of hypoglycemia were comparable between patients on iGlarLixi and insulin glargine. GI adverse effects were greater in patients on iGlarLixi compared to those on insulin glargine but less compared to those taking lixisenatide alone (3,4).

IDegLira has been examined in five pivotal clinical trials (5–9). Patient populations studied in each of the trials differed (insulin-naive in DUAL I, III, and IV; insulin-experienced in DUAL II and V; and GLP-1 receptor agonist–experienced in DUAL III). Over 26 weeks, a greater reduction in mean A1C and a larger proportion of patients achieving an A1C <7.0% were observed in those taking IDegLira compared to those taking insulin degludec alone, liraglutide alone, any GLP-1 receptor agonist, metformin with or without a sulfonylurea, or insulin glargine (5–9). In general, rates of serious adverse effects were similar between IDegLira and comparator agents. The DUAL-IV trial reported a higher rate of serious adverse effects in the IDegLira group (20.3 vs. 8.0 events per 100 patient-years of exposure), but a unifying distinguishing factor could not be determined (8). Greater reductions in weight were seen in patients on IDegLira compared to those on insulin degludec or insulin glargine (5,6,9). A similar number of patients experienced hypoglycemia on IDegLira compared to insulin degludec (5,6). When no maximum was placed on the comparator basal insulin, hypoglycemia events were far less frequent in patients on IDegLira (9). Patients on IDegLira experienced more GI adverse effects than patients on basal insulin comparators but fewer than patients on liraglutide alone (5–9).

No head-to-head trials comparing the efficacy of FRCs with that of sequential basal insulin with a GLP-1 receptor agonist have been conducted.

Bottom Line

These agents are approved for patients not meeting target A1C goals on basal insulin or the respective GLP-1 receptor agonist alone. FRCs offer another option to patients with type 2 diabetes with inadequate glycemic control, especially for those desiring a simplified method of treatment intensification to improve adherence. FRCs are titratable based on the basal insulin dose. Previous basal insulin therapy should be discontinued before initiation of an FRC (1,2). Prandial insulin has not been studied with these agents. The use of FRCs provides the benefits of greater efficacy with blood glucose control and weight loss while decreasing the risk of principal side effects associated with each individual agent (i.e., hypoglycemia with insulin therapy and GI adverse effects with GLP-1 receptor agonists).

Duality of Interest

No potential conflicts of interest relevant to this article were reported.

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