Insulin/Glucagon-Like Peptide-1 Receptor Agonist Combination Therapy for the Treatment of Type 2 Diabetes: Are Two Agents Better Than One?

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IN BRIEF Given the progressive nature of type 2 diabetes, treatment intensification is usually necessary to maintain glycemic control. However, for a variety of reasons, treatment is often not intensified in a timely manner. The combined use of basal insulin and a glucagon-like peptide-1 receptor agonist is recognized to provide a complementary approach to the treatment of type 2 diabetes. This review evaluates the efficacy and safety of two co-formulation products, insulin degludec/liraglutide and insulin glargine/lixisenatide, for the treatment of type 2 diabetes inadequately controlled on either component agent alone. We consider the benefits and limitations of these medications based on data from randomized clinical trials and discuss how they may address barriers to treatment intensification.

Type 2 diabetes is a progressive disease characterized by multiple pathological defects, including declining β-cell function, worsening insulin resistance, increased hepatic glucose output, decreased glucose uptake, increased lipolysis, and a decreased incretin effect (1,2). The importance of good glycemic control has been well established and has been shown to reduce the risk of long-term diabetes complications such as retinopathy and nephropathy (3,4). To avoid these complications, it is important to intensify treatment in a timely manner. Guidelines from the American Diabetes Association and American Association of Clinical Endocrinologists recommend iterative evaluation and treatment intensification (5,6), with metformin and lifestyle management recommended as initial therapy. Additional oral antidiabetic agents or injectable therapies (i.e., a glucagon-like peptide-1 [GLP-1] receptor agonist and/or a basal insulin) can be used as required to achieve and maintain glycemic control.

Despite these consensus guidelines and the plethora of available type 2 diabetes treatments, many patients have inadequately controlled glycemia. For example, data from the National Health and Nutrition Examination Survey showed that, while mean A1C improved over time across three different time periods (1999–2000, 2001–2002, and 2003–2004), 43% of patients had an A1C >7% between 2003 and 2004 (7). A more recent 2013 study showed that 54% of patients in the United States had an A1C >7% (8).

Understanding and addressing potential barriers to treatment intensification is crucial (9,10). Lack of sufficient optimization and timely intensification (sometimes referred to as clinical inertia) in patients on basal insulin therapy is well documented (9–13). Poor adherence to insulin regimens is also common. Two studies found adherence rates of 63 and 70.6% and a correlation between adherence and glycemic control (14,15). A study in the United States found that, during

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the first year of insulin therapy, 18% of patients discontinued treatment and an additional 62% had gaps of ≥30 days between prescriptions (16). Additional barriers to intensification include fear of hypoglycemia and/or weight gain, both of which may lead to discontinuation or insufficient titration; late initiation; poor persistence to treatment; lack of time for health care providers to educate patients; the burden of a complex regimen; and fear of increasing out-of-pocket costs (9,10,16–20).

Furthermore, for patients on basal insulin, clinical experience highlights the challenge of optimizing doses and titration. The multiple concomitant pathophysiologic defects challenge the approach of pure stepwise treatment on a practical level because many patients have other factors contributing to hyperglycemia throughout the day, for which further intensification with basal insulin alone is inappropriate. For example, fasting hyperglycemia may result in part from inadequate prandial control during the preceding day or evening, for which up-titration of basal insulin is inappropriate and may result in over–basal insulinization.

This review assesses the efficacy and safety of two insulin/GLP-1 receptor agonist co-formulations that are available in the United States: insulin degludec/liraglutide (IDegLira) and insulin glargine/lixisenatide (iGlarLixi) for patients with type 2 diabetes inadequately controlled on basal insulin or a GLP-1 receptor agonist. Insulin is recognized as the most effective glucose-lowering therapy (21,22), with basal insulin predominately lowering A1C as a result of its action on fasting plasma glucose (FPG) (23). GLP-1 receptor agonists can partly restore the β-cell insulin response that is impaired in type 2 diabetes (24,25). They lower both postprandial glucose (PPG) and FPG, with shorter-acting GLP-1 receptor agonists predominantly lowering PPG from the meal after dosing and long-acting GLP-1 receptor agonists having a relatively greater action on FPG.

GLP-1 receptor agonists are associated with a low rate of hypoglycemia and weight loss, whereas hypoglycemia and weight gain are the main side effects associated with insulin therapy. As a result of their efficacy and complementary modes of action, there is a rationale for combining these two injectable drug classes (26,27). Numerous trials have demonstrated that addition of basal insulin to a GLP-1 receptor agonist or vice versa is an efficacious treatment option (28–31), and the co-use of these therapies is supported by guidelines (5,6). Treatment options that address a range of underlying pathological deficits in type 2 diabetes are attractive and have the potential to address some commonly seen barriers to achieving and maintaining glycemic control.

Introduction to IDegLira and iGlarLixi

The two new co-formulations comprising a long-acting basal insulin and a GLP-1 receptor agonist are IDegLira (Xultophy 100/3.6) and iGlarLixi (Soliqua 100/33). In the United States, both are indicated as treatment for patients with type 2 diabetes inadequately controlled on basal insulin (<50 units for IDegLira and <60 units for iGlarLixi) or a GLP-1 receptor agonist (≤1.8 mg liraglutide for IDegLira or lixisenatide for iGlarLixi) (32,33). In Europe, both are also indicated for patients with type 2 diabetes inadequately controlled on oral antidiabetic agents (34,35). IDegLira comprises the basal analog insulin degludec (100 units/mL) and the once-daily GLP-1 receptor agonist liraglutide (3.6 mg/mL) (32); iGlarLixi comprises the basal analog insulin glargine 100 units/mL (U100) and the short-acting GLP-1 receptor agonist lixisenatide (33 µg/mL) (33). Both are available as single once-daily injections, with IDegLira recommended to be dosed at the same time each day with or without food and iGlarLixi dosed within the hour before the first meal of the day (32,33). Effective co-use of insulin degludec and liraglutide as separate injections (28,29) and of insulin glargine and lixisenatide as separate injections (31) has been demonstrated.

Comparison of the Monocomponents

Basal Insulins

Insulin glargine is produced by substituting an asparagine residue with glycine at position A21 of the human insulin A-chain and adding two arginine-residues at positions B31 and B32 on the B-chain. These modifications shift the isoelectric point, making insulin glargine less soluble at a physiological pH. This delays its absorption after subcutaneous injection, resulting in a half-life of ~12 hours (36). Insulin degludec is a modified human insulin lacking the B30 threonine residue and acylated with a hexadecandioyl fatty diacid moiety on the B29 lysine (37). These modifications enable insulin degludec to form stable, soluble multihexamer chains after subcutaneous injection. This slowly releases monomers into the bloodstream, resulting in an extended half-life of ~25 hours (38). The different mechanisms of protraction result in less day-to-day variability in blood glucose with insulin degludec than with insulin glargine (39).

Head-to-head trials have shown that A1C reductions were noninferior with insulin degludec compared with insulin glargine, but hypoglycemia rates were lower with insulin degludec (40,41). The cardiovascular safety of insulin glargine was investigated in the ORIGIN (Outcome Reduction with an Initial Glargine Intervention) trial, in which it did not significantly alter the rate of major cardiovascular events compared with standard care (42). Similarly, the cardiovascular safety of insulin degludec was investigated in the cardiovascular outcomes trial (CVOT) DEVOTE (Trial Comparing Cardiovascular Safety of Insulin Degludec versus

Insulin Glargine in Patients with Type 2 Diabetes at High risk of Cardiovascular Events), in which it was shown to be noninferior to insulin glargine with respect to the time to first occurrence of a major adverse cardiovascular event (MACE) (43).

GLP-1 Receptor Agonists

Liraglutide is a long-acting human GLP-1 receptor agonist suitable for once-daily dosing, with a half-life of 13 hours. Lixisenatide is a short-acting GLP-1 receptor agonist, with a half-life of ~3 hours. Lixisenatide predominantly exerts its effect at the meal after dosing, causing a reduction in PPG, whereas liraglutide has a glucose-lowering effect over 24 hours, reducing both PPG and FPG (44,45). In a head-to-head phase 3 trial, A1C and FPG reductions were significantly greater with liraglutide than with lixisenatide, but the PPG increment at the meal after dosing was significantly lower with lixisenatide (45). In the ELIXA (Evaluation of Lixisenatide in Acute Coronary Syndrome) CVOT, lixisenatide did not significantly alter the rate of major cardiovascular events compared with placebo in patients with recent acute coronary syndrome (46). In the LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) CVOT, liraglutide was superior to placebo with respect to the time to first occurrence of a MACE (43).

Clinical Trial Overview

This review will focus on clinical trials with IDegLira or iGlarLixi relevant to patients with type 2 diabetes inadequately controlled on basal insulin or a GLP-1 receptor agonist. Although trials of IDegLira and iGlarLixi in patients with type 2 diabetes uncontrolled on oral agents have also been conducted, these will not be covered in this review. Three randomized trials have been completed in patients with type 2 diabetes uncontrolled on basal insulin: two with IDegLira (DUAL II [NCT01392573] and V [NCT01952145]) and one with iGlarLixi (LixiLan-L [NCT02058160]). One trial has been completed in patients with type 2 diabetes uncontrolled on a GLP-1 receptor agonist (DUAL III [NCT01676116]) (Table 1).

DUAL II was a double-blind trial comparing IDegLira with insulin degludec (dose capped at 50 units) conducted in adults previously treated with 20–40 units of basal insulin plus metformin, with or without a sulfonylurea or glinide (sulfonylureas and glinides discontinued at randomization) (47) DUAL V was an open-label trial comparing treatment intensification with IDegLira versus up-titration of insulin glargine U100 in adults previously treated with 20–50 units of insulin glargine plus metformin (48). DUAL III was an open-label trial comparing IDegLira with unchanged GLP-1 receptor agonist therapy (liraglutide once daily or exenatide twice daily) conducted in adults previously treated with a GLP-1 receptor agonist (maximum tolerated dose) plus metformin, with or without pioglitazone or a sulfonylurea. Oral agents were continued at the pretrial dose (49). All three DUAL trials were 26 weeks in duration. IDegLira was initiated at a dose of 16 units (16 units insulin degludec/0.58 mg liraglutide) and the maximum dose was 50 units (50 units insulin degludec/1.8 mg liraglutide). IDegLira and basal insulin comparators were titrated twice weekly to an FPG target of 72–90 mg/dL using a 2-0-2 algorithm, whereby there was no dose change if FPG was at target and a dose change of –2 or +2 units if FPG was below or above target, respectively.

LixiLan-L was a 30-week, open-label trial comparing iGlarLixi with insulin glargine U100 (dose capped at 60 units) conducted in adults previously treated with basal insulin and up to two oral agents (50). Basal insulin was standardized to insulin glargine and further titrated by protocol during a 6-week run-in phase, after which patients still requiring treatment intensification (A1C 7.0–10.0%, FPG ≤140 mg/dL, dose 20–50 units), were randomized to iGlarLixi or continued titration with insulin glargine. All oral agents other than metformin were discontinued at the start of the run-in period.

During LixiLan-L, two co-formulations of iGlarLixi were used (3 units insulin:1 µg lixisenatide and 2 units insulin:1 µg lixisenatide), depending on the dose required. The starting dose of iGlarLixi was determined by the final dose of insulin glargine received before randomization. Individuals requiring <30 units were initiated at a starting dose of iGlarLixi of 20 units, using the 2:1 co-formulation; individuals requiring ≥30 units were initiated at a starting dose of iGlarLixi of 30 units using the 3:1 co-formulation so as not to exceed the recommended starting dose of 10 µg for the lixisenatide component. Titration was conducted once weekly to an FPG target of 80–100 mg/dL, with dose adjustments of 0, 2, or 4 units depending on FPG. The maximum dose was 60 units insulin glargine/20 µg lixisenatide.

There are several major differences in the DUAL and LixiLan-L trial designs worth noting, limiting the ability to directly compare the two treatments and results. First, the FPG target was higher for LixiLan-L (80–100 mg/dL) than for the IDegLira trials (72–90 mg/dL). The titration frequency differed (twice weekly for IDegLira compared with once weekly for iGlarLixi, although the dose of each could be adjusted by up to 4 units/week). The DUAL trials were 26 weeks in duration compared with 30 weeks for LixiLan-L. Additionally, a higher maximum insulin dose was feasible with iGlarLixi (60 units vs. 50 units for IDegLira). Most notably, LixiLan-L included a 6-week insulin glargine run-in period, randomizing only patients with a suggested need for better prandial control (FPG ≤140 mg/dL and A1C 7.0–10.0%), whereas the DUAL trials randomized patients whose diabetes was

TABLE 1. Overview of Trials Evaluating IDegLira and iGlarLixi in Patients With Type 2 Diabetes Uncontrolled on Basal Insulin or a GLP-1 Receptor Agonist

Population	Patients With Type 2 Diabetes Uncontrolled on Basal Insulin			Patients With Type 2 Diabetes Uncontrolled on a GLP-1 Receptor Agonist
Trial	**DUAL II (47)**	**DUAL V (48)**	**LIXILAN-L (50)**	**DUAL III (49)**
Patients	Type 2 diabetes uncontrolled on basal insulin + oral agents (*n* = 398)	Type 2 diabetes uncontrolled on basal insulin glargine U100 + metformin (*n* = 557)	Type 2 diabetes uncontrolled on basal insulin + oral agents (*n* = 736)	Type 2 diabetes uncontrolled on GLP-1 receptor agonist + oral agents (*n* = 438)
Inclusion criteria	Basal insulin (20–40 units for ≥3 months) + metformin ± sulfonylurea or glinides; A1C: 7.5–10.0%; BMI ≥27 kg/m^2	Insulin glargine U100 (20–50 units for ≥56 days) + metformin; A1C 7.0–10.0%; BMI ≤40 kg/m^2	At run-in: basal insulin ≥6 months (stable dose of 15–40 units for ≥2 months) with ≤2 oral agents (metformin sulfonylurea, glinide, SGLT2 inhibitor, DPP-4 inhibitor); FPG ≤180 mg/dL if on 2 oral agents or 1 oral agent other than metformin; ≤200 mg/dL if on metformin or 0 oral agents At randomization: A1C 7.0–10.0%; FPG ≤140 mg/dL; insulin glargine U100 20–50 units; calcitonin ≤20 pg/mL; amylase/lipase levels <3 times ULN	GLP-1 receptor agonist (maximum tolerated dose of liraglutide once daily or exenatide twice daily) + metformin ± sulfonylurea or pioglitazone; A1C 7.0–9.0%; BMI ≤40 kg/m^2
Treatment groups	IDegLira + metformin; insulin degludec (maximum dose 50 units) + metformin	IDegLira + metformin; insulin glargine U100 + metformin	iGlarLixi + metformin; insulin glargine U100 + metformin	IDegLira + metformin ± sulfonylurea ± pioglitazone; unchanged GLP-1 receptor agonist + metformin ± sulfonylurea ± pioglitazone
Blinding	Double-blinded	Open-label	Open-label	Open-label
Randomization	1:1	1:1	1:1	2:1
Duration (weeks)	26	26	Run-in: 6; after randomization: 30	26
Baseline characteristics*				
Age (years)	57–58	58.4–59.1	59.6–60.3	58.3–58.4
A1C (%)	8.7–8.8	8.2–8.4	8.1	7.7–7.8
BMI (kg/m^2)	33.6–33.8	31.7	31.0–31.3	32.9–33.0
Diabetes duration (years)	10–11	11.3–11.6	12.0–12.1	10.4
Basal insulin dose (units)	29	31–32	35	NA
Completers (%)	IDegLira: 85; insulin degludec: 83	IDegLira: 89.9; insulin glargine U100: 95.0	iGlarLixi: 91.6; insulin glargine U100: 96.2	IDegLira: 94.5; unchanged GLP-1 receptor agonist: 80.1

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TABLE 1. Overview of Trials Evaluating IDegLira and iGlarLixi in Patients With Type 2 Diabetes Uncontrolled on Basal Insulin or a GLP-1 Receptor Agonist, ***continued from p. 141***

Population	Patients With Type 2 Diabetes Uncontrolled on Basal Insulin			Patients With Type 2 Diabetes Uncontrolled on a GLP-1 Receptor Agonist
Trial	**DUAL II (47)**	**DUAL V (48)**	**LIXILAN-L (50)**	**DUAL III (49)**
Starting dose	IDegLira: 16 units; insulin degludec: 16 units	IDegLira: 16 units; insulin glargine U100: pretrial dose	iGlarLixi: 20 units/10 mg (given with pen A) if the insulin glargine U100 dose was <30 units at the end of run-in or 30 units/10 mg (given with pen B) if the insulin glargine U100 dose was ≥30 units at the end of the run-in; insulin glargine U100: pretrial dose	IDegLira: 16 units; unchanged GLP-1 receptor agonist: pretrial dose
Titration frequency	Twice weekly	Twice weekly	Once weekly	Twice weekly
FPG titration target (mg/dL)	72–90	72–90	80–100	72–90

**Range of mean values across treatments. DPP-4, dipeptidyl peptidase 4; NA, not applicable; SGLT2, sodium–glucose cotransporter 2; ULN, upper limit of normal.*

inadequately controlled on the basis of A1C. Hypoglycemia definitions also differed; in the DUAL trials, "overall hypoglycemia" was defined as severe or confirmed (<56 mg/dL) hypoglycemia, whereas "documented symptomatic hypoglycemia" (≤70 mg/dL) was the definition in LixiLan-L. Baseline characteristics of the populations were similar with respect to BMI and disease duration. The pretrial insulin dose was lower in DUAL II compared with LixiLan-L; baseline A1C was lower in LixiLan-L compared with DUAL II. Baseline A1C was lowest in DUAL III.

Efficacy

In the three trials in patients with type 2 diabetes previously uncontrolled on basal insulin (DUAL II, DUAL V, and LixiLan-L), both co-formulations were associated with significantly greater improvements in A1C compared with continued titration of basal insulin therapy (Table 2). In DUAL II, IDegLira resulted in a significantly greater reduction in A1C compared with insulin degludec at an equivalent insulin dose (estimated treatment difference [ETD] –1.1%, P <0.0001). There was also a significantly greater reduction in FPG with IDegLira compared with insulin degludec (ETD –13 mg/dL, P = 0.0019) (47). In DUAL V, A1C reduction was significantly greater with IDegLira compared with insulin glargine (ETD –0.59%, P <0.001), with no difference in FPG reduction (48). In LixiLan-L, A1C reductions were significantly greater with iGlarLixi compared with insulin glargine (ETD –0.5%, P <0.0001), with no significant difference in FPG reduction (50). In all three trials, significantly more patients reached the A1C targets of <7% and ≤6.5% with the co-formulation compared with the basal insulin comparator.

In patients with type 2 diabetes previously uncontrolled on a GLP-1 receptor agonist (DUAL III), IDegLira resulted in a significantly greater A1C reduction compared with unchanged GLP-1 receptor agonist (ETD –0.94%, P <0.001), with significantly more patients achieving an A1C <7% and ≤6.5% (both P <0.001, Table 2). There was a greater FPG reduction with IDegLira than with unchanged GLP-1 receptor agonist (P <0.001) (49).

Dose

In both DUAL II and LixiLan-L, end-of-trial doses were equivalent in the co-formulation and the basal insulin groups, likely related to the capping of the basal insulin dose as part of the trial design. In DUAL V, after 26 weeks, the daily dose of IDegLira was significantly lower than that of up-titrated insulin glargine (ETD 25.5 units, P <0.001), despite significantly lower A1C with IDegLira (Table 2).

Safety

Body Weight

Overall, IDegLira and iGlarLixi were associated with a weight benefit when used in patients with type 2 diabetes previously uncontrolled on basal insulin compared with weight gain with continued basal insulin therapy (Table 3). In DUAL II, IDegLira was associated with weight loss, whereas insulin degludec was weight neutral (ETD –2.5 kg, P <0.0001) (47). In DUAL V, IDegLira was associated with weight loss, whereas insulin glargine up-titration was associated with weight gain (ETD –3.2 kg, P <0.001) (48). In LixiLan-L, there

TABLE 2. Efficacy and Dose of IDegLira and iGlarLixi in Phase 3 Trials

Population	Patients With Type 2 Diabetes Uncontrolled on Basal Insulin						Patients With Type 2 Diabetes Uncontrolled on a GLP-1 Receptor Agonist	
Trial	DUAL II (47)		DUAL V (48)		LixiLan-L (50)		DUAL III (49)	
Treatment	IDegLira	Insulin degludec	IDegLira	Insulin glargine U100	iGlarLixi	Insulin glargine U100	IDegLira	Unchanged GLP-1 receptor agonist
n	199	199	278	279	367	369	292	146
A1C (%)								
Baseline	8.7 (0.7)	8.8 (0.7)	8.4 (0.9)	8.2 (0.9)	8.1 (0.7)	8.1 (0.7)	7.8 (0.6)	7.7 (0.5)
End of trial	6.9 (NR)	8.0 (NR)	6.6 (0.9)	7.1 (0.9)	6.9 (0.9)	7.5 (0.9)	6.4 (0.8)	7.4 (1.0)
Change	–1.9* (NR)	–0.9 (NR)	–1.81 (1.08)	–1.13 (0.98)	–1.1 (SE 0.06)*	–0.6 (SE 0.06)	–1.3 (0.9)*	–0.3 (0.9)
Responders (%)								
A1C <7%	60.3*	23.1	71.6*	47.0	55*	30	75*	36
A1C ≤6.5%	45.2*	13.1	55.4*	30.8	34*	14	63*	23
FPG (mg/dL)								
Baseline	175 (52)	173 (56)	160.6 (47.5)	159.8 (52.0)	131.5 (36.0)	133.3 (37.8)	161.7 (38.2)	169.1 (41.7)
End of trial	112 (NR)	126 (NR)	109.5 (38.4)	110.2 (38.6)	122.5 (41.4)	120.7 (37.8)	108.5 (29.3)	158.4 (48.7)
Change	–62 (53)*	–46 (60)	–50.9 (NR)	–49.9 (NR)	–7.2 (SE 1.8)	–9.0 (SE 1.8)	–53.6 (41.1)*	–10.7 (49.3)
End of trial dose (units)	45	45	41	66	47	47	43	NA

*Data are mean (SD) unless otherwise stated. *Significant difference between treatments in favor of IDegLira/iGlarLixi. NA, not applicable; NR, not reported; SE, standard error.*

was a mean body weight decrease with iGlarLixi compared with a mean increase with insulin glargine (ETD –1.4 kg, P <0.0001) (50).

When patients with type 2 diabetes uncontrolled on a GLP-1 receptor agonist were switched to IDegLira, a significant increase in weight was observed compared with those with unchanged GLP-1 receptor agonist therapy, which resulted in weight loss (ETD 2.89 kg, P <0.001 in favor of GLP-1 receptor agonist therapy; Table 3) (49).

Hypoglycemia

In patients with type 2 diabetes previously uncontrolled on basal insulin, the rates of overall and nocturnal hypoglycemia were significantly lower with IDegLira compared with uptitration of insulin glargine (estimated rate ratios [ERRs] 0.43 and 0.17, respectively, both P <0.001), despite lower A1C with IDegLira (Table 3) (48). In contrast, there were no significant differences in hypoglycemia between the co-formulation and basal insulin in the two trials in which the basal insulin dose was capped (DUAL II and LixiLan-L), although the rate was numerically lower with iGlarLixi than with insulin glargine (Table 3) (47,50).

In patients with type 2 diabetes previously uncontrolled on a GLP-1 receptor agonist, rates of overall and nocturnal hypoglycemia were significantly higher with IDegLira than with unchanged GLP-1 receptor agonist therapy (ERRs 25.36, P <0.001, and 32.82, P <0.001, respectively) (49). Hypoglycemia rates with IDegLira were higher in patients concomitantly treated with a sulfonylurea compared with those who were not taking a sulfonylurea (6.34 vs. 1.75 events/patient-year of exposure) (49).

Adverse Events

Rates of adverse events and serious adverse events were similar across trials and treatments. As expected, the rate of nausea was higher with co-formulations compared with bas-

TABLE 3. Safety of IDegLira and iGlarLixi in Phase 3 Trials

Population	Patients With Type 2 Diabetes Uncontrolled on Basal Insulin						Patients With Type 2 Diabetes Uncontrolled on a GLP-1 Receptor Agonist	
Trial	**DUAL II (47)**		**DUAL V (48)**		**LixiLan-L(50)**		**DUAL III (49)**	
Treatment	IDegLira	Insulin degludec	IDegLira	Insulin glargine U100	iGlarLixi	Insulin glargine U100	IDegLira	Unchanged GLP-1 Receptor Agonist
n	199	199	278	279	365	365	292	146
Hypoglycemia (% [events/PYE])								
Overall	24.1 (1.5)	24.6 (2.6)	28.4 (2.23)*	49.1 (5.05)	40.0 (3.03)	42.5 (4.22)	32 (2.82)	2.8 (0.12)†
Nocturnal	6.0 (0.22)	8.5 (0.32)	6.1 (0.22)*	24.4 (1.23)	NR	NR	11 (0.454)	0.7 (0.015)†
Severe	*n* = 1‡	*n* = 0‡	*n* = 0‡	*n* = 1‡	1.1 (0.02)	0.3 (<0.01)	0.3 (0.007)	0 (0)
Body weight (kg)								
Baseline (SD)	95.4 (19)	93.5 (20)	88.3 (17.5)	87.3 (15.8)	87.7 (14.5)	87.1 (14.8)	95.6 (16.6)	95.5 (17.3)
End of trial (SD)	NR	NR	86.9 (17.2)	89.1 (15.9)	87.5 (14.4)	88.0 (15.1)	NR	NR
Change (SD)	–2.7 (NR)*	0.0 (NR)	–1.4 (3.5)*	1.8 (3.6)	–0.7 (SE 0.2)*	0.7 (SE 0.2)	2.0 (3.9)	–0.8 (3.0)†
Adverse event (% [events/PYE])	57.8 (4.0)	61.3 (3.6)	57.6 (3.43)	50.5 (2.86)	53.4 (NR)	52.3 (NR)	65.6 (4.10)	63.4 (3.64)
Serious adverse event (% [events/PYE])	3.5 (0.12)	5.5 (0.14)	1.8 (0.04)	3.2 (0.07)	5.5 (NR)	4.9 (NR)	3.1 (0.09)	2.1 (0.05)
Nausea (% [events/PYE])	6.5 (0.22)	3.5 (0.08)	9.4 (0.26)	1.1 (0.02)	10.4 (NR)	0.5 (NR)	3.1 (0.08)	4.1 (0.11)
MACE (*n*)	1	2	1	1	similar %	similar %	2	0
Pancreatitis (*n*)	0	0	0	0	0	0	0	0
Pancreatic carcinoma (*n*)	0	1	0	0	0	0	0	0
Medullary thyroid carcinoma/thyroid neoplasm (*n*)	0	0	0	0	NR	NR	0	0

**Significant difference between treatments in favor of IDegLira/iGlarLixi. †Significant difference in favor of comparator. ‡Rate of severe hypoglycemia was not reported. NR, not reported; PYE, patient-year of exposure; SE, standard error.*

al insulin but lower compared with a GLP-1 receptor agonist (Table 3). In the double-blind trial (DUAL II), there was less of a difference in rates of nausea between co-formulation and basal insulin compared with the two open-label trials (DUAL V and LixiLan-L). There was no increase in the frequency of major adverse cardiovascular events with the co-formulations, and no pancreatitis or medullary thyroid carcinoma events were reported (Table 3). No CVOTs are currently planned for the co-formulations because the cardiovascular safety of their monocomponents has been investigated extensively in their respective CVOTs (42,43,46,51).

Immunogenicity

Across the DUAL program, after treatment with IDegLira, 11.1% of patients were positive for insulin degludec–specific antibodies compared with 2.4% at baseline; 30.8% were positive for human insulin–specific antibodies compared with 14.6% at baseline; and 2.1% were positive for anti-liraglutide antibodies compared with none at baseline. Antibody formation has not been associated with reduced efficacy of IDegLira (32). It has been reported that patients may develop antibodies to insulin glargine and lixisenatide, and if there is a worsening of glycemic control or allergic reaction, alternative treatment should be considered. After treatment with iGlarLixi in clinical trials, anti–insulin glargine antibodies were detected in 21.0–26.2% of patients, 93% of which cross-reacted with human insulin. Anti-lixisenatide antibodies were detected in 43% of patients (33).

Discussion

The DUAL and LixiLan trial programs compared two treatment strategies reflective of current clinical care decisions for patients on basal insulin: continuing up-titration of basal insulin or switching to a basal insulin/GLP-1 receptor agonist combination. Both found superiority in switching to the co-formulation compared to up-titrating basal insulin. Furthermore, DUAL III demonstrated the efficacy of switching patients with type 2 diabetes inadequately controlled on GLP-1 receptor agonist therapy to IDegLira.

In all trials, a high proportion of patients were able to achieve glycemic control with the co-formulations. Additionally, in patients with type 2 diabetes uncontrolled on basal insulin, the co-formulations were associated with a low frequency of hypoglycemia and weight loss, making them an attractive option compared to up-titration of basal insulin or intensification with prandial insulin, both of which increase hypoglycemia and weight gain (29,48). Preliminary results from DUAL VII (NCT02420262), a trial comparing IDegLira with basal-bolus therapy, were recently presented, showing noninferior A1C reductions after 26 weeks, a lower rate of hypoglycemia (ERR 0.11, P <0.0001), weight loss compared with weight gain (ETD –3.57 kg, P <0.0001), and a significantly lower insulin dose (P <0.0001) with IDegLira compared with basal-bolus therapy, respectively (52).

In patients with type 2 diabetes uncontrolled on a GLP-1 receptor agonist, IDegLira resulted in improved glycemic control, although, as expected with the introduction of insulin, with a higher rate of hypoglycemia and weight gain compared with GLP-1 receptor agonist therapy without insulin. At present, there are no data for patients converting from a GLP-1 receptor agonist to iGlarLixi, but a trial is currently recruiting participants (LixiLan-G: NCT02787551).

Several advantages of the co-formulation approach versus monocomponent approach emerged from these trials. Glycemic efficacy was consistently superior with the co-formulations compared with intensification of basal insulin or continuation of a GLP-1 receptor agonist. Furthermore, the co-formulations were able, to a large extent, to mitigate the main side effects associated with the monocomponents, namely hypoglycemia and weight gain with insulin and nausea with a GLP-1 receptor agonist. At the patient level, the co-formulations may offer appeal based on the need for fewer injections, less required self-monitoring compared to basal-bolus or premixed insulin regimens, and the potential to limit excess use of basal insulin through the incorporation of GLP-1 receptor agonist therapy. In addition to limiting the risk of using more basal insulin than required, there is also potential for insulin-sparing, as seen with IDegLira compared to insulin glargine up-titration (48).

On a practical level, which patients might be good candidates for treatment with the insulin/GLP-1 receptor agonist co-formulations? Consistent with their approved indications, these co-formulations would likely address treatment gaps in patients who are on basal insulin but are not at glycemic goal by targeting complementary pathophysiologic aberrancies while minimizing the risk of hypoglycemia and weight gain associated with insulin up-titration. Although not approved for this indication in the United States, the co-formulations have also demonstrated efficacy as initial injection therapy in patients currently taking oral agents and requiring treatment intensification. Finally, the once-daily dosing and simple titration of these co-formulations may provide practical benefit for patients for whom treatment adherence is a concern and treatment simplification is desired.

Questions remaining to be addressed include if there is a long-term advantage of earlier introduction of combined insulin/GLP-1 receptor agonist therapy through these co-formulations and if an early combined approach offers an overall benefit compared to eventual combined insulin/GLP-1 receptor agonist therapy through a step-wise approach. Furthermore, direct head-to-head comparisons of IDegLira and iGlar-

Lixi under a common trial design and population may help tease out comparative differences. Given the recent approval of both IDegLira and iGlarLixi, the extent to which these trials and their findings are translated to clinical practice, as well as the long-term efficacy of these products, remain to be seen. Cost and insurance coverage of the co-formulations compared with separate injections or the addition of other therapies will also likely influence how widely they are used. Data are also needed on patient adherence and long-term persistence and if there is a patient preference for the co-formulations over separate injections.

Summary

Combination therapy with a basal insulin and a GLP-1 receptor agonist is already used in clinical practice and recommended by guidelines as a result of the efficacy and complementary modes of action of these agents (5,6). The availability of insulin/GLP-1 receptor agonist co-formulations and the depth of trial evidence now available provide yet another viable and attractive approach for the management of patients with type 2 diabetes inadequately controlled on basal insulin or GLP-1 receptor agonist treatment.

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Author Contributions

All authors made substantial contributions to the design and interpretation of data and drafting of the manuscript and approved the final version. V.R.A. is the guarantor of this work and, as such, takes responsibility for the integrity and accuracy of this review.

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