Co-Formulations as the First Injectable in Type 2 Diabetes: A Review of Efficacy, Safety, and Implications in Clinical Practice

Mathew John Deepa Gopinath Tittu Oommen

Providence Endocrine and Diabetes Specialty Centre, Trivandrum, India

Keywords

Co-formulations · Diabetes mellitus · IDegAsp · IDegLira · IGLarLixi

Abstract

Background: Progression of type 2 diabetes will necessitate the use of injectable therapies in a significant number of people. Co-formulations of degludec with liraglutide (IDegLira) and glargine with lixisenatide (IGlarLixi) are currently recommended for intensification in people with type 2 diabetes on basal insulin or glucagon-like peptide receptor agonist (GLP-1RA) alone or in people with type 2 diabetes who are naïve to insulin with very high glycated haemoglobin. Co-formulation of aspart with degludec (IDegAsp) is recommended as a substitute for premixed insulin. The aim of this article is to review the evidence in the use of co-formulations as the first injectable in type 2 diabetes and its clinical implications. **Summary:** In people with type 2 diabetes who are naïve to insulin or GLP-1RA, IDegLira and IGLarLixi achieved stable and durable glycaemic control over a wide range of baseline glycated haemoglobin (HbA1c) levels. People on IDegLira and IGLarLixi had lesser risk of hypoglycaemia and weight gain in studies compared to basal insulin and lesser

gastrointestinal adverse effects in comparison to GLP-1RA. IDegAsp achieved similar glycaemic control to basal and premixed insulin with lesser risk of nocturnal hypoglycaemia. **Key Messages:** IDegLira, IGLarLixi, and IDegAsp can be used as the first injectable in people with type 2 diabetes with very high glycated haemoglobin on oral antidiabetic drugs. These co-formulations combine efficacy and durability with lesser injection burden. The components of these agents have proven cardiovascular and renal safety. Their limitations in flexibility of dosing, renal and cardiovascular considerations, and adverse effects are discussed.

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Published by S. Karger AG, Basel

Introduction

Type 2 diabetes is a major public health problem worldwide with the disease and its complications leading to high healthcare costs [1]. Glycaemic control along with the control of blood pressure and lipids form the cornerstone in preventing microvascular and macrovascular complications. As the duration of diabetes increases, more people require the use of injectable therapies for optimisation of their glycaemic control. Although insulin

is the traditional injectable, new guidelines recommend glucagon-like peptide receptor agonist (GLP-1RA) as the preferred injectable in people with type 2 diabetes [2–4]. For people who require further optimisation of glycaemic control, insulin is preferred although a significant number of people would be initiated on insulin directly [2]. However, co-formulations of insulin and fixed ratio combinations of GLP-1RA and basal insulin are newer options which are increasingly used in clinical practice. This review focuses on the use of these novel agents as the first injectable for people with type 2 diabetes.

Position of GLP-1RA, Basal Insulin Analogues, and Co-Formulations in the Current Guidelines

The early introduction of insulin should be considered if there is evidence of ongoing catabolism, if symptoms of hyperglycaemia are present, or when A1C levels ($>10\%$ [86 mmol/mol]) or blood glucose levels (≥ 300 mg/dL [16.7 mmol/L]) are very high. In appropriate high-risk individuals with established type 2 diabetes, the decision to treat with a GLP-1 receptor agonist or SGLT2 inhibitor to reduce major adverse cardiovascular events, hospitalisation for heart failure, cardiovascular death, or chronic kidney disease progression should be considered independently of baseline HbA1c or individualized HbA1c target. In others, the choice of the second agent after metformin is less empiric and is driven by consideration of adverse effects: hypoglycaemia, weight gain, renal function, and so on [2–5].

Due to the progressive nature of the disease, most people with type 2 diabetes will need injectable agents as they offer better glycaemic reduction than most oral agents. GLP-1RAs have consistently shown better glycaemic efficacy, lower risk of hypoglycaemia and weight loss in comparison to basal insulin in people with type 2 diabetes [6–9]. This makes them the choice as first injectable for most people with type 2 diabetes. Basal insulin is added to GLP-1RA if glycaemic targets are not met [2, 3].

Most guidelines recommend basal insulin as the first insulin preparation and advancing to prandial or premixed insulin for intensification [2–5]. The advantages of a single injection, a flat pharmacokinetic profile, easy titration, and less incidence of hypoglycaemia in comparison to premixed insulins, make basal insulins an ideal choice for initiation [10]. In trials comparing different insulins for initiation, premixed analogues resulted in a higher reduction in HbA1c and more people reaching the goal. However, the overall risk of hypoglycaemia and weight gain was also more with premixed insulin [10, 11].

Adding and titrating a basal insulin or GLP-1RA alone to oral agents have various limitations. Basal insulin targets the fasting hyperglycaemia by suppressing hepatic glucose output. Treat-to-target regimens continue to up-titrate basal insulin based on fasting plasma glucose (FPG) to reach target levels of 3.9–5.0 mmol/L [12]. However, in these studies, the achieved levels of FPG are higher than the target values, probably limited by the increased risk of nocturnal hypoglycaemia, and a significant percentage of people do not reach the HbA1c goals [12, 13]. In a meta-analysis of 48 basal insulin analogue trials, only 41% of the study participants attained an HbA1c of <53 mmol/mol (7.0%) [14]. Despite optimum titration in trials, basal insulin has less durability and limited benefits on postprandial glucose (PPG) [15, 16]. With increasing doses, basal insulin has a diminishing impact on glycaemic control with weight gain [17]. Similarly, adding a GLP-1RA alone to oral agents has limitations in terms of gastrointestinal adverse effects and less people reaching the HbA1c goals. In studies where the highest approved doses of semaglutide, liraglutide, dulaglutide, and exenatide QW were added on to oral glucose-lowering agents in people with type 2 diabetes, the percentages of people achieving HbA1c <53 mmol/mol (7.0%) were 73, 53, 53, and 40%, respectively [6–9]. Intensification of people started on one injectable (basal insulin or GLP-1RA) is done with the other injectable for further lowering of HbA1c.

As per recent guidelines, degludec with liraglutide (IDegLira) and glargine with lixisenatide (IGlarLixi) are recommended as a replacement for people on GLP-1RA or basal insulin if they fail to reach targets [2]. Aspart with degludec (IDegAsp), the first insulin co-formulation, is considered as a substitute for premixed analogues with lesser risk of nocturnal hypoglycaemia [18–20].

Types of Co-Formulations

Injectable co-formulations are preparations where 2 distinct drugs are combined, with each maintaining their distinct pharmacodynamic and pharmacokinetic properties [21]. The co-formulations currently available include insulin-based co-formulation, IDegAsp and GLP-1RA-basal insulin fixed ratio combinations, IDegLira, and IGlarLixi (Table 1).

IDegAsp

IDegAsp is a co-formulation of short-acting insulin analogue aspart with long-acting basal insulin degludec in a fixed dose of 30:70 proportion (100 U/mL). The unique pharmacokinetic and pharmacodynamic pro-

Table 1. Overview of co-formulations

Co-formulation	Components and proportion	Dosing	Maximum dose of individual components delivered in a single injection	Delivery per dosing change	Cartridge volume	Year of approval (FDA/EMA)
IDegAsp	70% ultra-long-acting insulin degludec (IDeg) and 30% rapid-acting insulin aspart (IAsp)	Starting dose in insulin-naïve people with type 2 diabetes mellitus is 10 units once daily along with the largest meal It can also be used twice daily	The disposable pen/cartridge can deliver 80 units The permanent device can deliver 60 units	0.7 unit degludec and 0.3 unit aspart in 1 unit IDegAsp It is dosed as units	3 mL	2015/2013
IDegLira	100 U/mL degludec and 3.6 mg/mL liraglutide	Starting dose is 10 dose steps in insulin-naïve people (10 units of insulin degludec and 0.36 mg liraglutide) administered at any time of the day, preferably at the same time of the day When transferring from basal insulin therapy, the recommended starting dose of IDegLira is 16 dose steps (16 units insulin degludec and 0.58 mg liraglutide)	50 units of degludec and 1.8 mg of liraglutide	1 unit of insulin degludec and 0.036 mg liraglutide in 1 dose step of IDegLira	3 mL	2016/2014
IGlarLixi	Glargine (100 U/mL) and lixisenatide (33 µg/mL)	It is available in a 3:1 dosing ratio of 3 units insulin glargine to 1 µg lixisenatide per mL Starting dose is 15 units glargine/5 µg lixisenatide (15 units dlargin in dial) for people on lixisenatide or <30 units glargine The starting dose is 30 units glargine and 10 µg lixisenatide for people on >30 units glargine Administered once daily within 1 hour before the first meal of the day	60 units glargine and 20 µg lixisenatide	1 dose step delivers 1 unit of glargine and 0.3–0.4 µg of lixisenatide	3 mL	2016/2017

file help it in using it either once daily or twice daily according to the glycaemic fluctuations [20] (Table 1).

IDegLira

IDegLira is a fixed-ratio combination of insulin degludec and liraglutide, containing 100 U/mL of IDeg and 3.6 mg/mL of liraglutide. Liraglutide is a long-acting GLP-1RA which reduces both FPG and PPG excursions via its glucose-dependent effects on β - and α -cell function. The dose should be titrated according to the mean of 3 or 4 consecutive pre-breakfast self-measured plasma glucose results, and according to the individual's glycaemic target range [22–24] (Table 1).

IGlarLixi

IGlarLixi contains insulin glargine U100 (IGlarU100), a long-acting basal insulin analogue, and lixisenatide, a short-acting GLP-1RA. It is currently approved for improving glycaemic control in adults with type 2 diabetes

inadequately controlled on basal insulin (<60 U daily) or lixisenatide [25]. As IGlarLixi is currently approved only for individuals with type 2 diabetes on basal insulin or lixisenatide, the starting dose is also decided based on the current dose [23, 25, 26] (Table 1).

Search Strategy

We searched PubMed through November 2019 for trials involving IDegAsp, IDegLira, and IGlarLixi. Eligible studies were randomised controlled trials of IDegAsp, IDegLira, or IGlarLixi compared with placebo or active comparators (GLP-1RA, insulin, or oral glucose-lowering drugs) in people with type 2 diabetes mellitus who were naïve to injectable therapies (see online suppl. File 1, www.karger.com/doi/10.1159/000509045).

Table 2. Efficacy of IDegAsp in studies where it was used as a first injectable therapy

Reference	Comparator	Duration of trial	Mean change in HbA1c (vs. comparator)	Estimated treatment difference in HbA1c	Percentage of patients reaching target HbA1c (vs. comparator)	Percentage of patients reaching target HbA1c without hypoglycaemia (vs. comparator)	Estimated treatment difference in fasting blood glucose
Kumar et al. [27]	IGlarU100	26 weeks' core phase and extension phase to 52 weeks	−17 mmol/mol (1.65%) at 26 weeks and −15 mmol/mol (1.39%) at 52 weeks (−19 mmol/mol [1.72%] at 26 weeks and −14 mmol/mol [1.34%] at 52 weeks)	0.03% (95% CI −0.14 to 0.20) at 26 weeks 0.08% (95% CI −0.26 to 0.09) at 52 weeks	45.9% at 26 weeks, 33.1% at 52 weeks (vs. 45.6% at 26 weeks, 29.7% at 52 weeks)	NA	0.51 mmol/L (95% CI 0.09 to 0.93) at week 26 and 0.28 mmol/L (95% CI −0.14 to 0.69) at week 52
Onishi et al. [28]	IGlarU100	26 weeks	−15 mmol/mol (1.4%; vs. −13 mmol/mol [1.2%])	−0.28% (95% CI −0.46 to −0.10)	59% (vs. 40%) (<i>p</i> value <0.01)	43% (vs. 25%) (<i>p</i> value <0.01)	0.15 mmol/L (95% CI, −0.29 to 0.60) <i>p</i> = not significant
Shimoda et al. [29]	Basal insulin (IDeg or IGlarU300)	12 weeks	−14 mmol/mol (1.29%; vs. −18 mmol/mol [1.6%]) [#]	0.31% [#]	57.7% ^{##} (vs. 69.2% ^{##}) (<i>p</i> value 0.388)	NA	NA
Franek et al. [30]	BIAsp30	26 weeks	−19 mmol/mol (1.71%; vs −19.2 mmol [1.73%])	0.02% (95% CI −0.12 to 0.17)	NA	NA	−1.0 mmol/l (95% CI −1.4 to −0.6) <i>p</i> < 0.001
Park et al. [31]	Comparison of two self-titration algorithms of IDegAsp OD (IDegAsp _{simple} vs. IDegAsp _{stepwise})	26 weeks	−15 mmol/mol (1.4%*) and −11 mmol/mol (1.0%**)	−0.2% (95% CI −0.4 to 0.02)	58.1%*, 49.3%**	39.5%*, 30.7%**	−0.4 mmol/l (95% CI −0.9 to 0.09)

* Twice weekly titration, based on a single pre-breakfast self-monitored plasma glucose (SMPG) measurement. ** Weekly titration, based on the lowest of three consecutive pre-breakfast SMPG measurements. [#] Indirectly derived from the parameters used in the study. ^{##} The target HbA1c was <8% in Shimoda et al.'s study [29], in the rest, it was <7%. NA, not reported in the text or supplementary appendix.

Glycaemic and Metabolic Outcomes with Co-Formulations

Evidence with IDegAsp (Tables 2, 3)

In an open-label, parallel-group, treat-to-target trial, people with type 2 diabetes who were naïve to insulin (*n* = 530, BMI: 30.9, mean age: 57.4 years, duration of diabetes: 8.7 years) were randomised (1:1) to receive IDegAsp OD (breakfast, *n* = 266) or IGlarU100 OD (as per label, *n* = 264) lasting 26 weeks. Participants then entered a 26-week extension phase (IDegAsp OD, *n* = 192; IGlarU100 OD, *n* = 221). IDegAsp was non-inferior to IGlarU100 for the primary endpoint of difference of HbA1c from the baseline at 52 weeks. The percentage of people reaching target HbA1c was also similar in both groups at 26 and 52 weeks [27].

In a phase 3 treat-to-target study in Japanese people with type 2 diabetes who were naïve to insulin (*n* = 296, 26-week duration, mean BMI: 25, duration of diabetes: 10.9 years, mean age: 60 years), the efficacy and safety of IDegAsp before the main meal was compared to IGlar-

U100 as an initiation strategy. The study showed superiority of IDegAsp in reducing HbA1c from baseline with a clinically relevant treatment difference of 0.28% in favour of IDegAsp. More people in the IDegAsp arm (59%) reached an HbA1c of <53 mmol/mol (7.0%) and more people (43%) reached HbA1c <53 mmol/mol (7.0%) without hypoglycaemia (*p* < 0.01) [28].

In a small trial (*n* = 52) in Japanese people, IDegAsp was compared to basal insulins IGlarU300 and IDeg. The reduction in HbA1c and proportion of people reaching a target HbA1c of 64 mmol/mol (8%) were similar. In a subgroup analysis of people stratified by baseline HbA1c, IDegAsp fared better than basal insulins in people with baseline HbA1c <69 mmol/mol (8.5%), whereas basal insulins fared better in people with HbA1c >69 mmol/mol (8.5%). These conclusions were limited by the small number of people enrolled and the less stringent targets for FPG and HbA1c [29].

In a trial lasting 26 weeks (BMI: 31.2, duration of diabetes: 9.5 years, baseline HbA1c: 68 mmol/mol [8.4%]),

Table 3. Safety, doses, and weight changes in trials of IDegAsp when used as the first injectable

Reference	Comparator	Duration of trial	Percentage of overall confirmed hypoglycaemia (vs. comparator)	Percentage of nocturnal hypoglycaemia (vs. comparator)	Mean total insulin dose (U/kg) at the end of therapy (vs. comparator)	Weight change (in kg) at the end of therapy (vs. comparator)
Kumar et al. [27]	IGlarU100	26 weeks' core phase and extension phase to 52 weeks	57.7 (52.1) at 52 weeks	7.5 (20.3)	0.78 (0.70)	4.4 (2.8)
Onishi et al. [28]	IGlarU100	26 weeks	44.2 (44.3)	8.2 (16.3)	0.41 (0.41)	0.7 (0.7)
Shimoda et al. [29]	Basal insulin (IDeg or IGlarU300)	12 weeks	3.8 (3.8)	0 (0)	0.154 (0.157)	NA
Franek et al. [30]	BIAsp30	26 weeks	61 (69)	19 (40)	0.80 (0.82)	3.53 (2.74)
Park et al. [31]	Comparison of two self-titration algorithms of IDegAsp OD (IDegAsp _{simple} vs. IDegAsp _{stepwise})	26 weeks	46.3*, 38.6**	13.4*, 12.9**	0.70*, 0.70**	2.6*, 1.9**

* Twice weekly titration, based on a single pre-breakfast self-monitored plasma glucose (SMPG) measurement. ** Weekly titration, based on the lowest of three consecutive pre-breakfast SMPG measurements. NA, not reported in the text or supplementary appendix.

IDegAsp ($n = 197$) was compared with BIAsp30 ($n = 197$). IDegAsp showed superior fasting glucose reduction and reduced overall and nocturnal confirmed hypoglycaemia at a similar overall insulin dose [30]. In a trial testing various titration regimens of IDegAsp, simple titration regimens fared as well as a step-wise titration regimen [31]. In most trials with self-monitoring of blood glucose, people on IDegAsp had lower PPG compared to the other arm [27, 28].

Evidence with IDegLira (Tables 4, 5)

DUAL VIII ($n = 1,012$, mean age: 56.8 years, duration of diabetes: 10.0 years), a 104-week duration study, was designed to test the durability of IDegLira in comparison with IGlarU100. IDegLira was found to be more durable by the metric of time from randomisation to inadequate glycaemic control and treatment intensification. At 104 weeks, 37% of the people on IDegLira required treatment intensification compared to 66% of the people on IGlarU100 [32].

In DUAL I ($n = 1,663$, mean age: 55.1 years, duration of diabetes: 6.6 years), IDegLira was compared to degludec and liraglutide in a 3-arm randomised controlled trial of 26 weeks' duration in insulin-naïve people with type 2 diabetes on metformin and pioglitazone. The mean HbA1c reduction was -1.9 , -1.4 , and -1.3% in the IDegLira, IDeg, and liraglutide arm, respectively. Significantly more people achieved target HbA1c of 53 mol/mol (7%) on IDegLira (81%) compared to IDeg (65%, $p < 0.0001$)

or liraglutide (60%, $p < 0.0001$). More people in the IDegLira arm (36%) achieved target HbA1c without hypoglycaemia and weight gain compared to IDeg (14%, $p < 0.0001$) [33]. During an extension phase of the DUAL I study, at 52 weeks, significantly more people achieved target HbA1c of 53 mol/mol (7%) on IDegLira (78.2%) compared to IDeg (62.5%, $p < 0.0001$) or liraglutide (56.5%, $p < 0.0001$) [34].

In a 52-week trial (DUAL I Japan) in Japanese people ($n = 819$, mean age: 56.9 years, duration of diabetes: 9.2 years), IDegLira was compared to both IDeg and liraglutide in a 1:1:1 randomisation. IDegLira was found to be superior to IDeg and liraglutide for reaching the primary endpoint of HbA1c reduction [35].

In a 26-week trial ($n = 420$, mean age: 56.1 years, duration of diabetes: 9.8 years), IDegLira was compared to IGlarU100 in people with type 2 diabetes on oral glucose-lowering drugs including SGLT2 inhibitors. In this trial, IDegLira was non-inferior to IGlarU100 for the primary endpoint of reduction of HbA1c from baseline to end of trial and superior for change in HbA1c [36].

In a 26-week double-blind trial, adults with type 2 diabetes were randomised to IDegLira ($n = 289$) or placebo ($n = 146$) as add-on to pre-trial sulphonylureas $\pm$ metformin (DUAL IV). The study showed that IDegLira was superior to placebo with regard to HbA1c reduction from baseline (-14 mmol/mol [1.5%] vs. -5 mmol [0.5%], $p < 0.001$) and proportion of people attaining the targets (79.2 vs. 28.8%, p value < 0.001) [37].

Table 4. Efficacy of IDegLira and IGLarLixi in trials as the first injectable

Reference	Comparator(s)	Duration of trial	Mean change in HbA1c (vs. comparator)	Estimated treatment difference in HbA1c	Percentage of patients		Estimated treatment difference in fasting blood glucose
					reaching target HbA1c <7% (vs. comparators)	target HbA1c of <7% (without hypoglycaemia gain (vs. comparators)	
Aroda et al. [32] (DUAL VIII)	IGlarU100	104 weeks	-22 mmol/mol (2.01%) (vs. -19 mmol/mol (1.69%))	-0.47% (95% CI 0.58 to -0.36), $p < 0.0001$	55.5 (28.5) $p < 0.0001$	51.8 (25.5) $p < 0.0001$	-0.48 (95% CI -0.76 to -0.19), p value = 0.0010
Gough et al. [33, 34] (DUAL I and DUAL I Extension)	IDeg. Lira	26 weeks' core phase and extension phase to 52 weeks	-21 mmol/mol (1.91%); vs. 15 mmol/mol (1.4%), -14 mmol/mol (1.3%) at 26 weeks; -20.2 mmol/mol (1.84%); vs. -15.3 mmol/mol (1.4%), -13.2 mmol/mol (1.21%) at 52 weeks	At 26 weeks, non-inferiority to insulin degludec -0.47% (95% CI -0.58 to -0.36, $p < 0.0001$) and superiority to liraglutide -0.64% (95% CI -0.75 to -0.53, $p < 0.0001$) At 52 weeks, with insulin degludec -0.46% (95% CI -0.57 to -0.34, $p < 0.0001$) with liraglutide -0.65% (95% CI -0.76 to -0.53, $p < 0.0001$)	81 (65.60) at 26 weeks $p < 0.0001$ 78.2 (62.5-56.5) at 52 weeks $p < 0.0001$	60 (41 [14.52] at 26 weeks 58 [15.7] $p < 0.0001$, 61.1 (44.1 [14.52] at 52 weeks 52.9 [15.7] $p < 0.0001$)	At 26 weeks with degludec -0.17 mmol/L (95% CI -0.41 to 0.07, $p = 0.16$) with liraglutide -1.76 mmol/L (95% CI -2.00 to -1.53, $p < 0.0001$) At 52 weeks with degludec -0.20 mmol/L (95% CI -0.45 to 0.05; $p = 0.11$) with liraglutide -1.67 mmol/L (95% CI -1.92 to -1.42; $p < 0.0001$)
Kaku et al. [35] (DUAL JAPAN)	IDeg. Lira	52 weeks	-26 mmol/mol (2.42%) (vs. -20 mmol/mol [1.8%]), -20 mmol/mol [1.8%])	with degludec -0.63% (95% CI -0.75 to -0.52), $p < 0.0001$ with liraglutide -0.48% (95% CI -0.60 to -0.37), $p < 0.0001$	NA	NA	-1 mmol/L with degludec -1.5 with liraglutide
Philis Tsimikas et al. [36] (DUAL IX)	IGlarU100	26 weeks	-20 mmol/mol (1.9%) (vs. -19 mmol/mol [1.7%])	-0.36% points (95% CI -0.50 to -0.21), $p < 0.0001$	84.8 (71.3) $p = 0.0107$	79.2 (56.4) $p < 0.0001$	-0.33 mmol/L (95% CI -0.64 to -0.01), $p = 0.0400$
Rodbard et al. [37] (DUAL IV)	Placebo	26 weeks	-14 mmol/mol (1.5%) (vs. -5 mmol [0.5%])	-1.02% (95% CI -1.18 to -0.87), $p < 0.001$	79.2 (28.8) $p < 0.001$	NA	-2.30 mmol/L (95% CI -2.72 to -1.89), $p < 0.001$
Harris et al. [38] (DUAL VI)	IDegLira, titrated either once weekly, based on the mean of 2 pre-breakfast plasma glucose (PG) readings, compared to twice weekly, based on the mean of 3 pre-breakfast PG readings	32 weeks	-22 mmol/mol (2.01%*) (vs. -22 mmol/mol [2.02%*])	0.12% (95% CI -0.04 to 0.28)	89.9*, 89.5**	85.7*, 83.5**	0.22 mmol/L (95% CI -0.11 to 0.55), $p = 0.194$
Rosenstock et al. [39] (Lixi Lan O)	IGlar, Lixi	30 weeks	-18 mmol/mol (1.63%) (vs. -14 mmol/mol [1.34%]) for IGLar, -9.5 mmol/mol [0.85%] for Lixi	with IGLar -0.3% (95% CI -0.4 to -0.2%), $p < 0.0001$ with Lixi -0.8% (95% CI -0.9 to -0.7%), $p < 0.0001$	74 (59.33) $p < 0.0001$	53.6 (44.4-30.5)	-0.2±0.1 (95% CI -0.4 to 0.04), p value 0.1 vs. IGLar -0.2±0.1 (95% CI -2.2 to -1.7), p value <0.0001 vs. Lixi
Rosenstock et al. [40] (proof of concept study)	IGlar	24 weeks	-20 mmol/mol (1.82%) (vs. 17.4 mmol/mol [1.64%])	-0.17% (95% CI -0.31 to -0.04), p value 0.01	84 (78)	68 (59)	0.16 (95% CI -0.14 to 0.47), p value = 0.2940

* Once weekly titration. ** Twice weekly titration.

Table 5. Safety, doses, and weight changes in trials of IDegLira and IGLarLixi when used as the first injectable

Reference	Comparator(s)	Duration of trial	Overall confirmed hypoglycaemia (vs. comparators)	Percentage of patients affected by GI side effects (vs. comparators)	Mean dose of GLP 1 analogue in co-formulation at the end of therapy	Weight change (in kg) at the end of therapy (vs. comparators)
Aroda et al. [32] (DUAL VIII)	IGlarU100	104 weeks	25.7% (31%)	14 (4)	1.296 mg	1.7 (3.4)
Gough et al. [33, 34] (DUAL I and DUAL I Extension)	IDeg, Lira	26 weeks' core phase and extension phase to 52 weeks	32% (39%, 7%) at 26 weeks 176.7 episodes/100 PYE (279.1/100 PYE, 19.1 episodes/100 PYE) at 52 weeks	21 (10.41) at 26 weeks	1.4±0.5 mg	−2.80 kg (vs. IDeg) +2.66 kg (vs. Lira)
Kaku et al. [35] (DUAL JAPAN)	IDeg, Lira	52 weeks	38.5% (54.6%, 2.2%)	18.6 (10.6, 31.1)	1 mg	−3.2 kg (vs. IDeg) +2.2 kg (vs. Lira)
Philis-Tsimikas et al. [36] (DUAL IX)	IGlarU100	26 weeks	12.9% (19.5%)	NA	1.3±0.48 mg	0 (2)
Rodbard et al. [37] (DUAL IV)	Placebo	26 weeks	41.7% (17.1%)	11.1 (10.9)	1 mg	0.5 (−1.0)
Harris et al. [38] (DUAL VI)	IDegLira, titrated either once weekly, based on the mean of 2 pre-breakfast plasma glucose (PG) readings, compared to twice weekly, based on the mean of 3 pre-breakfast PG readings	32 weeks	5.7%*, 16.2%*	NA	1.476 mg	−1*, −2**
Rosenstock et al. [39] (Lixi Lan O)	IGlar, Lixi	30 weeks	25.6% (23.6%, 6.4%)	21.7 (12.6, 36.90)	13.1	−0.3 (1.1 to −2.3)
Rosenstock et al. [40] (proof of concept study)	IGlar	24 weeks	21.7% (22.8%)	15.5 (9.3)	NA	0.39 (−1.16)

* Once weekly titration. ** Twice weekly titration.

The DUAL VI trial ($n = 420$, BMI: 32.4, duration: 7.3 years) compared the 2 different titration regimens of IDeg-Lira and showed that once weekly and twice weekly dose titration regimens were similar in safety and efficacy [38].

In trials where PPG was evaluated, IDegLira reduced the PPG significantly compared to the other arm [32, 33, 36, 38].

Evidence with IGLarLixi (Tables 4, 5)

IGlarLixi has been compared to IGLar and lixisenatide as the initial injectable in people with type 2 diabetes on metformin monotherapy or oral glucose-lowering agents. In a trial lasting 30 weeks, IGLarLixi was associated with a larger reduction in HbA1c and more people in the IGLar-Lixi arm (74%) reaching an HbA1c <53 mol/mol (7%) in comparison to IGLar (59%, p value <0.0001) and Lixi (33%, p value <0.0001). People on IGLarLixi had less risk of weight gain and better PPG in comparison to IGLar (−2.4 mmol/L ± 0.2) [39]. In a proof of concept study lasting 24 weeks in people on metformin, HbA1c reduced from 64 mmol/mol (8%) at baseline to 45 mmol/mol

(6.3%) in people on IGLarLixi vs. to 48 mmol/mol (6.5%) in people on IGLarU100 ($p = 0.01$). IGLarLixi improved 2-h post-meal glucose vs. IGLarU100 (−3.2 mmol/L, $p < 0.0001$) and body weight [40].

Clinical Considerations with the Use of Co-Formulations

Hypoglycaemia

The trials of co-formulations defined hypoglycaemia in various ways: confirmed hypoglycaemia (plasma glucose <3.1 or 3.8 mmol/L), severe hypoglycaemia (requiring assistance), and nocturnal hypoglycaemia (occurring between 00:01 and 05:59). The number of people reporting hypoglycaemia and number of hypoglycaemic episodes/patient years (100 patient years) were also reported in most studies. When the comparator was basal insulin analogue, there was no significant benefit of IDegAsp on the reduction of overall or confirmed hypoglycaemia. However, fewer episodes of nocturnal hypoglycaemia

were seen in people on IDegAsp in comparison to those on basal insulin [27–29]. However, in a trial comparing IDegAsp to BIAsp30, people randomised to the IDegAsp arm fared better in terms of overall confirmed hypoglycaemic episodes, nocturnal hypoglycaemic episodes, and number of people experiencing hypoglycaemia [30] (Table 3).

In trials comparing IDegLira to IGLarU100, people on IDegLira had a significantly lower risk of overall hypoglycaemia and nocturnal hypoglycaemia [32, 36]. In trials where IDegLira was compared to liraglutide, people on IDegLira experienced more episodes of hypoglycaemia than those on liraglutide [33, 35]. In a study on LixiLan O, the number of hypoglycaemic events was low and was similar in the IGLarLixi and IGLar groups [40] (Table 5). The lower HbA1c and higher overall hypoglycaemia rates in trials of IDegLira in comparison to IGLarLixi are related to lower FPG titration targets in the IDegLira studies, variable definitions of hypoglycaemia, and a higher FPG reduction of liraglutide.

Weight Gain

Obesity is one of the major risk factors for cardiovascular disease. People who gain weight during insulin therapy have an adverse cardiometabolic profile as evidenced by higher body fat, trunk fat, abnormal lipid profiles, elevated transaminases, and a worse cardiovascular profile [41, 42]. In most trials comparing IDegAsp to basal insulin or BIAsp30, weight gain was similar in people in both arms [28, 30]. In one trial, higher weight gain was noted with IDegAsp, associated with a higher dose of insulin and a higher risk of hypoglycaemia [27]. In trials comparing IDegLira or IGLarLixi with basal insulin, people on these drugs experienced less weight gain in comparison to those on basal insulin [32, 33, 35, 36, 39]. Liraglutide has been shown to attenuate insulin-induced weight gain [43]. In trials where a GLP-1RA was used as comparator, weight loss was more pronounced in GLP-1RA alone groups [33, 35, 40].

Drug Dosages

In most trials of IDegAsp in comparison with basal insulins or BIAsp30, the dose of insulin was similar. In one treat-to-target trial involving multi-ethnic populations, IDegAsp doses were higher than IGLarU100. This trial used IDegAsp before breakfast and had a higher risk of overall and confirmed hypoglycaemia and weight gain than people using IGLarU100 [27]. The doses of insulin (U/kg body weight) were lower in trials involving a Japanese population [28]. Although a possible effect of ethnic

variations on insulin doses cannot be excluded, one of the trials used a conservative target of FPG (4.4–7.16 mmol/L) for titrations. In a trial where some of the people used IGLarU300, the doses of IGLarU300 were 26% more than those of IDegAsp [29]. In trials where IDegLira and IGLarLixi were compared to basal insulin, the doses of insulin used were significantly lower in the co-formulation group. This effectively translated into lower weight gain and hypoglycaemia [32, 33, 35, 36]. Studies have shown that one of the determinants of weight gain was the insulin dose [44]. In studies where IDegLira or IGLarLixi was compared to GLP-1RA, the effective dose of liraglutide/lixisenatide was lesser in the former [33, 35, 39].

Cardiovascular Effects

Co-formulations contain components that have proven cardiovascular safety. The cardiovascular safety of glargine and degludec were demonstrated in the Outcome Reduction with Initial Glargine Intervention (ORIGIN) trial and in the Trial Comparing Cardiovascular Safety of Insulin Degludec versus Insulin Glargine in Patients with Type 2 Diabetes at High Risk of Cardiovascular Events (DEVOTE), respectively [45, 46]. In DEVOTE, 8% of all people were on GLP-1RA at baseline. In a subgroup analysis of DEVOTE, there was no difference in primary outcome by baseline cardiovascular status, insulin use, diabetes duration, or baseline HbA1c [46]. No comparison by baseline use of GLP-1RA was done. Although aspart has not been included in any cardiovascular outcome trial, the Nippon Ultra-Rapid Insulin and Diabetic Complication Evaluation (NICE) study showed a significant 43% decrease in the cumulative cardiovascular event rate for the insulin aspart group in comparison to the human regular insulin group [47].

The cardiovascular safety of lixisenatide and liraglutide were demonstrated in the Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) and the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trials, respectively which enrolled people with diabetes and a high cardiovascular risk [48, 49]. In a subgroup analysis of LEADER, there was no difference in the primary outcome for people stratified by baseline use of insulin [49]. The mean daily dose of liraglutide used in LEADER was 1.78 mg/day in comparison to a mean dose of 1.0–1.48 mg in phase 3 trials of IDegLira. In a post hoc analysis of the DEVOTE trial, the use of liraglutide was associated with a significantly lower risk of major adverse cardiovascular events and death in patients with type 2 diabetes and a high cardiovascular risk using basal insulin [50]. IDegLira had fa-

avourable effects on various cardiovascular risk factors in a post hoc analysis of various DUAL trials [51, 52]. In trials of co-formulations, the cardiovascular events were small in number and balanced between the groups. Although none of the co-formulations are included in a cardiovascular outcome trial, the cardiovascular safety of these combinations can be reassured due to the safety of these molecules in their individual trials.

Gastrointestinal Adverse Effects

One of the major reasons for drop out of people in trials using GLP-1RA is the risk of gastrointestinal adverse effects. In trials of IDegLira, 1.1 people per 100 patient years reported gastrointestinal adverse effects, and 0.5% dropped out due to these. In studies where liraglutide was the comparator, this was lower than in the IDegLira arm in the initial 10 weeks but stabilised later [53]. The smaller likelihood of gastrointestinal adverse effects in the co-formulations involving GLP-1RA is likely due to the slow titration of GLP-1RA and lower final dose. In DUAL I, the mean dose of liraglutide in the IDegLira arm was 1.4 mg and in the liraglutide arm it was 1.8 mg daily [33].

Although pancreatic enzymes like amylase and lipase were increased in people using liraglutide in LEADER (mean dose: 1.78 mg/day) and SCALE (mean dose: 3 mg/day), a meta-analysis involving GLP-1RA failed to show any increased risk of pancreatitis or pancreatic cancer [54–56]. In regulatory trials involving IDegLira, there was no increased risk of pancreatitis although an elevation of lipase and amylase was documented [53]. In trials involving IDegLira, the mean dose of liraglutide ranged from 1.0 to 1.48 mg. No imbalance of adverse effects between the groups related to the pancreas was seen in trials involving IDegLira or IGLarLixi. People with previous pancreatic diseases were not enrolled in trials involving co-formulations of GLP-1RA.

In the LEADER trial, acute gallbladder or biliary disease occurred more often with liraglutide, with similar trends for uncomplicated gallbladder stones, complicated gallbladder stones, cholecystitis, biliary obstruction, and the need for cholecystectomy [57]. The number of cases with gall bladder disease was also increased in people in the lixisenatide arm of ELIXA [48]. The mechanism for this effect is unclear but may relate to the saturation of bile during weight loss as well as the alterations in biliary motility [57]. Gall bladder-related events are few in people in trials of IDegLira and IGLarLixi and were balanced between the arms [26, 53]. Gastrointestinal adverse effects can limit the use of these co-formulations in people with these adverse effects.

Adherence and Injection Burden

Adherence to antidiabetic therapies is associated with a reduction in HbA1c, hypoglycaemia, hospitalisation, and acute complications [58]. In trials involving IDegAsp, the discontinuation rates were low and fairly matched in both arms [27, 28]. In trials where IDegLira was compared to basal insulin, the discontinuation rates were low and were similar in most trials [32, 33]. However, the discontinuation rates were higher with GLP-1RA (liraglutide or lixisenatide) when compared to co-formulations (IDegLira and IGLarLixi) apart from one trial which involved Japanese people [35]. The continuation rates for drugs like liraglutide in real world registries are much smaller than those in randomised trials [59, 60]. The possible reasons include adverse effects, inability to reach glycaemic or weight loss targets, and cost of therapy.

As first injectables, co-formulations offer the advantage of a smaller number of injections in comparison to GLP-1RA added to basal insulin, prandial insulin, and premixed insulin. In a multinational audit of GLP-1RA prescriptions, a lower injection frequency translated to a better adherence to medications [61]. Intensifying basal insulin is one of the areas in glycaemic management with significant clinical inertia. In people studied from the UK Clinical Practice Research Datalink database, the median time of intensification from basal insulin initiation was 4.3 years [62]. By substituting basal insulin with a co-formulation, this bridge of clinical inertia can be significantly reduced.

Dosing and Flexibility Limitations

The flexibility of co-formulations is limited by the fixed ratio of its components. In most studies of IDegAsp, the dose titrations were governed by FPG targets. A target FPG of 4.0–5.0 mmol/L or hypoglycaemia can limit the upward titration of IDegAsp. In studies where IDegAsp was used twice daily, the pre-breakfast dose of IDegAsp was titrated using the pre-dinner plasma glucose [30]. Unlike the protaminated aspart in BIAsp30, the IDeg component of IDegAsp lasts beyond 24 h making pre-dinner monitoring redundant for dose titrations of morning dose of IDegAsp [63]. Using the plasma PPG after the meal where IDegAsp is given or the pre-prandial plasma glucose before the subsequent meal is more appropriate. The controlled post-meal plasma glucose after the meal, where IDegAsp was given, or a target pre-meal plasma glucose before the next meal will limit the up-titration of the dose of a short-acting component (aspart). Most of the studies that used one daily IDegAsp used it before the largest meal

of the day, although one study used it before breakfast in all people. In this study, there was an increased risk of hypoglycaemia in the 4 h subsequent to the dose, proving the limitation of using FPG for titrating IDegAsp [27]. This remains one of the limitations of IDegAsp when people can have hypoglycaemia due to the short-acting component (aspart) of the co-formulation with the FPG still remaining high due to inadequacy of the long-acting component (degludec). The mean doses of IDegAsp required in treat-to-target trials of initiation range from 28 to 75 units.

Dose titration of co-formulations are limited by the maximum capacity of their disposable and reusable pens and the maximum permissible doses of their GLP-1RA components (Table 1): FPG remaining uncontrolled after these ceiling doses should be managed with additional basal insulin. There is a theoretical risk of uncontrolled post-prandial hyperglycaemia in the face of normal FPG in people using IDegLira or IGLarLixi. This may require the use of short-acting insulin analogues. Further, in these combinations, a significant percentage of people may not reach the maximal dose of GLP-1RA due to limitations imposed by dose titrations of basal insulin.

Cost Effectiveness

Cost is a major cause of drug non-adherence [64]. Drugs with benefits like lesser hypoglycaemia, less weight gain, and cardiovascular protection may reduce the overall risk of hospitalisation and cardiovascular events resulting in cost savings for the health care system. A short-term cost-effectiveness model showed that IDegAsp is a cost-effective treatment compared with BIAsp30 for people with type 2 diabetes mellitus. This result was driven by significant reductions in severe hypoglycaemia and lower insulin doses observed with IDegAsp versus BIAsp30 [65]. The cost-effectiveness of IDegLira (against basal bolus regimen, the addition of liraglutide, and up-titration of basal insulin) and IGLarLixi (against premixed insulin) was also shown in populations uncontrolled on basal insulin [66–68]. In a study on an Italian population, IDegLira was found to be cost-effective in comparison to IGLarLixi due to a delay in diabetes complications despite the high acquisition costs of IDegLira [69]. The cost-effectiveness of these drugs in injection-naïve people is not available. However, the generalisability of health-economic analyses in one population to various populations and payer models are questionable [70].

Renal Effects

Changes in renal function may affect the clearance of drugs leading to accumulation and adverse effects. Changes in eGFR did not affect the pharmacokinetic and pharmacodynamic characteristics of IDegAsp [71]. The eGFR cut-off of liraglutide and lixisenatide applies to their respective co-formulations. No overall differences in safety or efficacy were seen in these people with reduced renal function in the LEADER trial compared to people with normal renal function. Data for liraglutide is limited in people with end-stage renal disease [71].

Progression to macro-albuminuria was reduced in people enrolled in the GLP-1RA arm of the LEADER and ELIXA trials [48, 72]. Since a significant number of subjects in these trials were on maximum approved doses of the drug, the effect of lesser doses of GLP-1RA used in patients on IDegLira and IGLarLixi cannot be equated.

Conclusion

Co-formulations involving insulin and insulin-GLP-1RA are valuable additions to the current armamentarium of glucose-lowering agents. IDegAsp has a place as the first injectable in all people requiring insulin for initiation, intensification from basal insulin, or as a reasonable substitute to basal-bolus insulin in people with type 2 diabetes. Since IDegAsp is more expensive than IGLarU100, physicians should weigh the relative benefits of IDegAsp in comparison to IGLarU100 and BIAsp30 while choosing this drug. Insulin-GLP-1RA fixed drug combinations are important drugs which help more people achieve target HbA1c without weight gain and a low risk of hypoglycaemia. They can be used as the first injectable in all people with type 2 diabetes or as intensification for people initiated on GLP-1RA or basal insulin. These agents help simplify injectables so that better and durable glycaemic control can be achieved safely with minimal injection burden and improved adherence. The cost of these agents in comparison to basal insulin may limit their widespread use.

Conflict of Interest Statement

M.J. served on the speaker bureau for Novo Nordisk, Eli Lilly, Sanofi India, Astra Zeneca, Boehringer Ingelheim, and MSD. D.G. served on the speaker bureau for Novo Nordisk, Astra Zeneca, and MSD. T.O. served on the speaker bureau for Novo Nordisk, Eli Lilly, Sanofi India, Astra Zeneca, MSD, and Boehringer Ingelheim.

Funding Sources

There are no funding sources to be reported.

Author Contributions

M.J.: conception of the work, searching for articles, preliminary draft, analysis, interpretation, and drafting of the article. D.G.: writing the preliminary draft, data analysis, interpretation, and final drafting of the article. T.O.: writing the preliminary draft, data analysis, interpretation, and final drafting of the article.

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