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Review Article

Efficacy and Safety of Once-Weekly Insulin ICODEC

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Abstract

Insulin icodec is a long-acting once-weekly basal insulin analog that is currently under investigations. Efficacy and safety of insulin icodec were assessed in a series of 6 phase 3 clinical trials known as the ONWARDS Program; 5 trials in type 2 diabetes, and 1 trial in type 1 diabetes. In 4 of the 6 ONWARDS trials, reductions in glycated hemoglobin (HbA1c) levels were slightly greater with insulin icodec compared with once-daily insulin glargine or degludec with a mean difference of 0.19-0.38 percentage points. In the other 2 trials, insulin icodec was not inferior to insulin degludec in reducing HbA1c levels. Data analysis of continuous glucose monitoring (CGM) showed greater or similar time spent in range (TIR) with insulin icodec versus insulin glargine or degludec. In type 2 diabetes, patient satisfaction and compliance were superior with insulin icodec compared with insulin glargine or degludec. However, in type 1 diabetes, satisfaction score was lower with insulin icodec than with degludec. Incidence of level 1 hypoglycemia [blood glucose (BG) levels 54-69 mg/dl] was higher with insulin icodec compared with insulin glargine or degludec with estimated rate ratio (ERR) ranging from 1.25 to 1.88. In 3 of the 6 ONWARDS trials, incidence of combined level 2 hypoglycemia (clinically significant hypoglycemia with BG < 54 mg/dl) and level 3 hypoglycemia (severe hypoglycemia with cognitive impairment requiring external assistance) was significantly higher (by 71-89%) with insulin icodec vs insulin glargine or degludec. In patients with type 1 diabetes, incidence of hypoglycemia (levels 1, 2, 3, and nocturnal) was substantially higher with insulin icodec versus insulin. In general, no significant differences in weight were recorded between subjects receiving insulin icodec and those receiving insulin degludec. Allergic reactions were not increased with use of insulin icodec. In conclusion, insulin icodec may be a convenient basal insulin that is administered once weekly. It is similar or slightly higher in efficacy compared with insulin glargine or degludec. Yet, it is associated with increased incidence of hypoglycemia, particularly in type 1 diabetes.

Keywords: insulin; icodec; glargine; degludec; hypoglycemia; diabetes; glycated hemoglobin

Introduction

Insulin icodec has a half-life of 196 hours (8.1 days) allowing its administration once weekly [1,2]. After reaching a steady state 3-4 weeks following its initiation, insulin icodec exhibits an evenly distributed glucose-lowering activity throughout the 7 days of the week [1,2]. The long duration of action of insulin icodec is attributed to 2 main factors. First, binding to albumin through addition of a C20 fatty acid-containing side chain to form an albumin-binding depot from which icodec is slowly released in the circulation. Second, 3 amino acid substitutions that decreases affinity of icodec to insulin receptors leading to its decreased rate of clearance. Normally, insulin clearance occurs primarily through internalization following binding of insulin to its receptors at cell surface. Thus, reduced binding of insulin icodec to insulin receptors will lead to its reduced clearance and further prolongation of its action [1,2]. Importantly, the reduced affinity of icodec to insulin receptor does not compromise its potency but slows its action [1,2]. The concentration of formulation of insulin icodec is 7 times higher than that of the standard insulin U100 formulation. Consequently, the volume of insulin icodec administered once weekly is similar to other basal insulin dosing volumes given once daily [1,2]. The ONWARDS Program consists of 6 phase 3 clinical trials to evaluate insulin icodec versus insulin degludec and gargine [1]. In a previous article, the author reviewed the pharmacologic properties of insulin icodec as well as its efficacy and safety in 5 of the 6 trials of the ONWARDS Program including patients with type 2 diabetes [1]. More recently, insulin icodec was evaluated in subjects with type 1 diabetes in the 6th and last trial of the ONWARDS Program [3-8]. The main objective of this article is to review the efficacy and safety of insulin icodec in patients with type 1 and type 2 diabetes.

Summary of the ONWARDS studies

Table 1 summarizes the main features and results of the 6 ONWARDS trials [3-8]. The 6 trials were randomized, multinational and treat-to target [3-8]. The primary endpoint was the change in HbA1c levels from baseline to the end of the study. The target of fasting self-measured BG was 80-130 mg/dl. Thus, doses of insulin icodec, glargine and degludec were modified

weekly based on 3 pre-breakfast BG readings to attain this glycemic target [1]. The process of titration was mentioned in detail in a previous article of the author [1]. Briefly, if the mean of the self-measured 3 BG values are > 130 mg/dl, insulin icodec dose is increased by 20 units weekly and doses of glargine or degludec are increased by 3 units daily. On the other hand, if the lowest of the 3 fasting BG values is < 80 mg/dl, doses of insulin icodec are decreased by 20 units/week and those of glargine or degludec by 3 units per day [3]. In terms of study duration, ONWARDS 1 trial is the longest-term trial of the ONWARDS Program lasting 78 weeks followed by 5-week follow-up period for safety monitoring [3]. The latter study compared insulin icodec with insulin glargine in insulin-naïve patients with type 2 diabetes [3]. ONWARDS 2 trials compared insulin icodec and degludec in subjects with type 2 diabetes already treated with a basal insulin [4]. ONWARDS 3 trials evaluated insulin icodec versus insulin degludec in insulin-naïve patients [5]. ONWARDS 4 trials compared insulin icodec with insulin glargine in subjects with type 2 diabetes already on basal-bolus insulin regimen [6]. The largest study was the ONWARDS 5 trial (n=1,805), compared insulin icodec titrated with a dosing guide app with degludec, glargine U100, or glargine U300 titrated per standard practice in insulin naïve patients [7]. Finally, the ONWARDS 6 trial, dedicated exclusively for patients with type 1 diabetes, compared insulin icodec with degludec, both in combination with meal-time insulin as part (≥2 injections/day) [8].

	ONWARDS 1 [3]	**ONWARDS 2 [4]**	**ONWARDS 3 [5]**	**ONWARDS 4 [6]**	**ONWARDS 5 [7]**	**ONWARDS 6 [8]**
Main purpose	Compare insulin icodec (n=492) with once-daily glargine (n=492) in insulin-naïve patients with type 2 diabetes	Compare icodec (n=262) vs once-daily degludec (n=294) in basal-insulin treated patients with type 2 diabetes	Compare icodec (n=293) vs once-daily degludec (n=294) in insulin naïve-patients with type 2 diabetes	Compare icodec (n=291) vs once-daily glargine (n=291) in patients with type 2 diabetes treated with basal-bolus regimen	Compare icodec (n=542) titrated with app vs once daily OD glargine or degludec (n=538) titrated per standard practice in insulin-naïve patients	Compare icodec (n=290) vs once-daily degludec (n=292) both in combination of with insulin aspart (≥2 injections/day) in patients with type 1 diabetes
Design	Randomized, open-label, treat-to-target multi-national	Randomized, open-label, treat-to-target, multi-national	Randomized, double-masked, treat-to-target, multinational	Randomized, open-label, treat-to-target, multi-national	Randomized, open-label, parallel-group, multinational	Randomized, open-label, treat-to-target, multi-national
Duration	Main phase: 52 weeks. Extension phase 26 week. Safety monitoring until 83 weeks	26 weeks.	26 weeks. Safety monitoring up to 31 weeks.	26 weeks	52 weeks	Main phase: 26 weeks. Safety extension phase 26 weeks
Patients	N=984, 60% men in icodec group higher than 53% in the glargine group, 59-year-old, type 2 diabetes of 11 year-duration	N=526, 57% men, 62-year-old, type 2 diabetes of 16 year-duration	N=598, 63% men, 58-year-old, type 2 diabetes of 10 year-duration	N= 582, 52% men, 60-year-old, type 2 diabetes of 17 year-duration	N= 1,085, 57% men, 59-year-old, type 2 diabetes of 12 year-duration	N=582, 58% men, 44-year-old, type 1 diabetes of 19.5 year-duration
Baseline HbA1c	8.5%	8.1%	8.5%	8.3%	8.9%	7.6%
Total insulin doses per week	214 units (30.5 units/d) with icodec vs 222 units (31.7 units/d) with glargine (no significant difference)	268 units (38.2 units/d) with icodec vs 244 units (34.8 units/d) with degludec, ETR 1.10 (95% CI, 1.01 to 1.20) P=0.03	204 units (29.1 units/d) with icodec vs 187 units (26.7 units/d) with degludec (no significant difference)	514 units (73 units/d) with icodec vs 559 units (80 units/d) with glargine. ETR 0.92 (95% CI, 0.85 to 0.99, P=0.034).	227 units (32 units/d) with icodec vs 185 units (26.5 units/d) with OD insulin analogues. ETD 1.22 (95% CI, 1.12 to 1.33)	311 units (44 units/d) with icodec vs 323 units (46 units/d) with degludec. ETD 0.94 (95% CI, 0.88 to 1.01)

Effects on HbA1c	Superior HbA1c reduction with icodec vs glargine at week 52, ETD -0.19%, 95% CI, -0.36 to -0.03, P=0.02	Superior HbA1c reduction with icodec vs degludec, ETD -0.22% (95% CI, -0.37 to -0.08), P=0.003	Superior HbA1c reduction with icodec vs degludec, ETD -0.2% (95% CI, -0.1 to -0.3), P=0.002	Icodec was non-inferior to glargine. ETD 0.02% (95% CI, -0.11 to +0.15), P<0.0001. Icodec was not superior to degludec.	Superior HbA1c reduction with icodec vs OD insulins, ETD -0.38% (95% CI, -0.66 to -0.09), P=0.009	Icodec was non-inferior to degludec. ETD 0.05% (95% CI, -0.13 to 0.23), P=0.0065.
Percentage of time of glucose in range (70-180 mg/dl) in CGM	71.9% with icodec vs 66.9% with glargine, ETD 4.27% (95% CI, 1.92 to 6.62), p<0.001	63.1% with icodec vs 59.5% with degludec, ETR 1.10 (95% CI, -0.84 to +5.65) p=0.15	Not evalusated	66.9% with icodec vs 66.4% with glargine	Not evaluated	59.1% with icodec vs 60.8% with degludec. ETD -2% (95% CI, -4.38 to 0.38), P=0.099.
Hypoglycemia level 1 (BG 54-69 mg/dl)	At week 83: 2308 events with icodec (3.02/PYE) vs 1067 events with glargine (1.39/PYE), statistical significance not mentioned)	1209 episodes with icodec vs 589 episodes with degludec. ERR 1.88 (95% CI, 1.4 to 263, p=0.0002)	28% (359 events in 84 patients) with icodec vs 20.1% (159 events in 59 patients) with degludec. At week 31: rates are 2.3/PYE with icodec vs 1.08 with degludec	84% with icodec vs 86% with glargine. Yet, rate of hypoglycemic episodes was higher with icodec than glargine, ERR 1.25 (95% CI, 1.03 to 1.52), P 0.025	37% with icodec vs 28% with OD insulin	At week 57: 20406 events with icodec vs 14819 events with degludec (statistical significance not mentioned)
Incidence of combined hypoglycemia level 2 (BG <54 mg/dl) and level 3 (cognitive impairment)	At week 83: 226 events in 12.4% of patients receiving icodec vs 114 events in 13.4% receiving glargine. Event rate 0.30 with icodec vs 0.15/PYE with glargine. ERR 1.71 (95% CI, 1.06 to 2.76)	14% with icodec vs 7% with degludec, EOR 1.89 (95% CI, 1.05 to 3.41, p=0.034).	At 26 weeks: 8.2% with icodec vs 4.4% with degludec. ERR, 3.12 (95% CI, 1.30 to 7.51, P=0.01). At 31 weeks difference was not significant.	52% with icodec vs 56% with glargine. 7 events of level 3 hypoglycemia with icodec vs 3 events with glargine. ERR 0.99 (95% CI, 0.73 to 1.33). Difference not significant.	12% with icodec vs 8% with OD insulins. 0.19 events/ PYE with icodec vs 0.14 events/PYE with OD insulins, ERR 1.17 (95% CI, 0.73 to 1.86). Difference not significant.	At week 57: 5103 events in 91% of patients with icodec vs 2836 events in 86% of patients with degludec. ERR 1.80 (95% CI, 1.48 to 2.18), P<0.0001
Weight changes	+2.2 kg with icodec at week 52 vs +1.83 kg with glargine (no significant difference)	+1.4 kg with icodec vs -0.30 kg with degludec, ETD, 1.7 kg (95% CI, 0.76 to 2.63, P=0.0004)	+2.8 kg with icodec vs +2.3 kg with degludec, ETD 0.46 kg (no significant difference)	+ 2.7 kg with icodec vs +2.2 kg with glargine (no significant difference)	+2.3 kg with icodec vs +1.4 with OD insulin, ETD 0.83 kg (no significant difference)	At week 52: + 1.25 kg vs +1.67 with degludec, ETD -0.42 (95% CI, -1.20 to 0.37), P=0.30

Patient satisfaction score	Not evaluated	DTSQ score increased +4.22 with icodec vs +2.96 with degludec, ETD 1.25 (95% CI, 0.41 to 2.100, P=0.0035)	Not evaluated	Not evaluated	DTSQ score increased +4.68 with insulin icodec vs +3.90 with OD insulins, ETD 0.78 (95% CI, 0.10 to 1.47)	DTSQ score increased 1.41 with icodec vs 3.00 with degludec, ETD -1.59 (95% CI -2.51 to -0.67), P=0.0007
Compliance with insulin administration	Not evaluated	Not evaluated	Not evaluated	Not evaluated	TRIM-D score was 90.4 with icodec vs 87.4 for OD insulins, ETD 3.0 (95% CI, 1.28 to 4.81)	Not evaluated

Effects of insulin icodec on glycemic control

In ONWARDS 1, 2, 3, and 5 insulin icodec was shown to be slightly but statistically superior to both glargine glargine and degludec in reducing HbA1c values, with estimated treatment difference (ETD) of approximately 0.19 to 0.38 percentage points (table 1) [3-5,7]. In ONWARDS 4 and 6, insulin icodec was not inferior than degludec with respect to HbA1c reduction (table 1) [6,8]. In the 5 studies including patients with type 2 diabetes, reductions in HbA1c levels were evident 10-13 weeks after starting insulin in all treatment groups, then attained a trough at week 26 followed by a plateau [3-7]. Meanwhile, in type 1 diabetes, HbA1c levels reached a trough earlier after 10 weeks followed by gradual rebound [8]. Information from CGM was used for a duration of 4 weeks in ONWARDS 1, 2 and 6 trials to identify the diurnal glycemic trajectory [3,4,8]. In general, no significant differences in time spent in range (70-180 /dl) was recorded between icodec groups and glargine or degludec [3,4,8]. Meanwhile, in ONWARDS 1 trial, the percentage of time spent with BG levels above the range (ie. > 180 mg/dl) was approximately 1 hour less with insulin icodec than with insulin glargine [3]. While insulin efficacy depends largely on its doses, there was no consistent trend with respect to differences in insulin doses between insulin icodec and other basal insulins (table 1).

Patient satisfaction with insulin icodec

Patient satisfaction with insulin icodec versus degludec was assessed in ONWARDS 2, 5,6 and 8 studies using the validated "Diabetes Treatment Satisfaction Questionnaire" (DTSQ) with higher score indicating greater satisfaction [4,7,8]. In ONWARDS 2, at week 26, the DTSQ score was slightly but significantly higher in patients randomized to insulin icodec than insulin degludec 4.22 and 2.96, respectively; ETD 1.25 (95% CI, 0.41 to 2.10, P=0.003) (table 1) [4]. In ONWARDS 5, the corresponding ETD was smaller, but still statistically significant; ETR 0.78 (95% CI, 0.10 to 1.47) (table 1) [7]. On the contrary, in type 1 diabetes, total satisfaction score was significantly lower with insulin icodec compared with insulin degludec; ETD at 52 weeks -1.59 (95% CI, -2.5 to -0.67) (table 1) [8]. Compliance with insulin administration, evaluated by the Treatment Related Impact Measure for Diabetes [TRIMP-D] compliance domain score, was conducted in only 1 of the 6 studies, the ONWARDS 5 trial. The latter trial showed that compliance score was significantly higher with insulin icodec vs once-daily insulin analogues, ETD 3.04 (95% CI, 1.28 to 4.81) [7].

Safety of insulin icodec

1. Hypoglycemia

A. Type 2 diabetes

The main concern related to safety of insulin icodec is hypoglycemia. This concern is justified given the prolonged duration of action of insulin icodec that could potentially lead to intractable hypoglycemia and recurrence of hypoglycemic episodes. Results of one short-term (7 weeks) study including 43 patients with type 2 diabetes did not show significant differences between insulin icodec and insulin glargine in terms of symptoms and hormonal response to induced hypoglycemia [9]. Despite these preliminary reassuring findings, results derived from the ONWARDS Program clearly showed increased risk of hypoglycemia with insulin icodec versus either insulin glargine or degludec. Thus, in ONWARDS 1 trial, at week 83, the rates of combined clinically significant (level 2) or severe hypoglycemia (level 3) were significantly greater with insulin icodec compared with glargine, 0.30 and 0.15 hypoglycemic events per person-year of exposure (PYE), respectively, ERR 1.71 (95% CI, 1.06 to 2.76) [3]. Moreover, the gap of hypoglycemia between insulin icodec and glargine widened with the duration of insulin use [3]. In ONWARDS 3 trial, combined level 2 and 3 hypoglycemia from baseline to week 26 was approximately 3-fold higher with insulin icodec compared with insulin degludec; ERR 3.12 (95% 1.30 to 7.51, P=0.01) [5]. In addition, in ONWARDS 2, 3 and 5 trials, there was increased risk of hypoglycemia (level 1, and combined level 2 and 3) with insulin icodec compared with insulin degludec or glargine (table 1) [4,5,7]. However, frequency of level 3 hypoglycemia and nocturnal hypoglycemia, when reported separately, was not increased with insulin icodec in the ONWARDS 1,3-5 trials [3-5,7].

B. Type 1 diabetes

In type 1 diabetes, results of ONWARDS 6 trials showed that rates of level 2 and 3 hypoglycemia with insulin icodec were approximately double the rates with degludec at 57 weeks, 17.0 versus 9.2 events per PYE [8]. Furthermore, percentage of time below 54 mg/dl measured by CGM was significantly higher with icodec than degludec, 1.0% and 0.7%, respectively; ETR 1.46 (95% CI, 1.16 to 1.85, P=0.0014) [8]. It should be emphasized that, irrespective of insulin regimen, frequency of hypoglycemia in general is much higher in patients with type 1 diabetes compared with those with type 2 diabetes. Therefore, when expressed in absolute values, the increase in number of hypoglycemic episodes related to insulin icodec was substantially greater in patients with type 1 diabetes compared with those with type 2 diabetes (table 1) [4-8].

2. Weight gain

Overall, no significant differences in weight gain were observed between patients treated with insulin icodec versus degludec or glargine except in ONWARDS 2 trials where patients randomized to insulin icodec had a mean weight gain of 1.4 kg compared to 0.3 kg weight loss in subjects receiving insulin degludec, ETD 1.7 kg (95% CI, 0.76 to 2.63, P=0.0004) (table 1) [4].

3. Allergic reactions

Frequency of allergic events and injection site skin reactions were not increased with the use of insulin icodec compared with insulin degludec or glargine [3-8].

4. Medication errors

Medication errors were defined as misuse or abuse of insulin that had the potential to harm the participant (e.g., overdosing insulin to maximize its effects or with the intention to cause harm) [7]. In general, no increase in medication errors was recorded with insulin icodec in patients with type 2 diabetes. Meanwhile, in patients with type 1 diabetes, 18 events of medication errors were reported in 6% of patients randomized to icodec compared with 7 such events in 2% of patients randomized to insulin degludec [8]. The causes of the latter finding were unclear but could have contributed to the increase rates of hypoglycemia in patients with type 1 diabetes who received insulin icodec in the ONWARDS 6 trial [8].

Advantages of insulin icodec

The main advantage of insulin icodec resides in its once-weekly administration. Moreover, there is some flexibility in timing of injection such that the day of administration may be changed by up to 3 days ensuring a minimum of 4 days between injections [6,7]. Additionally, a single dose-study showed that pharmacokinetics and pharmacodynamics of insulin icodec did not change significantly whether injected in the thigh, abdomen or upper arm [10]. It was not surprising therefore that in patients with type 2 diabetes satisfaction was higher with insulin icodec compared to one-daily insulin analogues. However, in type 1 diabetes, for unclear reasons, satisfaction with insulin icodec was lower than other basal insulin analogues [8]. As far as efficacy is concerned, data suggest that insulin icodec is at least as effective as once-daily insulin glargine and degludec. It is reassuring that current information suggests that insulin icodec is no more immunogenic than other basal insulins. This was reflected by the low number of allergic and injection site reactions that were generally similar to insulin glargine and degludec [3-7].

Limitations of insulin icodec

Despite the above advantages, insulin icodec suffers from the following limitations. First, the increased risk of hypoglycemia. Indeed, in patients with type 1 diabetes, the absolute difference in hypoglycemic events between insulin icodec and degludec was unacceptably high (table 1) [8]. Hence, it is unsafe at present to recommend insulin icodec for patients with type 1 diabetes. Second, insulin icodec was not studied in patients with end-stage kidney disease and those with baseline HbA1c levels > 11.0% in type 2 diabetes and HbA1c ≥ 10% in type 1 diabetes because these patients were excluded from the ONWARDS program [3-8]. Third, insulin icodec may not be convenient for use in the hospital setting where rapid variations in BG levels are expected. For instance, patients already on insulin icodec before hospital admission should be monitored closely for hypoglycemia for 7 days from the day of last icodec injection. Fourth, all available trials of insulin icodec are sponsored by the manufacturer and all ONWARDS trials, except ONWARDS 3, are open label (table 1) [3-8]. Therefore, these investigations might be virtually prone for several bias in favor of insulin icodec. Panel 1 depicts advantages and limitations of insulin icodec.

Conclusions and current directions

Insulin icodec is a new basal insulin formulation that can be given once-weekly. Whereas data derived from the ONWARDS Program suggests that insulin icodec may have similar or slightly superior efficacy than once-daily insulin glargine or degludec, its use may be associated with increased risk of hypoglycemia, particularly in patients with type 1 diabetes. The increased propensity for hypoglycemia with the use of insulin icodec may be attributed to its long duration and possibly inappropriate dose titration. Indeed, the up-titration schedule of icodec doses by 20 units per week, as suggested by the investigation conducted by Lingvay et al [11] and adopted in the ONWARDS Program, may be too aggressive [3-8]. Thus, less aggressive titration of insulin icodec, e.g., an increase of its dose by 10 units per week instead of 20 units, might result in less frequency of hypoglycemia. Several clinical trials are underway to assess the combination of once-weekly icodec with the once weekly glucagon-like peptide-1 receptor agonist (GLP-1 RA) semaglutide in one single formulation [12-14]. The latter combination may be an attractive therapeutic strategy that potentially lowers icodec doses and therefore incidence of hypoglycemia. Moreover, the weight reduction effect of the GLP-1 RA may help lessening or even reversing the weight gain induced by insulin icodec. Importantly, large randomized trials with adequate power are required to examine the long-term effects of insulin icodec on cardiovascular events and mortality.

Conflict of interest

The author does not have a conflict of interest to declare.

Panel 1: Advantages and limitations of insulin icodec

Advantages

1. Once-weekly dosing.
2. Higher patient satisfaction when compared with insulin degludec in patients with type 2 diabetes.
3. Increased compliance when compared with once-daily insulin analogues (degludec, glargine U100 and glargine U300) in patients with type 2 diabetes.
4. May be injected in abdomen, thigh or upper arm.
5. No increase in allergic reactions compared with insulin glargine or degludec.
6. Administration with once-weekly glucagon-like 1 receptor agonists in one formulation may be potentially effective and convenient.

Limitations

1. Increased risk of hypoglycemia compared with insulin glargine and degludec, particularly in patients with type 1 diabetes.
2. Lower patient satisfaction when compared with insulin degludec in patients with type 1 diabetes.
3. Unknown long-term effects (safety was studied up to 83 weeks).
4. Propensity for hypoglycemia in cases of hospital admissions and intermittent sickness
5. Limited flexibility in dose-adjustment during days with of exercise or variable lifestyle.
6. Not studied in patients with glycated hemoglobin levels > 11.0% in type 2 diabetes and ≥10.0% in type 1 diabetes.
7. Not studied in patients with end-stage kidney disease.
8. Most clinical trials were open-label prone for bias.

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