Insulin degludec U100 is associated with lower risk for severe and symptomatic hypoglycemia as compared with insulin glargine U100 in subjects with type 1 diabetes

Anastasios Tentolouris, Ioanna Eleftheriadou, Nikolaos Tentolouris

Diabetes Center, First Department of Propaedeutic Internal Medicine, Medical School, National and Kapodistrian University of Athens, Laiko General Hospital, Athens, Greece

Correspondence to: Nikolaos Tentolouris. First Department of Propaedeutic Internal Medicine, Medical School, National and Kapodistrian University of Athens, Laiko General Hospital, 17 Agiou Thoma St, Athens 11527, Greece. Email: ntentol@med.uoa.gr.

Provenance: This is a Guest Editorial commissioned by Section Editor Kaiping Zhang, PhD (AME College, AME Group, Hangzhou, China).

Comment on: Lane W, Bailey TS, Gerety G, *et al.* Effect of Insulin Degludec *vs* Insulin Glargine U100 on Hypoglycemia in Patients With Type 1 Diabetes: The SWITCH 1 Randomized Clinical Trial. JAMA 2017;318:33-44.

Submitted Dec 18, 2017. Accepted for publication Dec 26, 2017.

doi: 10.21037/atm.2017.12.28

View this article at: http://dx.doi.org/10.21037/atm.2017.12.28

Hypoglycemia is defined non-numerically by the American Diabetes Association as "all episodes of an abnormally low plasma glucose concentration that expose the individual to potential harm" (1). The threshold for clinically significant hypoglycemia is 54 mg/dL (3.0 mmol/L), while severe hypoglycemia is defined as an episode with severe cognitive impairment that requires assistance for recovery (1).

Hypoglycemia remains the main barrier of intensifying insulin therapy and optimizing glycemic control in patients with type 1 diabetes mellitus (T1DM) (2). The Diabetes Control and Complications Trial (DCCT) showed that intensive treatment of patients with T1DM increases significantly the rate of severe hypoglycemia (3). Hypoglycemia leads to poor treatment adherence, weight gain due to increased food intake for avoiding or recovering from hypoglycemia, as well as to poor quality of life; in addition, hypoglycemia increases cardiovascular, psychological and all cause morbidity and mortality in patients with diabetes (2,4). Moreover, nocturnal hypoglycemia has been associated with poor quality of sleep and decreased productivity throughout the day (5,6).

Insulin degludec U100 (IDeg U100) is a long-acting basal insulin analogue with a half-life >25 h and a duration of action that exceeds 42 h (7). IDeg U100 compared to insulin glargine U100 (IGlar U100) has lower pharmacodynamic variability under steady-state conditions as it has been shown with euglycemic clamp techniques and therefore, a more predictable glucose-lowering effect (8). Furthermore, the stable pharmacodynamic profile of IDeg U100 applies to different populations including children, adults, older people, patients from different race and ethnic backgrounds, as well as in those with renal or hepatic disease (7). Lately, IDeg U100 was proven to be non-inferior in comparison with IGlar U100 regarding cardiovascular safety (9).

A Randomised, Double Blind, Cross-over Trial Comparing the Safety and Efficacy of Insulin Degludec and Insulin Glargine, Both With Insulin Aspart as Mealtime Insulin in Subjects With Type 1 Diabetes (SWITCH 1) was the first study designed to examine the impact of IDeg U100 on hypoglycemia as a primary outcome (10). In this study 501 individuals with T1DM were recruited. Inclusion criteria required that participants were ≥18 years old treated with basal-bolus regimen or continuous subcutaneous insulin infusion using insulin pump for at least 26 weeks, had glycosylated hemoglobin (HbA1c) ≤10%, body mass index ≤45 kg/m^2; and at least one of the following risk factors for hypoglycemia: (I) ≥1 severe hypoglycemic episode within the last year; (II) moderate chronic renal failure (estimated glomerular filtration rate 30–59 mL/min/1.73 m^2); (III) history of hypoglycemia unawareness; (IV) diabetes duration ≥15 years; and (V) an episode of hypoglycemia (symptoms and/or blood glucose level of ≤70 mg/dL) within the last 12 weeks before recruitment.

This was a phase 3 randomized, double-blind, 2-period

crossover, multicenter, treat-to target study. The trial spanned 65 weeks, consisting of treatment with once-daily IDeg U100 or IGlar U100, both with preprandial insulin aspart 2–4 times daily for two consecutive 32-week periods and 1 week of follow-up. Each 32-week treatment period consisted of a 16-week titration period and a 16-week maintenance period. In the first 16 weeks, the optimal titration of the basal insulin dose (titration period) was performed once weekly according to the trial algorithm and aiming for a pre-defined fasting blood glucose (FBG) target of 71–90 mg/dL. The following 16 weeks were the maintenance period. Titration of bolus insulin was either performed twice weekly based on the previous 3 or 4 days' readings according to the study algorithm or several times daily based on the insulin-to-carbohydrate ratio and insulin sensitivity factor, to achieve a preprandial blood glucose target of 71–108 mg/dL. Non-inferiority for the primary outcome was achieved if the upper limit of the 95% confidence interval (CI) for the estimated odds ratio (OR) was ≤1.10, while superiority was achieved when the upper bound of the 2-sided 95% CI was <1.00.

The primary endpoint of the study was the rate of overall severe or blood glucose-confirmed (<56 mg/dL) symptomatic hypoglycemic episodes during the maintenance period of the study. Secondary end points were the rate of nocturnal (severe or blood glucose confirmed episodes between 12:01 am and 5:59 am, both inclusive) symptomatic hypoglycemic episodes, and the proportion of patients experiencing severe hypoglycemia, both occurring during the maintenance period. Other hypoglycemic end points included rates of severe hypoglycemia; overall symptomatic and nocturnal symptomatic hypoglycemia in the full treatment period; rate of severe hypoglycemia in the maintenance period; and the proportion of patients with severe hypoglycemia, overall symptomatic, and nocturnal symptomatic hypoglycemia during the maintenance period and the full treatment period. Other efficacy secondary end points were adverse events and glycemic control estimated by HbA1c and FBG.

Regarding the primary objective, IDeg U100 achieved superiority, since the rates of the overall severe or blood glucose-confirmed symptomatic hypoglycemia were significantly lower with IDeg U100 as compared to IGlar U100 (OR: 0.89, 95% CI: 0.85–0.94, P<0.001). With regards to the secondary end points, nocturnal severe or symptomatic blood glucose-confirmed hypoglycemia episodes were significantly lower in the IDeg U100 group in comparison with the IGlar U100 group (OR: 0.64, 95% CI: 0.56–0.73, P<0.001). Additionally, the proportion of patients that experienced severe hypoglycemia during the maintenance period and the overall symptomatic hypoglycemia episodes in the full treatment period were lower in the group treated with IDeg U100 in comparison with those treated with IGlar U100. Glycemic control, estimated with HbA1c determination, did not differ significantly between the two groups. However, in the post hoc analysis, FBG was significantly lower in the IDeg U100 group as compared to the IGlar U100 after 32 weeks of treatment and the estimated treatment difference was –17.0 mg/dL (95% CI: –25.5 to –8.41 mg/dL, P<0.001). Moreover, there was no difference between the two groups in terms of weight change in the first treatment period (2.6 *vs.* 2.7 kg; difference, –0.25 kg; 95% CI: –0.99 to 0.49 kg; P=0.51) and in the second treatment period (0.7 *vs.* 0.0 kg; difference, 0.75 kg; 95% CI: –0.04 to 1.55 kg; P=0.06).

The SWITCH 1 trial was the first study designed to evaluate the impact of IDeg U100 *vs.* IGlar U100 on hypoglycemia in patients with T1DM at increased hypoglycemia risk as the primary objective (10). Hence, it is difficult to compare the results of the SWITCH 1 trial with the findings of other studies that examined rates of hypoglycemia as a secondary outcome. In addition, the definition of hypoglycemia was different from most of the previous studies, since in SWITCH 1 only symptomatic and/or severe hypoglycemic episodes were reported. It is surprising, though, that hypoglycemia unawareness was an inclusion criterion in the SWITCH 1 study, while in other studies hypoglycemia unawareness was an exclusion criterion (11,12). Therefore, a number of asymptomatic hypoglycemic events may have not been reported by the patients and self-reported hypoglycemic episodes may underestimate the number of true hypoglycemic events. Nevertheless, since the study had a cross-over designed and participants were exposed to both basal insulins of the study, this fact has probably not influenced much the results.

The *Comparison of NN1250 Plus Insulin Aspart With Insulin Glargine Plus Insulin Aspart in Type 1 Diabetes (BEGIN Basal Bolus Type 1)* study, was a phase 3 open-label study in patients with T1DM that reported non-inferiority of IDeg U100 in comparison with IGlar U100 in terms of glycemic control (11). Overall hypoglycemic episodes that were examined as a secondary outcome, did not differ significantly between the two groups (OR: 1.07, 95% CI: 0.89–1.28, P=0.48). In addition, there was no significant difference in severe hypoglycemia (OR: 1.38, 95% CI: 0.72–2.64, P=0.34), but similarly to the SWITCH

1 trial, nocturnal episodes were 25% lower in the IDeg U100 group as compared to IGlar U100 (OR: 0.75, 95% CI: 0.59–0.96) (11). When comparing these two studies, except for the different outcomes, we should also take into consideration that the BEGIN trial was an open label trial and therefore, there was greater caution in the titration of the IDeg U100 dose (10,11). Moreover, the FBG target was 71–90 mg/dL in both studies, but the pre-prandial was 71–90 mg/dL in the BEGIN and 71–108 mg/dL in the SWITCH 1 trial. Hence, hypoglycemia rates cannot be compared between the two studies, since the pre-prandial target was stricter in the BEGIN trial.

Similar results were reported from the 52-week extension of the BEGIN trial; nocturnal hypoglycemia was significantly lower in the group treated with IDeg U100, in comparison with the group treated with IGlar U100, while the overall confirmed hypoglycemia did not differ between the two groups (13). On the other hand, in a small open label study by Birkeland *et al.*, IDeg U100 was compared to IGlar U100 in terms of glycemic control and showed non-inferiority. Regarding hypoglycemia, the results were similar to the SWITCH 1 trial since overall hypoglycemia episodes and nocturnal episodes were significantly lower in the IDeg U100 than in the IGlar U100 group (12).

Most of the published studies agree that IDeg U100 decreases nocturnal hypoglycemia but data are still scarce about overall hypoglycemia rates. Several meta-analyses have been published so far to answer the question if IDeg U100 induces less hypoglycemia in comparison with IGlar U100; however, the examined studies had large heterogeneity with different inclusion criteria, different endpoints and different definitions of hypoglycemia (14-16). Ratner *et al.* demonstrated that among patients with T1DM, the rate of overall confirmed episodes was similar between IDeg U100 and IGlar U100, while the nocturnal hypoglycemia was lower in the maintenance period for IDeg U100 (14). Furthermore, Vora *et al.* showed that nocturnal and not daytime, non-severe hypoglycemias were significantly lower among patients treated with IDeg U100 as compared to IGlar U100 (15). Another meta-analysis by Dzygalo *et al.* showed that IDeg U100 was associated with reduced nocturnal hypoglycemia episodes in contrast to IGlar U100 and insulin detemir, but overall hypoglycemia could not be assessed because the available studies had large heterogeneity (16).

Independently of the efficacy and the safety of IDeg U100, many have raised concerns about the strict fasting plasma glucose targets in subjects at high risk for hypoglycemia in the SWITCH 1 trial and the potential risk of these patients (17), since it is known that severe hypoglycemia increases cardiovascular morbidity and mortality (4). Nevertheless, more interesting would be a comparison between IDeg U100 or U200 and IGlar U300, since these are the latest basal insulin analogues that have lower pharmacodynamic variability under steady state conditions and therefore, can reduce significantly hypoglycemia risk in comparison with IGlar U100 (8,18). Noteworthy, a recent study demonstrated that at steady state conditions IGlar U300 resulted in 20% less within-day variability in comparison with IDeg U100 at the same dose (0.4 U/kg/day) (19).

In the era of new basal insulin analogues, it seems possible to achieve safely a FBG target of less than 110 mg/dL and a HbA1c target less than 7% and to reduce the risk of diabetes complications. Such targets have been difficult to be achieved in past with older insulins, that were shorter acting and with more variable and less-predictable time-action profiles than newer basal insulin analogues, including IDeg U100.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. International Hypoglycaemia Study Group. Glucose Concentrations of Less Than 3.0 mmol/L (54 mg/dL) Should Be Reported in Clinical Trials: A Joint Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2017;40:155-7.
2. Cryer PE. The barrier of hypoglycemia in diabetes. Diabetes 2008;57:3169-76.
3. Diabetes Control and Complications Trial Research Group, Nathan DM, Genuth S, et al. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329:977-86.
4. Frier BM. Hypoglycaemia in diabetes mellitus:

epidemiology and clinical implications. Nat Rev Endocrinol 2014;10:711-22.
5. King P, Kong MF, Parkin H, et al. Well-being, cerebral function, and physical fatigue after nocturnal hypoglycemia in IDDM. Diabetes Care 1998;21:341-5.
6. Frier BM. How hypoglycaemia can affect the life of a person with diabetes. Diabetes Metab Res Rev 2008;24:87-92.
7. Haahr H, Heise T. A review of the pharmacological properties of insulin degludec and their clinical relevance. Clin Pharmacokinet 2014;53:787-800.
8. Heise T, Hermanski L, Nosek L, et al. Insulin degludec: four times lower pharmacodynamic variability than insulin glargine under steady-state conditions in type 1 diabetes. Diabetes Obes Metab 2012;14:859-64.
9. Marso SP, McGuire DK, Zinman B, et al. Efficacy and Safety of Degludec versus Glargine in Type 2 Diabetes. N Engl J Med 2017;377:723-32.
10. Lane W, Bailey TS, Gerety G, et al. Effect of Insulin Degludec vs Insulin Glargine U100 on Hypoglycemia in Patients With Type 1 Diabetes: The SWITCH 1 Randomized Clinical Trial. JAMA 2017;318:33-44.
11. Heller S, Buse J, Fisher M, et al. Insulin degludec, an ultra-longacting basal insulin, versus insulin glargine in basal-bolus treatment with mealtime insulin aspart in type 1 diabetes (BEGIN Basal-Bolus Type 1): a phase 3, randomised, open-label, treat-to-target non-inferiority trial. Lancet 2012;379:1489-97.
12. Birkeland KI, Home PD, Wendisch U, et al. Insulin degludec in type 1 diabetes: a randomized controlled trial of a new-generation ultra-long-acting insulin compared with insulin glargine. Diabetes Care 2011;34:661-5.
13. Bode BW, Buse JB, Fisher M, et al. Insulin degludec improves glycaemic control with lower nocturnal hypoglycaemia risk than insulin glargine in basal-bolus treatment with mealtime insulin aspart in Type 1 diabetes (BEGIN((R)) Basal-Bolus Type 1): 2-year results of a randomized clinical trial. Diabet Med 2013;30:1293-7.
14. Ratner RE, Gough SC, Mathieu C, et al. Hypoglycaemia risk with insulin degludec compared with insulin glargine in type 2 and type 1 diabetes: a pre-planned meta-analysis of phase 3 trials. Diabetes Obes Metab 2013;15:175-84.
15. Vora J, Christensen T, Rana A, et al. Insulin degludec versus insulin glargine in type 1 and type 2 diabetes mellitus: a meta-analysis of endpoints in phase 3a trials. Diabetes Ther 2014;5:435-46.
16. Dzygalo K, Golicki D, Kowalska A, et al. The beneficial effect of insulin degludec on nocturnal hypoglycaemia and insulin dose in type 1 diabetic patients: a systematic review and meta-analysis of randomised trials. Acta Diabetol 2015;52:231-8.
17. Zulewski H, Keller U. Insulin Analogues and Hypoglycemia in Patients With Type 1 Diabetes. JAMA 2017;318:1828.
18. Becker RH, Dahmen R, Bergmann K, et al. New insulin glargine 300 Units mL-1 provides a more even activity profile and prolonged glycemic control at steady state compared with insulin glargine 100 Units mL-1. Diabetes Care 2015;38:637-43.
19. Bailey TS, Pettus J, Roussel R, et al. Morning administration of 0.4U/kg/day insulin glargine 300U/mL provides less fluctuating 24-hour pharmacodynamics and more even pharmacokinetic profiles compared with insulin degludec 100U/mL in type 1 diabetes. Diabetes Metab 2017. [Epub ahead of print].

Cite this article as: Tentolouris A, Eleftheriadou I, Tentolouris N. Insulin degludec U100 is associated with lower risk for severe and symptomatic hypoglycemia as compared with insulin glargine U100 in subjects with type 1 diabetes. Ann Transl Med 2018;6(3):63. doi: 10.21037/atm.2017.12.28

