A Review of New Ultra-long-Acting Basal Insulin: Insulin Glargine 300 Units

นิพนธ์ปริทัศน์

นอร์ จุนา พอว์[1*] และ เนติ สุขสมบูรณ์[2]

[1] นักศึกษาหลักสูตรเภสัชศาสตรมหาบัณฑิต สาขาเภสัชกรรมคลินิก (หลักสูตรนานาชาติ)
[2] ภาควิชาเภสัชกรรม
[1-2] คณะเภสัชศาสตร์ มหาวิทยาลัยมหิดล กรุงเทพฯ 10400

* ติดต่อผู้นิพนธ์: juna.s07@gmail.com

Review Article

Naw Juna Paw[1*] and Naeti Suksomboon[2]

[1] Master of Pharmacy Student (Clinical Pharmacy International Program)
[2] Department of Pharmacy
[1-2] Faculty of Pharmacy, Mahidol University, Bangkok, 10400, Thailand

* **Corresponding author:** juna.s07@gmail.com

บทคัดย่อ

การใช้อนุพันธ์อินสุลินที่ให้ฤทธิ์ตลอดเวลา (basal insulin analogs) มีความสำคัญมากขึ้นกับการควบคุมโรคเบาหวาน ในปัจจุบันมียาอนุพันธ์อินสุลินที่ออกฤทธิ์ยาว เช่น อินสุลินกลาร์จีน 100 ยูนิต (insulin glargine 100 units; IGla 100U) และอินสุลินดีเทอเมียร์ (detemir insulin) ซึ่งทั้งสองชนิดนี้ยังให้ผลสรีรวิทยาที่ต่างจากการหลั่งของอินสุลินตามธรรมชาติ เมื่อให้ยาเหล่านี้ในขนาดสูงมักพบว่าให้ระดับยาพุ่งสูง และมักไม่สามารถให้ฤทธิ์ครอบคลุมตลอด 24 ชั่วโมงได้ ดังนั้นจึงพัฒนายา IGla 300U ซึ่งเป็นอนุพันธ์อินสุลินที่เป็นรูปแบบยาค่อยปลดปล่อย ทั้งนี้องค์การอาหารและยาของสหรัฐอเมริกาได้รับรอง IGla 300U เมื่อ 25 กุมภาพันธ์ 2558 เป็นยาที่ใช้ได้ทั้งเบาหวานชนิดที่ 1 และ 2 โดยให้ประสิทธิภาพและความปลอดภัยโดยมีความแปรปรวนทางเภสัชพลศาสตร์น้อยและให้ฤทธิ์ครอบคลุม 24 ชั่วโมง ทำให้เกิดภาวะน้ำตาลต่ำค่อนข้างน้อย น้ำหนักเพิ่มค่อนข้างน้อย และสามารถปรับขนาดยาได้ง่าย โดยสรุป IGla 300U สามารถใช้เป็นยารักษาเบาหวานที่มีประสิทธิภาพโดยลดความเสี่ยงต่อภาวะน้ำตาลในเลือดต่ำและน้ำหนักเพิ่ม

คำสำคัญ: อินสุลินกลาร์จีน, อินสุลินออกฤทธิ์ยาวที่ให้ฤทธิ์ตลอดเวลา

Abstract

Basal insulin analogs are essential for diabetes management. Currently available long-acting insulin (insulin glargine 100 units; IGla 100U) and insulin detemir still do not completely mimic physiological insulin secretion. When administered with high dose, their pharmacokinetic profile showed a peak concentration and a low dose may not be adequate to cover a 24-hour duration of action. Insulin glargine 300 units (IGla 300U) is a new basal insulin with a slow release formulation. The US Food and Drug Administration (FDA) approved IGla 300U in February 25, 2015. It can be used both in type 1 and type 2 diabetes mellitus. It offers efficacy and safety with less pharmacodynamic variability and duration of action over 24 hours, resulting in less hypoglycemic episodes, less weight gain and more flexible dosing regimen. In summary, IGla 300U would be an effective treatment option for diabetes while minimizing risks of hypoglycemia and weight gain.

Keywords: insulin glargine, ultra-long acting basal insulin

Introduction

In 2016, World Health Organization (WHO) reported that an estimated 422 million adults were living with diabetes in 2014 compared to 108 million in 1980, indicating the poor glycemic control of diabetic patients all around the world.[1] Insulin plays an important role in diabetes management and long-acting basal insulins are the standard of care in both type 1 (T1DM) and type 2 diabetes mellitus (T2DM). Insulin glargine (IGla) was a first once-daily, long-acting insulin analog which has been introduced in clinical practice for more than 10 years to provide required basal insulin. An ideal insulin regimen is to provide an optimal glycemic control with limited adverse events, and improve the patient's convenience.

Unfortunately, current basal insulin options (IGla 100U) and insulin detemir (IDet) do not fulfill the main requirements of the ideal basal insulin namely flat pharmacodynamic profile with low hypoglycemic risk, 24-hours duration of action and low inter-individual variability. Such undesirable properties could contribute to the fear to initiate insulin therapy because of concerns regarding the potential side effects, including hypoglycemia, weight gain and the inconvenient use of insulin. Therefore, additional consideration for new insulin formulations is required.

IGla 300U was a new formulation of IGla 100U which is designed to provide the same number of insulin units of IGla 100U with a third of its volume. It has more flat-line, prolonged pharmacokinetic and pharmacodynamic profile, longer duration of action and less variation in blood glucose control than IGla 100U. The less pronounced peak of action could result in a more gradual reduction of plasma glucose, reducing the risk of hypoglycemia while achieving the glycemic control.[2,3] The purpose of this review is to discuss about the development of IGla 300U and provide an insight of its potential role in diabetes treatment.

Formulation, Structure and Mechanism of Action

Insulin glargine (21^A-Gly-31^B-32^B-Di-Arg-human insulin) is a recombinant human insulin analog which is modified from

human insulin by replacing the asparagine amino acid at position A21 with glycine and two arginine amino acids are added to the C-terminus of the B-chain. IGla 300U is a new formulation of insulin glargine and available in the market as TOUJEO U-300, 1.5 mL. It is three times more concentrated, resulting in a two-thirds lower subcutaneous spheric depot with a surface area reduced by 50% as compared with IGla 100U. This results in a slower and prolonged absorption of insulin. It is less soluble in neutral pH and more soluble in acidic pH 4. After subcutaneous injection, IGla 300U functions essentially as a prodrug in subcutaneous tissue, with the majority of activity from its metabolites.[4,5]

Pharmacokinetic and Pharmacodynamic Properties

A multi-dose, two-treatment, two-period, two-sequence crossover study was conducted in T1DM by giving once-daily subcutaneous administrations of either 0.4 (cohort 1) or 0.6 units/kg (cohort 2) IGla 300U for 8 days in one treatment period and 0.4 units/kg Gla-100 for 8 days in the other. At steady state, pharmacokinetic profile of IGla 300U was more constant and evenly distributed over 24 hours compared with IGla 100U and lasted longer. The supporting data were at the time to 50% of area under the serum insulin and glucose infusion rate time curves from time 0 to 36 hours post-dosing. Maintenance of tight blood glucose control ($\leq$ 105 mg/dL) was approximately 5 hours longer with IGla 300U. At steady state, IGla 300U has a terminal half-life of 19 hours with a prolonged duration of activity (well beyond 24 hours). Steady state is reached after 3 - 4 days.[6] It has the same metabolism as IGla 100U and is metabolized into active metabolite such as M1 (Gly A21) and M2 (Gly A21, des-Thr B 30). M1 was the principal active moiety and it takes 4 days to reach the steady state concentration of M1 metabolite.[7] A multi-dose crossover study of IGla 300U 0.4U/kg, with six once-daily injections, in T1DM, showed that it has a low within-day variability with the peak-to-trough ratio of insulin concentration profile being < 2 and both swing and peak-to-trough fluctuation being < 1. It also has a high day-to-day reproducibility. The between-day within-subject coefficients of variation for total systemic exposure, with an area under the curve (AUC) from time 0 to 24 hours after dosing of 17.4% (95% confidence interval (or CI): 15 – 21%) and a maximum insulin concentration of 33.4% (95% CI: 28 – 41%).[8] Two single-dose studies conducted in

Japan and Europe with T1DM patients showed that serum glargine concentration and glucose infusion rate developed more gradually with a constant and prolonged action with IGla 300U than with IGla 100U.[8,9] The times to reach 50% glargine exposure and insulin activity were longer for all IGla 300U doses (0.4 U or 0.6 U or 0.9 U/kg) than IGla 100U during 36 hours clamp period. In the Japanese study, median $T_{50\%\text{-INS-AUC0-36,h}}$ was 14 hrs for 0.4 U/kg IGla 100U vs. 17 hrs for 0.4 U/kg, 18 hrs for 0.6 U/kg of IGla 300U.[9] In the European study, median $T_{50\%\text{-INS-AUC0-36,h}}$ was 13 hr for 0.4 U/kg IGla 100U vs. 15 hrs for 0.4 U/kg, 17 hrs for 0.6 U/kg and 19 hrs for 0.9 U/kg of IGla 300U.[8]

IGla 300U also allows flexible dosing (24 $\pm$ up to 3 hours) and does not compromise efficacy and safety profiles in people with T2DM. Although recommendation for a flexible-dosing schedule with IGla 300U was not included in the package insert, a substudy suggested that occasional flexibility (up to 3 hours) in dosing time is reasonable because there was no difference in efficacy and safety outcome between flexible and fixed dosing groups.[10] In T1DM, IGla 300U injected either in the morning or the evening provided similar overall glucose control and percentage time in target sensor glucose range (4.4 - 7.8 mmol/L) vs. IGla 100U. There was also less hypoglycemia and mean glucose profile for all subjects with less glucose excursion and lower within- and between-day glucose variability. It is indicated that IGla 300U can be given any time of the day.[11] In summary, IGla 300U has flat, stable and ultra-long-acting pharmacokinetic properties in both T1DM and T2DM with its modified slow-release formulation.

Starting Dose, Dose Adjustment and Switching Therapy

For T2DM insulin naïve patients, the recommended starting dose for IGla-300U is 0.2U/kg of body weight once daily. For T1DM insulin naive patients, 0.2 - 0.4 U/kg can be calculated as an initial total daily insulin dose and approximately 1/3 to 1/2 of the total daily insulin dose should be administered as basal insulin. The remainder is administered as short acting insulin, divided between each of the daily meals. Dose adjustment should be individualized. The dose of IGla 300U can range from 1 to 80 U per one injection. Dose should be titrated not more frequently than every 3 - 4 days to minimize the risk of hypoglycemia. For

switching therapy, unit-to-unit basis transition can be considered for patients receiving once daily long-acting or intermediate-acting insulin. For patients with twice daily isophane (NPH) regimen, the recommended starting dose of IGla 300U was 80% of the total daily NPH dose, given once daily to minimize the risk of hypoglycemia. Blood glucose should be monitored frequently in the first week of therapy and the dose of IGla 300U should be titrated accordingly. Other glucose lowering therapies should also be monitored and adjusted individually to minimize the risk of hypoglycemia. The maximum glucose lowering effect of a dose of IGla 300U may take 5 days to fully manifest and the first dose may be insufficient to cover metabolic needs in the first 24 hours of use.[12]

Special Populations

For elderly patients, in controlled clinical studies, 30 of 304 IGla 300U treated T1DM patients (9.8%) and 327 of 1242 IGla 300U treated T2DM patients (26.3%) were 65 years or older. Among these elderly, 2% of patients with T1DM and 3% of those with T2DM were 75 years or older. No overall differences in effectiveness and safety were observed in subgroup analysis of the age groups. However, caution should be taken when giving it to geriatric patients to avoid hypoglycemia.

For renal and hepatic impairment, there were no available clinical studies conducted for IGla 300U. However, as with all insulin products, glucose monitoring should be intensified and the dose should be adjusted on an individual basis in patients with renal or hepatic impairment.[12]

Efficacy

A series of EDITION studies were conducted to examine the efficacy and safety of IGla 300U. For T2DM patients, four EDITION studies (EDITION-1, EDITION-2, EDITION-3 and EDITION-JP 2) which included patients not achieving glycemic control with basal bolus meal time insulin, basal insulin plus oral antidiabetic drugs. The primary endpoint in all studies was non-inferiority for A1C change from baseline to month 6 and the main secondary endpoint in the trials of people with T2DM was the percentage of participants with at least 1 nocturnal confirmed or severe hypoglycemic event from week 9 to

month 6. According to such outcome, nocturnal meant midnight to 5:59 a.m., while confirmed hypoglycemia was defined as a blood glucose of $\leq$ 70 mg/dL. In addition, severe hypoglycemia was defined by the American Diabetes Association definition. All EDITION studies of T2DM showed a consistent efficacy of similar HbA1C reductions by IGla 300U, ranging from -0.45% to -1.42%, compared with -0.55% to -1.46% by IGla 100U. The data are summarized in Table 1. The patient level meta-analysis of EDITION 1,2,3 studies also confirmed that mean change in glycated hemoglobin was comparable between IGla 300U and IGla 100U, i.e., -1.02 with a standard error of 0.03% for both regimens, and a least square mean (LSM) difference of 0.00 with 95% CI of -0.08 to 0.07, for both regimens.[13] At the end of the 6-month study, a dosing increase was seen in IGla 300U when compared with IGla 100U as found in EDITION-1 study: 0.97 vs. 0.88 U/kg/day, LSM difference 0.09 U/kg/day (95% CI: 0.062-0.124), in EDITION-2 study: 0.92 vs. 0.84 U/kg/day, LSM difference 11 U/day (95% CI: 8-14), and in EDITION-3 study: 0.62 U/kg/day vs. 0.53 U/kg/day. This may be due to a slight decrease in bioavailability related to longer subcutaneous resistance time with exposure to tissue peptidase.[14-16]

For Type 1 DM, currently available data are derived from only 2 studies (EDITION-4 and EDITION-JP 1) which used IGla 100U as a comparator of IGla 300U. Both studies found non-inferiority in HbA1C reduction between IGla 300U and IGla 100U. Estimated treatment difference (ETD) of the HbA1C reduction between IGla 300U and IGla 100U was 0.04% (95% CI -0.10 to 0.19) in EDITION-4 study and 0.13% (95% CI -0.03 to 0.29) in EDITION-JP 1 study. The data are shown in Table 1.

Safety

Hypoglycemia

Six-month open-label extension studies of EDITION-1, -2, and -3 and EDITION-JP 2 showed that the use of IGla 300U resulted in a significant reduction in the nocturnal hypoglycemia in T2DM when compared with IGla 100U. The risk ratios (RRs) were 0.78 (95% CI 0.68-0.89), 0.71 (95% CI 0.58-0.86), 0.71 (95% CI 0.58-0.86), and 0.62 (95% CI 0.44-0.88) for EDITION-1, -2, -3, and EDITION-JP 2, respectively.

Table 1 Efficacy of IGla 300U on HbA1C and FPG reduction.

Study	Population, concomitant therapy, duration	Treatment arm	Baseline mean HbA1C % (SD)	Mean HbA1C reduction % (SE)	ETD (%) for HbA1C reduction (95% CI)	Baseline mean FPG (mmol/L) (SD)	Mean FPG reduction (mmol/L) (SE)	ETD (mmol/L) for FPG (95% CI)
EDITION-1 (2014)[14]	- T2DM - Basal + mealtime insulin ± MET - 6 months	- IGla 300U (N = 404) - IGla 100U (N = 403)	- 8.15 (0.78) - 8.16 (0.77)	- 0.83 (0.06) - 0.83 (0.06)	- 0.00 (-0.11, 0.11)	- 8.8 (2.9) - 8.9 (2.9)	-1.48 (SD = 3.11) -1.69 (SD = 3.21)	- NA
EDITION-2 (2014)[15]	- T2DM - Basal insulin + OADs (discontinued SU) - 6 months	- IGla 300U (N = 404) - IGla 100U (N = 407)	- 8.26 (0.86) - 8.22 (0.77)	- 0.57 (0.09) - 0.56 (0.09)	-0.01 (-0.14, 0.12)	- 8.24 (2.97) - 7.89 (2.67)	- 1.14 (SD = 3.42) - 1.06 (SD = 3.02)	- 0.19 (-0.15, 0.52)
EDITION-3 (2015)[16]	- T2DM - Insulin naïve, (discontinued SU) - 6 months	- IGla 300U (N = 432) - IGla 100U (N = 430)	- 8.49 (1.04) - 8.58 (1.07)	- 1.42 (0.05) - 1.46 (0.05)	- 0.04 (-0.09, 0.17)	- 9.93 (2.86) - 10.21 (2.90)	- 3.41 (0.10) - 3.8 (0.11)	- 0.39 (0.10, 0.68)
EDITION-JP 2 (2016)[20]	- T2DM Japanese - Basal insulin + OADs, - 6 months	- IGla 300U (N = 121) - IGla 100U (N = 120)	- 7.99 (0.72) - 8.06 (0.77)	- 0.45 (0.06) - 0.55 (0.06)	- 0.10 (-0.08, 0.27)	- 7.7 (2.1) - 7.4 (1.9)	−1.21 (0.16) - 1.25 (0.16)	- 0.04 (-0.40, 0.49)
EDITION-4 (2015)[18]	- T1DM - Basal + mealtime insulin - 6 months	- IGla 300U (N = 274) - IGla 100U (N = 275)	- 8.11 (0.77) - 8.14 (0.79)	- 0.42 (SD = 0.98) - 0.44 (SD = 0.72)	- 0.04 (-0.10, 0.19)	- NA - NA	- NA - NA	- NA - NA
EDITION-JP 1 (2016)[19]	- T1DM Japanese - Basal + mealtime insulin - 6 months	- IGla 300U (N = 122) - IGla 100U (N = 121)	- 8.06 (0.64) - 8.07 (0.74)	- 0.30 (0.06) - 0.43 (0.06)	- 0.13 (-0.03, 0.29)	- NA - NA	- 0.75 (0.4) - 1.2 (0.4)	- 0.4 (-0.6, 1.4)

Abbreviations: T2DM: type 2 diabetes mellitus, T1DM: type 1 diabetes mellitus, IGla 300U: insulin glargine 300U, IGla 100U: insulin glargine 100U, SD: standard deviation, SE: standard Error, OADs: oral antidiabetic drugs, NA; not available, SU: sulphonylurea, MET: metformin, ETD: estimated treatment difference.

The percentage of people experiencing severe hypoglycemia and hypoglycemia at any time of the day over the six-month period was also lower with IGla 300U (Table 2). In addition, a network meta-analysis was conducted to compare the efficacy and safety of IGla 300U with other basal insulins including NPH insulin, pre-mixed insulin, insulin detemir and insulin degludec. The analysis found that IGla 300U was associated with a significantly lower nocturnal hypoglycemia rate when compared with NPH (RR = 0.18; 95% Credible interval (CrI): 0.05 to 0.55), and with premixed insulin (RR = 0.36; CrI: 0.14 to 0.94), and no significant difference when it was compared with detemir (RR = 0.52; CrI: 0.19 to 1.36) or degludec (RR = 0.66; CrI: 0.28 to 1.50).[17]

In EDITION-4 study, during the 6-month period, rate of one or more confirmed (FPG ≤ 70 mg/dl) or severe hypoglycemic events was similar both for IGla 300U and IGla 100U, 93% and 94%, respectively, among T1DM patients. Equal percentage of nocturnal hypoglycemia was also found in both groups (69% vs. 70%). However, for the first 8 weeks of the study, there was a reduced rate of nocturnal confirmed or severe hypoglycemia (FPG ≤ 70 mg/dL) in IGla 300U group (RR = 0.69, 95% CI: 0.53 - 0.91).[18]

Table 2 Safety of IGla 300U in confirmed hypoglycemia and nocturnal hypoglycemia.

Study, study arm	Confirmed or severe hypoglycemia†				Severe hypoglycemia, baseline to month 6
	Nocturnal, baseline to week 8	Nocturnal, week 9 to month 6	Nocturnal, baseline to month 6	Any time of the day, baseline to month 6	
EDITION-1 (2014)[14] - IGla 300U (N = 404) - IGla 100U (N = 403)	- 26.2% - 33.3% - RR = 0.79 (95% CI: 0.64 - 0.98)	- 36.1% - 46.0% - RR = 0.78 (95% CI: 0.67 - 0.93)	- 44.6% - 57.5% - RR = 0.93 (95% CI: 0.68 - 0.89)	- 81.9% - 87.8% (95% CI: 0.88-0.99)	- 5.0% - 5.7% - RR = 0.87 (95% CI: 0.48-1.55)
EDITION-2 (2014)[15] - IGla 300U (N = 404) - IGla 100U (N = 407)	- 13.2% - 24.6% - RR = 0.53 (95% CI: 0.39 - 0.72)	- 21.6% - 27.9% - RR = 0.77 (95% CI: 0.60 - 0.97)	- 28.3% - 39.9% - RR = 0.71 (95% CI: 0.58 - 0.86)	- 70.0% - 77.3% - RR = 0.90 (95% CI: 0.83-0.98)	- 1.0% - 1.5% - NA
EDITION-3 (2015)[16] - IGla 300U (N = 432) - IGla 100U (N = 430)	- 7.4% - 10.0% - RR = 0.74 (95% CI: 0.48 - 1.13)	- 15.4% - 17.1% - RR = 0.9 (95% CI: 0.67 - 1.22)	- 17.9% - 23.5% - RR = 0.76 (95% CI: 0.59 - 0.99)	- 46.2% - 52.5% - RR = 0.88 (95% CI: 0.77 - 1.01)	- 0.9% - 0.9% - NA
EDITION-JP 2 (2016)[20] - IGla 300U (N = 121) - IGla 100U (N = 120)	- 13.3% - 16.7% - RR = 0.83 (95% CI: 0.45 - 1.52)	- 25.4% - 43.7% - RR = 0.58 (95% CI: 0.40 - 0.85)	- 28.3% - 45.8% - RR = 0.62 (95% CI: 0.44 - 0.88)	- 65.0% - 76.7% - RR = 0.86 (95% CI: 0.73 - 1.01)	- 2.5% - 1.7% - RR = 1.25 (95% CI: 0.31 - 4.98)
EDITION-4 (2015)[18] - IGla 300U (N = 274) - IGla 100U (N = 275)	- 46.7% - 57.1% - RR = 0.82 (95% CI: 0.7 - 0.96)	- 59.1% - 55.6% - RR = 1.06 (95% CI: 0.92 - 1.23)	- 68.6% - 70.2% - RR = 0.98 (95% CI: 0.88 - 1.09)	- 93.1% - 93.5% - RR = 1 (95% CI: 0.95 - 1.04)	- 6.6% - 9.5% - RR = 0.71 (95% CI: 0.41 - 1.24)
EDITION-JP 1 (2016)[19] - IGla 300U (N = 122) - IGla 100U (N = 121)	- 43.4% - 61.2% - RR = 0.71 (95% CI: 0.56 - 0.91)	- 61.7% - 73.7% - RR = 0.84 (95% CI: 0.70 - 1.00)	- 68.9% - 81.0% - RR = 0.85 (95% CI: 0.73 - 0.99)	- 96.7% - 97.5% - RR = 1 (95% CI: 0.95 - 1.04)	- 5.7% - 9.9% - RR = 0.58 (95% CI: 0.24 - 1.42)

Abbreviation: T2DM: type 2 diabetes mellitus, T1DM: type 1 diabetes mellitus, IGla 300U: insulin glargine 300U, IGla 100U: insulin glargine 100U, RR: relative risk comparing IGla 300U to IGla 100U.

* People experiencing ≥ 1 hypoglycemic event (safety population), SU: Sulphonylurea.

† confirmed hypoglycemia = ≤ 3.9 mmol/L or ≤ 70 mg/dl.

Weight gain

IGla 300U was also associated with less weight gain compared with IGla 100U in EDITION studies. In EDITION-1, weight gain is similar in both groups. In EDITION-2, -3 and -4, lower weight gain was found in IGla 300 group compared with IGla 100U, although not significant in EDITION-3 study (Table 3).

Table 3 Change in weight in IGla 300U versus IGla-100U in EDITION Phase 3 trials.

| Study | Least Square Mean Change (kg) | | |
	IGla 300 U	IGla 100 U	*P*-value
EDITION-1[15]	0.9	0.9	NA
EDITION-2[16]	0.08 (SD = 3.45)	0.66 (SD = 3.01)	0.015
EDITION-3[17]	0.49 (95% CI: 0.14 to 0.83)	0.71 (95% CI: 0.36 to 1.06)	NS
EDITION-4[18]	0.5 (SE = 3.3)	1.0 (SE = 3.2)	0.037
EDITION-JP 1[19]	-0.1 (SE = 0.2)	0.4 (SE = 0.2)	0.035
EDITION-JP 2[20]	-0.6 (SE = 0.2)	0.4 (SE = 0.2)	0.0003

Abbreviations: IGla 300U: insulin glargine 300U/ml, IGla 100U: insulin glargine 100U/ml, NA: data not available, NS: not significant, SD: standard deviation, SE: standard error.

Conclusion

Overall, according to the existing data, IGla 300U was a new formulation of IGla 100U which has a more flat and stable pharmacokinetic profile than IGla 100U. Although IGla 300U has the similar efficacy of HbA1C reduction with IGla 100U, it offers a benefit of less hypoglycemia and less weight gain.

References

1. World Health Organization. Global report on diabetes. 2016. World Health Organization, Geneva. [Internet]. (Accessed on Apr. 27, 2016, at http://www.who.int/diabetes/en/)

2. Eliaschewitz FG, Barreto T. Concepts and clinical use of ultra-long basal insulin. *Diabetol Metab Syndr* 2016;6;8:2.

3. Goldman J, White JR, Jr. New insulin glargine 300 U/mL for the treatment of type 1 and type 2 diabetes mellitus. *Ann Pharmacother* 2015;49(10):1153-1161.

4. Hilgenfeld R, Seipke G, Berchtold H, Owens DR. The evolution of insulin glargine and its continuing contribution to diabetes care. *Drugs* 2014;74(8):911-927.

5. Bolli GB, DeVries JH. New long-acting insulin analogs: from clamp studies to clinical practice. *Diabetes Care* 2015;38(4):541-543.

6. Becker RH, Dahmen R, Bergmann K, Lehmann A, Jax T, Heise T. 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(4):637-643.

7. Steinstraesser A, Schmidt R, Bergmann K, Dahmen R, Becker RH. Investigational new insulin glargine 300 U/ml has the same metabolism as insulin glargine 100 U/ml. *Diabetes Obes Metab* 2014; 16(9):873-876.

8. Becker RH, Nowotny I, Teichert L, Bergmann K, Kapitza C. Low within- and between-day variability in exposure to new insulin glargine 300 U/ml. *Diabetes Obes Metab* 2015;17(3):261-267.

9. Shiramoto M, Eto T, Irie S, et al. Single-dose new insulin glargine 300 U/ml provides prolonged, stable glycaemic control in Japanese and European people with type 1 diabetes. *Diabetes Obes Metab* 2015; 17(3):254-260.

10. Riddle MC, Bolli GB, Home PD, et al. Efficacy and safety of flexible versus fixed dosing intervals of insulin glargine 300 U/mL in people with type 2 diabetes. *Diabetes Technol Ther* 2016;18(4):252-257.

11. Bergenstal RM, Bailey TS, Rodbard D, et al. Insulin glargine 300 U/ml vs 100 U/ml: glucose profiles of morning vs evening injections in adults with type 1 diabetes mellitus measured with continuous glucose monitoring (CGM). [abstract no. 949 plus poster]. EASD VIRTUAL MEETING 2014. (Accessed on Apr. 27, 2016, at http://www.easdvirtualmeeting.org/resources/insulin-glargine-300-u-ml-vs-100-u-ml-glucose-profiles-of-morning-vs-evening-injections-in-adults-with-type-1-diabetes-mellitus-measured-with-continuous-glucose-monitoring-cgm—2)

12. European Medicines Agency. Toujeo U300 (insulin glargine 300U/ml). EU summary of product characteristics [Internet]. Update 2015. (Accessed on Apr. 23, 2016, at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000309/WC500047935.pdf)

13. Ritzel R, Roussel R, Bolli GB, et al. Patient-level meta-analysis of the EDITION 1, 2 and 3 studies: glycaemic control and hypoglycaemia with new insulin glargine 300 U/ml versus glargine 100 U/ml in people with type 2 diabetes. *Diabetes Obes Metab* 2015;17(9):859-867.

14. Riddle MC, Bolli GB, Ziemen M, Muehlen-Bartmer I, Bizet F, Home PD. New insulin glargine 300 units/mL versus glargine 100 units/mL in people with type 2 diabetes using basal and mealtime insulin: glucose control and hypoglycemia in a 6-month randomized controlled trial (EDITION 1). *Diabetes Care* 2014;37(10):2755-2762.

15. Yki-Jarvinen H, Bergenstal R, Ziemen M, et al. New insulin glargine 300 units/mL versus glargine 100 units/mL in people with type 2 diabetes using oral agents and basal insulin: glucose control and hypoglycemia in a 6-month randomized controlled trial (EDITION 2). *Diabetes Care* 2014;37(12):3235-3243.

16. Bolli GB, Riddle MC, Bergenstal RM, Ziemen M, Sestakauskas K, Goyeau H, et al. New insulin glargine 300 U/ml compared with glargine 100 U/ml in insulin-naive people with type 2 diabetes on oral glucose-lowering drugs: a randomized controlled trial (EDITION 3). Diabetes Obes Metab 2015;17(4):386-394.

17. Freemantle N, Chou E, Frois C, et al. Safety and efficacy of insulin glargine 300 u/mL compared with other basal insulin therapies in patients with type 2 diabetes mellitus: a network meta-analysis. *BMJ Open* 2016;6(2):e009421.

18. Home PD, Bergenstal RM, Bolli GB, et al. New insulin glargine 300 Units/mL versus glargine 100 Units/mL in people with type 1 diabetes: A randomized, phase 3a, open-label clinical trial (EDITION 4). Diabetes Care 2015;38(12):2217-2225.

19. Matsuhisa M, Koyama M, Cheng X, et al. New insulin glargine 300 U/ml versus glargine 100 U/ml in Japanese adults with type 1 diabetes using basal and mealtime insulin: glucose control and hypoglycaemia in a randomized controlled trial (EDITION JP 1). *Diabetes Obes Metab* 2016;18(4):375-383.

20. Terauchi Y, Koyama M, Cheng X, et al. New insulin glargine 300 U/ml versus glargine 100 U/ml in Japanese people with type 2 diabetes using basal insulin and oral antihyperglycaemic drugs: glucose control and hypoglycaemia in a randomized controlled trial (EDITION JP 2). *Diabetes Obes Metab* 2016;18(4):366-374.