Effects of Switching from Degludec to Glargine U300 in Patients with Type 1 Diabetes Having Large Day-to-Day Glycemic Variability: A Retrospective Study

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Abstract

Background: Degludec (Deg) and Glargine U300 (Gla-300) are new insulin analogues with longer and smoother pharmacodynamic action than Glargine U100. Both improve glycemic variability (GV) unlike Glargine U100. However, it is not clear which insulin analogue has a better effect on GV in insulin-dependent type 1 diabetes. We evaluated the effects of switching from Deg to Gla-300 on day-to-day GV in patients with insulin-dependent type 1 diabetes treated with Deg.

Methods: We conducted a retrospective study on 22 insulin-dependent type 1 diabetes patients having large day-to-day GV or frequent hypoglycemia who were treated with multiple insulin injection therapy including Deg and were advised to switch from Deg to Gla-300. We evaluated day-to-day GV and frequency of hypoglycemia in two groups. The first group included patients whose treatment was changed to Gla-300, and the second group included patients who opted to continue receiving Deg. We evaluated the change in standard deviation (SD) of fasting blood glucose (SD-FBG) calculated from self-monitoring of blood glucose (SMBG) and frequency of hypoglycemia (total, severe, and nocturnal).

Results: SD-FBG and frequency of nocturnal hypoglycemia decreased in Gla-300 group compared to those in Deg group. The change in SD-FBG had a negative correlation with SD-FBG and hemoglobin A1c (HbA1c) at baseline and positive correlation with serum albumin levels at baseline in Gla-300 group. On the other hands, the change in SD-FBG had no correlation with these markers in Deg group.

Conclusions: Switching from Deg to Gla-300 effectively stabilized blood glucose levels and decreased nocturnal hypoglycemia in insulin-dependent type 1 diabetes treated with Deg, especially in cases with low serum albumin, large GV, and high HbA1c.

Background

Strict blood glucose control is important to prevent micro- and macro-vascular diabetic complications in patients with diabetes [1, 2]. However, overly intensive control induces hypoglycemia and increases the risk of cardiovascular events and mortality [3–5]. Similar to hypoglycemia, glycemic variability (GV) and diabetic complications are closely related. Large day-to-day GV of fasting blood glucose (FBG) leads to micro- and macro-vascular events [6–8].

There are many factors that worsen GV. Dysfunction of β -cells is one of these factors [9]. Patients with type 1 diabetes have weaker β -cells function compared with type 2 diabetes. Thus, larger GV and more frequent hypoglycemia are observed in type 1 diabetes compared with these parameters in type 2 diabetes [10]. In patients with type 1 diabetes treated with multiple insulin injection therapy, basal insulin has an important role in the stability of blood glucose level. Insulin Glargine U100 (Gla-100) is a long-acting insulin that is widely used in both type 1 and type 2 diabetes. Recently, two new basal insulin analogues with prolonged pharmacodynamic action, called insulin Glargine U300 (Gla-300) and insulin Degludec (Deg) were developed. Gla-300 is known to have a longer and smoother pharmacokinetic action, estimated to be over 24 h. It also achieves smoother GV and decreased frequency of

hypoglycemia than Gla-100 in type 1 [11, 12] and type 2 [13, 14] diabetes. On the other hand, Deg is another ultra-long-acting insulin, and pharmacokinetic data show an insulin terminal half-life of more than 25 h and a duration of action of approximately 42 h. Clinical data has shown that users achieve smoother GV and decreased frequency of hypoglycemia than users of Gla-100 for type 1 [15, 16] and type 2 [17, 18] diabetes. Because Deg has a longer pharmacodynamic action profile than Gla-300, Deg tends to be more commonly used for type 1 diabetes. However, large GV and frequent hypoglycemia in type 1 diabetes can often be observed, despite the use of Deg [10].

Previous reports on type 2 diabetes have shown that Gla-300 decreases the frequency of hypoglycemia compared with Deg [19, 20]. However, the data on these insulin analogues in type 1 diabetes are limited. Further, it is not clear whether it is better to continue Deg or switch from Deg to Gla-300 in patients with type 1 diabetes treated with Deg and exhibiting large GV or frequent hypoglycemia.

Standard deviation (SD) of FBG (SD-FBG) in self-monitoring of blood glucose (SMBG) is used as the marker of day-to-day GV [21]. We hypothesized that switching from Deg to Gla-300 will improve GV in type 1 diabetes and evaluated the efficiency of switching from Deg to Gla-300 on SD-FBG in SMBG and frequency of hypoglycemia.

Methods

Study Design and Participants

This study utilized a retrospective design and was approved by the ethics committee at Fukui Prefectural Hospital (No. 18–70) with a waiver of consent obtained from the committee. We investigated the outpatients who attended the Endocrinology and Diabetic unit of Fukui Prefectural Hospital from April 2017 to March 2019. All procedures were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

The eligible patients were male and female patients including the follows: (1) patients with insulin-dependent type 1 diabetes (2) patients treated with multiple insulin injection therapy containing Deg (3) patients who were instructed to perform SMBG four times/day and more than 90% of instructed SMBG data was obtained (4) patients whose day-to-day GV were large or who experienced frequent hypoglycemia or severe hypoglycemia (5) patients advised to change their medication from Deg to Gla-300 expecting for improvement of hypoglycemia and glucose variability. Among these patients, we excluded patients as follows: (1) patients who had changed antidiabetic agents or received new nutrition guidance during the observation period (2) patients who were introduced to flash glucose monitoring (FGM) and continuous glucose monitoring (CGM) during the observation period. Large day-to-day GV was defined as SD-FBG calculated from the records of SMBG of more than 66.3mg/dL. This SD-FBG level was the criteria used for assigning patients to the high GV group in the SWITCH trial [10]. Frequent hypoglycemia was defined as hypoglycemic events occurring more than 3 times in 30 days according to records of SMBG. This is similar to the frequency detected in the high GV group in the SWITCH trial.

After the recommendation of switching their insulin analogue, some changed from Deg to Gla-300, while the others opted to continue treatment with Deg. We evaluated the difference in change of followed items between two groups. The first group included patients who switched from Deg to Gla-300 (Gla-300 group), whereas the second group included patients who opted to continue Deg after the recommendation of switching from Deg to Gla-300 (Deg group). In Gla-300 group, the first evaluation points were the days on which Deg was switched to Gla-300, and the second evaluation points were 4 ± 1 months after switching to Gla-300. In Deg group, the first evaluation points were the days on which patients were advised to switch from Deg to Gla-300, and the second evaluation points were 4 ± 1 months after the first evaluation points.

Data Collection

SD-FBG was calculated from the records of SMBG in the previous 30 days for evaluating day-to-day GV. Some of the parameters evaluated in hypoglycemia were the change in the frequency of total, severe, and nocturnal hypoglycemic events recorded in SMBG. The prevalence of hypoglycemic events was evaluated as rate of per person/month. Both symptomatic and documented asymptomatic hypoglycemia were considered as total and severe hypoglycemia. Conversely, all nocturnal hypoglycemic events were symptomatic. Hypoglycemia is defined as having glucose levels being < 70 mg/dL or manifestation of hypoglycemic symptoms. Severe hypoglycemia is defined as having glucose levels being < 54 mg/dL or hypoglycemia that requires treatment assistance from another person. Nocturnal hypoglycemia was defined as the hypoglycemia occurring from 0000 h until the next breakfast. In addition, we evaluated the fasting plasma glucose (FPG), hemoglobin A1c (HbA1c), serum creatinine (s-Cr), estimated glomerular filtration rate (eGFR), serum albumin (s-Alb), body mass index (BMI), and the dose of bolus and ultra-long-acting insulin. The blood samples were collected before breakfast.

Statistical Analysis

The data are expressed as mean $\pm$ SD and were analyzed using a commercially available statistical software (SPSS version 22.0 for Windows, IBM, Chicago, IL); P -values < 0.05 indicated statistical significance. Comparisons of the variables were analyzed by a non-pairwise t -test or Wilcoxon test. Correlation analysis was performed using Pearson test to validate the correlation factors affecting the change in SD-FBG. We calculated that sample size of 22 was necessary to provide up to 80% power to detect a difference in change of SD-FBG between two groups, assuming a mean difference of 15 and SD of 12 according to our previous research with significance of 0.05.

Results

A total of 22 type 1 diabetes patients were matched to our inclusion criteria. Of the remaining 22 patients, there were 11 patients matched to Gla-300 group and other 11 patients matched to Deg group. The clinical characteristics of the 22 patients are summarized in Table 1. Between two groups, there were no statistical differences in all parameters.

As shown in Table 2, day-to-day GV indicated by SD-FBG in SMBG ($p = 0.04$) and frequency of nocturnal hypoglycemia ($p = 0.02$) significantly decreased in Gla-300 group unlike in Deg group. The frequency of total and severe hypoglycemia tended to decrease in Gla-300 group compared to that in Deg group without statistically significant difference.

As shown in Fig. 1, the change in SD-FBG had a negative correlation with SD-FBG ($r = -0.81$, $p = 0.002$) and HbA1c ($r = -0.66$, $p = 0.01$) at baseline and a positive correlation with s-Alb ($r = 0.69$, $p = 0.03$) at baseline in Gla-300 group. However, there were no correlations between the change in SD-FBG and these markers in Deg group. Despite the decrease in frequency of nocturnal hypoglycemia, FPG and HbA1c levels in Gla-300 group were not elevated compared to those in Deg group. The changes in dose of insulin and BMI had no difference between two groups.

Discussion

Herein, we evaluated the effect of switching from Deg to Gla-300 in insulin-dependent type 1 diabetes patients treated with Deg on the GV and frequency of hypoglycemia. Switching from Deg to Gla-300 improved day-to-day GV expressed in SD-FBG and decreased the frequency of nocturnal hypoglycemia. The change of SD-FBG had negative correlation with SD-FBG and HbA1c values at baseline and positive correlation with s-Alb at baseline.

Both Deg and Gla-300 improve day-to-day GV unlike Gla-100, owing to their longer pharmacodynamic effect [11–18]. However, the action mechanisms of these two ultra-long-acting insulin analogues are different. Deg forms a soluble multi-hexameric chain after subcutaneous injection and the zinc moiety of the insulin molecule diffuses slowly from the terminal ends of Deg and gets absorbed into circulation. After absorption into the circulatory system, almost all Deg bind to albumin and is slowly released from albumin in the target tissue to achieve hypoglycemic effect [22]. In contrast, Gla-300 does not bind to albumin in circulation [23]. S-Alb levels fluctuate daily with high values in daytime, and low values at night [24]. The decreased in s-Alb level increases free insulin level at night and decreases blood glucose level. Thus, large GV and frequent nocturnal hypoglycemia are observed in patients treated with Deg.

Kawaguchi et al. reported lower GV and frequency of hypoglycemia with Gla-300 treatment than that with Deg treatment in type 2 diabetes [20]. Their findings indicated that the frequency of nocturnal hypoglycemia with Deg therapy was associated with low levels of s-Alb [20]. Another report on type 2 diabetes showed that Gla-300 decreased total and nocturnal hypoglycemia compared with Deg in the cases with s-Alb < 3.8 g/dL [25]. However, another clinical real-world study on type 2 diabetes showed that the first injection of Deg achieved larger reduction of HbA1c and frequency of hypoglycemia compared to these markers in Gla-300 therapy [26]. This report showed controversial results to that reported by Kawaguchi et al [20], and the superiority of Gla-300 and Deg based on their effectiveness are not clear even in type 2 diabetes.

Similar studies on type 1 diabetes are even more limited than on type 2 diabetes. However, a few reports have compared Deg therapy with Gla-300 therapy in type 1 diabetes. A double-blind crossover euglycemic

clump study showed that Gla-300 induced 20 % less fluctuation in steady state glucose infusion rate profiles than that of Deg in once-daily morning dosing regimen of 0.4 U/kg/day [27]. However, another double-blind crossover euglycemic clump study showed that Deg exhibited lower day-to-day and within-day GV than that of Gla-300 in type 1 diabetes [28]. Recently, Miura et al. conducted multicenter crossover trial on type 1 diabetes in which the efficiency of Deg and Gla-300 were compared [29]. In this study, SD-FBG by CGM were evaluated as the marker of day-to-day GV. The results showed that there was no difference of SD-FBG between these two insulin analogues. However, time below the target range (< 70mg/dL) were shorter in Gla-300. On the other hand, time above the target range (> 180mg/dL) were shorter in Deg. As conclusion, they identified that these two insulins have comparable glucose stabilizing effects in patients with type 1 diabetes. Although this study is similar to ours, there were several differences. The first difference is the target patients. In the study described by Miura et al., the target patients included all insulin-dependent type 1 diabetes. Our target patients were insulin-dependent type 1 diabetes patients exhibiting large GV or frequent hypoglycemia, despite the use of Deg. The second difference was in the evaluation of factors having correlation with the change in GV. Miura et al. did not evaluate the factors influencing the superiority of these ultra-long-acting insulin analogues. In contrast, our study showed that low s-Alb, high HbA1c, and high SD-FBG are predictors of the superiority of Gla-300 over Deg in type 1 diabetes. Knowing these predictors of superiority may lead to the personalization of treatment in patients with type 1 diabetes patients .

Our study has several limitations. First, this study adopted a retrospective design and was conducted in a small number of patients. The second is the method used to evaluate the GV and frequency of hypoglycemia. The evaluation of GV and hypoglycemia by FGM or CGM is better than that by SMBG. The third is the points without the data of switching from Deg to Gla-300. Therefore, larger prospective crossover studies using FGM or CGM are necessary for supporting our results.

Conclusions

Switching from Deg to Gla-300 is effective for stabilizing blood glucose levels and decreasing nocturnal hypoglycemia in patients with insulin-dependent type 1 diabetes treated with Deg exhibiting large GV or frequent hypoglycemia. The effectiveness of improving day-to-day GV is greater in cases with low serum albumin, large day-to-day GV, and high HbA1c level, despite the use of Deg. We should conduct prospective crossover study intended for insulin-dependent type 1 diabetes.

Abbreviations

Deg
Degludec
Gla-300
Glargine U300
GV
glycemic variability

SD
standard deviation
SD-FBG
standard deviation of fasting blood glucose
SMBG
self-monitoring of blood glucose
HbA1c
hemoglobin A1c
FBG
fasting blood glucose
Gla-100
Glargine U100
FGM
flash glucose monitoring
CGM
continuous glucose monitoring
FPG
fasting plasma glucose
s-Cr
serum creatinine
eGFR
estimated glomerular filtration rate
s-Alb
serum albumin
BMI
body mass index

Declarations

Ethics approval and consent to participate

The study was approved by the ethics committee of Fukui Prefectural Hospital (No. 18-70) with a waiver of consent being obtained from the ethics committee. All procedures were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Consent for publication

Not applicable

Availability of data and materials

All the data generated and analyzed during this study are available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

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The study did not receive any funding.

Authors' contributions

TS, SK, AO drafted the manuscript, designed and coordinated the study together with TH and YK collected retrospectively patient data. TS, SK, RY, and DA performed statistical analysis. SK, MK, YT, and TY edited the manuscript. TY is guarantor of this work and had full access to all the data in the study and the accuracy of the data analysis. All authors read and approved the final manuscript.

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Tables

Due to technical limitations, tables 1 and 2 is only available as a download in the Supplemental Files section.

Figures

Figure 1 (i)

Figure 1 (ii)

Figure 1

Correlation between the change in SD-FBG and s-Alb, HbA1c, and SD-FBG at baseline. The data of Gla-300 group is indicated in Figure 1(i) and Deg group in 1(ii), respectively. SD-FBG: standard division of fasting blood glucose; HbA1c: hemoglobin A1c.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Table1XRDeg.xlsx](#)
- [Table2XRDeg.xlsx](#)