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CLINICAL TRIAL

Comparison of insulin glargine 300 U/mL and insulin degludec using flash glucose monitoring: A randomized cross-over study

Mizuho Yamabe[1]*, Mami Kuroda[1], Yasuyo Hirosawa[1], Hiromi Kamino[1], Haruya Ohno[2], Masayasu Yoneda[2]

[1]Department of Internal Medicine, Murakami Memorial Hospital, Onomichi, and [2]Department of Endocrinology and Diabetic Medicine, Hiroshima University Hospital, Hiroshima City, Hiroshima, Japan

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***Correspondence**
Mizuho Yamabe
Tel.: +81-848-22-3131
Fax: +81-848-23-3508
E-mail address:
mizuhoy@urban.ne.jp

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ABSTRACT

Aims/Introduction: We compared the efficacy and safety of insulin glargine 300 U/mL (Gla300) and insulin degludec U100 (Deg) using a flash glucose monitoring system.

Materials and Methods: A total of 24 Japanese patients with type 2 diabetes were randomized to receive once-daily Gla300 (n = 12) or Deg (n = 12) in the morning. The primary end-points were the mean percentage of time in the target glucose range (70–179 mg/dL) and hypoglycemia (<70 mg/dL), as measured using flash glucose monitoring during the last 7 days of each 14-day period.

Results: The percentages of time with glucose levels <70 mg/dL were not significantly different between the two insulin treatments. No significant differences were observed in the percentages of time with glucose levels of 70–179 mg/dL or ≥180 mg/dL. The percentage of time with nocturnal hypoglycemia with Gla300 was significantly lower than that with Deg treatment (P = 0.021). This difference might be attributable to the difference in the duration of action between the two formulations, and the incidence of nocturnal hypoglycemia with Deg treatment was associated with the concomitant use of metformin (P = 0.035).

Conclusions: The two formulations were comparable in efficacy, whereas the incidence of nocturnal hypoglycemia was significantly lower with Gla300. Thus, the present study suggests that, although Gla300 and Deg are comparable long-acting insulin analogs, Gla300 is safer with respect to the incidence of hypoglycemia.

INTRODUCTION

In patients with type 2 diabetes, implementation of strict glycemic control at disease onset is well-known to be effective for preventing diabetic complications[1]. However, strict glycemic control has been reported to increase the risk of hypoglycemia[2,3]. Severe hypoglycemia and nocturnal hypoglycemia are considered to be important limiting factors in strict glycemic control, and they are risk factors for adverse events, cardiovascular disease and mortality[4–6]. Furthermore, hypoglycemia, which can be a serious problem for patients, has been shown to negatively impact treatment outcomes[6,7] and reduce quality of life[8,9]. Thus, in the treatment of diabetes, it is critical to achieve favorable glycemic control while preventing hypoglycemia.

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Insulin glargine 300 U/mL (Gla300) and insulin degludec U100 (Deg) are long-acting, once-daily, basal insulin analogs. Both reduce the risk of hypoglycemia over a 24-h period, including nocturnal hypoglycemia, compared with insulin glargine 100 U/mL (Gla100), which is the most widely used dose of basal insulin analog at present[10–13]. However, only a few studies have been carried out to compare Gla300 and Deg to determine which is more effective and safe. Therefore, in the present study, we compared the efficacy and safety of Gla300 and Deg with respect to glycemic control in type 2 diabetes patients.

METHODS

The present single-center, randomized, open-label, parallel-group, two-period, cross-over study of patients with type 2 diabetes was conducted from March to July 2017. This study was carried out in accordance with the Declaration of Helsinki

(1975, revised in 2013). Before the study, the protocol was approved by the ethics committee of Murakami Memorial Hospital (No. 2017-2). A total of 24 type 2 diabetes patients who had been treated with Deg in the morning and oral hypoglycemic agents at the outpatient clinic at Murakami Memorial Hospital, Onomichi, Hiroshima, Japan, for ≥3 months were included. All participants provided written informed consent. The protocol is shown in Figure 1. The patients were randomly divided into two groups: Gla300-Deg and Deg-Gla300. In the Gla300-Deg group, the pretrial Deg was replaced with the same dose of Gla300, and a FreeStyle Libre Pro® – a flash glucose monitoring (FGM) system (Abbot Diabetes Care, Chicago, Illinois, USA) – was worn to begin measurements. The doses were adjusted during the first week of wearing the FGM system, and measurements were obtained for 1 week thereafter. The algorithm for dose adjustment was as follows. When the blood glucose level before breakfast was ≥250 mg/dL, the dose was increased by 3 units; when the level was 200–249 mg/dL, the dose was increased by 2 units; when the level was 150–199 mg/dL, the dose was increased by 1 unit; when the level was 100–149 mg/dL, the dose was not changed; and when the level was <100 mg/dL, the dose was decreased by 1 unit. The dose was adjusted daily.

We used a titration that we believed would not cause hypoglycemia, but would be conducive to the experimental timeline. Because the FGM was limited to 14 days and adjustments within that time period were necessary, we carried out daily, rather than weekly adjustments. At an outpatient visit 1 month later, Gla300 was switched to the same dose of Deg, and FGM was restarted. As with Gla300, the Deg dose was adjusted during the first week of monitoring, and measurements were obtained for 1 week thereafter. The Deg-Gla300 group was treated and monitored in the same manner, but with the dosage schedules reversed. During the study period, the patients received individualized instructions on proper diet and compliance.

Outcome measures and measurements

The primary end-points of the present study were the efficacy and safety outcomes based on the FGM parameters. The efficacy outcome was calculated as the mean percentage of time within the FGM glucose range of 70–179 mg/dL for the seven consecutive days of each treatment period. The safety outcome was calculated as the mean percentage of time with glucose levels of <70 mg/dL. Secondary end-points based on FGM included the standard deviation, coefficient of variation, mean glucose level and mean percentage of time with severe hypoglycemia (<54 mg/dL), nocturnal (00.00–05.59 hours) hypoglycemia (<70 mg/dL), and hyperglycemia (≥180 mg/dL) for the seven consecutive days. The mean of daily difference for a 24-h period was used as an index of day-to-day glucose variability. According to the ADA guideline and 2018–2019 Diabetes treatment guide, we defined <70 mg/dL as the hypoglycemic range, <54 mg/dL as the severely hypoglycemic range and 70–179 mg/dL as the normal range[14,15].

Statistical analysis

The data are expressed as the mean ± standard deviation, unless otherwise stated. The findings were compared between the two treatments using Student's *t*-tests or χ^2-tests. A *P*-value of <0.05 was considered significant for all analyses. Statistical analyses were carried out using JMP 10 software (SAS Institute Inc., Cary, North Carolina, USA).

RESULTS

The overall patient composition is shown in Figure S1. Table 1 shows the patient characteristics. There were no significant differences in any of the patient parameters between the two

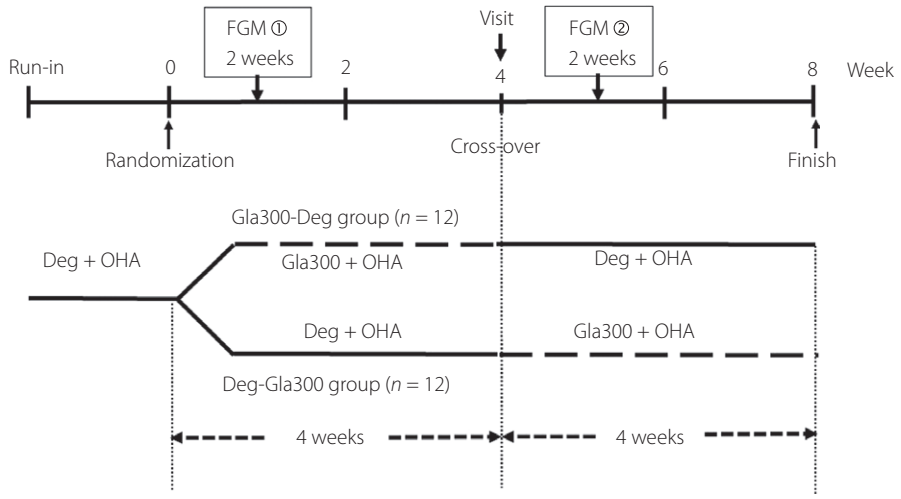

Figure 1 | Study design. Deg U100, insulin degludec U100; FGM, flash glucose monitoring; Gla300, insulin glargine 300 U/mL; OHA, oral hypoglycemic agent.

Table 1 | Baseline characteristics of randomized patients

	Overall (n = 24)	Gla300-Deg (n = 12)	Deg-Gla300 (n = 12)	P-value
Age (years)	70.7 ± 7.6	69.5 ± 9.5	71.9 ± 5.2	0.447
Duration of diabetes (years)	14.0 ± 9.3	11.6 ± 9.1	16.5 ± 9.1	0.199
Male, n (%)	12 (50.0)	5 (41.7)	7 (58.3)	0.436
BMI (kg/m^2)	23.1 ± 3.3	24.0 ± 2.4	22.3 ± 3.6	0.179
HbA1c (%)	6.80 ± 0.35	6.78 ± 0.33	6.83 ± 0.34	0.780
S-CPR (ng/mL)	1.1 ± 0.6	1.3 ± 0.7	0.9 ± 0.4	0.057
Basal insulin dosage (U)	6.0 ± 3.0	5.9 ± 2.5	6.2 ± 3.5	0.843
Antidiabetic agents				
DPP4 inhibitor (n)	20	10	10	0.500
Metformin (n)	11	7	4	0.313
SGLT2 inhibitor (n)	6	4	2	0.394
Sulfonylurea (n)	1	1	0	0.322
Glinides (n)	16	7	9	0.550
α-GI	14	5	9	0.212

Values are expressed as mean ± standard deviation. α-GI, alpha-glucosidase inhibitor; BMI, body mass index; Deg, insulin degludec U100; DPP4, dipeptidyl peptidase-4; Gla300, insulin glargine 300 U/mL; HbA1c, glycated hemoglobin; S-CPR, serum C-peptide; SGLT2, sodium–glucose cotransporter 2.

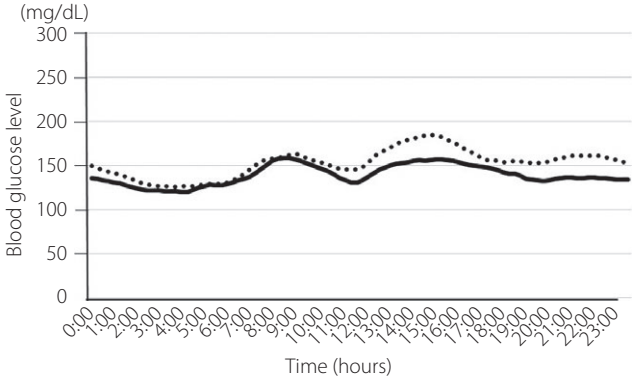

Figure 2 | Glycemic variability over 24 h in patients during treatment with insulin glargine 300 U/mL or insulin degludec. Glucose levels were calculated from the flash glucose monitoring on the seventh measurement day. Dotted line, insulin glargine 300 U/mL; solid line, insulin degludec.

treatment groups. Figure 2 shows the average daily glucose profiles for the seven consecutive days of measurement using FGM. The glucose variations were similar between the two treatment groups. The percentages of time with blood glucose levels of 70–179 mg/dL (normal range), which indicates effective glycemic control, were 73.4 ± 14.9% with Gla300 treatment and 77.3 ± 11.8% with Deg treatment (Table 2). The percentages of time with blood glucose levels of ≥180 mg/dL (hyperglycemic range) were 26.4 ± 15.1% and 21.1 ± 12.6%, respectively. No significant differences were observed between the two treatments in either parameter. During the 7-day FGM, the mean blood glucose levels were 153.5 ± 22.2 mg/dL with Gla300 treatment and 146.2 ± 19.3 mg/dL with Deg treatment; the coefficient of variation was 26.0 ± 4.7% and 26.9 ± 5.4%, respectively, and the mean of daily difference was 32.2 ± 13.0 and 35.6 ± 15.9 mg/dL, respectively. No significant differences were observed in any of these parameters. The basal insulin doses did not significantly differ between the two groups.

The percentages of time with blood glucose levels <70 mg/dL (hypoglycemic range) were 0.22 ± 0.50% with Gla300 treatment and 1.58 ± 3.93% with Deg treatment, showing no significant difference. The percentages of time with blood glucose levels <54 mg/dL (severe hypoglycemic range) were 0.01 ± 0.03% and 0.20 ± 0.77%, respectively, showing no significant difference. The percentages of time in the nocturnal hypoglycemic range (blood glucose <70 mg/dL at 00.00–05.59 hours) were 0.03 ± 0.10% and 0.68 ± 1.34%, respectively. This percentage was significantly lower with Gla300 treatment than with Deg treatment (P = 0.021).

The hourly frequency of hypoglycemia (event/patient) with Gla300 and Deg treatment was 0.04 and 1.08 (from 00.00 to 00.59 hours), 0 and 0.79 (from 03.00 to 03.59 hours), and 0 and 0.58 (from 04.00 to 04.59 hours). The frequency of hypoglycemia was significantly lower with Gla300 treatment (P < 0.05; Figure 3). When the factors associated with nocturnal hypoglycemia during Deg treatment were investigated, a significant difference was observed in the concomitant use of metformin. Nine patients treated with Deg and metformin developed nocturnal hypoglycemia, whereas two did not (P = 0.035).

In addition, the percentage of time with nocturnal hypoglycemia in the group using metformin (n = 11) was 1.45 ± 1.72%, and that in the group not using metformin (n = 13) was 0.03 ± 0.12%. The time with nocturnal hypoglycemia was significantly higher in the group using metformin (P = 0.007).

Table 2 | Flash glucose monitoring parameters of glucose variability in patients treated with insulin glargine 300 U/mL or degludec U100

	Gla300 (n = 24)	Deg (n = 24)	P-value
Mean percentage of time in target glucose range 70–179 mg/dL, (%)	73.4 ± 14.9	77.3 ± 11.8	0.314
Mean percentage of time with hyperglycemia ≥180 mg/dL (%)	26.4 ± 15.1	21.1 ± 12.6	0.194
Mean percentage of time with hypoglycemia <70 mg/dL (%)	0.22 ± 0.50	1.58 ± 3.93	0.100
Mean glucose level (mg/dL)	153.5 ± 22.2	146.2 ± 19.3	0.226
SD (mg/dL)	39.7 ± 8.8	40.1 ± 9.1	0.810
CV (%)	26.0 ± 4.7	26.9 ± 5.4	0.539
MODD (mg/dL)	32.2 ± 13.0	35.6 ± 15.9	0.430
Mean percentage of time with severe hypoglycemia <54 mg/dL (%)	0.01 ± 0.03	0.20 ± 0.77	0.213
Mean percentage of time with nocturnal hypoglycemia <70 mg/dL (%)	0.03 ± 0.10	0.68 ± 1.34	0.021
Mean basal insulin dose (U/day)	6.2 ± 3.3	6.1 ± 3.3	0.895

Values are expressed as means ± standard deviation. CV, coefficient of variation; Deg, insulin degludec U100; Gla300, insulin glargine 300 U/mL; MODD, mean of daily difference; SD, standard deviation of the glucose levels.

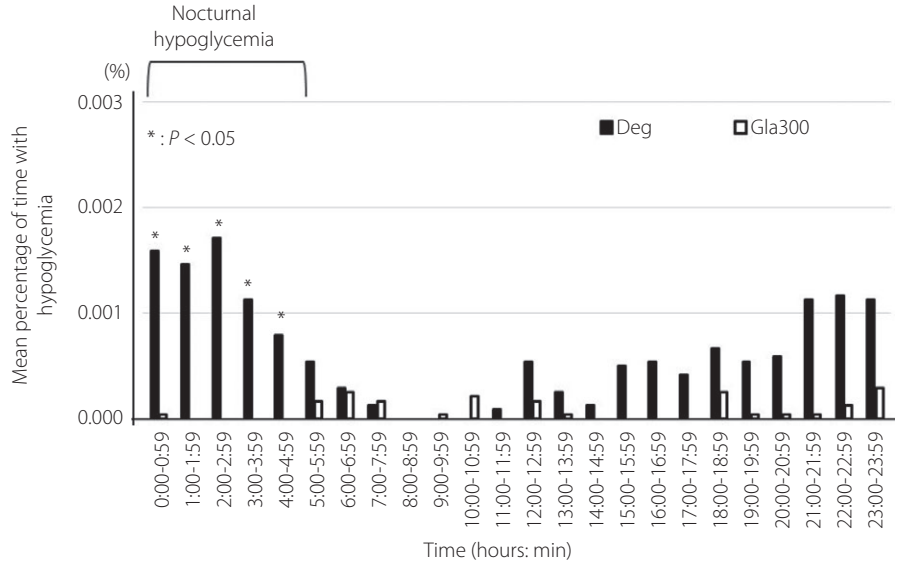

Figure 3 | Mean percentage of time at <70 mg/dL measured by flash glucose monitoring. Deg, insulin degludec U100 (black bar); Gla300, insulin glargine 300 U/mL (white bar). *P < 0.05.

No association was observed with the concomitant use of other drugs. With Gla300 treatment, no concomitant drugs were associated with nocturnal hypoglycemia (data not shown).

DISCUSSION

To optimize glycemic control while minimizing the risk of hypoglycemia, basal insulin analogs, with more constant and long-acting pharmacokinetics and pharmacodynamics, have been developed[16,17]. Gla100 is the most commonly used basal insulin analog. Since Gla300 and Deg were approved as long-acting, once-daily, basal insulin analogs, many clinical studies have compared the efficacy and safety of Gla300 and Gla100 or of Deg and Gla100. In type 2 diabetes patients treated with either basal supported oral therapy or basal–bolus insulin therapy, Gla300 and Deg have been reported to be associated with a lower risk of hypoglycemia than Gla100[18–23]. However, few clinical studies have directly compared the efficacy and safety of Gla300 and Deg.

Using an FGM system, the present study showed that Gla300 and Deg were comparable in efficacy, without significant differences in the percentages of time in the normal and hyperglycemic ranges, mean blood glucose levels, standard deviation, coefficient of variation or day-to-day variation. However, with respect to safety, Gla300 tended to be associated with a lower incidence of hypoglycemia than Deg, and the incidence of nocturnal hypoglycemia was significantly lower for Gla300. Differences between Gla300 and Deg have been reported in their mechanism of action[24,25], half-life[26], duration of action[16,27] and fluctuations in blood glucose levels due to glucose clamp[28]. When we investigated the causes for the higher incidence of

nocturnal hypoglycemia with Deg treatment, no differences were observed in age, body mass index, glycated hemoglobin levels, C-peptide immunoreactivity or basal insulin doses (data not shown). However, although no differences were observed in the Gla300 group in the concomitant use of oral hypoglycemic agents, the Deg group showed a significant difference between patients treated with and without metformin. Metformin is known to inhibit hepatic gluconeogenesis[29,30]. It has been reported that Deg has a half-life of 25 h and a duration of action of >42 h[26,27], whereas Gla300 has a half-life of 18 h and a duration of action of >24 h[16,26]. In the present study, because both formulations were administered in the morning, the difference in duration of action presumably contributed to the difference in the incidence of nocturnal hypoglycemia. Specifically, we assumed that nocturnal hypoglycemia occurred in the Deg group, because residual Deg activity and metformin inhibition of hepatic gluconeogenesis exacerbated night-time glucose homeostasis. In the present study, we could not measure gluconeogenesis during the night, so this remains a speculation.

Rather than standard weekly adjustments, our insulin titrations utilized daily adjustments to allow optimization within the limited, 14-day time-period of the FGM. However, the average number of units of insulin was very small in both groups. In addition, no significant difference was observed between the number of units of insulin administered at the beginning and the end of the study. Therefore, it is unlikely that the frequency of hypoglycemia increased due to daily insulin adjustment. During the study period, no hypoglycemic symptoms were reported by any patient in either group.

The present study had several limitations. The first limitation is that this was a single facility, open label study. The second limitation is that low glucose events were confirmed only by FGM and not by another device, raising the possibility that the actual blood glucose level was not low. Because there was another report of the occurrence of hypoglycemia in asymptomatic patients measured using continuous glucose monitoring[31], regular monitoring of night-time blood glucose levels is important even for patients with well-controlled blood glucose. Although long-acting insulin analogs stabilize blood glucose levels and provide favorable glycemic control through their extended duration of action, this prolonged activity might also adversely affect night-time blood glucose levels. The present study indicates that the drugs used in combination with Deg should receive more consideration. Despite the study limitations, we believe that important information can be garnered from the data, which warrant, at least, further study.

In the present randomized cross-over study using an FGM system, we compared and analyzed the efficacy and safety of Gla300 and Deg in type 2 diabetes patients. Although these two insulin formulations were comparable in efficacy, Gla300 was safer than Deg in terms of the incidence of nocturnal hypoglycemia, especially with concomitant metformin treatment. This difference seems to be caused by the difference in pharmacodynamics of each drug. In the case of Deg, when metformin is used in combination, the present data suggest that attention should be paid to night-time hypoglycemia, of which the patient might be unaware.

DISCLOSURE

M Yamabe has received honoraria for lectures from Novo Nordisk and Sanofi. The other authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1| Flow diagram of study participants. The numbers in parentheses indicate the numbers of study participants at each step.