Endocrine Journal 2019, **66** (8), 745-752

RAPID COMMUNICATION

Comparison of the efficacy and safety of once-daily insulin degludec/insulin aspart (IDegAsp) and long-acting second-generation basal insulin (insulin degludec and insulin glargine 300 units/mL) in insulin-naïve Japanese adults with type 2 diabetes: a pilot, randomized, controlled study

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Abstract. To examine the efficacy and safety of once-daily insulin degludec/insulin aspart (IDegAsp) or once-daily second-generation basal insulin analogs (insulin degludec and insulin glargine 300 units/mL) in insulin-naïve Japanese adults with type 2 diabetes in routine clinical practice. A 12-week multicenter, open-label, randomized, pilot study was performed in 52 subjects with type 2 diabetes treated with oral antidiabetic drugs (OADs). Subjects were randomized to once-daily IDegAsp ($n = 26$) or basal insulin ($n = 26$). The primary endpoint was percent change in HbA1c from baseline to week 12. Furthermore, it was analyzed *post hoc* in subgroups stratified by baseline HbA1c. During a follow-up period, percent change in HbA1c was not significantly different between the two groups ($p = 0.161$). Daily insulin doses and frequency of overall hypoglycemia were also similar in the two groups. In *post hoc* analyses, once-daily basal insulin was more effective than IDegAsp in subjects with HbA1c more than or equal to 8.5% ($p < 0.05$); however, in subjects with HbA1c less than 8.5%, once-daily IDegAsp showed a significant improvement in percent change in HbA1c at week 12, compared with basal insulin ($p < 0.01$). Although there was no apparent difference in the HbA1c-lowering effects between two groups, when compared in subjects with HbA1c less than 8.5%, once-daily IDegAsp showed a significant effect in comparison with once-daily basal insulin. These findings suggest that the baseline HbA1c level might provide the important information for choosing IDegAsp or basal insulin in patients insufficiently controlled with OADs. This trial was registered with UMIN (no. UMIN000035431).

Key words: Insulin degludec/insulin aspart (IDegAsp), Long-acting basal insulin, Insulin degludec, Insulin glargine U300

ONCE-DAILY BASAL INSULIN INJECTION is one of the optimal initiating methods with a relatively low frequency of hypoglycemic events, and widely used in the world [1]. It is also an ideal way because the frequency of injections required is low and the algorithm used to titrate the dose is not complex. The consensus statement by the American Diabetes Association and the European Association for the Study of Diabetes recommends once-daily basal insulin injection therapy as the first step in the introduction of insulin for the treatment of type 2 diabetes [2]. Mimicking physiological insulin

Submitted May 2, 2019; Accepted Jun. 22, 2019 as EJ19-0179
Released online in J-STAGE as advance publication Jul. 12, 2019
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secretion by adding insulin boluses in a sequential fashion (evolving from basal insulin injection to basal-plus-one bolus to basal-plus-two boluses to basal-bolus therapy), but the increase in the frequency of injections required adds an additional burden for patients.

Pharmacokinetic/pharmacodynamics (PK/PD) improvements have been made with the even longer-acting second-generation basal insulin analogs, insulin degludec (IDeg) and insulin glargine 300 units/mL (IGla-300) [3-5], which have smoother PK/PD profiles than insulin glargine 100 units/mL (IGla-100) with lower variability [3, 5]. The BEGIN and EDITION clinical trial development programs for IDeg and IGla-300, respectively, demonstrated similar HbA1c reductions to IGla-100 but with less hypoglycemia in subjects with type 2 diabetes [6, 7].

Insulin degludec/insulin aspart (IDegAsp) is a new combination of insulin consisting of 70% of IDeg and 30% of the rapid-acting prandial insulin aspart (IAsp), in which each component maintains its original independent characteristics without interacting each other [8, 9]. Use of IDegAsp has been associated with lower fasting blood glucose and less frequency of hypoglycemia than other premixed insulin preparations [10]. Moreover, once-daily IDegAsp has a significantly greater effect on reducing glycated hemoglobin (HbA1c) in the phase 3 study than once-daily first-generation basal insulin (IGla-100), and without causing more frequent hypoglycemia [11].

However, direct clinical comparisons between IDegAsp and second-generation basal insulin analogs are to be remained. Here we report the first randomized controlled trial designed to compare the efficacy and safety of once-daily IDegAsp with once-daily second-generation basal insulin analogs (IDeg or IGla-300) in insulin-naïve Japanese adults with type 2 diabetes inadequately controlled with oral antidiabetic drugs (OADs) alone in a clinical setting.

Materials and Methods

Subjects and study design

The pilot trial recruited Japanese insulin-naive subjects with type 2 diabetes, aged ≥20 years with HbA1c ≥7% and a body mass index of ≤35 kg/m^2. All subjects had been treated with ≥1 OAD(s) for >16 weeks and qualified for treatment intensification. Subjects with type 1 diabetes, secondary diabetes, severe renal disease, severe hepatic disease, alcoholism, severe depression or a severe psychological condition, malignancy or abnormal hemoglobinemia were excluded. Subjects who had received a blood transfusion within 4 months before the start of the study, and pregnant and nursing women were also excluded. OADs, antihypertensive agents, statins or fibrates were not newly administered, and their doses were not changed from 8 weeks before the start until the end of the study. Subjects were asked not to alter their lifestyle, including diet, exercise and habits, during the study.

This study, which was carried out in a "real-world" clinical setting, which was a 12-week, open-label, randomized, parallel-group, multicenter, intervention trial conducted in Japan (10 sites) between June 2017 and August 2018. The trial was conducted in accordance with the Declaration of Helsinki and its amendments, and Good Clinical Practice Guidelines. The protocol was approved by the ethics committee of Prefectural University of Kumamoto (approved on 13 June 2017, approval number 29-06). Written informed consent was obtained from all participants before the trial enrollment.

Subjects were randomized 1:1 to treatment with either once-daily IDegAsp or once-daily basal insulin, using a computer-generated allocation schedule. Subjects in the basal insulin group were randomized 1:1 to receive once-daily IDeg or IGla-300 in the same way.

The starting dose was 0.15 units/kg for both trial products. Either IDegAsp or basal insulin was administered subcutaneously either before breakfast or dinner; the injection timing was chosen at the discretion of each subject and maintained throughout the trial. All subjects were scheduled to visit each clinic every 4 weeks and expert physicians adjusted insulin dosage according to the recommendation of the Japan Diabetes Society described as follows. Target plasma glucose level was set between 80 and 129 mg/dL before breakfast and between 80 and 179 mg/dL at 2-hour after meal without causing hypoglycemia [12-16]. Insulin titration was then performed according to the attending physician's instruction to achieve the target plasma glucose level without using insulin titration algorithm, taking into consideration that this study was conducted in a "real-world" clinical setting.

The primary endpoint was percent change in HbA1c from baseline to week 12, calculated as (posttreatment value – baseline value) × 100/baseline value. Other efficacy endpoints included change in daily insulin requirement. The proportion of subjects achieving HbA1c <8% at end of trial was also determined.

Subjects in each group were divided into two subgroups by baseline HbA1c levels (8.5%) according to Monnier *et al.* [17], and the percent change in HbA1c was analyzed *post hoc* in these subgroups.

Safety was assessed on the basis of hypoglycemic episodes and body mass index (BMI). Hypoglycemia was defined as any of the following criteria: (i) the presence of symptoms that were alleviated by oral ingestion of

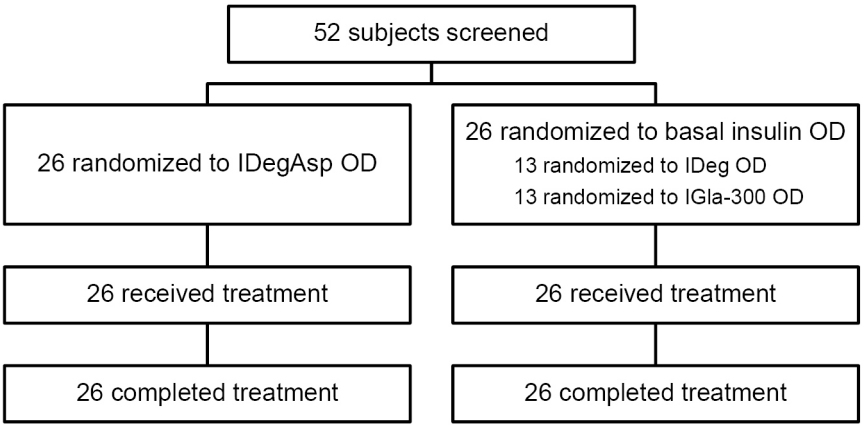

Fig. 1 Flow chart of study participants throughout the trial. Data are the number of study participants. OD: once-daily.

carbohydrates, an intramuscular injection of glucagon or other resuscitative actions; and (ii) a blood glucose level less than 70 mg/dL, regardless of the presence or absence of symptoms [18]. Nocturnal hypoglycemia was defined as hypoglycemia occurring between 0:01 a.m. and 5:59 a.m. Severe hypoglycemia was defined as hypoglycemia accompanied by severe central nervous system symptoms that could not be resolved by the patient and required assistance [6].

Statistical analysis

Data are expressed as median (interquartile range) or number (%). Changes in clinical parameters were evaluated by Wilcoxon signed-rank test or Mann-Whitney U-test. p-values <0.05 were considered to be statistically significant. Data analysis was performed using SPSS v. 11.5 for Windows (SPSS Inc., Chicago, IL, USA).

Results

Clinical baseline characteristics

A total of 52 Japanese subjects were randomized and exposed to IDegAsp (n = 26) or basal insulin (n = 26, IDeg; n = 13, IGla-300; n = 13). All 52 participants completed the trial (Fig. 1). Baseline HbA1c levels in the IDegAsp group and the basal insulin group were 8.9 and 9.6%, respectively. No statistically significant differences in demographics and baseline characteristics were observed between the groups (Table 1).

Overall 70% of participants performed SMBG at baseline. However, participants were not obliged to record their glucose levels with SMBG in the present study.

Glycemic control

Both treatment regimens resulted in similar improvement in HbA1c levels during 12 weeks of the trial (Fig. 2A). There was no significant difference in percent change in HbA1c between the two groups (IDegAsp; –14.5% *vs.* basal insulin; –16.7%, p = 0.227).

In both groups, there was no significant difference in percent change in HbA1c between the subgroup that was injected insulin before breakfast and the subgroup that injected insulin before dinner.

There was no statistical difference between the two groups in the proportion of patients with an HbA1c <8% at week 12 (IDegAsp; 57.7% *vs.* basal insulin; 69.2%, p = 0.388).

In the subgroup analyses, HbA1c levels were significantly decreased in all subgroups (p < 0.05; Fig. 2B, 2C). However, in subjects with more than or equal to 8.5%, percent change in HbA1c at week 12 in the basal insulin subgroup [n = 19 (IDeg, n = 9, IGla-300, n = 10), –21.5%] significantly decreased compared with that in the IDegAsp subgroup (n = 19, –13.1%, p < 0.05). By contrast, in subjects with less than 8.5%, the percent change in HbA1c at 12 weeks in the IDegAsp subgroup (n = 7, –15.2%) significantly decreased than that in the basal insulin subgroup [n = 7 (IDeg, n = 4, IGla-300, n = 3), –7.5%, p < 0.01].

In the basal insulin group, HbA1c levels improved significantly in both subgroups (p < 0.05; Fig. 2D). The percent change in HbA1c was similar between the IDeg and IGla-300 subgroups (IDeg –18.5% *vs.* IGla-300 –14.1%, p = 0.545).

Insulin requirement profiles

The daily insulin requirement profiles are summarized in Table 2. Daily insulin dose increased significantly in both groups (p < 0.05). At the end of the trial, daily insulin doses were similar between the treatment groups: 0.154 U/kg/day for IDegAsp and 0.157 U/kg/day for basal insulin.

In the basal insulin group, daily insulin dose increased significantly in the IGla-300 subgroup at the end of study

Table 1 Demographic and baseline characteristics of the study subjects

Characteristics	IDegAsp ($n = 26$)	Basal insulin			*p*-value (IDegAsp *vs.* basal)	*p*-value (IDeg *vs.* IGla-300)
		Total ($n = 26$)	IDeg ($n = 13$)	IGla-300 ($n = 13$)		
Males/Females	17/9	17/9	10/3	7/6	1.000	0.411
Age (years)	64.0 (56.0–71.0)	54.5 (46.0–66.8)	57.0 (48.0–68.0)	49.0 (45.0–60.0)	0.062	0.390
BMI (kg/m^2)	26.0 (22.5–28.0)	25.6 (23.6–28.7)	25.4 (23.4–28.8)	25.9 (25.0–26.7)	0.840	0.762
HbA1c (%)	8.9 (8.4–10.2)	9.6 (8.6–10.5)	9.5 (8.0–9.9)	9.7 (9.0–10.7)	0.464	0.687
Duration of diabetes (years)	11.0 (5.5–15.5)	7.0 (4.0–10.8)	8.0 (3.0–10.0)	5.0 (4.0–9.0)	0.354	0.920
Fasting C-peptide (ng/mL)	2.72 (1.95–3.28)	1.89 (1.60–2.73)	1.87 (1.74–2.80)	2.04 (1.54–2.48)	0.224	0.801
Creatinine (mg/dL)	0.70 (0.55–0.70)	0.81 (0.67–0.90)	0.78 (0.67–0.78)	0.85 (0.68–0.85)	0.079	0.457
eGFR (mL/min per 1.73 m^2)	66.7 (57.0–85.1)	68.8 (64.9–87.3)	68.1 (64.9–82.5)	69.3 (65.4–88.5)	0.260	0.521
Injection timing						
Morning/Evening	15/11	18/8	10/3	8/5	0.565	0.673
Antidiabetic agents, *n*						
Sulphonylurea	15 (57.7%)	11 (42.3%)	6 (46.2%)	5 (38.5%)	0.406	1.000
α-glucosidase inhibitor	6 (23.1%)	2 (7.7%)	0 (0.0%)	2 (15.4%)	0.249	0.480
Biguanide	13 (50.0%)	19 (73.1%)	8 (61.5%)	11 (84.6%)	0.099	0.378
Thiazolidinedione	3 (11.5%)	1 (3.8%)	0 (0.0%)	1 (7.7%)	0.610	1.000
DPP4 inhibitor	20 (76.9%)	19 (73.1%)	11 (84.6%)	8 (61.5%)	1.000	0.378
SGLT2 inhibitor	7 (26.9%)	8 (30.8%)	2 (15.4%)	6 (46.2%)	1.000	0.202

Data are median (interquartile range) or *n*. BMI: body mass index.

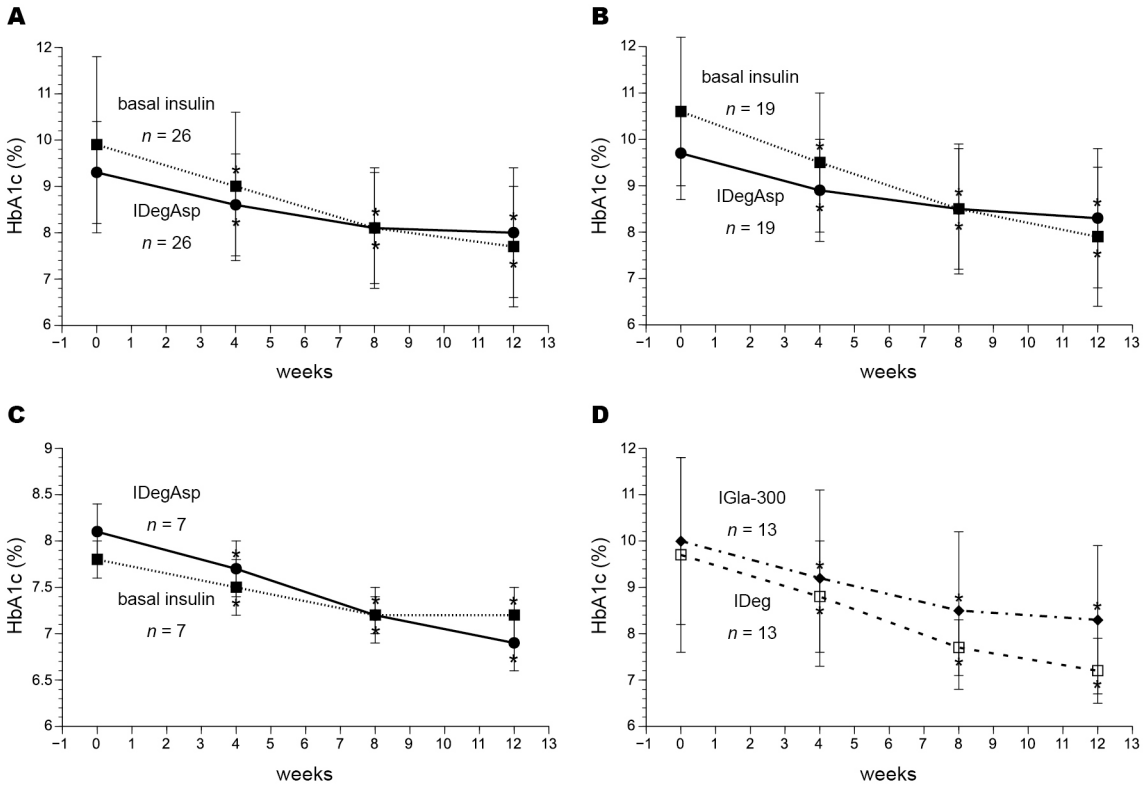

Fig. 2 Time course of HbA1c during the 12-week study. (A) IDegAsp group (closed-circles) *vs.* basal insulin group (closed-squares). (B) IDegAsp subgroup (baseline HbA1c ≥8.5%, closed-circles) *vs.* basal insulin subgroup (baseline HbA1c ≥8.5%, closed-squares). (C) IDegAsp subgroup (baseline HbA1c <8.5%, closed-circles) *vs.* basal insulin subgroup (baseline HbA1c <8.5%, closed-squares). (D) IDeg subgroup (open-squares) *vs.* IGla-300 subgroup (closed -diamonds). Data are means ± SD. *$p < 0.05$ *vs.* baseline.

Table 2 Changes of the daily insulin requirement profiles (unit/kg/day)

	0 week	4 week	8 week	12 week
IDegAsp (n = 26)	0.148 (0.144–0.152)	0.152 (0.144–0.175)*	0.155 (0.144–0.198)*	0.154 (0.143–0.198)*
Basal insulin (n = 26)	0.147 (0.143–0.153)	0.155 (0.145–0.184)*	0.157 (0.148–0.189)*	0.157 (0.145–0.197)*
IDeg (n = 13)	0.146 (0.142–0.152)	0.151 (0.140–0.158)	0.151 (0.140–0.158)	0.145 (0.128–0.158)
IGla-300 (n = 13)	0.147 (0.143–0.155)	0.172 (0.155–0.189)*#	0.172 (0.157–0.199)*#	0.189 (0.160–0.220)*#

Data are median (interquartile range). * $p < 0.05$ *vs.* baseline (0 week). # $p < 0.05$ *vs.* IDeg.

Table 3 Frequency of hypoglycemic episodes during the 12-week study

	IDegAsp	Basal insulin		
		Total	IDeg	IGla-300
Overall				
Participants, *n*	1 (3.8%)	1 (3.8%)	1 (7.7%)	0 (0.0%)
Episodes	1	2	2	0
Rate#	0	0	0	0
Nocturnal				
Participants, *n*	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Episodes	0	0	0	0
Rate#	0	0	0	0
Severe				
Participants, *n*	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Episodes	0	0	0	0
Rate#	0	0	0	0

Data are median or *n*. Rate #, the rate of hypoglycemic episodes per patient-month of exposure.

($p < 0.05$), but not significantly in the IDeg subgroup. Basal insulin dose in the IGlar-300 subgroup was significantly higher than that in the IDeg subgroup at week 4, 8, and 12 ($p < 0.05$, $p < 0.01$ and $p < 0.01$). At 12 weeks, daily dose was 0.145 U/kg/day for IDeg and 0.189 U/kg/day for IGlar-300. The mean daily dose in the IGlar-300 subgroup was 26.9 percent higher than that in the IDeg subgroup.

Hypoglycemia

No severe adverse event was observed during the study period. Frequency of hypoglycemic episodes is summarized in Table 3. Although one episode in the IDegAsp group and 2 episodes in the basal insulin group were recorded during 12 weeks of the trial (difference between groups: $p = 0.978$), neither nocturnal nor severe hypoglycemia episodes were observed in both groups. There was no statistically significant difference in the frequency of overall hypoglycemia between the IDeg and IGlar-300 subgroups ($p = 0.317$).

BMI change

BMI levels were significantly increased at the end of the trial in both groups (IDegAsp; 26.0 kg/m^2 to 26.8 kg/m^2, $p < 0.05$, basal insulin; 25.6 kg/m^2 to 26.6 kg/m^2, $p < 0.01$). There was no statistically significant difference in percent change in BMI between the two groups (IDegAsp 1.19% *vs.* basal insulin 2.04%, $p = 0.475$).

Discussion

The main objective of this pilot, randomized, controlled trial in a clinical setting was to assess the feasibility of insulin initiation with once-daily administration of IDegAsp in patients with type 2 diabetes insufficiently controlled with OADs.

Several studies have reported the comparison of once-daily IDegAsp and once-daily first-generation basal insulin (IGla-100) in patients with type 2 diabetes [11, 19-22]. However, there has been no comparative study between once-daily IDegAsp and once-daily second-generation basal insulin analogs, *i.e.* IDeg and IGla-300. Therefore, our clinical trial focused on the efficacy and safety of these insulin preparations in insulin-naïve subjects.

We observed no significant difference in percent change in HbA1c level from baseline to week 12 between IDegAsp and basal insulin groups in this study. Daily insulin dose was similar between groups at the end of the trial, as were increased in BMI from baseline. Basal insulin administered once-daily was more effective than IDegAsp in subjects with HbA1c more than or equal to 8.5%, however, our study demonstrated the advantage of IDegAsp administered once-daily in subjects with HbA1c less than 8.5%, inducing a significant improvement in the percent change in HbA1c level at week 12, compared with basal insulin. These findings highlight possible differences of the efficacy of IDegAsp among populations, suggesting that the baseline HbA1c level might provide the important information for selecting IDegAsp or basal insulin in patients insufficiently controlled with OADs. As is well known, the relative contribution of the postprandial glucose increment to HbA1c level is larger than that of the fasting glucose increment at HbA1c level in the range below 8.5%, and

fasting hyperglycemia plays a major role as soon as the HbA1c level rises above 8.5% [17]. Nagai *et al.* reported that IDegAsp was more effective than basal insulin in reducing postprandial glucose levels after test meal loading [22]. Although we did not evaluate postprandial glucose levels or 1,5-anhydroglucitol in the present study, this improvement in subjects with HbA1c less than 8.5% was likely due to reduction in postprandial glucose levels caused by IAsp, the bolus component of IDegAsp.

Interestingly, in the basal group, the IGla-300 insulin dose at week 12 was significantly higher than the IDeg dose, although IGla-300 and IDeg provided similar glycemic control improvement with relatively low hypoglycemia risk. These results seemed consistent with the result of the BRIGHT trial [23], a head-to-head trial comparing between IGla-300 and IDeg in insulin-naïve patients with type 2 diabetes, in which IGla-300 was non-inferior to IDeg in reducing HbA1c, whereas the daily dose of IGla-300 was approximately 25 percent higher than that of IDeg group. This difference was to be expected, given the similar doses of IDeg and IGla-100 observed in the BEGIN trial [24] and the higher dose of IGla-300 *vs.* IGla-100 in the EDITION trials [7, 25, 26]. Rosenstock *et al.* described that the greater dose of IGla-300 after subcutaneous injection was needed to compensate for its lower bioavailability owing to the longer residence time of its microprecipitates in the subcutaneous space and subsequent local degradation by tissue proteases [23]. Based on these findings, it seems possible that IGla-300 requires larger amount of insulin than IDeg in order to obtain similar glucose-lowering effect.

In the present study, few diurnal hypoglycemic episodes were observed during 12 weeks in both groups. This is one of the reasons why the increases in insulin dose were small. In the basal insulin group, there was no statistically significant difference in the frequency of overall and nocturnal hypoglycemia between the IDeg and IGlar-300 subgroups. However, two diurnal hypoglycemic episodes were observed in the IDeg subgroups but not in IGla-300 subgroup. In the BRIGHT trial, event rates of anytime and nocturnal confirmed hypoglycemia were lower with IGla-300 than with IDeg during the initial titration period (0–12 weeks) [23]. Recently, Yamabe *et al.* also reported that the incidence of nocturnal hypoglycemia, of which patients might be unaware, with IGla-300 (n = 24) was significantly lower than that with IDeg (n = 24) in crossover study using a flush glucose monitoring (FGM) system [27]. The low-level hypoglycemia might have been overlooked in our study because of lacking daily glucose profile by FGM or continuous glucose monitoring, we might underestimate the frequency of hypoglycemia unawareness but did not observe any serious episodes of hypoglycemia throughout the observation.

There are several limitations in the current trial. First, the number of study subjects is small (n = 52), and the observation period is short (12 weeks). Second, the study was designed as a randomized and parallel-group study. It should have more appropriately conducted as a crossover study. Third, we did not evaluate the daily glucose profile and ask all the participants to perform SMBG in our study. Regardless of the limitations, our study suggests the cutting point of HbA1c level (<8.5%) to choose the use of once-daily IDegAsp.

In conclusion, once-daily IDegAsp and once-daily second-generation basal insulin analogs were comparable in efficacy and safety. However, once-daily IDegAsp was more effective than once-daily basal insulin in subjects with HbA1c less than 8.5%. With respect to efficacy and safety, we propose a novel basal insulin-supported oral therapy regimen with once-daily IDegAsp for patients whose HbA1c level is less than 8.5% and inadequately controlled with OADs in clinical practice. However, the sample size of the current study is small, and thus further studies are required to confirm these findings.

Acknowledgments

The current study was self-funded.

Disclosure

No funding or sponsorship was received for this study or publication of this article. Seiya Shimoda has received honoraria for lectures from Daiichi Sankyo Inc, Ono Pharmaceutical Co. Ltd. and Novo Nordisk Pharma. Eiichi Araki has received honoraria for lectures from Astellas Pharma, MSD, Ono Pharmaceutical, Novo Nordisk Pharma and Sanofi, and scholarship grants from Astellas Pharma, Daiichi Sankyo, Mitsubishi Tanabe Pharma, Nippon Boehringer Ingelheim, Novo Nordisk Pharma, Ono Pharmaceutical, Sanofi, Shionogi, Sumitomo Dainippon Pharma and Takeda Pharmaceutical. The other authors declare no conflicts of interest.

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