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# Efficacy and safety of switching from basal insulin to once-daily insulin degludec/insulin aspart in Japanese patients with inadequately controlled type 2 diabetes: A 4-week, randomized, open-label, treat-to-target study

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## ABSTRACT

**Aims/Introduction:** A prospective, 4-week, single-center, randomized, open-label, parallel-group, treat-to-target study was carried out to develop an algorithm for safe and effective switching from basal insulin to once-daily insulin degludec/insulin aspart (IDegAsp) in patients with inadequately controlled type 2 diabetes.

**Materials and Methods:** Patients were randomly assigned to continue their current basal insulin therapy ($n$ = 10) or to switch to IDegAsp on a 1:1 unit basis ($n$ = 10). The insulin dose could be titrated once weekly, targeting a self-measured blood glucose of 80–100 mg/dL before breakfast. A mixed meal test was carried out at baseline and after 4 weeks.

**Results:** After 4 weeks, the mean daily dose of insulin was similarly increased by 60% in both groups, and there was a significant decrease of mean plasma glucose and glucose area under the glucose concentration vs time curve for 2 h in the meal test. The mean estimated treatment difference (IDegAsp group − basal insulin group) of the mean plasma glucose level was −28 mg/dL (95% confidence interval −47 to −8, $P$ = 0.008) after 4 weeks and that of the area under the glucose concentration vs time curve for 2 h was −2,800 mg/min/dL (95% confidence interval −5,300 to −350, $P$ = 0.028), confirming the superiority of IDegAsp to basal insulin. In the IDegAsp group, the 2-h postprandial plasma glucose level was significantly decreased to the fasting plasma glucose range. There were no confirmed hypoglycemic episodes in either group during the 4-week study period.

**Conclusions:** After switching from basal insulin, the IDegAsp dose can be uptitrated by 60% based on fasting plasma glucose data. However, monitoring of postprandial glucose should be considered before further uptitration of IDegAsp.

## INTRODUCTION

Basal insulin-supported oral therapy (BOT) is commonly used to initiate insulin therapy when oral hypoglycemic agents (OHA) do not achieve adequate glycemic control in patients with type 2 diabetes[1,2]. It involves the addition of once-daily long-acting insulin, such as insulin glargine or insulin degludec, to ongoing OHA therapy. Several clinical trials have supported the efficacy of BOT[3–5]. While supplementing basal insulin is expected to reduce the fasting plasma glucose level, some patients still fail to achieve the target hemoglobin A1c (HbA1c), probably because of postprandial hyperglycemia. Elevated postprandial glucose levels make an important contribution to overall hyperglycemia in patients with diabetes[6,7], suggesting that treatment targeting postprandial glucose in addition to fasting

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plasma glucose might be able to improve glycemic control. Various rapidly acting insulin analogs have been introduced to control postprandial glucose excursions, such as insulin glulisine, lispro and aspart[8]. However, the requirement for additional insulin injections may reduce adherence to treatment[9,10].

Insulin degludec/insulin aspart (IDegAsp) is a novel combination drug (70% insulin degludec [IDeg] and 30% insulin aspart [IAsp]). IDeg and IAsp exist separately in solution[11], allowing formulation as a single injection. After subcutaneous injection, IDeg immediately forms stable multihexamers that create a tissue depot from which IDeg monomers slowly dissociate[12], whereas IAsp monomers are rapidly released into the circulation[13].

Based on the pharmacokinetic and pharmacodynamic profile of IDegAsp, it might be a novel option for BOT that could improve postprandial plasma glucose (although only after one meal a day).

However, IDegAsp has a 30% lower content of basal insulin, suggesting that the fasting plasma glucose level might increase after switching from basal insulin to IDegAsp on a 1:1 unit basis.

Accordingly, the present study was carried out to develop an algorithm for safe and effective switching from basal insulin to once-daily insulin IDegAsp in patients with inadequately controlled type 2 diabetes.

## METHODS

### Study design

The present prospective, 4-week, single-center, randomized, open-label, parallel-group, treat-to-target study[14] was carried out to compare the efficacy and safety of IDegAsp or basal insulin in combination with OHA therapy.

### Participants

Between April 2016 and March 2017, patients with type 2 diabetes were recruited at the outpatient clinic of St. Marianna University Hospital (Kawasaki, Japan). The inclusion criteria were as follows: (i) age ≥20 years; (ii) inadequate glycemic control (HbA1c 7.0–9.0%, and variation of HbA1c by <0.5% within 3 months before recruitment); (iii) body mass index ≤35 kg/m$^2$; and (iv) current treatment for diabetes with once-daily basal insulin (insulin glargine or insulin degludec, which were both widely used basal insulin in Japan) plus oral hypoglycemic agents. The exclusion criteria were as follows: (i) age ≥75 years; (ii) hospital admission to improve glycemic control within the past 1 year; (iii) a history of coronary artery disease, coronary revascularization, stroke or transient ischemic attacks within the past 1 year; (iv) malignancy; (v) severe renal dysfunction (estimated glomerular filtration rate <30 mL/min/1.73 m$^2$); (vi) women who were pregnant, possibly pregnant, planned to become pregnant or were breast-feeding; and (vii) other patients who were considered to be ineligible for the study by the attending doctor. Written informed consent was obtained from all patients. This study was carried out in accordance with the Declaration of Helsinki[15], and was approved by the ethics committee of St. Marianna University School of Medicine. This study was registered with the University Hospital Medical Network Clinical Trials Registry (registration number: UMIN000021629).

### Intervention

None of the 23 participants enrolled in the present study skipped breakfast on a regular basis. At screening, patients were instructed to inject insulin before breakfast irrespective of the usual timing, and then were randomly assigned to continue their basal insulin ($n$ = 11) or switch to IDegAsp ($n$ = 12) on a 1:1 unit basis. A computer-generated list of random numbers was used for allocation of the patients. The insulin dose was titrated weekly at hospital visits or by telephone. Based on the mean self-measured blood glucose (SMBG) level before breakfast during the preceding 7 days, the dose was increased by two units if SMBG was >100 mg/dL or was reduced by two units if it was <80 mg/dL. Glucose was measured using a OneTouch® Ultra™ glucometer (Johnson & Johnson, Tokyo, Japan). Apart from insulin, treatment of the patients was not changed throughout the study period.

### Mixed meal tolerance test

At baseline and after 4 weeks, a standard meal test (total caloric content of 460 kcal, including 53% carbohydrate, 16% protein and 31% fat) was carried out to evaluate the plasma glucose profile (fasting, and 30 min, 60 min, 90 min and 120 min postprandially). The test meal was ingested within 15 min. The total area under the glucose concentration vs time curve for 2 h (glucose $AUC_{0\text{-}2\ h}$) after starting the mixed meal tolerance test (MMTT) was calculated by the trapezoidal rule. HbA1c and other standard laboratory parameters were measured at 0 min in the meal test.

### Outcomes

The primary efficacy end-point was the change of glucose $AUC_{0\text{-}2\ h}$ from baseline in the MMTT carried out after 4 weeks. Secondary efficacy end-points included changes of fasting plasma glucose and HbA1c from baseline. Safety was assessed from the insulin dose, hypoglycemic events and other adverse events. Hypoglycemic events included episodes with a confirmed plasma glucose level <70 mg/dL or severe episodes requiring assistance (plasma glucose confirmation not required).

### Statistical analysis

It was calculated that a sample size of 20 patients was required to detect a decrease of prandial glucose corresponding to that reported in a phase 3 trial[16] with a 5% level of significance (two-sided) and a power of 80%.

Categorical variables were expressed as numbers, and continuous variables were expressed as the mean ± standard deviation or standard error. The Shapiro–Wilk normality test was used to assess whether variables had a normal distribution. Analysis

of the significance of within-group differences of normally distributed data was carried out by using the two-tailed paired *t*-test, whereas the unpaired *t*-test was used to assess differences between groups. Differences were considered to be significant if the *P*-value was <5%. All statistical analyses were carried out with SPSS 21.0 software (IBM Japan Ltd, Tokyo, Japan).

## RESULTS

A total of 23 patients were enrolled in the present study. Three patients did not complete the study because of protocol deviation ($n = 1$), scheduling difficulties ($n = 1$) and personal reasons ($n = 1$). The remaining 20 participants (14 men and 6 women) completed the study and formed the per protocol set for analysis. At screening, 11 participants were being treated with IDeg, and the other nine participants were receiving insulin glargine (IGlar).

Baseline clinical characteristics of the 20 participants are shown in Table 1. There were no differences between the two groups with regard to sex, age, duration of diabetes, body mass index, fasting plasma glucose, HbA1c, blood pressure and serum lipid profile. The mean daily dose of basal insulin was 16.8 U (0.22 U/kg) in the basal insulin group and 11.2 U (0.16 U/kg) in the IDegAsp group ($P = 0.120$). The glucose $AUC_{0\text{-}2\ h}$ during the baseline MMTT was also similar in the two groups (23,600 ± 4,300 mg/min/dL in the basal insulin group and 24,100 ± 4,800 mg/min/dL in the IDegAsp group, $P = 0.82$).

The insulin dose was titrated weekly at hospital visits or by telephone. In both groups, the mean daily dose of insulin was significantly increased by 60% from the baseline dose to 23.0 ± 7.8 U in the basal insulin group ($P < 0.001$ vs baseline) and 16.9 ± 6.8 U in the IDegAsp group ($P < 0.001$ vs baseline). There was no significant difference of the insulin dose between the two groups (estimated treatment difference [IDegAsp group − basal insulin group]: −0.5 U; 95% confidence interval [CI] −3.2 to 2.2, $P = 0.697$; Figure 1a). At the end of the study period, the SMBG before breakfast was significantly decreased from baseline by 29 ± 8 mg/dL in the basal insulin group ($P = 0.007$), and was decreased by 18 ± 9 mg/dL in the IDegAsp group ($P = 0.328$; Figure 1b).

The plasma glucose profile of each group during the MMTT is shown in Figure 2. After 4 weeks of basal insulin or IDegAsp, the mean plasma glucose level and glucose $AUC_{0\text{–}2\ h}$ were significantly decreased in both groups. At the end of the study period, the mean plasma glucose level showed a significant decrease of 22 ± 6 mg/dL in the basal insulin group ($P = 0.008$ vs baseline) and 49 ± 7 mg/dL in the IDegAsp group ($P < 0.001$ vs baseline). After 4 weeks, the mean

**Table 1** | Characteristics of the participants

| | Basal group $n = 10$ | IDegAsp group $n = 10$ | *P*-value |
|---|---|---|---|
| Female (*n*) | 5 | 1 | 0.06 |
| Age (years) | 68 ± 8 | 66 ± 13 | 0.73 |
| Duration of diabetes (years) | 16 ± 7 | 20 ± 11 | 0.39 |
| Body mass index (kg/m$^2$) | 28.8 ± 5 | 25.8 ± 5 | 0.21 |
| Fasting plasma glucose (mg/dL) | 155 ± 25 | 144 ± 37 | 0.42 |
| HbA1c (%) | 7.5 ± 1 | 7.6 ± 1 | 0.60 |
| Systolic blood pressure (mmHg) | 133 ± 13 | 132 ± 16 | 0.88 |
| Diastolic blood pressure (mmHg) | 80 ± 11 | 75 ± 10 | 0.30 |
| LDL cholesterol (mg/dL) | 91 ± 29 | 89 ± 40 | 0.60 |
| HDL cholesterol (mg/dL) | 53 ± 20 | 44 ± 8 | 0.58 |
| Triglycerides (mg/dL) | 138 ± 46 | 124 ± 47 | 0.26 |
| Basal insulin at screening (IGlar/IDeg) | 5/5 | 4/6 | 0.64 |
| Basal insulin dose at screening (U/day) | 16.8 ± 9.4 | 11.3 ± 5.3 | 0.12 |
| Oral hypoglycemic agents at screening (*n*) | | | |
| Biguanide | 8 | 7 | |
| Sulfonylurea | 2 | 0 | |
| Glinide | 5 | 4 | |
| α-Glucosidase inhibitor | 4 | 4 | |
| Thiazolidinedione | 2 | 0 | |
| DPP-4 inhibitor | 7 | 7 | |
| SGLT2 inhibitor | 0 | 0 | |

Data are expressed as the mean ± standard deviation for continuous variables or the number for categorical variables. Differences between two groups were assessed by the *t*-test for continuous variables and by Fisher's exact test for categorical variables. DPP-4, dipeptidyl peptidase-4; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein cholesterol; IDegAsp, insulin degludec/insulin aspart; IGlar/IDeg, insulin glargine/insulin degludec; LDL, low-density liporotein cholesterol; SGLT2, sodium–glucose cotransporter-2.

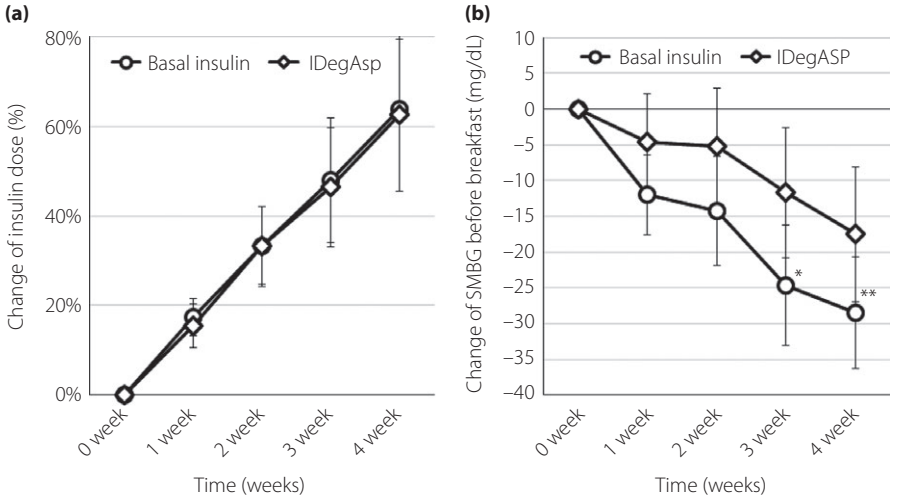


**Figure 1** | Change of (a) the insulin dose and the (b) mean self-measured blood glucose (SMBG) level before breakfast in the preceding 7 days in patients continuing basal insulin or switching to insulin degludec/insulin aspart (IDegAsp) for 4 weeks (W). Data are the mean ± standard error. **P* < 0.05, ***P* < 0.001 vs 0 W.

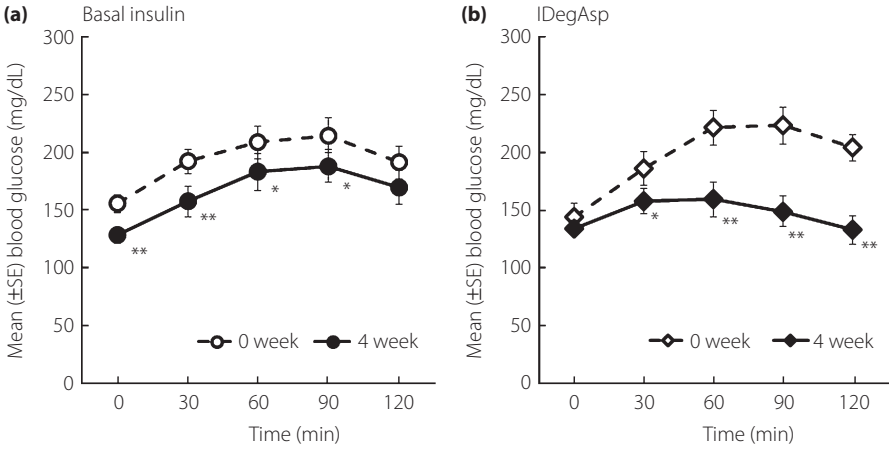


**Figure 2** | Mean plasma glucose level in the mixed meal tolerance test at baseline and after 4 weeks (W). Data are the mean ± standard error (SE). **P* < 0.05, ***P* < 0.001 vs 0 W. IDegAsp, insulin degludec/insulin aspart.

estimated treatment difference (IDegAsp group − basal insulin group) was −28 mg/dL (95% CI −47 to −8, $P = 0.008$; Figure 3a). At the end of the treatment period, the glucose $AUC_{0\text{-}2\ h}$ was 20,300 ± 4,500 mg/min/dL in the basal insulin group ($P = 0.004$ vs baseline) and 18,000 ± 4,100 mg/min/dL in the IDegAsp group ($P < 0.001$ vs baseline; Figure 3b). The mean estimated treatment difference (IDegAsp group − basal insulin group) was −2,800 mg/min/dL (95% CI −5,300 to −350, $P = 0.028$) after 4 weeks, confirming that IDegAsp was superior to basal insulin (Figure 3b). In the IDegAsp group, the 2-h postprandial plasma glucose level was significantly decreased from 204 ± 36 mg/dL to 133 ± 40 mg/dL ($P < 0.001$), which was in the fasting plasma glucose range.

In the basal insulin group, HbA1c decreased significantly ($P = 0.009$) from 7.5 ± 0.5% at baseline to 7.2 ± 0.5% at week 4, and it also decreased significantly ($P = 0.012$) from 7.6 ± 0.7% to 7.3 ± 0.5% in the IDegAsp group, but there was no significant difference between the two groups (estimated treatment difference: −0.04% point; 95% CI −0.28 to 0.20, $P = 0.74$). Within the IDegAsp group, there were no differences in treatment response between those previously treated with IGlar and those with IDeg (data not shown).

No severe adverse events occurred in either group during the study period, including confirmed hypoglycemic episodes.

## DISCUSSION

The present 4-week study explored the efficacy and safety of switching from once-daily basal insulin to once-daily IDegAsp on a 1:1 unit basis and then titrating the dose once a week using a simple algorithm in Japanese patients with inadequately

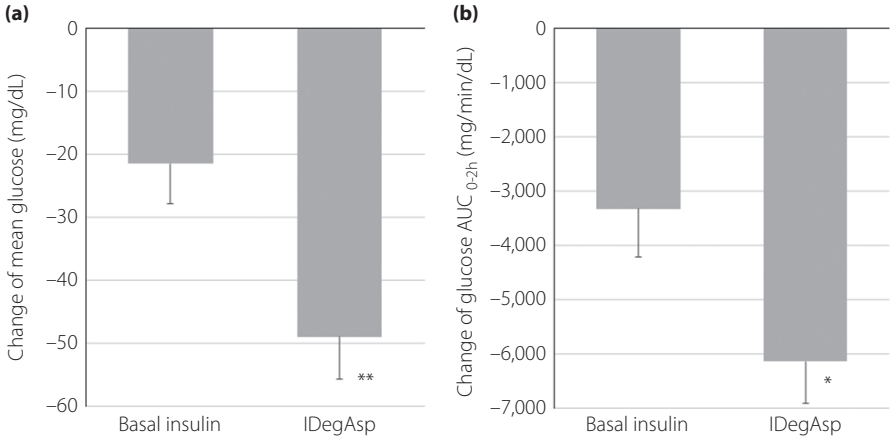


**Figure 3** | Change of (a) the mean blood glucose level and (b) glucose area under the concentration vs time curve $(AUC)_{0-2\ h}$ in the mixed meal tolerance test at baseline and after 4 weeks. Data are the mean ± standard error. *$P < 0.05$, **$P < 0.001$ vs basal insulin. IDegAsp, insulin degludec/insulin aspart.

controlled type 2 diabetes. Baseline characteristics of the two groups were similar. At the end of the study, the mean daily dose of insulin was increased by 60% in both groups after titration according to the SMBG before breakfast (Figure 1a). As expected in a trial with a treat-to-target design, glycemic control showed significant improvement in both groups, with no difference in the reduction of HbA1c from baseline between the two groups. However, plasma glucose profile differed in the 4-week MMTT (Figure 2a,b), as reflected by the differences of the mean glucose level (Figure 3a) and glucose $AUC_{0-2\ h}$ (Figure 3b). The fasting plasma glucose level was significantly decreased in the basal insulin group. In the IDegAsp group, fasting plasma glucose was also decreased (although not significantly), and postprandial plasma glucose was significantly decreased to the fasting plasma glucose range. There were no episodes of confirmed hypoglycemia in either group during the 4-week treatment period.

In a phase 3 treat-to-target trial of once-daily IDegAsp, no significant differences were reported in the postprandial changes of glucose other than after the largest meal at dosing time[17]. Together with the present findings, this report suggests that improving the postprandial plasma glucose level, even after only one meal a day, can decrease HbA1c. The present findings are supported by the report that the relative contribution of postprandial plasma glucose to HbA1c gradually increases as HbA1c becomes lower[18]. Thus, better glycemic control could have been achieved in the IDegAsp group if this study had been extended until fasting blood glucose reached the target value. Another phase 3 treat-to-target trial of once-daily IDegAsp therapy for 26 weeks in insulin-naïve Japanese patients showed that IDegAsp provided superior long-term glycemic control compared with IGlar, with a similar fasting plasma glucose level and insulin dose[16]. However, postprandial hypoglycemia would be expected to occur if we continued to titrate the dose of IDegAsp based on SMBG data before breakfast alone, because the postprandial plasma glucose level was decreased to the fasting plasma glucose range in the IDegAsp group (Figure 3b). The previous phase 3 trial also showed that weekly insulin dose titration to achieve a pre-breakfast target plasma glucose level of 70–89 mg/dL led to confirmed hypoglycemia in 52.6% of patients using IDegAsp, and the hypoglycemic episodes occurred in the evening (postprandial state)[17]. The titration algorithm used in the present study was less aggressive, with a target plasma glucose of 80–100 mg/dL before breakfast, and was found to be suitable for safe and effective switching to IDegAsp.

The present study had some limitations, including a small sample size and its single-center, open-label design. In addition, all of the participants were instructed to inject insulin before breakfast, so we were unable to assess the influence of other injection timing. Further study is warranted to determine the optimal timing of IDegAsp. Furthermore, the achieved fasting glucose levels were above the target range of 80–100 mg/dL in both groups, suggesting that a 4-week study was not long enough for titration of insulin. Despite these limitations and the potential for bias, the present results could assist physicians with titration of the IDegAsp dosage after switching from basal insulin.

With respect to efficacy and safety, we propose a novel BOT regimen with IDegAsp injected before breakfast for patients inadequately controlled by once-daily basal insulin. When switching from basal insulin, the IDegAsp dose can be uptitrated by 60% based on SMBG before breakfast. However, postprandial glucose monitoring should be considered to minimize the risk of postprandial hypoglycemia when uptitrating the IDegAsp dose beyond 60%.

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## DISCLOSURE

The authors declare no conflict of interest.

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