Efficacy of switching from insulin glargine to insulin degludec in patients with type 1 diabetes: a 16-week retrospective study

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Abstract We retrospectively investigated the effect of switching from insulin glargine (IGlar) to insulin degludec (IDeg) on glycemic control in Japanese patients with type 1 diabetes mellitus. We also evaluated the dose of IDeg, and assessed weight gain and the risk of hypoglycemia after switching. Forty-five patients with type 1 diabetes were switched from IGlar (once daily or twice daily) to IDeg (once daily) during routine medical care. Data were collected for 16 weeks after switching from IGlar to IDeg. The mean HbA1c (%) in weeks 4, 8, 12, and 16 was lower than it was in week 0 (8.0 ± 1.0 , 8.0 ± 1.4 , 7.9 ± 1.1 , 7.6 ± 1.0 vs. 8.3 ± 1.3 %, $p < 0.01$). The total basal insulin dose (TBD) was significantly lower after 16 weeks of IDeg as compared to IGlar treatment (0.30 ± 0.12 vs. 0.24 ± 0.11 U/kg/day, $p = 0.001$). In the twice-daily IGlar group, TBD showed a significant decrease from 0.33 ± 0.12 to 0.26 ± 0.11 U/kg/day ($p < 0.001$) after switching to IDeg. In the once-daily IGlar group, TBD showed a slight but not significant decrease from

0.23 ± 0.08 to 0.20 ± 0.09 U/kg/day ($p = 0.97$). Hypoglycemic episodes were transiently increased, but the change was not significant. The blood glucose fluctuation was evaluated from self-monitoring data and the coefficient of variation (CV) was calculated. The CV showed only a minimal change from 48.3 ± 17.1 to 48.6 ± 14.2 % at 12 weeks after switching to IDeg ($p = 0.73$). In conclusion, once-daily IDeg improved glycemic control in patients with type 1 diabetes compared to the control achieved with IGlar, without increasing the risk of hypoglycemia. When switching from IGlar (especially twice daily), it is recommended that the initial dose of IDeg should be reduced in order to decrease the risk of hypoglycemia.

Keywords Basal-bolus therapy · Blood glucose fluctuation · Type 1 diabetes

Introduction

In patients with type 1 diabetes mellitus, physiological replacement of insulin is challenging because exogenous insulin needs to cover both basal and postprandial (bolus) insulin requirements. In landmark trials, intensive basal-bolus therapy was demonstrated to improve glycemic control and reduce the risk of long-term complications associated with type 1 diabetes [1, 2]. Insulin degludec (IDeg) was developed as an ultra-long-acting basal insulin. New long-acting basal insulin analogues with more predictable pharmacodynamics may decrease the risk of hypoglycemia relative to current insulin analogues such as insulin glargine and insulin detemir [3]. After subcutaneous injection, IDeg forms soluble multihexamers that slowly dissociate into monomers, resulting in a flat and consistent

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insulin action profile. While insulin degludec has a half-life of 24 h, insulin glargine has a half-life of only 12 h, and its glucose-lowering effect is stronger during the first 12 h after injection than during the subsequent 12 h [4]. The flat insulin action curve and fourfold smaller variability of insulin degludec compared with insulin glargine [5] result in a similar efficacy but a lower risk of hypoglycemia [6].

It has been suggested that a dose conversion rate of 90 % should be employed when switching patients from insulin glargine to IDeg. Previous studies have indicated that this dose conversion rate is appropriate, but insulin doses were determined according to the algorithms in such trials. While the beneficial effects of IDeg have been demonstrated in several clinical trials, the optimum IDeg regimen for routine clinical practice in Japan remains unknown. In addition, patients with type 1 diabetes mellitus adjust their insulin dose according to their meals and level of activity. Therefore, it is important to compare the efficacy of insulin glargine and IDeg under real-life conditions.

The primary objective of the present study was to evaluate the dose of IDeg required when Japanese patients with type 1 diabetes mellitus switched from insulin glargine to IDeg, while the secondary objectives were to assess glycemic control, glucose fluctuation, weight gain, and the risk of hypoglycemia after switching.

Subjects and methods

This study retrospectively evaluated patients with type 1 diabetes who switched from insulin glargine (IGlar) to IDeg. Ninety-seven diabetic patients taking IDeg were screened during routine medical care at Yokohama City University Medical Center from March 1, 2013 to September 1, 2013. Patients were included if they were at least 18 years old and had type 1 diabetes mellitus, and were excluded if they had gestational diabetes. Type 1 diabetes was diagnosed by the detection of GAD antibodies and a fasting C-peptide level of <0.6 ng/ml. Forty-seven patients who fitted these criteria were enrolled in this study. Electronic medical records were used to identify patients, and data were collected from 4 weeks before to 16 weeks after switching insulin. Patients who experienced events that could influence the glucose level (such as hospitalization or intercurrent disorders) during the 4-month study period were also excluded. Two subjects discontinued IDeg due to hospitalization or transfer to a different hospital before completing 16 weeks of treatment and were excluded from this study. Therefore, this study evaluated 45 patients who switched from insulin glargine (IGlar) to IDeg. Institutional ethics committee approval was

obtained for this study, and it was performed in accordance with the Declaration of Helsinki.

The primary outcome measures were the mean basal insulin doses in units/kg/day on the index dates, which were the date of switching from IGlar to IDeg and 4, 8, 12, and 16 weeks after switching. The mean total insulin dose (basal plus bolus) was also determined in patients using more than one type of insulin. Secondary outcome measures were the changes in HbA1c and body weight up to 16 weeks after switching. In addition, the frequency of hypoglycemia was assessed from 4 weeks before to 16 weeks after switching, based on episodes in the electronic medical records.

Subjects were switched to IDeg at 90–100 % of the IGlar dose if they were on once-daily injection of IGlar, or at 80–90 % of the IGlar dose if they were on twice-daily IGlar, according to the method reported previously [4]. Treat-to-target therapy was performed for 16 weeks, and the insulin dose was varied with the aim of achieving a fasting plasma glucose level <130 mg/dl or HbA1c <7.0 % according to the 2013 *Evidence-based Practice Guideline for the Treatment for Diabetes in Japan* [7]. IDeg was injected once daily—either before breakfast, before dinner, or at bedtime—during the study period.

Blood samples were taken from an antecubital vein before switching and approximately every 4 weeks during the study. HbA1c was measured by high-performance liquid chromatography and the plasma glucose level was measured by the glucose oxidase method.

Glycemic control was evaluated 4 weeks before switching and 4, 8, 12, and 16 weeks after switching to IDeg, based on the blood glucose profile obtained from self-monitoring of blood glucose (SMBG) and the HbA1c level. To assess the blood glucose fluctuation, the coefficient of variation (CV; standard deviation of the glucose level divided by the mean value) was calculated over 28 days. Hypoglycemia was defined as a blood glucose level of <3.8 mmol/l (70 mg/dl).

Statistical analysis

Differences between normally distributed variables were assessed using a two-tailed Student's *t*-test (paired test within groups and unpaired test between groups). Differences between non-normally distributed variables were assessed using a Wilcoxon test for paired differences within groups.

Continuous variables are presented as the mean $\pm$ standard deviation (SD), while categorical variables are tabulated as frequencies and percentages. A *p* value of <0.05 was considered to indicate statistical significance. All statistical analyses were performed with SPSS version 22.0 for Windows (IBM Corporation, Armonk, NY, USA).

Results

Clinical and laboratory characteristics at baseline and after treatment

Forty-seven patients with type 1 diabetes who fitted the enrollment criteria entered this study, but two of those subjects were excluded as described in “Subjects and methods.” The remaining 45 patients (19 men and 26 women) were included in the analysis. The patients were 44.2 ± 12.7 years old and had a BMI of 21.5 ± 2.7 kg/m². Duration of diabetes was 14.8 ± 7.9 years and they had bad glycemic control (HbA1c 8.3 ± 1.3 %). No patient discontinued treatment due to deterioration of blood glucose levels. Seventeen subjects were treated with IGLar once daily (GLonce) and 28 subjects used IGLar twice daily (GLtwice). As shown in Table 1, mean HbA1c was significantly lower after 16 weeks. This improvement occurred quite rapidly (4 weeks: 8.0 ± 1.0 %, $p = 0.005$ vs. baseline, Tables 1, 2) without a significant increase in body weight. According to stratified analysis, both the GLtwice and the GLonce groups showed significant improvements in mean HbA1c. No significant change in body weight was observed in either group.

Mean basal insulin dose over time

The total basal insulin dose (TBD) was significantly lower after 16 weeks of IDeg treatment than after the corresponding IGLar treatment (Table 2). However, the total bolus insulin dose did not change during this study and the TBD/total daily insulin dose (TDD) ratio was also unchanged. In the twice-daily IGLar group, IDeg was initiated at around 80 % of the previous insulin dose and TBD showed a significant decrease from 0.33 ± 0.12 to 0.25 ± 0.12 U/kg/day ($p < 0.001$) after switching to IDeg, and this persisted to week 16. In addition, the TBD/TDD ratio showed a significant decrease.

In the once-daily IGLar group, IDeg was initiated at around 90–100 % of the IGLar dose and TBD was almost unchanged. While TBD and the TBD/TDD ratio were slightly but not significantly decreased after 16 weeks in the GLtwice group, these variables remained similar to baseline (4 weeks before switching) in the GLonce group.

SMBG and glucose fluctuation

The 6-point SMBG was performed in 30 patients for 16 weeks. The 6-point SMBG profile did not change significantly from baseline to 16 weeks after switching to IDeg (data not shown). The mean CV was also unchanged during the study period (Fig. 1).

Safety

IDeg was well tolerated, and no serious adverse events were reported in either group. The total number of episodes of hypoglycemia increased significantly in the first 4 weeks after switching compared with baseline (Table 3). However, the frequency of hypoglycemia was almost the same as the baseline frequency by the end of the study. Nocturnal hypoglycemia (0:00–6:00) tended to increase in frequency during the first 4 weeks after switching to IDeg, but this frequency did not change significantly over the course of the study.

Discussion

This retrospective observational study showed that switching patients with type 1 diabetes from an IGLar-based to an IDeg-based regimen led to significantly improved glycemic control without significant weight gain. IDeg was initiated at around 80–90 % of the prior insulin dose and TBD showed a significant decrease. Both total hypoglycemic episodes and nocturnal hypoglycemia showed transient increases, but the glucose CV did not change

Table 1 Changes in mean glycosylated hemoglobin (HbA1c) and body weight

	Baseline	4 weeks	8 weeks	12 weeks	16 weeks
HbA1c (%)					
Total (%) $n = 45$	8.3 ± 1.3	$8.0 \pm 1.0^{\dagger}$	$8.0 \pm 1.4^{\dagger}$	$7.9 \pm 1.1^{\ddagger}$	$7.6 \pm 1.0^{\dagger}$
GLonce (%) $n = 17$	8.0 ± 1.1	7.7 ± 0.7	$7.7 \pm 1.4^*$	$7.7 \pm 1.1^*$	$7.2 \pm 0.7^*$
GLtwice (%) $n = 28$	8.5 ± 1.3	$8.2 \pm 1.0^{\dagger}$	$8.2 \pm 1.3^*$	$8.1 \pm 1.1^{\dagger}$	$7.8 \pm 1.0^*$
Body weight (kg)					
Total $n = 45$	57.4 ± 10.3	57.7 ± 9.4	57.1 ± 7.4	57.2 ± 7.6	58.0 ± 7.6
GLonce $n = 17$	61.2 ± 8.4	61.9 ± 9.6	56.8 ± 6.1	58.7 ± 7.1	59.9 ± 6.5
GLtwice $n = 28$	55.2 ± 10.8	55.4 ± 8.9	57.3 ± 8.3	56.4 ± 8.1	57.0 ± 8.2

Data were compared with baseline values using the paired *t*-test

* $p < 0.05$, $^{\dagger} p < 0.01$, $^{\ddagger} p < 0.001$

Table 2 Mean basal and total insulin doses at baseline and at the conclusion of the study

	IGlar baseline	IDeg				Difference in 16 weeks (IGlar – IDeg) (% change)
		4 weeks	8 weeks	12 weeks	16 weeks	
Total						
Total insulin dose (U/day)	42.3 ± 16.5	38.1 ± 14.9 [†]	40.0 ± 13.7 [‡]	39.8 ± 13.5 [‡]	39.8 ± 13.5 [‡]	2.5 (−5.9) [‡]
Total insulin dose (U/kg/day)	0.72 ± 0.27	0.65 ± 0.25 [†]	0.69 ± 0.23 [†]	0.68 ± 0.22 [‡]	0.68 ± 0.22 [†]	0.04 (−5.5) [‡]
Bolus insulin dose (U/day)	25.2 ± 10.4	24.8 ± 10.3	25.0 ± 10.4	25.0 ± 10.5	24.9 ± 10.5	0.3 (−1.2)
Bolus insulin dose (U/kg/day)	0.43 ± 0.18	0.43 ± 0.18	0.43 ± 0.18	0.43 ± 0.18	0.43 ± 0.18	0.0 (0.0)
Basal insulin dose (U/day)	17.8 ± 7.5	15.1 ± 6.7 [‡]	15.4 ± 6.4 [†]	15.6 ± 5.8 [†]	15.2 ± 6.1 [‡]	2.6 (−10.1) [‡]
Basal insulin dose (U/kg/day)	0.30 ± 0.12	0.25 ± 0.10 [‡]	0.25 ± 0.11 [†]	0.25 ± 0.11 [†]	0.24 ± 0.11 [‡]	0.06 (−20.0) [‡]
TBD/TDD	0.46 ± 0.18	0.44 ± 0.19	0.44 ± 0.19	0.43 ± 0.18	0.43 ± 0.20	0.03(−7.0)
GLonce <i>n</i> = 17						
Basal insulin dose (U/day)	15.1 ± 6.0	13.7 ± 6.9	14.8 ± 5.4	14.2 ± 4.5	13.6 ± 4.5	1.5 (−10.0)
Basal insulin dose (U/kg/day)	0.23 ± 0.09	0.21 ± 0.10	0.22 ± 0.09	0.20 ± 0.10	0.20 ± 0.09	0.03 (−13.0)
TBD/TDD	0.43 ± 0.18	0.42 ± 0.19	0.42 ± 0.20	0.41 ± 0.20	0.41 ± 0.20	0.02 (−4.9)
GLtwice <i>n</i> = 28						
Basal insulin dose (U/day)	19.4 ± 8.0	14.8 ± 7.7 [†]	15.8 ± 7.0 [†]	16.4 ± 6.3 [†]	16.1 ± 6.7 [†]	3.3 (−17.0) [†]
Basal insulin dose (U/kg/day)	0.33 ± 0.12	0.25 ± 0.12 [†]	0.27 ± 0.11 [†]	0.27 ± 0.11 [†]	0.26 ± 0.11 [†]	0.07 (−21.2) [†]
TBD/TDD	0.49 ± 0.17	0.46 ± 0.19 [*]	0.46 ± 0.19 [*]	0.44 ± 0.18 [†]	0.44 ± 0.21 [*]	0.05 (−11.4) [*]

Values are mean ± standard deviation. The difference between the two groups in terms of the change from baseline was analyzed using two-sample *t*-tests.

GLonce IGlar once daily, *GLtwice* IGlar twice daily, *TBD* total daily dose of the basal insulin dose, *TDD* total daily dose of insulin.

* $p < 0.05$, [†] $p < 0.01$, [‡] $p < 0.001$

Fig. 1 Changes in the coefficient of variation (CV) for the 6-point self-monitored blood glucose profile over 16 weeks

significantly. These results suggest that it is necessary to reduce TBD when switching from IGlar to IDeg. Thus, once-daily IDeg improved glycemic control in patients with type 1 diabetes relative to IGlar, with a low risk of hypoglycemia and no significant increase in weight.

The improvement in glycemic control observed in the present study may have been due to the pharmacokinetic profile of IDeg, which has a slower and milder peak and a longer duration of action than IGlar [5]. Switching to IDeg from twice-daily IGlar administration resulted in an improvement in glycemic control that was potentially of

clinical significance. When once-daily IGlar is used as the basal insulin therapy in insulin-depleted patients, they often show large diurnal variations in blood glucose due to the dawn phenomenon or the Somogyi effect [8]. It has been reported that glycemic control can be improved in these patients by splitting the basal insulin dose and giving it twice daily [9]. In the present study, 27 patients were receiving twice-daily IGlar. Thus, our study also demonstrated that switching from twice-daily administration of IGlar to once-daily IDeg can maintain glycemic control with fewer injections. As shown in Table 1, 17 subjects were using IGlar once daily (*GLonce* group) and 28 subjects were on IGlar twice daily (*GLtwice* group) before switching. Two-thirds of the patients were switched to once-daily IDeg without any deterioration of glycemic control after 16 weeks. It was reported that patients who inject insulin less frequently have a higher QOL [10], which suggests that switching from twice-daily IGlar to once-daily IDeg may improve the QOL of patients with type 1 diabetes.

The manufacturer of IDeg suggests that a dose conversion rate of 90 % should be used when switching patients from IGlar to IDeg, but it is not clear whether this is the optimum conversion rate for switching from IGlar. In a previous study that compared IDeg with IGlar in patients with type 1 diabetes, the daily insulin dose was

Table 3 Episodes of total hypoglycemia and nocturnal hypoglycemia from baseline to week 16

	IGlar (baseline) −4 to 0 weeks	IDeg			
		0–4 weeks	4–8 weeks	8–12 weeks	12–16 weeks
Total hypoglycemia (events/4 weeks)					
Total	5.1 ± 7.7	6.8 ± 8.1, <i>p</i> = 0.61	7.7 ± 9.3, <i>p</i> = 0.008	7.9 ± 9.8, <i>p</i> = 0.01	6.3 ± 6.8, <i>p</i> = 0.07
GLonce <i>n</i> = 17	4.5 ± 9.7	6.4 ± 10.1, <i>p</i> = 0.37	6.4 ± 9.9, <i>p</i> = 0.24	6.2 ± 11.5, <i>p</i> = 0.16	4.9 ± 6.6, <i>p</i> = 0.64
GLtwice <i>n</i> = 28	5.46 ± 6.3	7.1 ± 6.8, <i>p</i> = 0.09	8.4 ± 9.0, <i>p</i> = 0.02	9.0 ± 8.7, <i>p</i> = 0.02	7.1 ± 6.8, <i>p</i> = 0.07
Nocturnal hypoglycemia (events/4 weeks)					
Total	0.29 ± 0.82	0.33 ± 0.95, <i>p</i> = 0.83	0.49 ± 1.18, <i>p</i> = 0.12	0.53 ± 1.12, <i>p</i> = 0.11	0.40 ± 0.94, <i>p</i> = 0.35

Values are mean ± standard deviation. The difference between the two groups in terms of the change from baseline was analyzed using the Wilcoxon signed rank test.

GLonce IGlar once daily, GLtwice IGlar twice daily

significantly lower in the IDeg group, with dose ratios (insulin degludec/insulin glargine) of 88 % [11] and 91 % [12] for basal insulin. According to recent Japanese reports, the dose of IDeg was 80 and 76 % of the IGlar dose, respectively [13, 14]. In the present study, the dose of IDeg was around 80 % of the IGlar dose in the twice-daily group and 90 % in the once-daily IGlar group, and blood glucose tended to decrease within a few days after starting IDeg, in agreement with previous reports. Since the conversion rate differed between the GLonce and GLtwice groups, it seems that the frequency of basal insulin administration should be taken into consideration when determining the optimum conversion rate for switching from IGlar.

According to recent reports, the dose of IDeg was equivalent to [15], 18 % lower than [16], and 10 % lower (this study) than baseline in the GLonce group. In addition, the dose of IDeg was reduced by 9 % [15], 13 % [12], 24 % [14, 16], and 21 % (this study) compared with baseline in the GLtwice group. These differences might be partly attributable to differences in handling the bolus insulin dose. Bolus insulin was increased in a previous study, while the bolus insulin dose was almost unchanged in the present study [15]. Thus, when patients are switched from once-daily IGlar to once-daily IDeg, it is recommended that the initial IDeg dose should be reduced by 10–20 % to reduce the risk of hypoglycemia. In addition, when patients are transferred from twice-daily IGlar to once-daily IDeg, it is recommended that the initial IDeg dose should be reduced by 20–30 % to reduce the risk of hypoglycemia, and then the dose should be adjusted based on the response of blood glucose.

Recent studies have indicated that glycemic variability might play a role in the pathogenesis of atherosclerosis,

and may be an independent risk factor for cardiovascular complications in diabetic patients [16–18]. In order to reduce hypoglycemic events, emphasis should be placed on efforts to control glucose fluctuations as well as HbA1c and FPG. Therefore, we need to find appropriate methods to improve glucose fluctuations. There have only been a few comparisons of the effects of IGlar and IDeg on glucose variability. In a clamp study, the day-to-day variability of the glucose-lowering effect was 4 times smaller in IDeg groups than in IGlar groups [5]. However, the glucose CV determined by SMBG did not change significantly from baseline to 16 weeks after switching to IDeg in the present study. This may have been because two-thirds of the patients switched from twice-daily injection of IGlar, since there is less intraday variability of BG levels with twice-daily IGlar compared with once-daily IGlar [9]. Recently, Komuro reported that there was no difference in glycemic variability when treatment with IGlar for 2 weeks was compared with treatment with IDeg for 2 weeks. Therefore, a prospective study that compares the effect on glucose fluctuation of twice-daily IGlar with that of once-daily IDeg is needed.

Hypoglycemia is of particular concern in diabetes because it influences cerebrovascular disease. It was not possible to determine the effect of IDeg on the overall risk of hypoglycemia because not all patients had sufficient SMBG data from the pre-study period. However, SMBG data did show that the frequency of hypoglycemia increased slightly in the first 4 weeks after switching, after which it gradually decreased due to adjustment of the insulin dose, and became comparable with baseline by 16 weeks after switching. There was no significant change in the frequency of hypoglycemia throughout the study.

Thus, it is possible to achieve good glycemic control by using lower doses of IDeg with the same risk of hypoglycemia.

Some limitations of this study should be noted. First, it was a retrospective analysis with a small patient population. Second, the effect of IDeg on the glucose fluctuation remains unknown. Third, the study period was short and it was not a crossover trial. Therefore, a larger-scale prospective, double-blind crossover study should be performed to confirm our data. In addition, continuous blood glucose monitoring may aid further investigations.

In conclusion, once-daily IDeg improved glycemic control with a low risk of hypoglycemia in patients with type 1 diabetes who switched from IGlax. When patients are switched from IGlax to IDeg, it is recommended that the initial IDeg dose should be reduced by 10–20 % to decrease the risk of hypoglycemia.

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Human rights statement and informed consent All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (Yokohama City University School of Medicine, an Ethical Committee) and with the Helsinki Declaration of 1964 and its subsequent revision.

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