Efficacy and safety of switching from insulin glargine to insulin degludec in young people with type 1 diabetes

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Abstract. We evaluated the efficacy and safety of switching to insulin degludec (IDeg) from insulin glargine (IGlar) as basal-bolus therapy in young people with type 1 diabetes. The subjects were 36 patients, 21.3±1.0 years of age, with type 1 diabetes. IGlar had previously been injected once daily in 25 patients and twice daily in 11. They were then switched from IGlar to once-daily injection of IDeg. Both fasting plasma glucose (FPG) and HbA1c levels decreased significantly from 134±3.9 mg/dL and 7.9±0.2% at baseline to 116±2.2 mg/dL and 7.4±0.2% at 12 months after starting IDeg (P<0.0001 and P<0.001, respectively). Overall and nocturnal hypoglycemia (PG<70 mg/dL) frequencies also decreased significantly from 4.9±0.7 and 2.0±0.3 times/month to 2.4±0.3 and 0.4±0.1 times/month at 12 months after starting IDeg (P<0.005 and P<0.0005, respectively). The daily basal insulin dose was significantly reduced from 0.48±0.04 units/kg/day at baseline to 0.38±0.03 units/kg/day at the end of the study period (P<0.0001), which corresponded to 79.2% of the baseline value. Trends were similar in patients receiving the once-daily injection and those given twice-daily injections, but basal-insulin value reductions from baseline were more marked in patients receiving twice-daily injections of basal insulin (76.0% vs. 82.6% of the baseline value). These results suggest that switching from IGlar to an appropriate dose of IDeg may effectively control hyperglycemia while reducing the frequency of hypoglycemia episodes in young Japanese people with type 1 diabetes.

Key words: Basal-bolus therapy, Glycemic control, Insulin degludec, Type 1 diabetes, Young people

MANAGEMENT of type 1 diabetes in adolescents and young adults is known to be more difficult than in mature adults, because of greater insulin resistance associated with endocrine changes and the often erratic lifestyles of young people which can contribute to poor adherence to self-management of diabetes [1]. In addition, glycemic control during this period is crucial for preventing future microvascular and macrovascular complications. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Investigation and Complications (DCCT/EDIC) studies demonstrated that appropriate glycemic control during adolescence and young adulthood can reduce the risks of developing these diabetic complications [2-4]. On the other hand, hypoglycemia, in particular nocturnal hypoglycemia, is considered to be the major barrier to achieving optimal glycemic control. Several studies have demonstrated that hypoglycemia has a detrimental effect on cognitive function. Fear of hypoglycemia can lead to reluctance to titrate to glycemic targets with sufficient doses of insulin, thereby resulting in hyperglycemia and suboptimal HbA1c levels [5]. Furthermore, an insufficient insulin supply can place patients at risk for metabolic deterioration, which can progress to diabetic ketoacidosis (DKA). DKA is still one of the major causes of mortality in young people with type 1 diabetes [6].

Basal-bolus regimens with insulin analogues have been widely used in patients of all ages with type 1 diabetes. Rapid acting insulin analogue (Ra), with a
rapid onset and shorter duration of action than regular insulin, is frequently used as pre-meal bolus regimen, whereas long acting insulin analogue (La), with a more stable effect and longer duration of action than neutral protamine Hagedorn (NPH) insulin, is usually used as the basal regimen [7]. La may contribute to achieving optimal glycemic control with fewer hypoglycemic episodes more effectively than Ra by providing a continual background level of insulin [8]. Insulin glargine (IGlar) has long been widely used as the main form of La, and reportedly lasts for up to 24 hours, though a waning effect can be seen at approximately 20 hours after the injection [9]. Approximately 70-80% of patients using IGlar give themselves a once-daily injection, whereas others require twice-daily injections to cover their 24-hour basal insulin supplementation [8-11]. Patients requiring twice-daily injections of basal insulin tend to need a higher dose of insulin to attain optimal glycemic targets, and experience more frequent episodes of hypoglycemia [8, 10].

Recently, insulin degludec (IDeg, Novo Nordisk, Bagsvaerd, Denmark), a new generation ultra-long acting insulin analogue, has become available in the European Union, Japan, and other countries. After subcutaneous injection, IDeg forms a deposit of soluble multihexamers from which insulin is slowly released into the circulation. It has a terminal half-life of approximately 25 hours, and its duration of action exceeds 42 hours [12, 13]. Phase 3 trials (BEGIN) demonstrated that IDeg reduced blood glucose levels in adult patients with diabetes, regardless of whether it was type 1 or type 2, and decreased nocturnal hypoglycemia as compared with IGlar, though the overall frequencies of hypoglycemia did not differ significantly [14, 15]. However, little is known about the pharmacokinetics or clinical use of IDeg in young people with type 1 diabetes. Biester et al. [16] reported only that the ultra-long pharmacokinetic properties of IDeg observed in adults were retained in children and adolescents with type 1 diabetes. Recently, Thalange et al. [17] reported that IDeg offered glycemic control and frequencies of hypoglycemia similar to those achieved with La of insulin detemir (IDet), but reduced hyperglycemia with ketosis at a once-daily daily injection when used in these age groups of patients with type 1 diabetes.

This study aimed to evaluate the efficacy and safety of IDeg as basal-bolus therapy after switching from IGlar during a 12-month period in young Japanese patients with type 1 diabetes.

Materials and Methods

The study subjects consisted of 36 young Japanese patients, 11 males and 25 females, 21.3±1.0 years of age (20 patients: 15-19 years of age, 13: 20-35 years of age) with a duration of diabetes, at the time of starting the study, of 10.1±1.5 years. All the patients were fully maturated in sexual development with Tanner stage 4 or 5. No patients were obese. The mean body weight was 52.0±1.8 kg and the body mass index (BMI) was 20.0±1.4 at the beginning of the study. FPG and glycated hemoglobin (HbA1c), as expressed by National Glycohemoglobin Standardization Program (NGSP) values, at baseline were 134±3.9 mg/dL and 7.9±0.2%, respectively. They had neither progressive microvascular complications, such as proliferative retinopathy and renal insufficiency, nor psychosocial problems.

The patients had previously been treated with basal-bolus regimens with insulin aspart or insulin lispro as the bolus insulin regimen injected at each meal, and IGlar as the basal insulin regimen injected once- or twice-daily, i.e., 25 patients injected IGlar once daily and 11 injected IGlar twice daily, before starting the study. Clinical characteristics in subjects, those receiving once-daily injection of IGlar and those receiving twice-daily injections IGlar before using IDeg, are shown in Table 1.

After obtaining informed consent from the patients and their parents, for those <20 years of age, the basal insulin preparation was switched from IGlar to IDeg with a once-daily injection in all subjects. IDeg was injected at bedtime in 25 patients, before breakfast in 7 and before dinner in 4, as previously prescribed for IGlar. The basal-injection doses of IDeg were initially equivalent to those previously prescribed for IGlar, but were then titrated to attain self-monitored FPG levels between 90-140 mg/dL, as conducted when use of IGlar before changing to IDeg. The bolus-injection doses were determined by a carbohydrate counting method, with the goal of achieving self-monitored 1- to 2-hour postprandial levels of plasma glucose (PG) below 180 mg/dL. Daily injection-doses of bolus insulin were changeable according to carbohydrate consumption in each patient, however, the insulin to carbohydrate ratio was not changed before and throughout the study period. Titration-role for determination of injection-doses in basal and bolus insulin were similarly adopted during the study period.

The patients were requested to continue daily self-
Monitoring of PG before each meal and at bedtime every day, postprandially once or twice a week, and when diurnal and/or nocturnal symptoms of hypoglycemia were recognized at any time. All the patients continued self-monitoring of PG regularly, and kept the rule of adopting insulin doses according to PG levels.

Confirmed hypoglycemia was defined as self-monitored PG levels <70 mg/dL. Hypoglycemic episodes occurring between 11 pm and 7 am were classified as nocturnal. Nocturnal hypoglycemia was estimated when the patients recognized symptoms of hypoglycemia and found self-monitored PG levels <70 mg/dL, Severe episodes as having impaired consciousness or seizure requiring assistance from other persons [7]. These definitions were similarly adapted before and throughout the study period.

We compared mean values in self-monitored FPG and HbA1c levels, frequencies of overall and nocturnal episodes of confirmed hypoglycemia per patient-month and basal insulin dose per kg·body weight·day at the 3rd, 6th and 12th months after starting IDeg to those at baseline. We also compared these indices between the patients receiving once-daily and twice-daily injections of IGlar prescribed before starting IDeg.

FPG was measured by each patient using a glucometer (One Touch Ultra, Johnson & Johnson, New Brunswick, USA) at home. HbA1c was determined by a high performance liquid chromatography method at the laboratory of Nihon University Hospital (reference NGSP value: 4.6-6.1%).

Table 1  Subjects characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All patients</th>
<th>Patients with OD</th>
<th>Patients with TD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects, n</td>
<td>36</td>
<td>25</td>
<td>11</td>
</tr>
<tr>
<td>Age, years</td>
<td>21.3 ± 1.0</td>
<td>21.5 ± 1.2</td>
<td>23.9 ± 1.7</td>
</tr>
<tr>
<td>Duration of diabetes, years</td>
<td>10.1 ± 1.5</td>
<td>10.0 ± 1.8</td>
<td>10.2 ± 1.9</td>
</tr>
<tr>
<td>Male/female</td>
<td>11/25</td>
<td>4/21</td>
<td>7/4</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>52.8 ± 2.0</td>
<td>52.3 ± 2.2</td>
<td>53.6 ± 2.4</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>20.0 ± 1.4</td>
<td>19.5 ± 1.2</td>
<td>21.0 ± 1.5</td>
</tr>
<tr>
<td>FPG, mg/dL</td>
<td>134.1 ± 3.9</td>
<td>138.2 ± 4.4</td>
<td>124.6 ± 7.8</td>
</tr>
<tr>
<td>HbA1c (NGSP), %</td>
<td>7.9 ± 0.2</td>
<td>8.1 ± 0.2</td>
<td>7.4 ± 0.4</td>
</tr>
<tr>
<td>CPR, ng/mL</td>
<td>0.2 ± 0.2</td>
<td>0.1 ± 0.1</td>
<td>0.2 ± 0.2</td>
</tr>
<tr>
<td>BID, U/kg/day</td>
<td>0.48 ± 0.04</td>
<td>0.46 ± 0.04</td>
<td>0.50 ± 0.09</td>
</tr>
</tbody>
</table>

OD, once-daily injection of IGlar before using IDeg; TD, twice-daily injections of IGlar before using IDeg; BID, basal insulin dose. The results are expressed as mean ± SE.

Statistical analyses

The results were expressed as mean ± SE. The Wilcoxon signed-rank test was used to statistically assess the differences between two independent values. One-way repeated measures ANOVA with Greenhouse-Geisser correction was used to statistically assess the differences in means of values over time, and post-hoc multiple comparisons were conducted to test the mean changes of values from baseline with Dunnett’s method. P<0.05 was taken to indicate a statistically significant difference. All statistical analyses were performed using IBM SPSS Statistics version 23.0 (IBM Corp, Armonk, New York, USA).

Results

Comparisons of FPG and HbA1c levels, hypoglycemia frequencies, and basal insulin doses between the values at baseline and those at the 3rd, 6th and 12th month after starting IDeg in all subjects (Table 2)

Both FPG and HbA1c levels decreased significantly after changing to IDeg as compared with the values at baseline, and these improvements were evident early in the study period, i.e., at the 3rd month, and were sustained for the entire 12 months.

Frequencies of confirmed overall and nocturnal hypoglycemic episodes per patient-month decreased significantly after changing to IDeg, and the decrease was more marked in nocturnal hypoglycemia. We found no difference in the frequencies of overall and nocturnal hypoglycemia according to the timing of IDeg injection (data not shown). No severe hypoglycemic episodes occurred at any time during the study period.

Basal insulin doses per kg·body weight·day were significantly decreased starting early in the study period, i.e., at the 3rd month, and were ultimately 79.2% of the baseline value.
There were no significant differences in FPG and HbA1c levels, frequency of hypoglycemia and basal insulin doses between the two-age groups; i.e. patients with 15-19 years of age and those with 20-35 years of age throughout the study period (data not shown).

Body weight and BMI did not change significantly. There were no adverse events associated with IDeg use, excluding mild hypoglycemia, at any time during the study period.

**Comparisons of FPG and HbA1c levels, hypoglycemia frequencies, and basal insulin doses between the values at baseline and those at the 3rd, 6th and 12th months after starting IDeg in patients receiving once-daily injection of IGlar before using IDeg (Table 3)**

In 25 patients treated with once-daily injection of IGlar before starting IDeg, FPG and HbA1c levels decreased significantly after changing to IDeg during the study period.

Frequencies of confirmed overall and nocturnal hypoglycemic episodes per patient-month decreased significantly after starting IDeg, and this decrease was more marked in the nocturnal period. Basal insulin doses per kg·body weight·day decreased significantly after starting IDeg, and were ultimately 82.6% of the baseline value.

**Comparisons of FPG and HbA1c levels, hypoglycemia frequencies, and basal insulin doses between the values at baseline and those at the 3rd, 6th and 12th months after starting IDeg in patients receiving twice-daily injections of IGlar before using IDeg (Table 4)**

Eleven patients receiving twice-daily injections of IGlar before starting IDeg were also evaluated with regard to changes in the same indicators. FPG and HbA1c levels showed significant improvement at the end of the study period as compared with the values at baseline.

Frequencies of confirmed overall hypoglycemic episodes per patient-month decreased significantly at the 12th month, and that during the nocturnal period decreased significantly from the 6th to the 12th month, as compared with the values at baseline. This decrease was more marked in the nocturnal period.

Basal insulin doses per kg·body weight·day decreased significantly after starting IDeg, and were ultimately 76.0% of the baseline value. Therefore, the reduction rate in the basal insulin dose from the baseline was greater in patients previously treated with once-daily injection of IGlar than in those given twice-daily injections of IGlar.

**Discussion**

The Japan Diabetes Society has recommended that glycemic targets for adults with diabetes should be set at HbA1c <7.0% to prevent long-term complications. On the other hand, the International Society for Pediatric and Adolescent Diabetes (ISPAD) has proposed HbA1c targets for children and adolescents with type 1 diabetes of <7.5% [18]. This glycemic target is likewise intended to prevent long-term complications, while also avoid-
and psychological burdens, which can create considerable challenges in adhering to self-management of diabetes. Fear of hypoglycemia is also a barrier to attaining the desired glycemic targets. Suboptimal glycemic control during these periods might be associated with an increased risk of microvascular and macrovascular complications [2-4]. Therefore, qualified intensive insulin therapy using suitable insulin preparations should be devised for patients in these age groups, with the ultimate goal of achieving optimal glycemic control while minimizing hypoglycemia.

In administering basal-bolus insulin regimens, the key issue may be how to use basal insulin and adjust its dose to achieve optimal glycemic control while minimizing frequent hypoglycemic episodes and the occurrence of severe hypoglycemia. Avoiding these hypoglycemic episodes should be given first priority for pediatric patients, because they can potentially cause brain damage such as decreases in neuropsychological or cognitive function [5]. Furthermore, adolescence and young adulthood are periods known to be particularly difficult for maintaining optimal glycemic control while minimizing hypoglycemia [1]. Patients in these age groups have insulin resistance due mainly to hypersecretion of growth hormone [19, 20], and need more basal insulin to achieve optimal glycemic control than young children and mature adults with type 1 diabetes [21, 22]. Furthermore, they often have erratic daily schedules and psychological burdens, which can create considerable challenges in adhering to self-management of diabetes. Fear of hypoglycemia is also a barrier to attaining the desired glycemic targets. Suboptimal glycemic control during these periods might be associated with an increased risk of microvascular and macrovascular complications [2-4]. Therefore, qualified intensive insulin therapy using suitable insulin preparations should be devised for patients in these age groups, with the ultimate goal of achieving optimal glycemic control while minimizing hypoglycemia.

### Table 3
Comparisons of FPG and HbA1c levels, hypoglycemia frequencies, and basal insulin doses between the values at baseline and those at the 3rd, 6th and 12th months after starting IDeg in patients receiving once-daily injection of IGlar before using IDeg

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>3rd month</th>
<th>6th month</th>
<th>12th month</th>
</tr>
</thead>
<tbody>
<tr>
<td>FPG (mg/dL)</td>
<td>138.2 ± 4.4</td>
<td>123.8 ± 3.0</td>
<td>121.0 ± 2.9</td>
<td>117.0 ± 2.8</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>8.1 ± 0.2</td>
<td>7.8 ± 0.1</td>
<td>7.7 ± 0.1</td>
<td>7.6 ± 0.2</td>
</tr>
<tr>
<td>Overall hypoglycemia (/month)</td>
<td>4.2 ± 0.9</td>
<td>3.0 ± 0.5</td>
<td>2.4 ± 0.4</td>
<td>2.2 ± 0.3</td>
</tr>
<tr>
<td>Nocturnal hypoglycemia</td>
<td>1.6 ± 0.4</td>
<td>0.6 ± 0.2</td>
<td>0.6 ± 0.2</td>
<td>0.4 ± 0.1</td>
</tr>
<tr>
<td>Basal insulin dose (U/kg/day)</td>
<td>0.46 ± 0.04</td>
<td>0.41 ± 0.04</td>
<td>0.39 ± 0.03</td>
<td>0.38 ± 0.04</td>
</tr>
<tr>
<td><strong>P</strong></td>
<td>&lt;0.05</td>
<td>&lt;0.005</td>
<td>&lt;0.01</td>
<td></td>
</tr>
</tbody>
</table>

Values are given as mean ± SE. *P* value < 0.05 was considered statistically significant compared between the values at baseline and those at the 3rd, 6th and 12th months after starting IDeg. NS, not significant.

### Table 4
Comparisons of FPG and HbA1c levels, hypoglycemia frequencies, and basal insulin doses between the values at baseline and those at the 3rd, 6th and 12th months after starting IDeg in patients receiving twice-daily injections of IGlar before using IDeg

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>3rd month</th>
<th>6th month</th>
<th>12th month</th>
</tr>
</thead>
<tbody>
<tr>
<td>FPG (mg/dL)</td>
<td>124.6 ± 7.8</td>
<td>113.2 ± 4.1</td>
<td>112.0 ± 3.2</td>
<td>114.1 ± 3.7</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>7.4 ± 0.4</td>
<td>7.2 ± 0.4</td>
<td>7.1 ± 0.3</td>
<td>6.9 ± 0.3</td>
</tr>
<tr>
<td>Overall hypoglycemia (/month)</td>
<td>6.5 ± 1.1</td>
<td>4.8 ± 1.1</td>
<td>4.3 ± 0.8</td>
<td>2.7 ± 0.5</td>
</tr>
<tr>
<td>Nocturnal hypoglycemia</td>
<td>2.7 ± 0.5</td>
<td>1.8 ± 0.8</td>
<td>1.1 ± 0.3</td>
<td>0.4 ± 0.1</td>
</tr>
<tr>
<td>Basal insulin dose (U/kg/day)</td>
<td>0.50 ± 0.09</td>
<td>0.40 ± 0.08</td>
<td>0.39 ± 0.03</td>
<td>0.38 ± 0.03</td>
</tr>
<tr>
<td><strong>P</strong></td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are given as mean ± SE. *P* value < 0.05 was considered statistically significant compared between the values at baseline and those at the 3rd, 6th and 12th months after starting IDeg. NS, not significant.
mizing hypoglycemic episodes, particularly in young people with type 1 diabetes [7, 8, 10]. The ideal basal-insulin preparation would exhibit stable pharmacodynamics with minimal day-to-day and between-subject variations. Several studies have demonstrated that IDeg has these desired pharmacokinetic properties with a low risk of occurrence of hypoglycemia in adults with type 1 diabetes and type 2 diabetes [14, 15, 23]. Heise et al. [23] reported that IDeg showed four times lower pharmacodynamic variability than IGlar under steady-state conditions in adults with type 1 diabetes. Biester et al. [16] demonstrated that the pharmacokinetic characteristics observed in adults were preserved in children and adolescents with type 1 diabetes [16]. Therefore, IDeg is considered to possibly have a more predictable glucose-lowering effect with fewer hypoglycemic events than IGlar.

On the other hand, most studies have reported comparable glucose-lowering effects, showing equivalent FPG and HbA1c levels, of IDeg as compared with IGlar in patients with type 1 diabetes [14, 17, 24-26]. In recent Japanese reports, Kusunoki et al. [27] demonstrated that PG levels during evening time tended to decrease after switching to IDeg from other Las as evaluated by CGM in patients with once-daily injection of La at baseline. Nakamura et al. [28] showed that the mean and SD of FPG were significantly smaller at lower dose of insulin with IDeg than with IGlar in a multicenter, randomised, crossover study for adults with type 1 diabetes. On the other hand, Thalange et al. [17] similarly reported that significant decrease of FPG with lower dose of insulin was observed with IDeg than with IDet in children and adolescents with type 1 diabetes. However, Kusunoki et al. and Thalange et al. did not find significant improvement of HbA1c and/or 8-point self-monitored PG profiles with IDeg. Nakamura et al. did not evaluate HbA1c. However, we observed significant reductions in both FPG and HbA1c levels after switching from IGlar to IDeg, and this improvement was apparent as early as 3 months after the switch to IDeg and was sustained for the entire 12-month study period. This significant glucose-lowering effect of IDeg, as observed in the present study, could be explained by more than one mechanism. Firstly, of 36 patients in the present study, 21 showed decreases in FPG levels by 10 mg/dL and 14 showed decreases by 20 mg/dL. Furthermore, 20 showed improvements in HbA1c levels by 0.2% and 15 by 0.3% at 12 months after switching to IDeg. Notably, 6 finally showed FPG decreases of 40 mg/dL or more, and 11 had HbA1c decreases of 0.5% or more. These remarkable improvement of FPG observed in more than half the patients might be well reflected by significant decrease in the HbA1c level. Whereas, 16 failed to significant improvement of glycemic control by switching basal insulin from IGlar to IDeg. There could be well-responders and non-responders to IDeg used for basal insulin preparation. On the other hand, the majority of patients, excluding 3, showed significant decrease in frequencies of hypoglycemia particularly during nighttime period after switching from IGlar to IDeg, which may be reflected by lower pharmacodynamic variability of IDeg, as various studies indicated [14, 17, 24-26]. Secondly, a new insulin product, IDeg, might display a distinct glucose lowering effect in young individuals as compared with elder persons. Switch to a new insulin product may introduce some bias to patients’ attitudes towards self-management of diabetes, such as frequencies of self-monitoring of PG and keeping appropriate lifestyles, which could be more notable in young people as compared with elder persons. Though adolescents tend to have irregular lifestyles, our patients mostly maintain adequate diabetes management during the study period. The investigators may also have been more vigilant in management of diabetes using a new insulin product. Furthermore, Biester et al. [16] reported that young people showed higher total exposures to and maximum concentrations of IDeg over 24 hours than adults with type 1 diabetes. This higher pharmacokinetic profile of IDeg in young people can be attributable to a greater glucose-lowering effect. These several factors could influenced on the effects of IDeg in the present study.

We found that confirmed frequencies of overall and nocturnal hypoglycemia decreased significantly after changing from IGlar to IDeg. The 2-year extension to the BEGIN main trial [26] demonstrated that the hypoglycemia-reducing benefit of IDeg was not observed during the day time, but rather at night, because diurnal hypoglycemia may be related to bolus insulin, whereas the ultra-long action and less variable glucose-lowering effect of IDeg might well reduce nocturnal hypoglycemia. In the present study, we also demonstrated the greater decrease in the frequency of nocturnal hypoglycemia than the overall decrease, which is consistent with the results in previous studies [14, 17, 24-26]. Reduction of nocturnal hypoglycemia in particular can augment titration to glycemic targets with a sufficient insulin supply, as well as enhancing adher-
ence and thereby contribute to achieving optimal glycemic control.

Upon switching from IGlar or IDet to IDeg, in the treatment of type 1 diabetes, it is of clinical importance to determine the appropriate replacement dose. We found that basal-insulin doses of IDeg decreased significantly early in the study period, i.e., at the 3rd month and 6th month, and were ultimately 85.4% and 81.2% of the value at baseline for our patients overall. The reduction rate was remarkable in patients receiving twice-daily injections of basal insulin (76.0% of the value at baseline) as compared with those given once-daily injections (82.6% of the value at baseline) before IDeg use. Previous studies of adults with type 1 diabetes have recommended reducing the dose of IDeg by <10-20% for patients who previously received once-daily injection of IGlar, and by 20-40% for those previously given twice-daily injections [14, 25, 26-28]. By contrast, Yamada et al. [29] reported that there was no need to reduce the dose of IDeg from those given initially in Japanese adults with type 1 diabetes. Nevertheless, we believe that it may be appropriate for young people with type 1 diabetes to begin replacement IDeg at a 10-20% lower dose when the previously-used IGlar was given once daily, or at a 20-30% lower dose when IGlar was given twice daily on the basis of consequence of the present study, and to then adjust the dose on the basis of self-monitored PG data. In addition, ultra-long acting insulin might cause unexpected hypoglycemic episodes in patients with previous episodes of severe hypoglycemia and/or unawareness of hypoglycemia. Therefore, for safety reasons, the IDeg replacement dose should be further decreased for these patients.

The major limitation of this study is that it was not a controlled study, but an only observation study, suggesting that there may be intervention bias in the results studied. There could be discrepancies in the results in changes of glycemic indicators, frequency of hypoglycemia and insulin doses between previously conducted control studies and our observation study. Another limitation is the small number of subjects for evaluating the efficacy and safety of IDeg in young people with type 1 diabetes. Small number of subjects and short duration of study limit the amount of data collected, in particular with regard to safety. In the present study, there were no problematic adverse events associated with IDeg, including occurrence of severe hypoglycemia, though such events might have occurred in larger number of participants and/or longer duration of study. Furthermore, there may be a selection bias in participants studied, who might have been particularly prone to alter their attitude to management of diabetes with a new insulin product. Therefore, further studies are needed to confirm the efficacy and safety of IDeg in young patients with type 1 diabetes. On the other hand, the crossover design study may be well suited to small number of participants. However, with a crossover design study, it seems difficult to obtain informed consent from participants, because this study design is complex. Achieving prolonged adherence to the procedure can become intolerable for many subjects. Moreover, seasonal variations can also influence HbA1c results.

Conclusions

Switching to IDeg from IGlar as basal-bolus therapy may effectively control hyperglycemia while reducing the frequencies of overall and nocturnal hypoglycemic episodes in young people with type 1 diabetes. Appropriate replacement doses may be lowered by 10-20% for patients who previously received once-daily injection of IGlar, and by 20-30% for those previously given twice-daily injections. Ambitious titration of glycemic targets with minimization of hypoglycemia may well be achieved by using IDeg as basal-bolus therapy for young people with type 1 diabetes.

Acknowledgements

This study was approved by the ethics committee of Nihon University School of Medicine (NO.140202), and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Part of the study was presented at the 74th Scientific Session of the American Diabetes Association held in San Francisco on June 13-17, 2014.

Author Disclosure Statement

T.U. received honoraria from Novo Nordisk and Sanofi as a speaker and for attendance at advisory boards. None of the other authors have any conflicts of interest associated with this research.
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