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CLINICAL TRIAL

Efficacy and safety of insulin degludec in Japanese patients with type 1 and type 2 diabetes: 24-week results from the observational study in routine clinical practice

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ABSTRACT

Aims/Introduction: Insulin degludec, a new long-acting insulin analog, showed its better glycemic control and reduced risk of hypoglycemia. This is the first prospective observational study that evaluated the efficacy and safety of insulin degludec in routine clinical practice.

Materials and Methods: Japanese patients with type 1 or type 2 diabetes mellitus receiving basal–bolus insulin therapy were switched their basal insulin to degludec, and prospectively observed over a 24-week course. The Diabetes Therapy-Related Quality of Life questionnaire was administered before and 12 weeks after switching.

Results: The participants were 80 diabetes patients = (type 1, 44; type 2, 36). In the type 1 group, there was no difference in glycated hemoglobin levels between the pre-switching and 24-week measurements (from 62 to 62 mmol/mol, $P = 0.768$), whereas the daily insulin dose (per kg of bodyweight) decreased significantly (basal, from 0.25 to 0.20 U/kg, $P < 0.001$; bolus, from 0.40 to 0.37 U/kg, $P = 0.001$). In the type 2 group, glycated hemoglobin levels decreased after switching (from 60 to 58 mmol/mol, $P = 0.028$). In the type 1 group, the frequency of hypoglycemia decreased significantly after switching, but not significantly in the type 2 group. Patient satisfaction with the control of hypoglycemia tended to improve in the type 1 group.

Conclusions: Compared with existing long-acting insulin, degludec can maintain glycemic control at a lower insulin dose and frequency of hypoglycemia in type 1 diabetes, while it can improve glycemic control at an equal insulin dose in type 2 diabetes..

INTRODUCTION

In recent years, a desirable approach to glycemic control might involve targeting satisfactory glycemic control while reducing the risk of hypoglycemia, because hypoglycemia is regarded as the main restricting factor leading to poor adherence to treatment and glycemic control, quality of life, and mortality[1–3]. In order to achieve this approach, short-acting or long-acting insulin analogs have been introduced, and these induce more physiologically accurate insulin secretion patterns compared with existing insulin preparations. As a result, the selection of appropriate drugs can reduce the risk of hypoglycemia when treating patients who frequently experience hypoglycemic episodes. Regarding long-acting insulin analogs (e.g., insulin detemir and insulin glargine), these treatments are associated with a lower incidence of nocturnal hypoglycemia than existing intermediate type insulin preparations[4–7]. However, there are cases where neither of these treatments, when administered

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using the daily basal insulin regimen, provides sufficient activity for 24 h, thus necessitating a twice-daily regimen[8, 9].

Accordingly, insulin degludec has been developed as a next-generation, long-acting, soluble insulin analog that provides a longer duration of activity[10]. In clinical pharmacological studies, insulin degludec exerted a long-lasting action (>42 h)[11], with a flat and stable insulin profile in the glucose-lowering effect for individual patients[12].

By a phase III clinical study, insulin degludec's ability to lower blood glucose levels has shown non-inferiority to the control drug in the magnitude of glycated hemoglobin (HbA_{1c}) reduction[13, 14]. However, these phase III studies tested a specific group of patients who were selected according to strict criteria regarding baseline HbA_{1c}, body mass index (BMI) and prior medication period, based on the regulatory authority's guidelines. Thus, the question arose, whether similar efficacy will be observed when insulin degludec is used during routine clinical practice. Furthermore, the insulin dose in previous studies was adjusted with a target fasting blood glucose level of 3.9–5.0 mmol/L (70–90 mg/dL), and direct application of this dose adjustment method would not be suitable in routine clinical practice.

The present study was thus undertaken to evaluate glycemic control and the incidence of adverse reactions (e.g., serious hypoglycemic episodes) when insulin degludec was used in clinical practice by physicians who specialize in treating diabetes mellitus.

METHODS

Study Design and Procedures

The study was designed as a multicenter, non-randomized, open-label, observational study involving prospective collection of data from clinical cases. The present study enrolled adult Japanese patients with type 1 diabetes mellitus (type 1) or type 2 diabetes mellitus (type 2) who were receiving outpatient care with the basal–bolus regimen at the Department of Endocrinology and Diabetic Medicine, Hiroshima University Hospital (Hiroshima Japan) or at 14 other medical facilities, between June 2013 and May 2014. The exclusion criteria were pregnancy, women hoping to achieve pregnancy, medication that might aggravate glucose metabolism (e.g., corticosteroid), duration of diabetes treatment less than 12 months and patients in whom degludec treatment was deemed inappropriate by the attending physician.

Basal insulin injection with the basal–bolus regimen was switched to once-daily degludec injection. The dose of basal and bolus insulin before and after switching was determined by the attending physician on an individual basis. Concomitant use of other antidiabetic drugs and unrelated medications was also decided by the attending physician, who suggested modifications if they were deemed necessary.

Bodyweight, HbA_{1c}, insulin dose, use of non-insulin antidiabetic drugs and adverse events were recorded during outpatient clinic visits at the time of switching to degludec, as well as at 4, 12 and 24 weeks after switching. Furthermore, self-monitoring of blood glucose (SMBG) records for preprandial (breakfast, supper) glucose levels were collected for 1 month before each visit.

In addition, the frequency of hypoglycemia during the 1 month before each visit was investigated. Hypoglycemia was defined as any of the following criteria: (i) the presence of symptoms that were alleviated by oral ingestion of carbohydrates, an intramuscular injection of glucagon or an intravenous injection of glucose; and (ii) a blood glucose level less than 3.1 mmol/L (56 mg/dL), regardless of the presence or absence of symptoms[15].

Nocturnal hypoglycemia was defined as hypoglycemia developing between the evening insulin injections and awaking the next morning. Serious hypoglycemia was defined as hypoglycemia accompanied by severe central nervous system symptoms that could not be resolved by the patient and required medical intervention.

The Diabetes Therapy-Related Quality of Life questionnaire[16] was administered at the time of switching to degludec and 12 weeks after switching.

The present study was carried out in accordance with the principles of the Declaration of Helsinki (amended in 2008 at Seoul). Prior review and approval regarding the ethical validity, scientific validity and the appropriateness of its implementation were obtained from the Hiroshima University Epidemiological Study Ethical Committee and the ethical committees of the other participating facilities. All patients provided written informed consent before their enrolment. This study was registered in June 2013 with the University hospital Medical Information Network Clinical Trials Registry (registration no. UMIN000011037).

Efficacy Measures

The primary end-point was the change in HbA_{1c} levels at 24 weeks after switching to degludec. The secondary end-points were changes in bodyweight, insulin dose (bolus, basal and total), mean fasting and pre-supper blood glucose levels, frequency of hypoglycemia, and patient satisfaction after switching to degludec.

Statistical Analysis

All data were expressed as either mean ± standard deviation or median (interquartile range). Of the patients registered, only those who were followed until week 24 were included in the analysis. In the statistical analysis (comparison pre- and post-treatment data), the paired *t*-test was used for continuous variables and the Chi squared-test for discrete variables. In all tests, *P*-values <0.05 were considered statistically significant.

Analysis of SMBG data was carried out for patients in whom pre-breakfast and pre-supper blood glucose level data were available on at least 5 days of the 1-month period. The analysis evaluated changes in pre-prandial (breakfast and supper)

glucose levels (at 5 points of time) during the pre- and post-switching periods.

The Diabetes Therapy-Related Quality of Life questionnaire data were analyzed for patients who answered all questions, using the method reported by Ishii *et al.*[16]. According to the report, we analyzed the total score and the score for each question, with 0–100 points assigned to each of the four quality of life subgroups (full score = 100).

RESULTS

There were 80 patients with diabetes mellitus (38 men and 42 women) included in the study and analyzed. Baseline patient characteristics are summarized in Table 1. A total of 44 patients had type 1 diabetes and 36 patients had type 2 diabetes. Before switching, the frequency of basal insulin injection was twice daily in 24 patients, which included 20 type 1 patients. The basal insulin analog used before switching was insulin glargine in 65 patients and insulin detemir in 15 patients. At the time of switching, the basal insulin dose was reduced in 29 type 1 patients (including 13 patients who received basal insulin twice daily, reduced 0.04 ± 0.03 U/kg of bodyweight) and 12 type 2 patients (including two patients who received basal insulin twice daily, reduced 0.03 ± 0.01 U/kg of bodyweight). In all other patients, the basal insulin dose was unchanged or increased at the time of switching.

In the type 1 group, the dose of oral antidiabetic drugs (OADs) was reduced in two patients, increased in one patient and newly started in two patients during the 24-week observation period. In the type 2 group, the dose of OADs was reduced in five patients, gained in five patients, newly started in two patients and discontinued in two patients (Table S1).

During the 24-week observation period, there was no significant change in HbA_{1c} levels in the type 1 group (62 ± 10 to 62 ± 9 mmol/mol [7.8 ± 0.9 to 7.8 ± 0.8%], $P = 0.768$), although it did decrease significantly in the type 2 group (60 ± 11 to 58 ± 10 mmol/mol [7.7 ± 1.0 to 7.4 ± 0.9%], $P = 0.028$; Table 2). No significant change in BMI was observed in either group (Table 2).

Regarding insulin dose, basal, bolus and total insulin doses (units of insulin per kg of bodyweight per day) were significantly lower at 24 weeks after switching in the type 1 group (basal 0.25 ± 0.11 to 0.20 ± 0.08 U/kg/day, $P < 0.001$; bolus 0.40 ± 0.15 to 0.37 ± 0.14 U/kg/day, $P = 0.001$; total 0.65 ± 0.21 to 0.57 ± 0.17 U/kg/day, $P < 0.001$). All insulin doses in the type 2 group remained essentially unchanged during the 24-week period (Table 2).

When the frequency of hypoglycemia was analyzed, the entire type 1 group showed a large reduction in the overall frequency of hypoglycemia and nocturnal hypoglycemia after switching (Table 3). Severe hypoglycemia was observed before switching in one patient with type 1 diabetes, although no instances were observed in this group after switching.

Of the 80 patients, SMBG records were available at five or more points of time for 47 patients (26 men and 21 women; 24 type 1 patients and 23 type 2 patients). In both the type 1 and 2 groups, there was no significant change in the mean of the pre-breakfast or pre-supper blood glucose levels over the 24-week period (Table S2).

Correctly completed questionnaires were collected from 70 patients (34 men and 36 women; 40 type 1 patients and 30

Table 1 | Baseline characteristics of the study participants

Characteristic	Overall (n = 80)	Type 1 (n = 44)	Type 2 (n = 36)
Sex (women/men)	42/38	27/17	15/21
Age (years)	59.0 ± 13.3	58.1 ± 14.3	60.0 ± 12.0
Duration of diabetes (years)	14.8 ± 9.9	14.9 ± 10.5	14.7 ± 9.3
BMI (kg/m^2)	22.9 ± 4.3	21.7 ± 3.1	24.4 ± 5.0
HbA_{1c} (mmol/mol)	61 ± 12	62 ± 10	60 ± 11
HbA_{1c} (%)	7.7 ± 0.9	7.8 ± 0.9	7.7 ± 1.0
Fasting serum CPR (nmol/L)	0.07 (0.03–0.17)	0.03 (0.03–0.07)	0.17 (0.11–0.40)
Basal insulin			
Injection twice a day (n)	24	20	4
Glargine/Detemir (n)	65/15	32/12	33/3
Patients receiving OADs (n)	31	6	25

Data are presented as mean ± standard deviation or median (interquartile). BMI, body mass index; CPR, C-peptide reactivity; HbA_{1c}, glycated hemoglobin; OADs, oral antidiabetic drugs.

Table 2 | Mean changes of glycated hemoglobin, body mass index and the daily insulin dose

	Baseline	4 weeks	12 weeks	24 weeks
HbA_{1c} (mmol/mol)				
Type 1 (n = 44)	62 ± 10	61 ± 10	60 ± 10	62 ± 9
Type 2 (n = 36)	60 ± 11	57 ± 13	59 ± 11	58 ± 10*
BMI (kg/m^2)				
Type 1 (n = 44)	21.7 ± 3.1	21.5 ± 2.7	21.4 ± 3.0	21.6 ± 2.9
Type 2 (n = 36)	24.4 ± 5.0	24.2 ± 5.4	24.2 ± 5.3	24.1 ± 5.2
Daily insulin dose (U/kg of bodyweight)				
Type 1 (n = 44)				
Basal	0.25 ± 0.11	0.22 ± 0.09*	0.20 ± 0.83*	0.20 ± 0.08*
Bolus	0.40 ± 0.15	0.39 ± 0.14	0.38 ± 0.14*	0.37 ± 0.14*
Total	0.65 ± 0.21	0.61 ± 0.18*	0.58 ± 0.18*	0.57 ± 0.17*
Type 2 (n = 36)				
Basal	0.20 ± 0.10	0.20 ± 0.10	0.20 ± 0.10	0.20 ± 0.09
Bolus	0.30 ± 0.16	0.29 ± 0.14	0.29 ± 0.16	0.28 ± 0.12
Total	0.50 ± 0.22	0.47 ± 0.19	0.49 ± 0.23	0.47 ± 0.18

Data are presented as mean ± standard deviation. *$P < 0.05$ by the paired t-test for differences from baseline. BMI, body mass index; HbA_{1c}, glycated hemoglobin.

Table 3 | Change of the frequency of hypoglycemic episodes

	Type 1 (n = 44)			Type 2 (n = 36)		
	Overall	Severe	Nocturnal	Overall	Severe	Nocturnal
Baseline						
Participants	19	1	9	1	0	1
Episodes	81	1	21	1	0	1
Rate†	22.09	0.27	5.72	0.33	0	0.33
24 weeks						
Participants	17	0	2	2	0	0
Episodes	39	0	3	3	0	0
Rate†	10.64*	0	0.82*	1	0	0

†Rate, the rate of hypoglycemic episodes per patient-year of exposure. *$P < 0.05$ by the paired t-test for differences from baseline. Participants, patients with hypoglycemic episodes.

Table 4 | Change of the score of Diabetes Therapy-Related Quality of Life questionnaire

	Baseline	12 weeks	P-value
Type 1 (n = 40)			
1) Burden on social activities and daily activities	59.2 ± 21.1	60.6 ± 19.5	0.56
2) Anxiety and dissatisfaction with treatment	48.8 ± 21.0	51.4 ± 20.4	0.25
3) Hypoglycemia	39.7 ± 26.3	44.9 ± 26.6	0.06
4) Satisfaction with treatment	46.5 ± 16.0	46.6 ± 16.2	0.97
Total	51.9 ± 17.6	54.0 ± 17.0	0.22
Type 2 (n = 30)			
1) Burden on social activities and daily activities	64.7 ± 23.0	62.3 ± 25.5	0.43
2) Anxiety and dissatisfaction with treatment	53.5 ± 25.4	53.6 ± 26.2	0.99
3) Hypoglycemia	58.7 ± 29.9	62.7 ± 25.5	0.32
4) Satisfaction with treatment	59.3 ± 24.2	60.6 ± 21.9	0.75
Total	59.8 ± 21.0	59.9 ± 21.7	0.99

Data are presented as mean ± standard deviation.

type 2 patients). A comparison of the questionnaire results between weeks 0 and 12 showed no significant difference in the overall score for both the type 1 and 2 groups (Table 4). When the questions were divided into four categories, and the answers for each category were compared between weeks 0 and 12, there was no significant difference in the scores for social activity/daily living, anxiety/discomfort with treatment or treatment satisfaction level. However, the scores for hypoglycemia showed a tendency towards increased satisfaction levels in the type 1 group, although this tendency was not statistically significant ($P = 0.06$).

During the 24-week follow-up period, two adverse events were reported. One patient complained of vomiting before the week 4 visit, which appeared to be associated with infectious gastroenteritis and was resolved by outpatient treatment; degludec treatment was subsequently continued. The other patient was hospitalized as a result of a seizure before the week 24 visit. This event appeared to represent a sequela of cerebral infarction (an unrelated event), rather than hypoglycemia. In this case, degludec treatment was discontinued after recovery from the seizure. A direct causal relationship to degludec treatment was not noted in either of these cases.

DISCUSSION

In the present study, Japanese patients with type 1 or type 2 diabetes were switched from conventional long-acting basal insulin to insulin degludec, and were observed for 24 weeks during routine clinical care. During the observation period, the type 1 group showed a significant reduction in both insulin dose and the frequency of hypoglycemia, although there was no significant change in HbA_{1c} levels. The type 2 group showed no reduction in insulin dose, but a significant reduction in HbA_{1c} levels.

In a previous phase III clinical study comparing insulin degludec with insulin glargine in a basal–bolus regimen, the degludec group showed a reduced frequency of hypoglycemia, particularly at night, while showing non-inferiority to glargine in its blood glucose-lowering effect[13, 17]. In a subsequent long-term observational study, the basal and total insulin doses were lower in the degludec group compared with the glargine group[18]. There is also a study that found that switching to degludec resulted in lower basal and total insulin dose among patients who had previously received twice-daily basal insulin injections, although that study only involved a small number of patients[19]. Unlike the findings of preceding studies, the present study found a reduction not only in the basal but bolus insulin doses among type 1 diabetic patients. The type 1 group contained a high percentage of patients who were receiving twice-daily basal insulin injections before switching, although the reduction in basal insulin dose after switching did not aggravate their glycemic control. This was likely caused by the long-acting degludec enabling sufficient replenishment of basal insulin through the daily injection.

Among type 2 diabetic patients, a previous phase III study has shown the non-inferiority of degludec compared with glargine, and found that degludec reduced the overall frequency of hypoglycemia and nocturnal hypoglycemia[14]. In the treat-to-target study of degludec and glargine in insulin therapy-naïve patients (with basal supported oral therapy), degludec allowed glycemic control, with a lower frequency of nocturnal hypoglycemia compared with glargine[20, 21]. In the present study, the frequency of hypoglycemia in the type 2

group was low before switching, and no significant change was detected after switching. In addition, a significant reduction in HbA_{1c} levels was achieved in the type 2 group, as it was possible to maintain the insulin dose because of the low frequency of hypoglycemia.

Regarding quality of life and patient satisfaction with their treatment, a meta-analysis of the data from phase III studies reported an increase in physical and mental scores[22]. In the present study, there was no significant difference in the overall scores, likely because our observation was confined to a short period of time (12 weeks after switching). Our analysis of the hypoglycemic episodes reported by patients, the SMBG data, and the questionnaire results showed that the subjective symptoms of hypoglycemia and related anxiety were alleviated, likely because the long-lasting activity of degludec was effective in reducing hypoglycemia.

The results of the present study are limited by the single-arm, non-controlled design; the small sample size; the exclusively Japanese patient population; and the short observation period (24 weeks). Furthermore, as the use of oral-dose antidiabetics was modified according to the discretion of the attending physicians, we cannot rule out the influence of changing oral medication on the results for type 2 diabetic patients. We are continuing this study, with the survey period extended to 52 weeks, and we plan to carry out further analysis while increasing the number of enrolled patients.

In conclusion, the present study showed that the use of insulin degludec in Japanese patients with type 1 diabetes enabled glycemic control with a significant reduction in both insulin dose and frequency of hypoglycemia. In contrast, in type 2 diabetes, insulin degludec did not change insulin dose and frequency of hypoglycemia, but it did show better glycemic control compared with existing long-acting insulin preparations. As a new basal insulin analog, insulin degludec might provide a useful alternative for diabetic patients who require insulin therapy.

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DISCLOSURE

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1 | Change of oral antidiabetic drugs.
Table S2 | Change of mean self-monitoring of blood glucose profile.