Clinical course of different long-acting insulin therapies—glargine U100, U300, degludec, and insulin degludec/insulin aspart—among Japanese patients with type 2 diabetes: a multicenter retrospective observational study (JDDM65 study)

Masahiro Iwamoto¹⁾*, Shuhei Nakanishi²⁾*, Hideyuki Iwamoto²⁾, Hideaki Kaneto²⁾, Hiroshi Maegawa³⁾ and Japan Diabetes Clinical Data Management Study Group (JDDM study group)

¹⁾ Iwamoto Clinic, Kagawa, Japan

²⁾ Division of Diabetes, Metabolism and Endocrinology, Kawasaki Medical School, Okayama, Japan

³⁾ Department of Medicine, Division of Diabetology, Endocrinology, and Nephrology, Shiga University of Medical Science, Shiga, Japan

Abstract. This study aimed to retrospectively compare the clinical efficacy of different types of long-acting insulin therapies—glargine U100, glargine U300, degludec, and insulin degludec/insulin aspart—among Japanese patients with type 2 diabetes after insulin use was initiated in an outpatient setting. The study consisted of 822 insulin-naïve patients in Japan who started using long-acting insulin for treatment of type 2 diabetes and continued for over 12 months. In addition, the impact of insulin type on insulin withdrawal was investigated by dividing the participants into two groups: those who achieved insulin withdrawal and those who did not, during the 12-month observation period based on a Cox proportional hazards model. As a result, HbA1c was decreased, and BMI was increased in all participants regardless of the insulin type used. A total of 185 participants succeeded in insulin withdrawal. After adjustment was made for several confounders, the positive determinant factors for withdrawal were short duration of diabetes and the choice of IDegAsp when compared with Glal00; the negative determinant factor was use of insulin secretagogues at the start of the study. In conclusion, all long-acting insulins were a powerful tool for treatment of type 2 diabetes, and patients with short duration of diabetes and/or no usage of insulin secretagogues resulted in favorable outcomes in terms of insulin withdrawal within a year in an outpatient setting. In addition, insulin degludec/insulin aspart was found to possibly be a better choice for treatment when it was compared with glargine U100 among the four types of insulin.

Key words: Long-acting insulin, Insulin therapy withdrawal, Type 2 diabetes

TYPE 2 DIABETES MELLITUS (T2D) is characterized by insulin resistance and impaired insulin secretion. T2D, a progressive, chronic metabolic disease, affects populations worldwide and, accordingly, has become an important public health challenge in Japan and other Asian countries [1, 2]. Insulin therapy is recognized as the most effective and established T2D treatment for

improvement of glycemic control, although it is associated with such drawbacks as bodyweight gain and potential for an increase in hypoglycemic events. Long-acting, basal insulin therapy is widely used and of considerable value in the treatment of T2D with a relatively low frequency of hypoglycemic events [3]. Recently, to guard against the risk of severe hypoglycemia, several oral antihyperglycemic agents (OAA) and injections of glucagon-like peptide 1 receptor agonists (GLP-1RA) have become readily available, and education about their use prior to initiation of basal insulin therapy is considered necessary [4].

Insulin glargine 100 U/mL (Gla100), insulin glargine 300 U/mL (Gla300), and insulin degludec 100 U/mL (Deg) are long-acting, once-daily, widely used basal

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Correspondence to: Shuhei Nakanishi, M.D., Ph.D., Division of Diabetes, Metabolism and Endocrinology, Kawasaki Medical School, 577 Matsushima, Kurashiki, Okayama 701-0192, Japan.

E-mail: n-shuhei@umin.net

*Masahiro Iwamoto and Shuhei Nakanishi contributed equally to this work.

insulin analogues in Japan. Insulin degludec/insulin aspart (IDegAsp), a soluble coformulation of 70% insulin degludec and 30% insulin aspart, the latter of which provides postprandial coverage, is also available for the treatment of diabetes mellitus in adults in many countries [5]. Although it is common to start these long-acting insulins as the first step in insulin therapy for patients with T2D in an outpatient setting at clinics or hospitals, continuation of insulin therapy can represent a physical, clinical, and economic burden for patients. In addition, although several studies have compared the analogues for assessment of their effectiveness and safety [6–14], no comparative studies concerning the clinical course and withdrawal of the use of these four insulin types in outpatient settings have been published.

The objective of this multicenter retrospective observational study using insulin-naïve Japanese T2D outpatients was to investigate any differences in clinical usefulness including the potential for withdrawal of insulin therapy by comparing the clinical course in study participants using the four long-acting insulin types Gla100, Gla300, Deg, and IDegAsp in clinical application.

Materials and Methods

Study population and patient preparation

This retrospective observational study analyzed data from the Computerized Diabetes Care database (CoDiC®) of the Japan Diabetes Clinical Data Management Study Group (JDDM). The database was specifically developed by the JDDM to promote research on medical care for diabetes in Japan [15]. CoDiC is a large, validated database containing anonymized, longitudinal, patient-level information, including diagnoses, laboratory results, and prescription data. All collected data were archived at a central analytical center established by the JDDM, at which patient data were anonymized prior to analysis. The annually updated database holds the medical records of approximately 60,000 patients from 98 institutions that specialize in diabetes treatment across Japan. The study protocol was approved by the JDDM Ethical Review Board (JDDM2021-3). All patients provided informed consent. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki 1964 and its later amendments, Good Pharmacoepidemiology Practices, and applicable local laws and regulations.

The study participants comprised 543 men and 279 women who had regularly visited outpatient JDDM member institutions for T2D treatment and who began to use daily injections of long-acting insulin—Gla100, Gla300, Deg, or IDegAsp—as outpatients at some point between October 2015 and April 2018, because of poor

glycemic control, based on the Treatment Guide for Diabetes 2010 (edited by the Japan Diabetes Society) [16]. All participants at the start of the study were insulin-therapy naïve and were regularly followed for a continuous period of at least 12 months. Excluded from the study in advance were participants currently using steroids, those with active retinopathy, end-stage renal disease, ongoing treatment for malignancies or autoimmune diseases, using glucagon-like peptide 1 receptor agonist (GLP-1RA), starting use of rapid acting insulin(s) concomitantly, younger than 20 years of age at the beginning of the follow-up period, hospitalized during the observation period, or deemed to be inappropriate for the study by the attending physician. To investigate the association between type of long-acting insulin and HbA1c, body mass index (BMI; calculated as body-weight [kg] divided by the square of standing height [m]), and insulin dose, in addition to insulin therapy withdrawal, a dataset including information about OAA medication was prepared retrospectively until a point in time 12 months after the initiation of long-acting insulin in the patients. Diabetes treatment, including medication and insulin dose during the follow-up period after initiation and withdrawal from the four long-acting insulin treatments, was determined by the attending physician based on a patient-centered approach considering the best available evidence in terms of benefit, harm, patient values, preferences, and context in time, not only target HbA1c level. Namely, the dose titration of insulin accompanying the choice of OAA was decided carefully by the attending physician to prevent hypoglycemia based on data derived from laboratory-measured or self-monitored plasma glucose. Outpatient review was mostly carried out every two-to-eight week to promote strict maintenance of glycemic control. Withdrawal of insulin therapy was defined when registered as an insulin dose of 0 at the point of observation during the follow-up period and continued for 12 months based on decisions made by the attending physician in consideration of glycemic control.

Statistical analysis

The data from the study are expressed as mean and standard deviation. Continuous variables at the start of the study were assessed using age- and gender-adjusted analysis of covariance (ANCOVA) to compare categories of clinical characteristics at baseline. Categorical variables were analyzed based on Fisher's exact test or chi-squared test. The measurements taken at the four visits (3, 6, 9, and 12 months) after initiation of basal insulin therapy were analyzed using Wilcoxon signed-rank test based on comparison with the data obtained at the initiation of insulin use. Since the value for BMI and HbA1c

were not normally distributed, these data were analyzed after logarithmic transformation. The trends over time of HbA1c, BMI, and medication used during the observation period were compared to analyze the clinical course of the four types of long-acting insulin and between the participants withdrawing from insulin and participants continuing insulin therapy for 12 months. In addition, to investigate the determining factors for withdrawal of insulin use, the success of withdrawal or the continuation of insulin therapy during the 12-month period was designated as the dependent variable (1, withdrawal; 0, continuation). Adjusted hazard ratios for several determinants related to withdrawal of insulin, such as age, gender, initial dose of insulin, HbA1c, BMI, duration of diabetes, and specific medication(s), as well as choice of long-acting insulin (in comparison to Gla100 as the standard), were estimated using the Cox proportional hazards model. Statistical analyses were performed using JMP software (version 13.2 for Windows, SAS Institute).

Results

Clinical characteristics of this study participants in Gla100, Deg, Gla300 and IDegAsp groups

Table 1 indicates the clinical characteristics of all participants. Mean age, duration of T2D, HbA1c, and BMI were 63.5 ± 13.4 years, 12.3 ± 9.4 years, $9.0 \pm 1.8\%$, and 24.6 ± 4.6 kg/m², respectively, at the start of the study. During the observation period, 248, 351, 135, and 88 participants started using insulin Gla100, Deg, Gla300, or IDegAsp, respectively. Age, duration of diabetes, HbA1c, and BMI did not statistically differ, but initial insulin doses of IDegAsp were higher than those used with the other three insulin types in this study.

Clinical course after initiation of the four long-acting insulin types

Among the participants, 56 using Gla100, 75 Deg, 28 Gla300, and 26 IDegAsp succeeded in withdrawal of insulin therapy during the 12-month period. The rate of withdrawal did not differ among the four different insulin types ($p = 0.39$). The clinical course of HbA1c showed significant decreases with all four insulin types during the observation period. In addition, no differences were observed in HbA1c value at the beginning, and after 3, 6, 9, and 12 months among the four categories. In terms of BMI value, only the category after 9 months was different (Table 1). However, the mean BMI in all participants combined using the four different insulin types significantly increased.

Table 1 also shows changes in medication(s) at the beginning of the study compared with 12 months later in participants prescribed insulin secretagogues, such as

sulfonylureas (SU) or glinides, biguanides (BG), α -glucosidase inhibitors (α -GI), dipeptidyl peptidase-4 inhibitors (DPP-4I), thiazolidinediones (TZD), sodium-glucose co-transporter 2 inhibitors (SGLT2I), and GLP-1RA, or rapid-acting insulin. Use of the insulin secretagogues, α -GI and SGLT2I at the beginning of the study and use of rapid-acting insulin after 12 months resulted in significant differences among the four insulin categories ($p = 0.038, 0.037, 0.025, \text{ and } 0.042$).

Clinical course after initiation of four insulin types in subject with and without achievement of insulin withdrawal

As presented in Table 2, the 185 participants that were able to withdraw from long-acting insulin therapy (W) were of significantly lower age and had a shorter duration of diabetes than the 637 participants that had to continue insulin therapy (C). The mean duration of insulin use among withdrawal patients ($n = 185$) was 3.94 ± 3.37 (mean and SD) months. In addition, the mean durations of withdrawal among the patients using Gla100 ($n = 56$), Deg ($n = 75$), Gla300 ($n = 28$) and IDegAsp ($n = 26$) were $3.63 \pm 3.23, 4.43 \pm 3.58, 3.54 \pm 3.04, \text{ and } 3.69 \pm 3.37$ months, respectively. At 3, 6, 9, and 12 months, the W participants had a significantly lower HbA1c than that of the C participants, although both participant groups showed significant improvement in HbA1c value. BMI value, on the other hand, did not differ at 3, 6, 9, and 12 months between the two categories of participants. BMI of the W participants did not change significantly during the observation period, but BMI of the C participants showed a continuous and significant increase.

Among W participants, HbA1c at the start of withdrawal, 1 month, 2, 3, 4, 5, 6, 7, 8, 9, 10, and 11 months after withdrawal were 7.36 ± 1.20 (mean and SD), $7.17 \pm 1.19, 7.14 \pm 1.32, 7.06 \pm 1.19, 7.06 \pm 1.07, 7.05 \pm 1.03, 7.19 \pm 1.19, 7.17 \pm 1.24, 7.21 \pm 1.16, 7.41 \pm 1.47, 7.39 \pm 1.62, \text{ and } 7.33 \pm 1.04\%$, respectively.

Concerning changes in medication(s), Table 2 presents data for the W and C participants using the insulin secretagogues, BG, α -GI, DPP-4I, TZD, SGLT2I, and GLP-1RA, or rapid-acting insulin at the beginning of the study and at 12 months. Use of the insulin secretagogues, TZD, and DPP-4I at the beginning of the study ($p < 0.0001, 0.002, \text{ and } 0.005$) and the insulin secretagogues, TZD, GLP-1RA, and rapid-acting insulin at 12 months ($p < 0.0001, 0.008, 0.005, \text{ and } 0.027$) resulted in significant differences between the two categories.

Hazard ratios for withdrawal of insulin use after adjustment for several confounders

To calculate hazard ratios, a Cox regression model was used, with withdrawal of long-acting insulin used as

Table 1 Changes in clinical characteristics for each group based on long-acting insulin type among patients with type 2 diabetes

	Initiation of basal insulin			
	Gla100	Deg	Gla300	IDegAsp
M/F (n, % male)	161 (65)/87	228 (65)/123	96 (71)/39	58 (66)/30
Insulin withdrawal (n, % male)	37 (66)/19	55 (73)/20	19 (68)/9	16 (62)/10
Age (years)	62.8 ± 12.8	64.1 ± 13.7	61.7 ± 12.9	65.9 ± 14.3
Duration of diabetes (years)	11.1 ± 9.0	12.7 ± 9.3	12.5 ± 10.0	13.9 ± 9.7
SBP (mmHg)	130 ± 18	132 ± 17	130 ± 16	133 ± 15
DBP (mmHg)	73 ± 12	75 ± 11	76 ± 13	76 ± 11
Dose of insulin (U/day) (n)				
First insulin dose	7.9 ± 5.7 (248)	8.3 ± 5.3 (351)	6.8 ± 3.9 (135)	10.6 ± 6.4 (88)*,****
At 3 months	7.4 ± 7.1 (213) [‡]	8.9 ± 7.5 (312) [‡]	8.3 ± 8.1 (118) [‡]	9.8 ± 6.7 (74) [‡]
At 6 months	8.1 ± 7.4 (204) [‡]	9.4 ± 8.7 (298) [‡]	10.2 ± 10.1 (112) [‡]	9.6 ± 8.5 (67) [‡]
At 9 months	8.0 ± 8.4 (197) [‡]	9.1 ± 8.7 (286) [‡]	9.7 ± 10.3 (109) [‡]	9.3 ± 8.4 (65) [‡]
At 12 months	8.8 ± 8.9 (192) [‡]	9.0 ± 8.4 (276) [‡]	9.5 ± 10.0 (107) [‡]	9.8 ± 8.4 (62) [‡]
HbA1c (%)				
At start of study	8.86 ± 1.78	9.10 ± 1.99	8.89 ± 1.55	8.98 ± 1.75
At 3 months	7.82 ± 1.40 [‡]	7.90 ± 1.27 [‡]	7.80 ± 1.25 [‡]	7.78 ± 1.40 [‡]
At 6 months	7.70 ± 1.27 [‡]	7.81 ± 1.21 [‡]	7.61 ± 1.14 [‡]	7.63 ± 1.60 [‡]
At 9 months	7.85 ± 1.33 [‡]	7.72 ± 1.13 [‡]	7.66 ± 1.18 [‡]	7.34 ± 1.00 [‡]
At 12 months	7.75 ± 1.36 [‡]	7.76 ± 1.07 [‡]	7.68 ± 1.07 [‡]	7.57 ± 1.04 [‡]
BMI (kg/m ²)				
At start of study	25.2 ± 4.9	24.4 ± 4.6	24.6 ± 4.7	23.6 ± 3.8
At 3 months	25.4 ± 5.0 [‡]	24.5 ± 4.5 [‡]	24.8 ± 4.7 [‡]	23.4 ± 3.3
At 6 months	25.4 ± 5.0 [‡]	24.6 ± 4.4 [‡]	24.6 ± 4.5 [‡]	23.5 ± 3.4
At 9 months	25.8 ± 5.2 [‡]	24.7 ± 4.5 [‡]	24.6 ± 4.4 [‡]	23.4 ± 3.0* [†]
At 12 months	26.0 ± 5.4 [‡]	25.0 ± 4.5 [‡]	24.7 ± 4.8 [‡]	23.7 ± 3.0 [‡]
Treatment with SU/glinide (n, %)				
At start of study	103 (42)/26 (10)	161 (46)/36 (10)	64 (47)/11 (8)	29 (33)/4 (5)
At 12 months	94 (38)/35 (14)	126 (36)/41 (12)	43 (32)/19 (14)	26 (30)/5 (6)
Treatment with BG/α-GI/DPP-4I (n, %)				
At start of study	122 (49)/44 (18)/ 183 (74)	167 (48)/88 (25)/ 253 (72)	76 (56)/25 (19)/ 113 (84)	45 (51)/12 (14)/ 63 (72)
At 12 months	134 (54)/38 (15)/ 172 (69)	180 (51)/81 (23)/ 253 (72)	78 (58)/28 (21)/ 101 (75)	48 (55)/18 (20)/ 64 (73)
Treatment with rapid-acting insulin/SGLT2I/GLP-1RA/TZD (n, %)				
At start of study	0/29 (12)/0/29 (12)	0/43 (12)/0/39 (11)	0/29 (21)/0/23 (17)	0/9 (10)/0/6 (7)
At 12 months	10 (4)/43 (17)/ 12 (5)/23 (9)	24 (7)/72 (21)/ 19 (5)/33 (9)	2 (1)/36 (27)/ 9 (7)/21 (16)	2 (2)/14 (16)/ 2 (2)/5 (6)

Data are shown as mean ± SD. *: $p < 0.05$ compared with insulin glargine U 100/mL (Gla100), after adjustment for age and gender; **: $p < 0.05$ compared with Deg, after adjustment for age and gender; ***: $p < 0.05$ compared with Gla300, after adjustment for age and gender; †: $p < 0.05$ compared with data at start of study; and ‡: $p < 0.01$ compared with data at start of study. Deg, insulin degludec 100 U/mL; Gla100, insulin glargine 100 U/mL; Gla300, insulin glargine 300 U/mL; IDegAsp, insulin degludec/insulin aspart; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; SU, sulfonylureas; TZD, thiazolidinedione; BG, biguanide; α-GI, alpha-glucosidase inhibitors; DPP-4I, dipeptidyl peptidase-4 inhibitors; SGLT2I, sodium-glucose co-transporter 2 inhibitors; GLP-1RA, glucagon-like peptide 1 receptor agonist.

a dependent variable. Independent variables were age, gender, duration of diabetes, HbA1c, BMI, initial dose of insulin, use of the insulin secretagogues, BG, TZD, α-GI,

DPP-4I, and SGLT2I at the beginning of the study, and type of long-acting insulin. As described in Table 3, the hazard ratios for duration of diabetes and use of any

Table 2 Comparison of clinical course after initiation of long-acting insulin therapy between patients withdrawing from and continuing insulin therapy

	Patients withdrawing from insulin	Patients continuing insulin
M/F (n, % male)	127 (69)/58	416 (65)/221
Age (years)	60.7 ± 15.1	64.4 ± 12.8*
Duration of diabetes (years)	7.2 ± 8.4	13.8 ± 9.2**
SBP (mmHg)	134 ± 17	131 ± 17
DBP (mmHg)	79 ± 12	74 ± 12
Dose of insulin (U/day)		
At start of study	8.5 ± 5.8	8.1 ± 5.4
At 3 months	2.4 ± 4.4	8.8 ± 7.6***‡
At 6 months	1.5 ± 3.8	9.4 ± 8.7***‡
At 9 months	0.8 ± 3.4	8.9 ± 8.9***‡
At 12 months	0	9.1 ± 8.8***‡
HbA1c (%)		
At start of study	8.91 ± 2.11	9.00 ± 1.75
At 3 months	7.29 ± 1.31‡	8.00 ± 1.28***‡
At 6 months	7.18 ± 1.16‡	7.87 ± 1.25***‡
At 9 months	7.14 ± 1.04‡	7.86 ± 1.18***‡
At 12 months	7.17 ± 0.99‡	7.86 ± 1.16***‡
BMI (kg/m ²)		
At start of study	25.2 ± 4.8	24.4 ± 4.6
At 3 months	24.9 ± 4.7	24.6 ± 4.6‡
At 6 months	24.4 ± 4.6	24.8 ± 4.5‡
At 9 months	24.7 ± 4.6	24.9 ± 4.6‡
At 12 months	24.8 ± 5.1	25.2 ± 4.6‡
Treatment with SU/glinide (n, %)		
At start of study	47 (25)/18 (10)	310 (49)/59 (9)
At 12 months	48 (26)/16 (9)	241 (38)/84 (13)
Treatment with BG/α-GI/DPP-4I (n, %)		
At start of study	82 (44)/33 (18)/123 (66)	328 (51)/136 (21)/489 (77)
At 12 months	91 (49)/30 (16)/124 (67)	349 (55)/135 (21)/466 (73)
Treatment with rapid-acting insulin/SGLT2I/GLP-1RA/TZD (n, %)		
At start of study	0/30 (16)/0/10 (5)	0/80 (13)/0/87 (14)
At 12 months	3 (2)/34 (18)/2 (1)/9 (5)	35 (5)/131 (21)/40 (6)/73 (11)

Data are shown as mean ± SD. *: $p < 0.01$ and **: $p < 0.0001$ compared with patients achieving withdrawal of long-acting insulin, after adjustment for gender; ***: $p < 0.0001$ compared with patients achieving withdrawal of long-acting insulin, after adjustment for age and gender; †: $p < 0.001$ and ‡: $p < 0.0001$ compared with data at start of study. SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; SU, sulfonylureas; TZD, thiazolidinedione; BG, biguanide; α-GI, alpha-glucosidase inhibitors; DPP-4I, dipeptidyl peptidase-4 inhibitors; SGLT2I, sodium-glucose co-transporter 2 inhibitors; GLP-1RA, glucagon-like peptide 1 receptor agonist.

insulin secretagogues were 0.911 (95% CI 0.889–0.933, $p < 0.0001$) and 0.647 (0.458–0.913, $p = 0.013$), respectively. In contrast, the hazard ratio of IDegAsp compared with Gla100 was 1.749 (1.078–2.837, $p = 0.024$). Other OAAs, initial insulin dose, and variables such as HbA1c or BMI did not affect withdrawal of basal insulin use in

this study. After making two other Cox models after adjustment for the same confounders, the hazard ratios of IDegAsp compared with Gla300 and Deg were 1.641 (0.932–2.887, $p = 0.086$) and 1.581 (0.997–2.505, $p = 0.052$), respectively.

Table 3 Adjusted hazard ratios of independent variables for insulin withdrawal within 12 months among patients with type 2 diabetes

	Adjusted hazard ratio (95% CI)	<i>p</i> value
Age	1.004 (0.992–1.017)	0.502
Men	0.858 (0.623–1.181)	0.348
Duration of diabetes	0.911 (0.889–0.933)	<0.0001
Deg (vs. Gla100)	1.017 (0.776–1.578)	0.576
Gla300 (vs. Gla100)	1.066 (0.669–1.698)	0.788
IDegAsp (vs. Gla100)	1.749 (1.078–2.837)	0.024
Initial dose of insulin	0.995 (0.968–1.023)	0.716
HbA1c at start	0.930 (0.856–1.010)	0.085
BMI at start	1.012 (0.978–1.048)	0.486
Use of insulin secretagogues at start	0.647 (0.458–0.913)	0.013
Use of BG at start	0.998 (0.728–1.367)	0.988
Use of α -GI at start	0.897 (0.602–1.338)	0.596
Use of TZD at start	0.585 (0.306–1.119)	0.105
Use of DPP-4I at start	0.772 (0.559–1.065)	0.115
Use of SGLT2I at start	1.434 (0.935–2.200)	0.099

CI, confidence interval; Deg, insulin degludec 100 U/mL; Gla100, insulin glargine 100 U/mL; Gla300, insulin glargine 300 U/mL; IDegAsp, insulin degludec/insulin aspart; BMI, body mass index; TZD, thiazolidinedione; BG, biguanide; α -GI, alpha-glucosidase inhibitors; DPP-4I, dipeptidyl peptidase-4 inhibitors; SGLT2I, sodium-glucose co-transporter 2 inhibitors.

Discussion

In this study, initiation of long-acting insulin therapy was found to be an effective strategy for treatment of T2D, regardless of selection among four long-acting insulin types—Gla100, Gla300, Deg, and IDegAsp—in a Japanese clinical setting. Short duration of diabetes and non-use of insulin secretagogues were significant determinants for success in withdrawal of insulin therapy, in addition to use of IDegAsp compared with Gla100.

The principal objective of this study, which to our knowledge is the first study to compare four long-acting insulins, was to assess the impact of initiation of long-acting insulin therapy among patients with T2D. After the study's participants began use of the insulin types, HbA1c value decreased consistently over time, regardless of the four different types of insulin used as treatment. Accordingly, the addition of long-acting insulin appears as if it could be a powerful strategy for managing T2D in clinical practice. In addition, 185 of the participants (22.5%) were able to withdraw from insulin therapy within 12 months. The characteristics of that withdrawal group included short duration of diabetes and non-use of insulin secretagogues such as sulfonylureas and glinides, the same factors as those observed in a previous study [17, 18]. Insulin therapy would be expected

to achieve “ β -cell rest,” which finally leads to the preservation and recovery of insulin secretory capacity in β -cells. In contrast, participants with long duration of diabetes and history of use of insulin secretagogues, which have stimulatory effects on pancreatic β -cells, might not have been successful in insulin withdrawal due to the increased burden on β -cells. Evidence from the UK Prospective Diabetes Study (UKPDS) showed that β -cell function worsened continuously over time in patients with T2D [19, 20]. In addition, it was previously reported that total pancreatic β -cell mass was decreased to approximately 50% of that in healthy persons at the onset of T2D [21]. The results of such studies suggest that T2D should be treated with medication at an early phase in the disease progression. In consideration of these findings, initiation of long-acting insulin therapy at an early phase of the disease might be beneficial for remission of glucose intolerance with respect to preservation and recovery of β -cell function.

Patients with high BMI, which is thought to typically be accompanied by hyperinsulinemia due to insulin resistance, experienced successful withdrawal of insulin use within six months in another previous study [17]. The contrast of these results with those of our study could be explained by differences in observational period between that study and our study, which was designed in

the form of a 12-month observation. Such results might indicate that insulin therapy exceeding six months might lead to long-term preservation of β -cell function, resulting in successful withdrawal of insulin, independent of BMI. To detect the effect on early withdrawal from use of insulin, further study is warranted.

No difference was observed among the four insulin types in terms of HbA1c and BMI changes over time, or rate of withdrawal of insulin treatment during the observation period in this study. Several previous randomized controlled trial (RCT) programs demonstrated that Gla300 and Deg provided similar reductions in HbA1c compared with Gla100 but with fewer hypoglycemic episodes in patients with T2D [8, 22, 23], because of improvements in the pharmacokinetic (PK)/pharmacodynamic (PD) properties of basal insulin analogs Gla300 and Deg compared with Gla100. In addition, some studies aimed to compare Gla300 and Deg/degludec U200 [6, 9]. In those RCT programs, basal insulins were titrated to target fasting glucose level, independent of risk of hypoglycemia, in contrast with two studies that used propensity-score matching analyses [9, 10]. The design used in those studies might have made a difference in the clinical outcomes among the basal insulin types. However, in this study, as well as in other Japanese prospective, observational studies [24, 25], long-acting insulins were titrated to target hypoglycemia-conscious glucose levels by attending physicians on an individual basis in routine clinical practice without titration resumes. The differences in titration design might be a reason why no differences were found in this study among the four insulin types, including the rate of withdrawal of use of insulin.

However, use of IDegAsp in comparison with Gla100 was a significant, positive factor for withdrawal of insulin use within 12 months, after adjustment for several confounding factors. As indicated above, IDegAsp is co-formulated with bolus insulin. As is understood, the relative contribution of the postprandial glucose increments to overall HbA1c levels is larger than that of fasting glucose increments [26]. It might therefore be difficult to find a clinical difference between Deg and IDegAsp containing 70% Deg. In addition, previous studies [12, 13] found similarly effective treatment using both IDegAsp and Gla300. However, of note, compensation with a certain dose of bolus insulin might be expected to lead to more effective regulation of postprandial glucose level than other basal insulins, although attending physicians might have begun with higher initial doses for that reason, as observed in this study (Table 1). When compared with Gla100, IDegAsp was found to be superior in terms of glycemic control [11] and nocturnal hypoglycemic events [14]. Accordingly, the benefit of the combination

of bolus insulin and basal insulin found in IDegAsp was apparent in comparison with Gla100, which is the fastest acting of the four insulins, even though the advantage observed when compared with Gla300 and Deg was not significant but consistent. For that reason, IDegAsp seems to be advantageous with respect to the goal of withdrawal of insulin use, especially when compared with Gla100, due to the potential clinical benefits associated with the pharmacological properties of IDegAsp.

The present study has several limitations. First, the study was observational and not randomized. Second, this study was not designed to obtain information on hypoglycemic events. It is therefore likely that the present study underestimated the efficacy of the four insulins in terms of prevention of hypoglycemic events, leading the authors to be unable to evaluate the precise efficacy of the four insulin types. Third, the study did not consider the timing of insulin injection. Fourth, the duration of diabetes was assessed based on the patient reported age at first diabetes diagnosis by the physician in charge, rather than based on the collection of original test results. Lastly, habitual, and comorbid factors such as smoking status and activities of daily life were not assessed, both before the study and during the observation period.

In conclusion, in this multicenter retrospective observational and clinical study, the initiation of long-acting insulin therapy was confirmed to be a powerful strategy for prompt glycemic management, regardless of insulin type, in a Japanese clinical setting. When initiating use of such insulins, patients with non-use of insulin secretagogues and a short duration of diabetes have the potential for withdrawal of insulin use within a one-year year period, even in an outpatient setting.

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