

[ORIGINAL ARTICLE]

Efficacy and Safety of Switching from Insulin Glargine 100 U/mL to the Same Dose of Glargine 300 U/mL in Japanese Type 1 and 2 Diabetes Patients: A Retrospective Analysis

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Abstract:

Objective Insulin glargine [300 U/mL (Gla-300)] achieved better glycemic control and reduced the risk of hypoglycemia in comparison to glargine [100 U/mL; (Gla-100)] in phase 3 trials. This is the first study to retrospectively evaluate the efficacy and safety of Gla-300 in Japanese type 1 and 2 diabetes patients in a routine clinical setting.

Methods We analyzed 20 type 1 diabetes patients and 62 type 2 diabetes patients who switched from Gla-100 to the same dose of Gla-300. Sixty type 2 diabetes patients who continued the use of Gla-100 during the study were included as controls.

Results At three months after switching, the HbA1c levels were decreased in the patients with type 1 diabetes, but not to a significant extent. In the type 2 diabetes patients, the HbA1c levels were significantly decreased after switching ($p < 0.01$). In contrast, there was no change in the HbA1c levels of the type 2 diabetes patients who continued the use of Gla-100 over the same period. The BMI values of the type 1 diabetes patients tended to decrease ($p = 0.06$) and there was a significant decrease in the BMI values of the type 2 diabetes patients ($p < 0.05$). There was no change in the BMI values of the type 2 diabetes patients who continued the use of Gla-100. The rates of hypoglycemia and adverse events did not change during the follow-up period.

Conclusion In the clinical setting, switching from Gla-100 to the same dose of Gla-300 had a favorable effect on glycemic control and body weight control in Japanese type 1 and type 2 diabetes patients, without any increase in adverse events; however, a prospective study should be performed to confirm these findings.

Key words: glargine 100 U/mL, glargine 300 U/mL, Japanese diabetes patients, outpatient clinic

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Introduction

Diabetes is a growing global health challenge. By 2040, it is predicted that worldwide population of diabetes patients will reach 642 million, which is equivalent to approximately 10% of the world's population (1). Insulin is important for the treatment of type 1 and 2 diabetes because of its efficacy

and its consistent results in controlling blood glucose levels. The application of recombinant DNA (rDNA) technology in the 1980s led to the development of insulin analogs with characteristics that confer additional benefits over native insulin. At present, the most widely used basal insulin is insulin glargine [100 U/mL (Gla-100)], which has a well-established mode of action, efficacy, and safety profile (2-6). However, to improve current treatment options, a basal insu-

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lin product that confers an even lower risk of hypoglycemia would be desirable. Insulin glargine [300 U/mL; (Gla-300)] was newly developed to optimize glycemic control, while minimizing the risk of hypoglycemia. After subcutaneous (s.c.) injection, the pharmacokinetic and pharmacodynamic action profiles of Gla-300 were more constant and were prolonged in comparison to those of Gla-100 because of the more gradual and extended release of Gla-300 from the s.c. depot, which translates into continued blood glucose control, even beyond 24 hours after injection (7). In Japan, Gla-300 became available in September 2015 and has been used as a clinical treatment option since that time. The expectations are high that type 1 and 2 diabetes patients who can switch from Gla-100 to the same dose of to Gla-300 will experience improved glycemic control.

A recent study of a Japanese population with type 1 and 2 diabetes, the EDITION JP1 and JP2 program, showed that the glycemic control offered by Gla-300 and Gla-100 did not differ to a statistically significant extent over a six-month time-period with scheduled titration procedures, but that patients who received Gla-300 had fewer hypoglycemic events than those who received Gla-100 (8, 9). Gla-300 was well tolerated, and the rates of other adverse events did not differ from those that were observed with the use of Gla-100. However, these trials (8, 9) used a modified TactiPen[®] injector (Sanofi, Paris, France) to administer Gla-300, and a SoloSTAR[®] pen injector (Sanofi) to administer Gla-100 (Lantus[®]; Sanofi). In Japan, Gla-300 is commercially available with the improved SoloSTAR[®] pen injector, which exhibits higher reproducibility and lower injection force (10) in comparison to the Gla-100 SoloSTAR[®] (11). In addition, the insulin dose in each study was adjusted in accordance with the targeted fasting glucose levels. Accordingly, it is necessary to investigate type 1 and 2 diabetes Japanese patients who received other medications, such as prandial insulin or oral anti-hyperglycemic drugs, when switching from Gla-100 to the same dose of Gla-300 to certify the effect of Gla-300 in the clinical setting.

The aim of the present study was to retrospectively evaluate - using outpatient data - the glycemic control, body weight, and incidence of adverse effects in Japanese type 1 and type 2 diabetes patients who switched from Gla-100 to the same dose of Gla-300.

Materials and Methods

Study patients

The study population included adult type 1 diabetes outpatients who were treated with basal-bolus insulin therapy using a rapid-acting insulin analog and Gla-100 as basal insulin, and type 2 diabetes outpatients treated with Gla-100 and oral anti-hyperglycemic drugs or rapid insulin and glucagon-like peptide-1 receptor agonists. With the exception of the dose of Gla-100, the patients' diabetes treatments had not changed for two consecutive consultations before

they were switched from Gla-100 to Gla-300 during the period from January to April 2016. The HbA1c level shows seasonal variation (12); thus, we monitored the patients who continued the use of Gla-100 during the same time-period, in an effort to mitigate the influence of this seasonal variation. The diagnoses of type 1 and type 2 diabetes were based on the Japan Diabetes Society criteria (13, 14). When switching from Gla-100 to Gla-300, the dose remained the same as that administered at regular outpatient visits (in all patients), while the patients who continued the use of Gla-100 without changing other medications during the observational period were retrospectively enrolled in the present study. After the basal insulin switch, insulin titration was carried out based on the instructions of the attending physician. The study protocol was approved by the hospital ethics committee (No. 2602).

Measurements

The body weight (kg), systolic and diastolic blood pressure (mmHg), blood glucose levels (mg/dL), and HbA1c (%) were extracted from the data obtained over five consecutive outpatient visits [the two visits before switching (Visits 1 and 2), the visit in which the switch was initiated (Visit 3), and two visits after switching (Visits 4 and 5)]. In addition, the medication status and information about symptomatic hypoglycemic episodes were extracted from the patients' medical records. The body mass index (BMI) was calculated as the body weight in kilograms divided by the height in meters squared. Because several of the patients had already been trained to use a blood glucose monitor to track their fasting blood glucose [self-monitored blood glucose (SMBG)] levels and recorded the information, asymptomatic hypoglycemia (<60 mg/dL) was also calculated using the laboratory and SMBG data.

Statistical analysis

The data are expressed as the mean and standard deviation. Continuous variables were compared using an age-adjusted analysis of variance (ANOVA) for comparisons between patients who switched from Gla-100 to Gla-300 and patients who continued the use of Gla-100. In the patients who switched to Gla-300, the measurements taken at Visits 1 and 2 and Visits 4 and 5 were compared to the measurements taken at Visit 3 using Wilcoxon's rank sum test. Among patients who continued the use of Gla-100, the measurements at Visits 1, 2, 4, and 5 were compared to the measurements at Visit 3 over the course of these five consecutive visits. Next, the patients were divided into tertiles based on their HbA1c and body weight levels at Visit 3; the patient numbers of the three categories differed because some patients had identical values. For the type 1 diabetes patients, we divided the HbA1c levels into the following three categories: <7.0 (n=6), 7.0-8.4 (7), and ≥8.5% (7). For the type 2 diabetes patients, we divided the HbA1c levels into the following categories: <7.7 (21), 7.7-8.4 (25), and ≥8.5% (16). For the patients who continued the use of Gla-

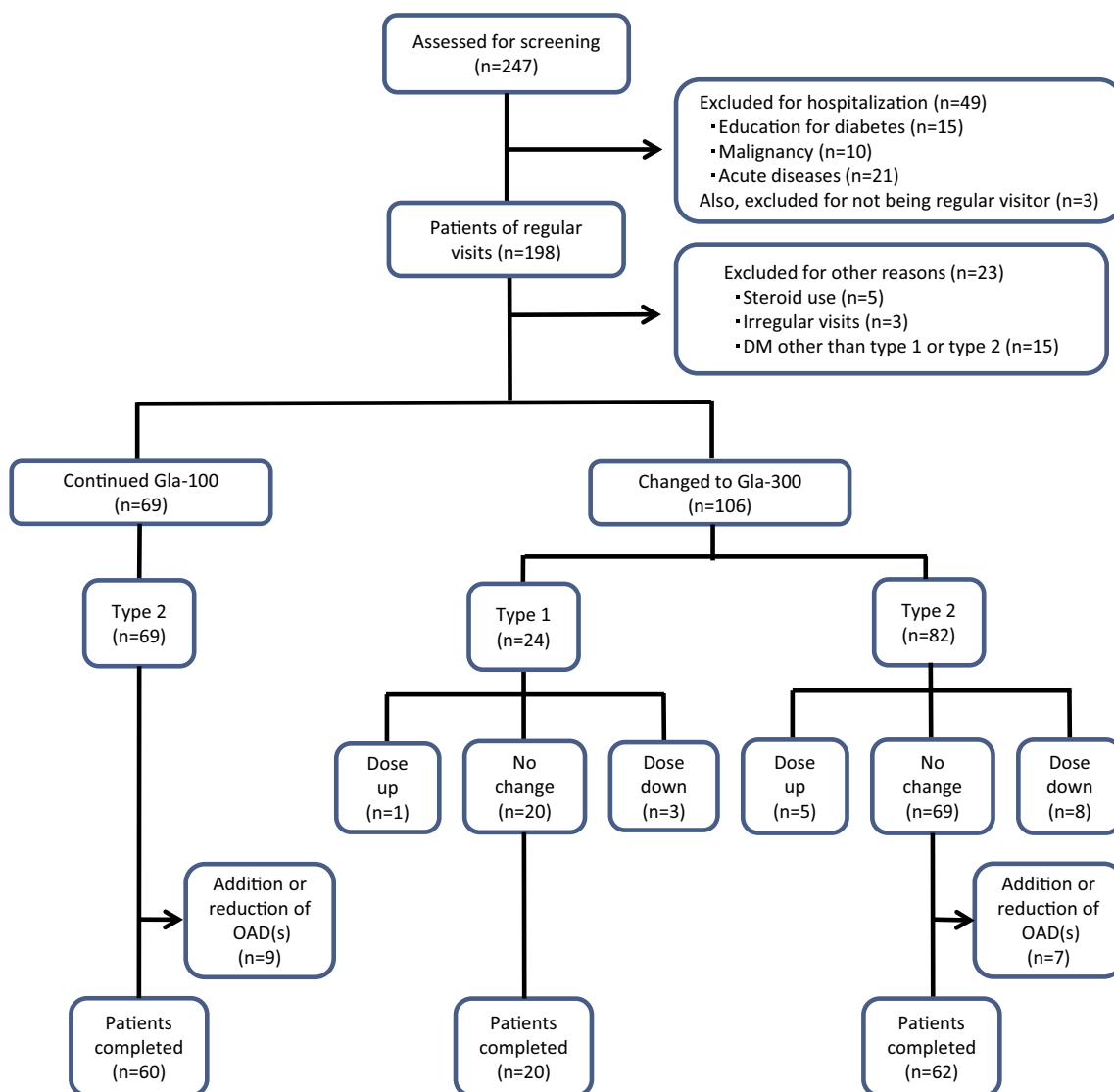


Figure 1. The flow of the study participants. The numbers indicate the numbers of study participants.

100, we divided the HbA1c levels into the following categories: 7.2 (22), 7.2-7.6 (20), and $\geq 7.7\%$ (18). For the type 1 diabetes patients, we divided the BMI values into the following categories: <19.9 (6), 20-23.3 (7), and ≥ 23.4 kg/m² (7). For the type 2 diabetes patients, we divided the BMI values into the following categories: <23.2 (21), 23.3-26.7 (20), and ≥ 26.8 kg/m² (21). For the patients who continued the use of Gla-100, we divided the BMI values into the following categories: <23.4 (19), 23.5-26.5 (20), and ≥ 26.6 kg/m² (21). The changes in HbA1c were compared among the three categories. In addition, the differences in the mean fasting glucose level were calculated using seven days of SMBG data before and after switching to evaluate the effect of basal insulin. *p* values of <0.05 were considered to indicate statistical significance. The statistical analyses were performed using the SAS software program (version 8 for Windows).

Results

The clinical characteristics of study patients

The overall patient composition is shown in Fig. 1. From the 247 patients who were screened for Gla-100 prescription data, 49 were excluded due to hospitalization at some point (for several reasons) during the five consecutive observation periods. In addition, 23 patients were excluded for steroid use, irregular physician visits, or types of diabetes other than type 1 or type 2. Finally, 20 type 1 diabetes patients and 62 type 2 diabetes patients were switched from Gla-100 to the same dose of Gla-300. In addition, we monitored 60 type 2 diabetes patients who continued the use of Gla-100 at the same dose during the same time period (Visits 2 and 3) to mitigate the effects of seasonal variation in the HbA1c level on the study results. Table shows the clinical characteristics and medication status at baseline in the type 1 and type 2

Table. Clinical Characteristics of Study Subjects.

	Switched to Gla-300		Continued Gla-100
	T1DM	T2DM	T2DM
M/F (n)	13/7	36/26	33/27
Time of injection (n)			
Morning	3	13	30
Morning and dinner	3	3	0
Dinner	13	39	27
Bedtime	1	7	3
Age (years)	51.5±21.0	62.1±14.7*	70.3±9.2*†
Dose of basal insulin (U)	10.9±7.8	8.7±6.0	11.1±4.9
Body weight (kg)	56.0±12.3	66.3±13.6*	63.5±11.3
BMI (kg/m ²)	22.1±3.1	25.4±4.1*	25.5±3.9*
SBP (mmHg)	130.7±21.3	134.2±17.3	131.9±18.0
DBP (mmHg)	70.2±14.0	74.7±12.6	70.6±11.2
AST (IU/L)	21.0±6.0	25.0±14.8	22.3±8.1
ALT (IU/L)	14.6±5.9	24.8±14.6*	19.1±13.8
BUN (mg/dL)	14.6±4.6	18.5±8.2	19.9±7.3*
Crea (mg/dL)	0.68±0.17	0.83±0.49	0.79±0.31
Blood glucose (mg/dL)	147.9±50.2	174.1±58.4	168.6±56.1
HbA1c (%)	7.96±1.31	8.07±0.97	7.55±0.82†
Treatment for DM in addition to basal insulin (n)			
Bolus	20	36	26
DPP4Is		35	45
Biguanides		33	18
Thiazolidinediones		21	4
Sulphonylureas		15	17
Glinides		7	6
α -glucosidase inhibitors		14	6
SGLT2Is		4	4
GLP-1 analogues		2	1

Data are shown as mean±SD. *p<0.05 compared to T1DM. †p<0.05 compared to T2DM in subjects who switched to Gla-300. T1DM: Type 1 diabetes patients, T2DM: Type 2 diabetes patients, BMI: Body Mass Index, DPP4I: Dipeptidyl peptidase-4 inhibitor, SGLT2I: Sodium-glucose co-transporter 2 inhibitor

diabetes patients who switched or continued to use Gla-100. Several patients were treated with Gla-100 twice daily. In the type 1 diabetes patients, the mean timing of Visits 4 and 5 (after switching from Gla-100 to Gla-300) was 6.0±2.8 weeks and 11.2±4.0 weeks after the baseline measurement, respectively. Similarly, in the type 2 diabetes patients, the mean timing of Visits 4 and 5 (after switching from Gla-100 to Gla-300) was 6.0±2.6 weeks and 12.4±4.3 weeks after the baseline measurement, respectively. In the type 2 diabetes patients who continued the use of Gla-100, the mean timing of Visits 4 and 5 was 5.0±1.9 weeks and 9.8±2.5 weeks after the baseline measurement, respectively. Because participants were not obligated to record their SMBG levels in our study, we only obtained fasting glucose data from the medical records of 47 patients (type 1, n=11; type 2, n=36).

Changes in glycemic control and insulin dose

After switching to Gla-300 at Visit 3, the HbA1c levels in the type 1 diabetes patients decreased from 7.96±1.31% at baseline, to 7.91±1.16% at Visit 4, and 7.81±1.25% at Visit 5; these changes were not statistically significant (Fig. 2A).

A significant change was observed in the HbA1c levels of the type 2 diabetes patients, which decreased from 8.07±0.97% at Visit 3, to 7.94±1.20% at Visit 4, and 7.79±1.20% at Visit 5 (p=0.023 and p<0.001, respectively) (Fig. 2B). In contrast, there was no such change in the HbA1c levels of the type 2 diabetes patients who continued the use of Gla-100: 7.55±0.82% at Visit 3, 7.57±0.83% at Visit 4, and 7.50±0.73% at Visit 5 (Fig. 2C). In addition, the doses of Gla-300 in the type 1 diabetes patients were 10.9±7.8 U/day when the switch was made (Visit 3), 10.9±7.8 U/day at Visit 4, and 11.2±7.8 U/day at Visit 5. The doses of Gla-300 in the type 2 diabetes patients were 8.7±6.0 U/day when the switch was made (Visit 3), 8.8±6.3 U/day at Visit 4, and 8.6±6.7 U/day at Visit 5. The doses of Gla-100 in the type 2 patients who continued the use of Gla-100 were 11.1±4.9 U/day at Visit 3, 10.8±4.3 U/day at Visit 4, and 10.8±4.3 U/day at Visit 5. The doses of bolus insulin in the type 1 diabetes patients were 17.2±9.6 U/day at Visit 3, 17.0±9.6 U/day at Visit 4, and 16.8±9.4 U/day at Visit 5. The doses of bolus insulin in the type 2 diabetes patients who switched to Gla-300 were 16.0±6.0 U/day at Visit 3, 15.9±5.7 U/day at

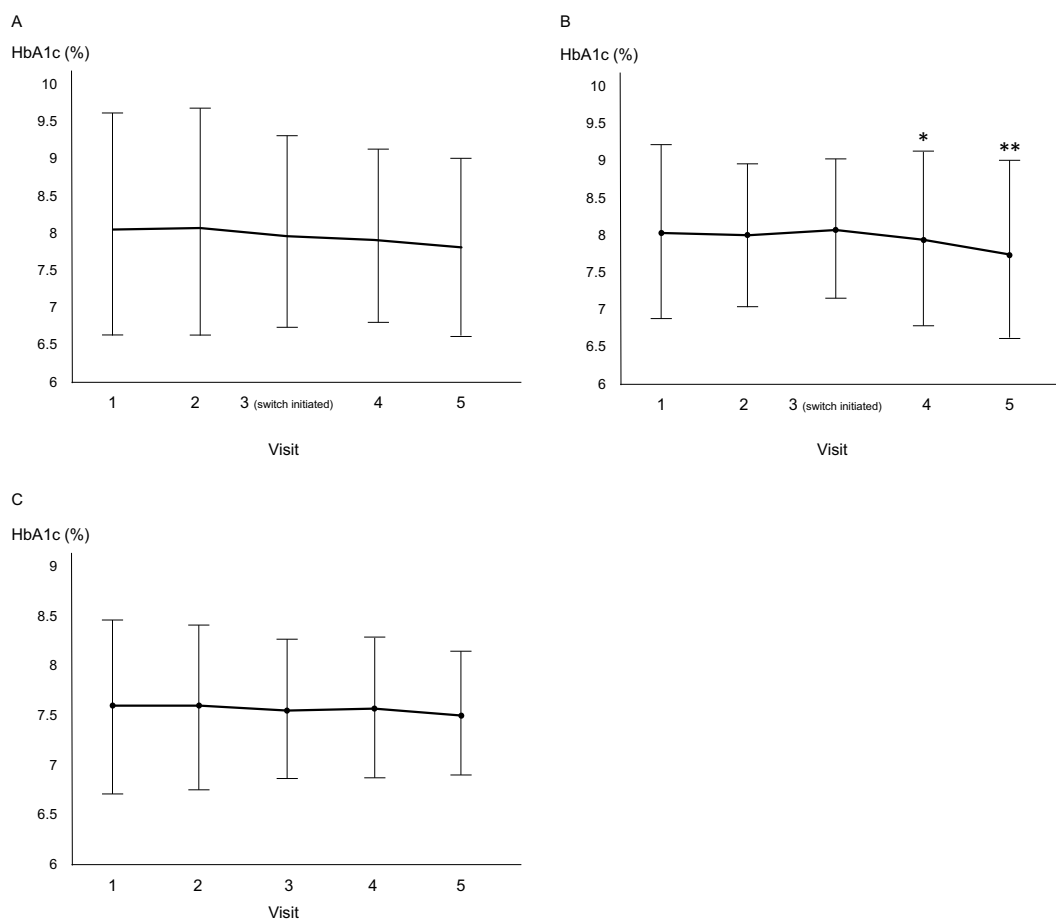


Figure 2. The time course of the HbA1c levels in the type 1 diabetes patients who switched from Gla-100 to Gla-300 (A), the type 2 diabetes patients who switched from Gla-100 to Gla-300 (B), and the type 2 diabetes patients who continued the use of Gla-100. * $p < 0.05$ in comparison to baseline. ** $p < 0.01$ in comparison to baseline.

Visit 4, and 15.2 ± 6.0 U/day at Visit 5. In the type 1 and 2 diabetes patients, the bolus insulin doses tended to decrease after switching to Gla-300; however, the decrease did not reach statistical significance. There was no such change in the bolus insulin doses of the type 2 diabetes patients who continued the use of Gla-100: 15.4 ± 5.5 U/day at Visit 3, 15.5 ± 5.3 U/day at Visit 4, and 15.3 ± 5.1 U/day at Visit 5.

Next, the patients were divided into tertiles according to the HbA1c level at Visit 3 (based on the population). In the high tertile group of type 1 diabetes patients, the HbA1c level was significantly decreased at Visit 4 (Fig. 3A). In the middle tertile group of type 2 diabetes patients, the HbA1c level was significantly decreased at Visit 5. In the low tertile group, the HbA1c levels were significantly decreased at Visits 4 and 5 (Fig. 3B). In contrast, there was no such change in the HbA1c levels of the middle and low tertile groups of the type 2 diabetes patients who continued the use of Gla-100; however, the HbA1c level was decreased in the high tertile group at Visit 5 (Fig. 3C).

Finally, patients were divided into tertiles according to their BMI value at Visit 3 (based on the population). In the middle tertile group of type 1 diabetes patients, the HbA1c levels tended to decrease at Visits 4 and 5 but the change

was not statistically significant (Fig. 4A). In the middle tertile group of type 2 diabetes patients, the HbA1c level was significantly decreased at Visit 5. In the low tertile group, the HbA1c levels were significantly decreased at Visits 4 and 5 (Fig. 4B). On the other hand, there was no change in any of the tertile groups of the type 2 diabetes patients who continued the use of Gla-100 (Fig. 4C).

BMI change

After switching to Gla-300 at Visit 3, the BMI values of the type 1 diabetes patients decreased from 22.1 ± 3.1 kg/m² at Visit 3, to 22.0 ± 3.2 kg/m² at Visit 4, and 21.9 ± 3.3 kg/m² at Visit 5; however, the decrease did not reach statistical significance ($p = 0.052$ and 0.059 , respectively) (Fig. 5A). The BMI values of the type 2 diabetes patients decreased significantly from 25.4 ± 4.1 kg/m² at Visit 3, to 25.4 ± 4.1 kg/m² at Visit 4, and 25.0 ± 4.3 kg/m² at Visit 5 ($p = 0.025$) (Fig. 5B). In contrast, there was no change in the BMI values of the type 2 diabetes patients who continued the use of Gla-100: Visits 3, 25.5 ± 3.9 kg/m²; Visit 4, 25.5 ± 4.0 kg/m²; Visit 5, 25.4 ± 4.0 kg/m² (Fig. 5C).

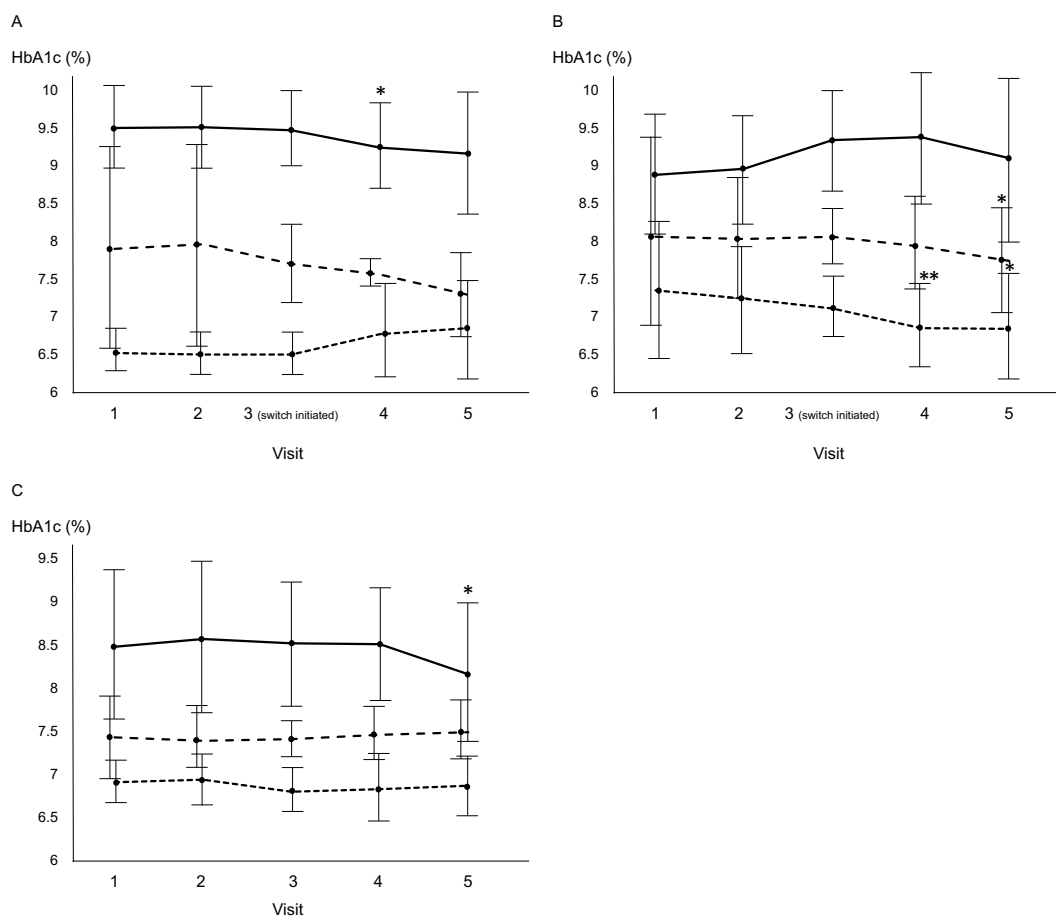


Figure 3. The time course of the HbA1c levels divided into HbA1c tertiles. (A) Type 1 diabetes patients who switched from Gla-100 to Gla-300. (B) Type 2 diabetes patients who switched from Gla-100 to Gla-300. (C) Type 2 diabetes patients who continued the use of Gla-100. Solid lines: patients in the high HbA1c tertile group; long dashed lines: patients in the middle HbA1c tertile group; short dashed lines: patients in the low HbA1c tertile group. * $p < 0.05$ in comparison to baseline. ** $p < 0.01$ in comparison to baseline.

The fasting glucose data from the patients' SMBG records

We obtained the fasting SMBG data for seven days before and after the switch of basal insulin from the medical records of 47 patients. The mean fasting glucose levels in the type 1 and type 2 diabetes patients decreased from 145.6 ± 23.6 mg/dL and 155.3 ± 35.7 mg/dL to 130.7 ± 20.1 mg/dL and 146.0 ± 30.8 mg/dL ($p = 0.15$ and 0.08), respectively; the decrease did not reach statistical significance.

Hypoglycemia and adverse events

During the follow-up period, no symptomatic hypoglycemic episodes or adverse events were noted in any of the patients' medical records. However, in the records of the type 1 diabetes patients, asymptomatic hypoglycemia (< 60 mg/dL) was noted (in the clinical and SMBG data) three times before switching and twice after switching. In the type 2 diabetes patients, asymptomatic hypoglycemia was noted three times before switching but was not noted after the switch. In the type 2 diabetes patients who continued the

use of Gla-100, asymptomatic hypoglycemia was observed only once during the follow-up period. In addition, no patients withdrew from the study due to adverse events, and no injection-site reactions were reported.

Discussion

In this observational, retrospective study, we examined the effectiveness of switching from Gla-100 to the same dose of Gla-300 in Japanese type 1 and 2 diabetes patients. As a result, we found that in the clinical setting, a switch from Gla-100 to the same dose of Gla-300 had a favorable effect on glycemic control and body weight reduction, without any adverse events.

In the recent EDITION JP2 trial (8), regarding the number of Japanese type 2 diabetes patients who switched from Gla-100 to Gla-300 compared to those who continued the use of Gla-100 over a 6-month period, the reduction in the HbA1c levels of the patients who switched to Gla-300 was found to be equal to that of the patients who continued to receive Gla-100. In addition, no inter-treatment differences

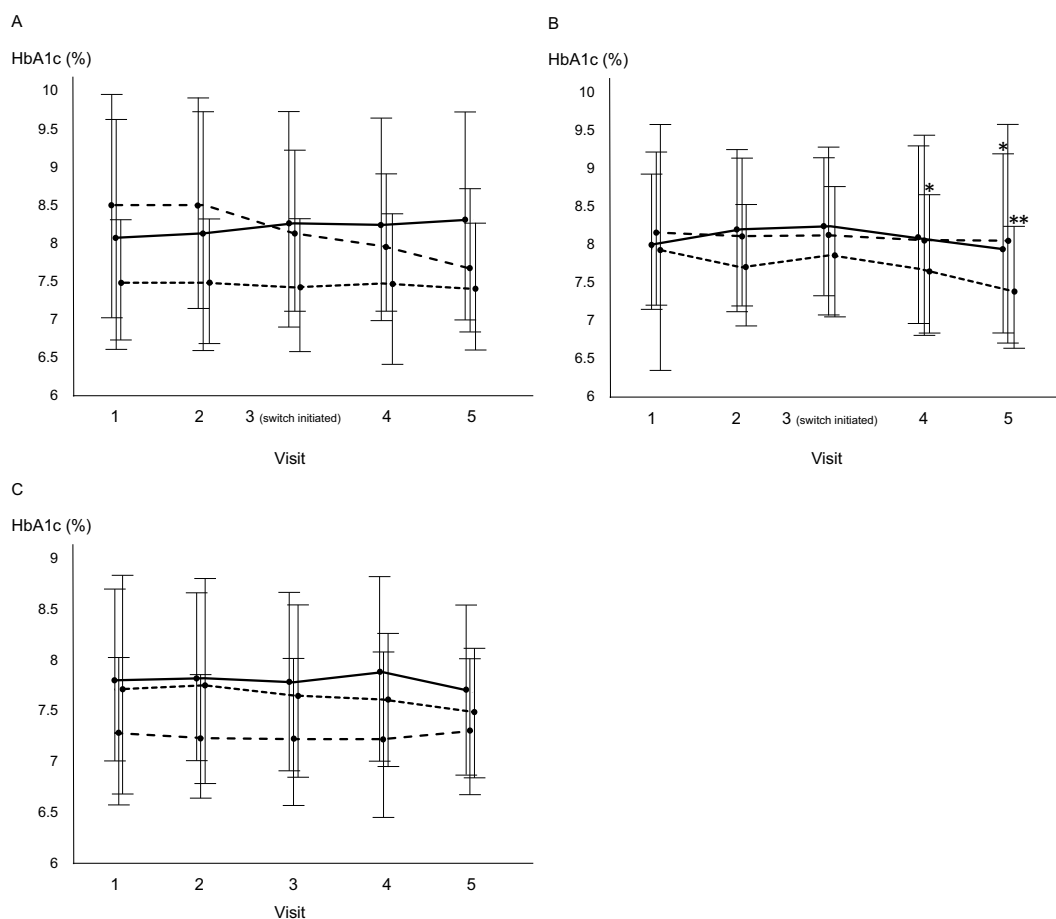


Figure 4. The time course of HbA1c levels divided into BMI tertiles. (A) Type 1 diabetes patients who switched from Gla-100 to Gla-300. (B) Type 2 diabetes patients who switched from Gla-100 to Gla-300. (C) Type 2 diabetes patients who continued the use of Gla-100. Solid lines: patients in the high BMI tertile group; long dashed lines: patients in the middle BMI tertile group; short dashed lines: patients in the low BMI tertile group. * $p < 0.05$ in comparison to baseline. ** $p < 0.01$ in comparison to baseline.

in glycemic control were observed. Furthermore, the changes in the HbA1c and fasting glucose levels in that trial were consistent with treat-to-target-based studies. However, a higher dose of Gla-300 was required in comparison to Gla-100 in order to maintain the same degree of glycemic control (8).

In our study, although the insulin dose administered to the type 2 diabetes patients by physicians was not often changed during the follow-up period, switching from Gla-100 to the same dose of Gla-300 provided beneficial effects, not only in terms of glycemic control but also in terms of body weight. These discrepancies in results might be - at least in part - due to the differences in the injection devices that were used for Gla-300. Gla-300 SoloSTAR, a disposable insulin pen that is currently available in Japan, was reported to be beneficial for patients with reduced hand strength (11) and accurately delivered the required dosage of insulin (10); the TactiPen was used in EDITION JP2 (8). We assume that this difference might have contributed to the improvement in the glycemic control of the patients in our study, even after they switched from Gla-100 to the same

dose of Gla-300, because the same benefits were not observed in previous studies that used other devices (8, 15).

In our study, the type 2 diabetes patients in the middle HbA1c tertile group showed a tendency for improved glycemic control at Visit 5, while those in the low HbA1c tertile group showed a tendency for improved glycemic control and Visits 4 and 5. These patients were thought to have been injected with sufficient doses of Gla-100 because they showed better fasting glucose levels than the patients in the high HbA1c tertile group. Accordingly, the pharmacological profile of Gla-300, which has stable and prolonged pharmacokinetic and pharmacodynamic profiles in comparison to Gla-100 (7, 16), might be effective for such patients. Interestingly, the type 2 diabetes patients in the middle BMI tertile group showed significantly improved HbA1c levels at Visit 5, while those in the low BMI tertile group showed significantly improved HbA1c levels at Visits 4 and 5. It was assumed that these patients had greater insulin sensitivity in comparison to the patients in the high BMI tertile group. Thus, we assume that patients whose fasting glucose levels are well controlled by Gla-100 or those with high insulin

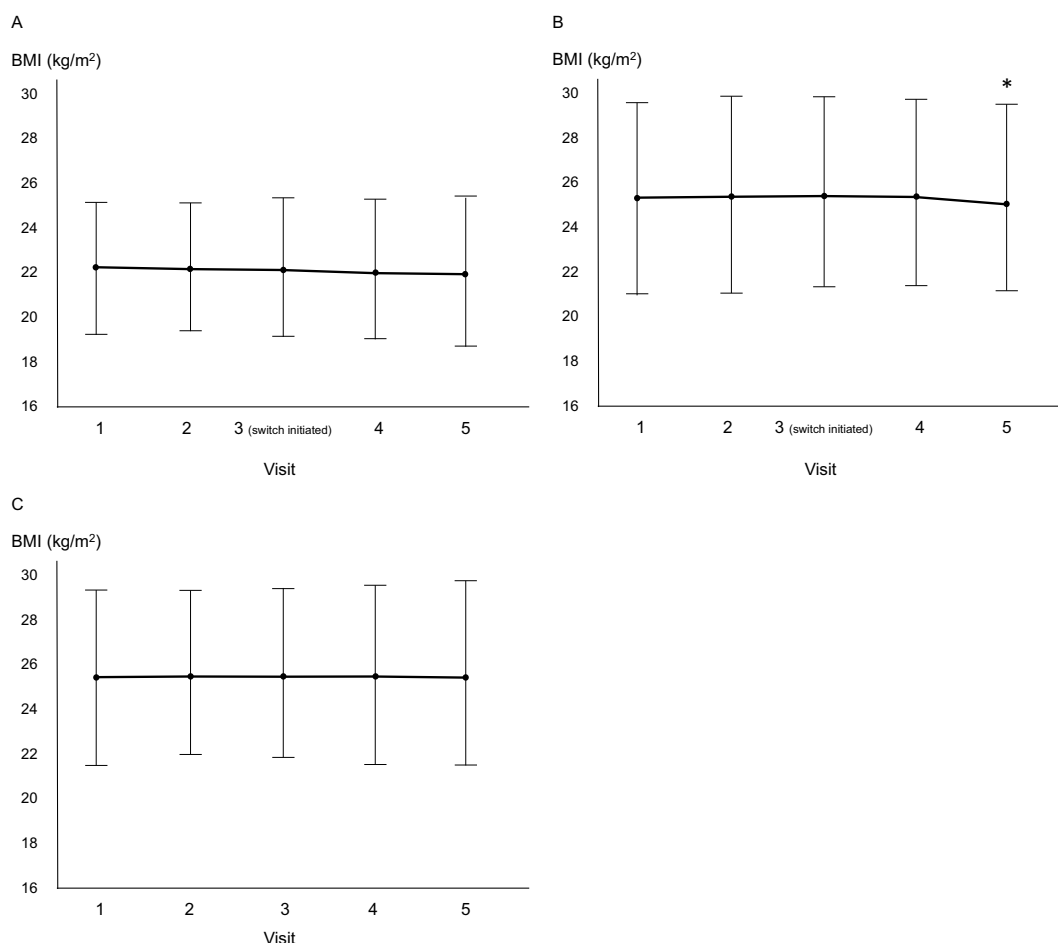


Figure 5. The time course of the BMI values in the type 1 diabetes patients who switched from Gla-100 to Gla-300 (A), the type 2 diabetes patients who switched from Gla-100 to Gla-300 (B), and the type 2 diabetes patients who continued the use of Gla-100. * $p < 0.05$ in comparison baseline.

sensitivity (*i.e.*, patients with lean physical profiles) are best suited for switching from Gla-100 to Gla-300.

In our study, a body weight reduction was observed in the type 2 diabetes patients who switched from Gla-100 to the same dose of Gla-300; this was consistent with the observations in previous reports (8, 15). In addition, although the mean fasting glucose levels obtained from the patients' SMBG records were decreased hypoglycemic events - including asymptomatic events - were rare in our study. In previous studies of type 1 (9, 17) and type 2 diabetes (8, 15, 18), Gla-300 was associated with a lower risk of hypoglycemia in comparison to Gla-100. In addition, although the result was not statistically significant, the reduction in the incidence of asymptomatic hypoglycemic events is of clinical relevance because it indicates more effective glucose control with less need for unnecessary meals, which could lead to body weight gain. However, further analyses are warranted to establish whether a reduction in hypoglycemic events contributes to a favorable change in body weight when using Gla-300 in comparison to Gla-100.

The present study was associated with several limitations, and thus caution is required when interpreting the results. First, it was a retrospective observational study with limited

study population. In addition, the observational period of approximately three months was short. In particular, there were no significant differences in the HbA1c levels or body weight changes among the type 1 patients. This lack of significance was likely due - at least in part - to the relatively small number of type 1 diabetes patients. In addition, no comparable type 1 patients who continued treatment with Gla-100 participated in our study. To make our results more reliable, it would be beneficial to perform further prospective studies with adequate statistical power over a longer study period. Second, this study was based on practical data without titration. Needless to say, both advances in insulin device technology and adjustments in the insulin dose are important for obtaining good glycemic control in the type 1 and 2 diabetes patients. Third, in this study we monitored 60 patients who continued to use the same dose of Gla-100 during the same period in order to mitigate the effects of seasonal variation in the HbA1c level. However, there were differences in several of the background parameters of the patients who switched from Gla-100 to Gla-300 and those who continued Gla-100; as shown in Table, these differences included age, the timing of injections, and the use of biguanides. Thus, we cannot exclude the possibility that the

results in this study were influenced by such differences. Fourth, the effects with respect to the HbA1c level and body weight that were observed in the type 2 patients who had changed from Gla-100 to Gla-300 may have been derived - in part - from a placebo effect due to the change in treatment.

In conclusion, switching from Gla-100 to the same dose of Gla-300 is likely to be safe for Japanese patients with type 1 or type 2 diabetes. This switch, which can be expected to have benefits on both glycemic control and body weight control, should be appropriate for use in the outpatient setting. However, a further prospective study should be performed to confirm the findings.

Author's disclosure of potential Conflicts of Interest (COI).

Shuhei Nakanishi: Honoraria, Sanofi. Masahiro Iwamoto: Honoraria, Sanofi, Kissei Pharma and Boehringer Ingelheim. Kohei Kaku: Advisory role, Novo Nordisk Pharma, Sanwa Kagaku Kenkyusho, Takeda, Taisho Pharmaceutical, MSD, Kowa, Sumitomo Dainippon Pharma, Novartis, Mitsubishi Tanabe Pharma, AstraZeneca, Nippon Boehringer Ingelheim, Chugai, Daiichi Sankyo and Sanofi; Honoraria, Novo Nordisk Pharma, Sanwa Kagaku Kenkyusho, Takeda, Taisho Pharmaceutical, MSD, Kowa, Sumitomo Dainippon Pharma, Novartis, Mitsubishi Tanabe Pharma, AstraZeneca, Nippon Boehringer Ingelheim, Chugai, Daiichi Sankyo and Sanofi; Others, Novo Nordisk Pharma, Sanwa Kagaku Kenkyusho, Takeda, Taisho Pharmaceutical, MSD, Kowa, Sumitomo Dainippon Pharma, Novartis, Mitsubishi Tanabe Pharma, AstraZeneca, Nippon Boehringer Ingelheim, Chugai, Daiichi Sankyo and Sanofi. Hideaki Kaneto: Honoraria, Sanofi, Novo Nordisk, Lilly, Boehringer Ingelheim, MSD, Takeda, Ono Pharma, Daiichi Sankyo, Sumitomo Dainippon Pharma, Mitsubishi Tanabe Pharma, Pfizer, Kissei Pharma, AstraZeneca, Astellas, Novartis, Kowa, Chugai and Taisho Pharma; Others, Sanofi, Novo Nordisk, Lilly, Boehringer Ingelheim, MSD, Takeda, Ono Pharma, Daiichi Sankyo, Sumitomo Dainippon Pharma, Mitsubishi Tanabe Pharma, Pfizer, Kissei Pharma, AstraZeneca, Astellas, Novartis, Kowa, Chugai and Taisho Pharma.

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