



Original Article

Insulin glargine in pediatric patients with type 1 diabetes in Japan

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Abstract **Background:** We evaluated the safety and effectiveness of insulin glargine in Japanese pediatric patients with type 1 diabetes in clinical settings based on post-marketing surveillance data.

Methods: Clinical data were collected from Japanese pediatric patients with type 1 diabetes for 24 weeks after initiation of glargine treatment. Baseline characteristics, hemoglobin A1c (HbA1c), fasting plasma glucose (FPG), previous/concomitant medication, height, bodyweight, and adverse events were analyzed.

Results: One-hundred and thirteen patients were enrolled from 20 medical institutions in Japan in 2003 and 2004. Of these patients, 73 were included in the safety analysis, and 70 of these patients were also included in the efficacy analysis. The 73 patients included 28 boys and 45 girls, with a mean age of 11.8 years at entry. Hypoglycemia occurred in three patients (three events) and was severe in two patients (two events); all patients recovered. In the efficacy evaluation, HbA1c at baseline and final assessment was 9.10% and 8.09% ($P < 0.001$) in all patients; 8.96% and 7.85% ($P < 0.001$) in patients aged 7–12 years (Group 1); and 9.28% and 8.37% ($P = 0.010$) in patients aged 13–15 years (Group 2). FPG significantly decreased in all patients and in Group 1. No significant changes were observed in body mass index or degree of obesity during the study.

Conclusions: Glargine therapy for Japanese pediatric patients with type 1 diabetes resulted in good glycemic control in terms of HbA1c and FPG as well as good safety in clinical settings. Glargine had little effect on the physical build of patients.

Key words degree of obesity, glycemic control, hypoglycemia, insulin glargine, pediatric patients with type 1 diabetes.

Good glycemic control to normalize fluctuations in blood glucose levels is important in the treatment of diabetes to prevent the development of complications.^{1,2} However, it is difficult to maintain stable blood glucose levels in pediatric patients with type 1 diabetes due to variations in food consumption and exercise levels; thus, children with type 1 diabetes may experience a higher incidence of hyperglycemia and hypoglycemia than adults.^{3–5}

Treatment of type 1 diabetes requires insulin therapy, and standard therapy should be designed to match the physiological insulin profile as closely as possible by combining a long-acting or intermediate insulin with a rapid-acting or regular insulin.⁶

Insulin glargine is a long-acting insulin analogue⁷ that is dissolved and absorbed slowly over time after subcutaneous administration, resulting in a consistent antihyperglycemic effect over almost 24 h with no peak; this action profile is different from conventional neutral protamine Hagedorn (NPH) insulin or long-acting zinc-based insulins.^{8,9} Due to these properties, glargine is one of the most common basal insulin preparations used in intensive insulin treatment, and extensive evidence supports its use.

Glargine was reported to be effective in Caucasian pediatric patients with type 1 diabetes.^{10–16} When an application was submitted for approval in Japan, however, its safety and effectiveness had not been established in Japanese pediatric patients, because no clinical studies had been conducted in this ethnic group. This post-marketing surveillance study was conducted to evaluate the safety and efficacy of insulin glargine in Japanese pediatric patients aged <16 years with type 1 diabetes.

Methods

This was a 24-week, prospective, open-label, multicenter, observational study. All pediatric patients aged <16 years who started to receive glargine for treatment of type 1 diabetes within 6 months of its launch in Japan (12 December 2003–11 June 2004) in medical institutions that agreed to participate in the study were surveyed. The planned sample size of 30 patients was selected because it appeared feasible during the 6-month period after launch.

The study was endorsed by the Health Authority in Japan, and was carried out as a special drug-use result surveillance study of Lantus in accordance with Good Post-Marketing Surveillance Practice (MHW Ordinance no. 10).

Data on actual usage of glargine in clinical settings were collected without intervention in terms of dose or regimen. Patients were followed for 24 weeks or until premature withdrawal from the study because of ineffectiveness or patient request.

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The following baseline characteristics were collected from medical charts at entry: sex; age; duration of diabetes; hospitalization or outpatient status; medical history; complications; and type and dose of previous medication (if applicable). The following information was collected about treatment during the observation period: administration time (before breakfast/before bedtime); dose of glargine; and type and dose of concomitant insulin.

Safety variables included adverse events and abnormal changes in laboratory test parameters (hematology, biochemistry, and urinalysis). An adverse event was defined as any untoward medical occurrence or clinically significant abnormal change in laboratory test parameters during the observation period. All adverse events were assessed by the investigator for the term, whether associated with hypoglycemia or not, seriousness, treatment, outcome, and causal relationship to glargine. An adverse event was handled as an adverse drug reaction unless considered to be unrelated to glargine. All adverse drug reactions were classified according to the Japanese version of the *Medical Dictionary for Regulatory Activities* 14.0. In this study, a diagnosis of hypoglycemia was made by the investigator based on the patient's condition, and severe hypoglycemia was defined as hypoglycemia with decreased consciousness requiring third-party intervention or intravenous administration of glucose.

Efficacy variables included hemoglobin A1c (HbA1c) (Japan Diabetes Society [JDS] value), fasting plasma glucose (FPG), height, and bodyweight. FPG was determined via self-monitoring of blood glucose before breakfast. The variables were measured before treatment (baseline: within 4 weeks before treatment) and after 24 ± 4 weeks of treatment.

For baseline characteristics, pre-study insulin, concomitant insulin and safety, and the percentage of each subject in each insulin group were calculated, and if necessary, descriptive sta-

tistics (mean \pm SD) were calculated to confirm the distribution. For effectiveness, mean \pm SD values were calculated for HbA1c, FPG, height, bodyweight, body mass index (BMI), and degree of obesity at baseline and final assessment (at the end of the 24-week treatment for patients who completed the 24-week treatment and at the time of discontinuation for those who were withdrawn or dropped out from the study). HbA1c was collected in JDS units and converted into National Glycohemoglobin Standardization Program (NGSP) units according to the following formula: HbA1c (NGSP) = $1.02 \times \text{HbA1c (JDS)} + 0.25$ (%; rounded to two decimal places).¹⁷ BMI was calculated according to the following formula: BMI = bodyweight/height squared (kg/m²). The degree of obesity was calculated based on the "Evaluation of Physical Build of Japanese Children" published by the Japanese Society for Pediatric Endocrinology (standard bodyweight was calculated by sex, age and height, and BMI calculator software version 1 was used).¹⁸ For the efficacy variables, the mean change from baseline to final assessment (final assessment – baseline) was calculated for patients aged 7–12 years (Group 1) and those aged 13–15 years (Group 2), divided by school age considering onset of puberty, and statistical analyses were performed by the paired *t*-test. All statistical tests were two-tailed and $P < 0.05$ was considered significant. Data were analyzed using IBM SPSS modeler (Version 15.0; IBM, Armonk, NY, USA) and R 2.15.1.¹⁹

Results

Patient composition

The patient composition is shown in Figure 1. A total of 113 patients were enrolled in the study from 20 medical institutions in Japan, and 107 patients completed the survey, excluding six patients from whom no case report form could be collected. Of

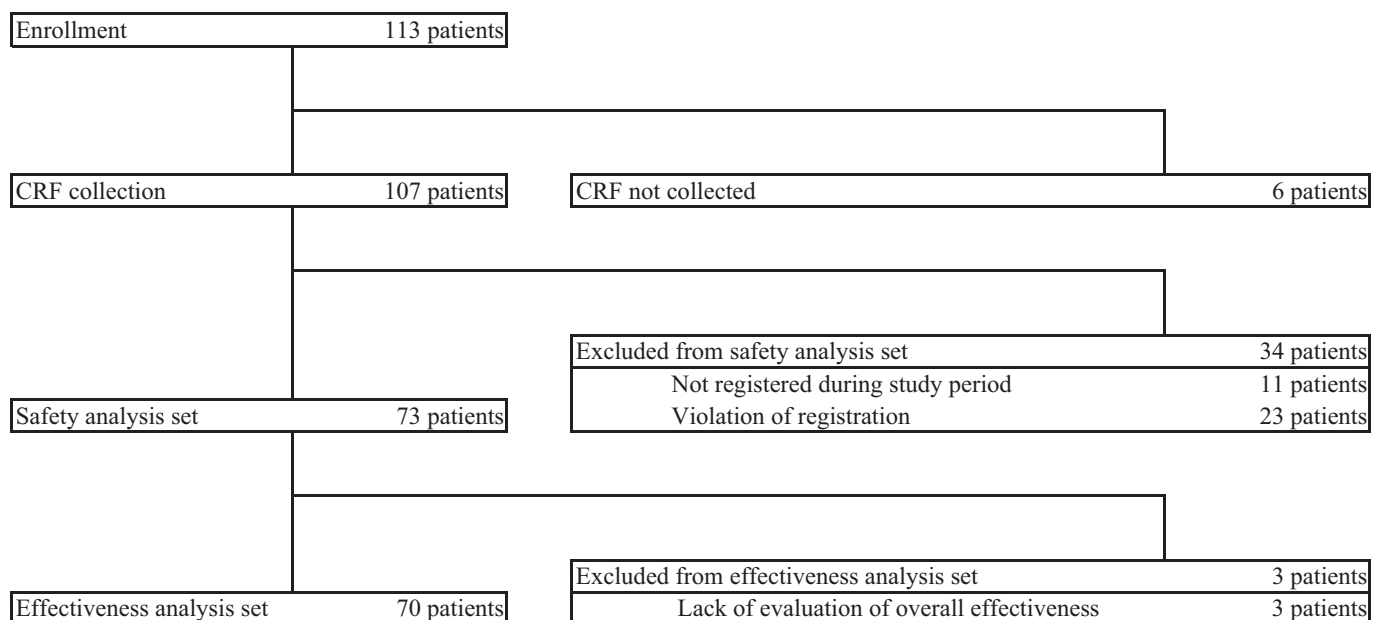


Fig. 1 Patient disposition. CRF, case report form.

the 107 patients, 73 patients were included in the safety analysis, excluding 34 patients who were not enrolled during the study period or were enrolled with violation of the registration. Of the 73 patients in the safety analysis, 70 patients were included in the efficacy analysis, excluding three patients who lacked evaluation of overall effectiveness.

Baseline characteristics

Baseline characteristics of patients in the safety analysis ($n = 73$) and efficacy analysis ($n = 70$) are shown in Table 1. Because the distribution of baseline characteristics of patients was similar in the two analysis sets, data from the safety analysis are provided hereafter. The patients comprised 28 boys (38.4%) and 45 girls (61.6%), and the mean age was 11.8 ± 2.7 years. The duration of diabetes was <1 year in three patients (4.1%), ≥ 1 year and <5 years in 36 patients (49.3%), and ≥ 5 years in 34 patients (46.6%). Two patients (2.7%) had other medical disorders (bronchial asthma and Kawasaki disease, respectively) and six patients (8.2%) had a complication of diabetes, including renal impairment in two patients (2.7%).

Previous therapy and insulin preparations after initiation of glargine

In this study, only two of 73 patients were insulin-naïve, newly diagnosed as type 1 diabetes; the remaining 71 patients had been treated with other insulin preparations. The most common previous insulin therapy was intermediate + rapid-acting insulin in 26 patients (35.6%), followed by intermediate + regular insulin in 22 patients (30.1%), and intermediate + rapid-acting + regular insulin in 12 patients (16.4%). Other previous therapies included premixed insulin alone, premixed + rapid-acting or regular insulin, and regular insulin alone (Table 2).

After start of treatment with glargine, the most common insulin therapy was glargine + rapid-acting insulin in 59 patients (80.8%), followed by glargine + intermediate + rapid-acting insulin in six patients (8.2%), and glargine + regular insulin in three patients (4.1%).

Figure 2 presents data on insulin dose pre-study, at baseline, and at study end-point. The mean \pm SD insulin dose at pre-study was 54.2 ± 26.4 U/day. During the study, total insulin dose and glargine dose started from 50.4 ± 22.3 U/day and 18.0 ± 9.5 U/day at baseline, and increased to 52.1 ± 22.7 U/day and 19.2 ± 9.7 U/day at end-point, respectively.

Adverse drug reactions

Five adverse drug reactions were reported in five of 73 patients (6.9%): hypoglycemia (three patients, 4.1%); asthenic conditions (one patient, 1.4%); and hyperglycemia (one patient, 1.4%). Of these, two adverse drug reactions in two patients were severe hypoglycemia with impaired consciousness (2.7%) and were serious, but all patients recovered. No patients were withdrawn from the study because of death (Table 3).

The first case of severe hypoglycemia was a 12-year-old girl who developed hypoglycemia 2 months after the start of treatment with glargine, which was used in combination with rapid-acting insulin (insulin aspart). She received an oral dose of glucose to treat mild impairment of consciousness in the early morning and recovered. The second case of severe hypoglycemia was a 12-year-old boy who developed hypoglycemia approximately 4 months after the start of treatment with glargine, which was used in combination with rapid-acting insulin (insulin aspart) and intermediate insulin (human insulin). He received an intravenous dose of 20% glucose to treat severe hypoglycemia with clouding of consciousness and recovered.

Table 1 Background characteristics

		Safety analysis set		Effectiveness analysis set	
		<i>n</i>	%	<i>n</i>	%
<i>n</i>		73	100.0	70	100.0
Sex	Boys	28	38.4	27	38.6
	Girls	45	61.6	43	61.4
Age	Mean \pm SD		11.8 ± 2.7		11.8 ± 2.7
	≥ 3 years, <7 years	3	4.1	2	2.8
	≥ 7 years, <13 years	36	49.3	34	48.6
	≥ 13 years, <16 years	34	46.6	34	48.6
Hospitalization/outpatient	Hospitalization	9	12.3	9	12.9
	Outpatient	63	86.3	61	87.1
	Unknown	1	1.4	0	0.0
Duration of diabetes	Less than 1 year	3	4.1	3	4.3
	1–5 years	33	45.2	30	42.9
	More than 5 years	37	50.7	37	52.9
Medical history	No	71	97.3	68	97.1
	Yes	2	2.7	2	2.9
Complications	Total	6	8.2	6	8.6
	Diabetic nephropathy	1	1.4	1	1.4
	Diabetic retinopathy	0	0.0	0	0.0
	Diabetic neuropathy	0	0.0	0	0.0
	Hyperlipidemia	1	1.4	1	1.4
	Other	4	5.5	4	5.7

Table 2 Pre-study and concomitant insulin

	Pre-study insulin		Concomitant insulin	
	<i>n</i>	%	<i>n</i>	%
Total	73	100.0	73	100.0
Intermediate + rapid-acting	26	35.6	6	8.2
Intermediate + regular	22	30.1	2	2.7
Intermediate + rapid-acting + regular	12	16.4	0	0.0
Intermediate + rapid-acting + premixed	1	1.4	0	0.0
Intermediate + rapid-acting + regular + premixed	1	1.4	0	0.0
Premixed	2	2.7	0	0.0
Premixed + rapid-acting	2	2.7	1	1.4
Premixed + regular	2	2.7	0	0.0
Premixed + rapid-acting + regular	2	2.7	0	0.0
Regular	1	1.4	3	4.1
Rapid-acting	0	0.0	59	80.8
Rapid-acting + regular	0	0.0	2	2.7
None	2	2.7	0	0.0

Efficacy

Glycemic control parameters, height, bodyweight, BMI, and degree of obesity at each time-point for the 70 patients in the effectiveness analysis are shown in Table 4.

HbA1c at baseline, final assessment, and its change from baseline to final assessment were $9.10 \pm 1.80\%$, $8.09 \pm 1.31\%$, and $-0.97 \pm 1.37\%$ ($P < 0.001$), respectively, in all patients; $8.96 \pm 1.62\%$, $7.85 \pm 0.79\%$, and $-1.14 \pm 1.45\%$ ($P < 0.001$), respectively, in Group 1; and $9.28 \pm 2.02\%$, $8.37 \pm 1.69\%$, and $-0.73 \pm 1.24\%$ ($P = 0.010$), respectively, in Group 2, showing significant decreases. Likewise, FPG at baseline, final assessment, and its change from baseline to final assessment were 180.53 ± 87.86 mg/dL, 135.03 ± 52.68 mg/dL, and -46.58 ± 83.36 mg/dL ($P = 0.012$), respectively, in all patients; 184.41 ± 90.64 mg/dL, 133.86 ± 53.92 mg/dL, and -55.00 ± 87.32 mg/dL ($P = 0.013$), respectively, in Group 1; and 172.00 ± 85.44 mg/dL, 140.39 ± 54.82 mg/dL, and -14.60 ± 63.52 mg/dL ($P = 0.634$),

respectively, in Group 2, showing significant decreases in all patients and Group 1.

Changes in bodyweight from baseline to final assessment were 1.97 ± 2.27 kg ($P < 0.001$) in all patients, 2.24 ± 1.99 kg ($P < 0.001$) in Group 1, and 1.52 ± 2.67 kg ($P = 0.032$) in Group 2, showing a significant increase in each group. Conversely, the change in BMI was 0.23 ± 0.95 kg/m² ($P = 0.123$) in all patients, 0.26 ± 0.80 kg/m² ($P = 0.107$) in Group 1, and 0.18 ± 1.20 kg/m² ($P = 0.563$) in Group 2, showing no significant changes. Similarly, the change in degree of obesity was $-0.39 \pm 5.41\%$ ($P = 0.640$) in all patients, $-0.72 \pm 4.73\%$ ($P = 0.437$) in Group 1, and $0.19 \pm 6.60\%$ ($P = 0.911$) in Group 2, showing no significant changes.

Table 3 Incidence rates of adverse drug reactions and severe drug reactions

	Adverse drug reaction	Serious adverse drug reaction
Safety analysis set	73	73
Patients with adverse drug reactions	5	2
Adverse drug reaction episodes	5	2
Percentage of patients with adverse drug reactions	6.9%	2.7%
Adverse drug reaction category	Percentage of patients with adverse drug reactions	
Metabolism and nutrition disorders		
Hypoglycemia	3 (4.1)	2 (2.7)
General disorders and administration site conditions		
[†] Asthenic conditions	1 (1.4)	–
Investigation		
Hyperglycemia	1 (1.4)	–

[†]Unexpected adverse drug reactions or infections according to the package insert. All adverse drug reactions were coded using the *Medical Dictionary for Regulatory Activities* 14.0.

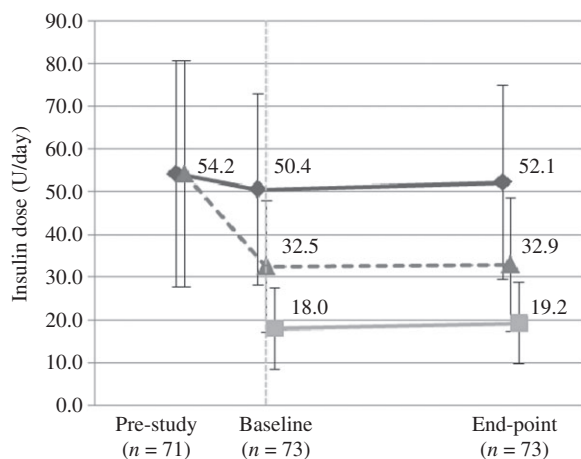


Fig. 2 Time course of insulin dose. The mean \pm SD dose for glargine (—●—), other insulin (---▲---) and total insulin (—■—) at pre-study, baseline, and end-point of the study.

Table 4 Changes in HbA1c, FPG, height, weight, BMI and degree of obesity

Item [†]	Mean \pm SD (<i>n</i>)			Paired <i>t</i> -test [†]
	Baseline	End-point	Change from baseline	
HbA1c (%)	9.10 \pm 1.80 (55)	8.09 \pm 1.31 (69)	-0.97 \pm 1.37 (54)	<i>P</i> < 0.001***
Group 1	8.96 \pm 1.62 (31)	7.85 \pm 0.79 (34)	-1.14 \pm 1.45 (31)	<i>P</i> < 0.001***
Group 2	9.28 \pm 2.02 (24)	8.37 \pm 1.69 (33)	-0.73 \pm 1.24 (23)	<i>P</i> = 0.010**
FPG (mg/dL)	180.53 \pm 87.86 (32)	135.03 \pm 52.68 (36)	-46.58 \pm 83.36 (24)	<i>P</i> = 0.012*
Group 1	184.41 \pm 90.64 (22)	133.86 \pm 53.92 (21)	-55.00 \pm 87.32 (19)	<i>P</i> = 0.013*
Group 2	172.00 \pm 85.44 (10)	140.39 \pm 54.82 (13)	-14.60 \pm 63.52 (5)	<i>P</i> = 0.634 NS
Height (cm)	149.23 \pm 13.00 (49)	150.55 \pm 15.33 (59)	2.51 \pm 1.80 (42)	<i>P</i> < 0.001***
Group 1	141.43 \pm 10.74 (28)	143.23 \pm 10.19 (31)	3.17 \pm 1.59 (27)	<i>P</i> < 0.001***
Group 2	159.63 \pm 7.17 (21)	162.73 \pm 6.35 (26)	1.33 \pm 1.58 (15)	<i>P</i> < 0.01**
Weight (kg)	44.43 \pm 12.80 (50)	45.72 \pm 13.90 (62)	1.97 \pm 2.27 (45)	<i>P</i> < 0.001***
Group 1	36.02 \pm 8.89 (28)	37.55 \pm 8.96 (32)	2.24 \pm 1.99 (28)	<i>P</i> < 0.001***
Group 2	55.15 \pm 8.11 (22)	57.02 \pm 8.75 (28)	1.52 \pm 2.67 (17)	<i>P</i> = 0.032*
BMI (kg/m ²)	19.37 \pm 2.99 (49)	19.38 \pm 3.10 (59)	0.23 \pm 0.95 (42)	<i>P</i> = 0.123 NS
Group 1	17.72 \pm 2.25 (28)	17.72 \pm 1.94 (31)	0.26 \pm 0.80 (27)	<i>P</i> = 0.107 NS
Group 2	21.56 \pm 2.39 (21)	21.59 \pm 2.92 (26)	0.18 \pm 1.20 (15)	<i>P</i> = 0.563 NS
Degree of obesity (%)	3.86 \pm 11.33 (49)	2.95 \pm 12.81 (59)	-0.39 \pm 5.41 (42)	<i>P</i> = 0.640 NS
Group 1	0.58 \pm 10.65 (28)	-0.81 \pm 10.33 (31)	-0.72 \pm 4.73 (27)	<i>P</i> = 0.437 NS
Group 2	8.22 \pm 10.95 (21)	7.25 \pm 14.66 (26)	0.19 \pm 6.60 (15)	<i>P</i> = 0.911 NS

P* < 0.05; *P* < 0.01; ****P* < 0.001. [†]Group 1: \geq 7 years and <13 years; Group 2: \geq 13 years and <16 years. BMI, body mass index; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; NS, not significant.

Discussion

In this study, treatment outcomes were collected from 73 Japanese pediatric patients aged <16 years who started to receive glargine for treatment of type 1 diabetes.

Multiple studies have been conducted to compare NPH and glargine as basal insulin treatments for glycemic control in pediatric patients with type 1 diabetes in Caucasian populations,^{10,11,13,15,20–22} and conflicting results have been reported. Hathout *et al.*¹¹ reported that the average HbA1c decreased from 9.5% to 8.6% (*P* < 0.001) after glargine administration, while the average glucose showed no significant change (210.67 mg/dL to 215.21 mg/dL, *P* > 0.5). Schober *et al.*¹³ reported that glargine significantly decreased FPG (glargine group: -1.29 mmol/L; NPH group: -0.68 mmol/L; *P* = 0.02), but had no effect on HbA1c (glargine group: 0.28%; NPH group: 0.27%; *P* = 0.9276) at the end of the study. However, Colino *et al.*²² reported that switching from NPH to glargine resulted in a significant decrease in HbA1c (from 7.63 \pm 0.81% to 7.14 \pm 0.71%, *P* < 0.001) and FPG (from 161 \pm 37 mg/dL to 150 \pm 35 mg/dL, *P* < 0.05) at 6 months. Moreover, similar results were reported in Japanese children and adolescents with type 1 diabetes. After changing from NPH to glargine, the average HbA1c significantly decreased from 8.06 \pm 0.85% to 7.36 \pm 0.95% (*P* < 0.01), and FPG significantly decreased from 142.5 \pm 39.3 mg/dL to 121.1 \pm 26.0 mg/dL (*P* < 0.01) at 12 months.²³

In the present study, HbA1c (-0.97 \pm 1.37%, *P* < 0.001) and FPG (-46.58 \pm 83.36 mg/dL, *P* = 0.012) significantly decreased after insulin glargine was started. These findings are consistent with findings from the studies by Colino *et al.*²² and Urakami *et al.*²³ and show that glargine can contribute to glycemic control

in Japanese pediatric patients with type 1 diabetes. It is possible that the reason a significant reduction in FPG was not seen in Group 2 is because these subjects were experiencing an increase in insulin resistance with the onset of puberty.

In terms of insulin dose, small reductions were observed with glargine compared with pre-study and end-of-study doses. Because glargine exhibits glucose-lowering in a stable manner for approximately 24 hours without showing an evident blood level peak,⁹ physicians might be able to adjust the insulin dose according to blood glucose levels when switching to glargine from NPH.

In this study, the incidence of adverse drug reactions was 6.9% (five of 73 patients), which was lower than the value of 10.34% (12 of 116 patients) reported in a special drug-use surveillance of glargine in Japanese adult patients with type 1 diabetes (unpublished data) and 10.14% (14 of 138 patients) in the glargine group in an open-label, parallel, comparative study in Japanese type 1 diabetes patients aged 16–65 years.²⁴ A similar tendency was observed in a clinical study of Caucasian pediatric patients with type 1 diabetes (incidence of 9.2%).¹³

Type 1 diabetes should be treated with special attention to hypoglycemia, particularly severe hypoglycemia in pediatric patients. Improvements in glycemic control, particularly when provided by intensive insulin treatment, reduce the risks of vascular complications. However, frequent hypoglycemia or severe hypoglycemia resulting in coma, which not only adversely affects the central nervous system, but also threatens the patient's life, should be avoided.²⁵ In our study, the incidence of severe hypoglycemia was 2.7% (two of 73 patients), compared with approximately 7% in surveys by the Japanese Study Group of Insulin Therapy for Childhood and Adolescent Diabetes in

1997 and 1998, when NPH was used as the basal insulin treatment,^{13,26,27} suggesting that glargine can contribute to better glycemic control without increasing the incidence of severe hypoglycemia.

In terms of weight gain, it is necessary to evaluate the physical build and consider not only bodyweight, but also sex, age, and height in growing children. One study showed a mean increase of 4.75 kg in the intensive treatment group of adult patients with type 1 diabetes with a mean follow-up of 6 years (range: 3–9 years).¹ In the present study, not only bodyweight, but BMI and degree of obesity were also assessed. Both BMI and degree of obesity were minimally changed at the final assessment, with no apparent differences from the standard BMI or degree of obesity in age-matched children.¹⁸

Because this study was a post-marketing surveillance of daily clinical practice, the results cannot be directly compared with those from active drug-controlled clinical studies.^{10,13,22} In addition, it is difficult to omit the influence of concomitant insulin from the evaluation of glargine. Moreover, a limitation regarding the safety assessment period must be addressed. During the observational period of 24 weeks, only short-term safety of glargine was evaluated; long-term safety, such as malignancy risk, was not assessed. Future research examining the long-term safety of glargine in pediatric patients with type 1 diabetes is needed. Nonetheless, our study showed that the safety and effectiveness of glargine in Japanese pediatric patients with type 1 diabetes in daily clinical practice were similar to findings in Caucasian children.

In conclusion, this study showed that glargine therapy for Japanese pediatric patients with type 1 diabetes resulted in better glycemic control in terms of HbA1c and FPG with a good safety profile. In addition, glargine appeared to have little effect on the physical build of subjects.

Acknowledgments

Authors' contributions

Sanofi was responsible for the study design, study conduct and statistical analysis. Y.N. performed the statistical analysis. T.U. and Y.S. made significant suggestions to the analysis and interpretation of data. Y.N. drafted the manuscript. T.U. and Y.S. reviewed and revised the manuscript. All authors reviewed and approved the final version of this manuscript.

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List of participating institutions

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