Predictors for achieving target glycemic control in Japanese patients with type 2 diabetes after initiation of basal supported oral therapy using insulin glargine: sub-analysis of the ALOHA2 study, drug use surveillance in Japan

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Abstract

Objectives We aimed to identify diabetes-related factors associated with achieving HbA1c <7.0 % after the initiation of basal supported oral therapy (BOT) in insulin-naïve type 2 diabetes patients with an HbA1c value of ≥6.5 % during the previous 4 weeks, using data from Add-on Lantus[®] to Oral Hypoglycemic Agents 2 (ALOHA2) study, a 24-week observational study on Japanese type 2 diabetes patients.

Methods Patients were categorized into two groups: HbA1c <7.0 % at the final evaluation point (at 24 weeks or the last visit) as HbA1c-target-achieved; HbA1c ≥7.0 % as target-not-achieved. Associations between baseline factors and HbA1c <7.0 % achievement were explored using logistic regression.

Results Of the 1520 patients in the study, 400 patients (26.3 %) achieved HbA1c <7.0 %. Patients with diabetes duration of <1 year and between ≥1 and <2 years [odds ratio (OR): 5.27, 95 % confidence interval (CI): 1.13–24.51; OR: 3.77, 95 % CI 1.19–11.93, respectively],

those on one pre-study orally administered antidiabetic agent (OAD) (OR: 2.42, 95 % CI 1.12–5.22), and those with absence of diabetic neuropathy (OR: 2.54, 95 % CI 1.12–5.76) were more likely to achieve HbA1c <7.0 % than those with duration of ≤15 years, ≥4 pre-study OADs, and neuropathy, respectively. Achievement of HbA1c <7.0 % among patients increased by approximately 20 % for each 1 % decrease in HbA1c level at baseline.

Conclusions Shorter diabetes duration, pre-study regimen of one OAD, absence of neuropathy, and lower HbA1c level at baseline were associated with achievement of HbA1c <7.0 %, suggesting that earlier initiation of BOT leads to good HbA1c control in insulin-naïve Japanese type 2 diabetes patients, consistent with our early ALOHA study.

Keywords Type 2 diabetes · Basal supported oral therapy · Insulin glargine · Real-life observational study

Introduction

Glycemic control is a key factor in the management of type 2 diabetes. Poor glycemic control is linked to the onset of micro- and macrovascular complications [1]. In order to reduce the risk of developing such diabetic complications, the achievement and maintenance of a glycosylated hemoglobin (HbA1c) level of <7.0 % has been recommended by the American Diabetes Association (ADA), European Association for the Study of Diabetes (EASD), Canadian Diabetes Association (CDA), and Japan Diabetes Society (JDS) [2–4]. The reality, however, is not rosy. Among individuals with diabetes, half are unable to reach the recommended glycemic target level, with or without insulin therapy [5–7]. In Japan, 40 % of patients with type

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2 diabetes mellitus treated with insulin therapy were able to achieve HbA1c <7.0 %, based on the Japanese disease registry [8].

Basal supported oral therapy (BOT) is a widely adopted treatment [9] whereby a long-acting insulin injection such as insulin glargine is merely added to ongoing treatment with orally administered antidiabetic agents (OADs) in patients with type 2 diabetes. The simple addition of insulin to OADs is regarded as a convenient strategy when monotherapy is unlikely to achieve and/or maintain a target HbA1c level [10].

In our earlier study, we assessed the safety and effectiveness of insulin glargine plus OADs, using a safety analysis dataset collected for 4219 Japanese type 2 diabetes patients between 2007 and 2009 in the Add-on Lantus® to Oral Hypoglycemic Agents (ALOHA) study [11–15]. The results of the sub-analysis indicated that shorter diabetes duration, lower HbA1c level, and absence of retinopathy at baseline were diabetes-related predictors significantly associated with achievement of HbA1c <7.0 % by the end of a 24-week observation period in insulin-naïve patients treated with BOT with insulin glargine [13]. The study suggests that earlier initiation of insulin therapy could increase the likelihood of type 2 diabetes patients achieving optimal glycemic control of HbA1c <7.0 %.

Today, a greater number of treatment options, including glucagon-like peptide-1 (GLP-1) analogs and dipeptidyl peptidase-4 inhibitors (DPP-4i), are available for type 2 diabetes than were available at the time the ALOHA study was conducted. Moreover, recent studies have revealed the efficacy of DPP-4i use with insulin therapy [16, 17]. Because the identification of factors affecting glycemic control in a current clinical setting is important, and as data are scarce, we conducted a 24-week prospective, open-label, multi-center observational assessment of the safety and effectiveness of BOT with insulin glargine for treating Japanese patients with type 2 diabetes, the Add-on Lantus® to Oral Hypoglycemic Agents 2 (ALOHA2) study [18]. Here, we conducted a sub-analysis using ALOHA2 study data to identify diabetes-related factors associated with achieving HbA1c <7.0 % at the final evaluation point after the initiation of BOT.

Materials and methods

Study design and patients

The ALOHA2 study was conducted as a special drug use surveillance in 2012 and 2013 among 619 hospitals and clinics across Japan [18]. Participating patients were observed in a clinical setting. The ALOHA2 study is a sequel

to the ALOHA study conducted between 2007 and 2009, the results of which have been previously reported [11–15]. Patients were eligible for enrollment in the ALOHA2 study, upon written consent, if they: (1) had type 2 diabetes and were 20 years or older, (2) were being treated with OAD therapy, (3) had HbA1c ≥ 6.5 % according to International Federation of Clinical Chemistry (IFCC) or National Glycohemoglobin Standardization Program (NGSP) values, or ≥ 6.1 % in JDS values, during the 4 weeks prior to the study, and (4) were to start BOT with insulin glargine. Data on HbA1c levels were originally collected and recorded as JDS, IFCC, or NGSP values. For data analysis, the JDS and IFCC values were converted into NGSP values utilizing the following respective formulas: NGSP (%) = $1.02 \times \text{JDS} (\%) + 0.25$ %; or NGSP (%) = $1.02 \times [\text{IFCC} (\%) - 0.4] + 0.25$ % [19]. Patients with a JDS HbA1c value of 6.1 % or IFCC value of 6.5 %, converted to an NGSP value of 6.47 %, were also enrolled.

The study conformed to the ethical principles of Good Post-marketing Study Practice in Japan.

Treatment, follow-up, and assessment

All treatment decisions were made by attending physicians. Data on patient characteristics, safety, and effectiveness was collected over 24 weeks. Effectiveness parameters comprised HbA1c level, fasting plasma glucose (FPG) level, 2-h postprandial plasma glucose (2-h PPG) level, and weight. All adverse events reported during the observation period were documented by the physicians based on patient-reported hypoglycemic episodes, including any hypoglycemic episodes and symptoms of hypoglycemia.

Summary results of ALOHA2 study

Of the 2630 patients enrolled, 2602 and 1629 patients constituted the safety and efficacy analysis sets, respectively (Fig. 1). The mean [$\pm$ standard deviation (SD)] age of patients in the safety analysis set was 62.6 ± 12.6 years, and the majority of patients were men (60.2 %). The mean ($\pm$ SD) duration of diabetes among patients was 12.6 ± 8.9 years. Their average HbA1c level, FPG level, 2-h PPG level, and body mass index (BMI) at baseline were 9.4 ± 1.9 %, 198.1 ± 80.6 mg/dL, 263.4 ± 103.3 mg/dL, and 24.8 ± 4.7 kg/m², respectively. During the observation period, 140 patients (5.38 %) reported hypoglycemic events, including 11 patients (0.42 %) with severe hypoglycemic events (0.019 event/patient-year). With regard to efficacy, HbA1c, FPG, and 2-h PPG levels significantly improved from baseline to final evaluation (9.6–7.9 %, 203.0–148.6 mg/dL, and 267.0–192.5 mg/dL, respectively).

Fig. 1 Patient disposition. **a** Patients who had ever been administered insulin glargine. **b** Patients who had not been treated with insulin previously and were treated with BOT throughout the observation

period. *CRF* case report form, *HbA1c* glycosylated hemoglobin, *OAD* orally administered antidiabetic agent

Statistical analysis

Data on insulin-naïve patients who had not been administered insulin at least 12 weeks prior to the study and who were treated with BOT using insulin glargine throughout the observation period were drawn from the ALOHA2 study ($n = 1629$) (Fig. 1). Patients, including those with $\text{HbA1c} \leq 7.0\%$ at baseline, were categorized into two groups based on HbA1c level at the final evaluation point (at 24 weeks or last visit): $\text{HbA1c} < 7.0\%$ as the HbA1c -target-achieved group, and $\text{HbA1c} \geq 7.0\%$ as the target-not-achieved group. Missing data were calculated using last observation carried forward (LOCF).

Descriptive statistics on demographic and clinical characteristics at baseline, including HbA1c , FPG, 2-h PPG levels and BMI (weight in kilograms divided by the square of height in meters), were assessed by group (target-achieved group vs. target-not-achieved group). In addition, average insulin glargine doses during the observation period were calculated at 4-week intervals by target-achieved and target-not-achieved groups.

Logistic regression analysis was performed to assess factors associated with the achievement of $\text{HbA1c} < 7.0\%$ at final evaluation after initiation of BOT. Data

including age, sex, duration of diabetes, number of pre-study OADs, diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, HbA1c level, FPG level, 2-h PPG level, and BMI collected at baseline were included in the model as potential predictors. Results of logistic regression were summarized using odds ratios (ORs) with 95 % confidence intervals (CIs). To assess model fit, a Hosmer–Lemeshow test was conducted, along with Cox and Snell R^2 and Nagelkerke R^2 assessing the extent to which variance was explained by the model.

Subsequently, factors found to be statistically significant predictors for achieving $\text{HbA1c} < 7.0\%$ were further examined individually. The proportion of the target-achieved patients was initially computed according to diabetes duration, baseline HbA1c level, and number of OAD medications taken prior to the ALOHA2 study.

For the assessment of safety, the likelihood of hypoglycemic episodes was assessed between the target-achieved and target-not-achieved groups using Fisher's exact test.

All statistical tests were two-tailed, and $p < 0.05$ was considered as indicating statistical significance. All statistical analyses were conducted using SAS for Windows, version 9.2. or higher (SAS Institute Inc., Cary, NC, USA).

Results

Overall patient characteristics in the present sub-analysis

Among the 2602 patients included in the safety analysis set of the ALOHA2 study, data were initially extracted for 1629 insulin-naïve patients who started BOT, and whose HbA1c levels at baseline were documented. Subsequently, data on 1520 patients with documented HbA1c levels at the final evaluation point were used for the present sub-analysis. The mean ($\pm$ SD) age of these 1520 patients was 61.8 ± 12.6 years, and the majority of patients were men (62.3 %). The mean ($\pm$ SD) duration of diabetes among patients was 11.7 ± 8.4 years. Their average ($\pm$ SD) BMI, HbA1c level, FPG level, and 2-h PPG level at baseline were 25.0 ± 4.7 kg/m², 9.6 ± 1.8 %, 201.0 ± 73.7 mg/dL, and 269.6 ± 92.8 mg/dL, respectively.

Baseline characteristics and dose of insulin glargine in target-achieved and target-not-achieved groups

Among 1629 insulin-naïve patients who started BOT and had documentation of baseline HbA1c level, data on HbA1c level at the final evaluation point were collected from 1520 patients, among whom 400 (26.3 %) achieved HbA1c <7.0 % at final evaluation. Descriptive statistics for the HbA1c-target-achieved and target-not-achieved groups are shown in Table 1. The target-achieved group tended to include more men (67.3 %) and more patients on only one concomitant OAD (35.0 %), with lower levels of renal dysfunction (18.8 %) and diabetic nephropathy (18.0 %), compared to the target-not-achieved group (60.5, 26.0, 24.9, and 24.3 %, respectively). The comparison between the two groups indicated statistically significant differences in sex, duration of diabetes, number of pre-study OAD, HbA1c level, BMI, and the presence of renal dysfunction, diabetic nephropathy, and ischemic cerebrovascular disorder (Fisher's exact test or Wilcoxon signed-rank test, $p < 0.05$).

Insulin glargine doses administered across the observation period were calculated by target-achieved and target-not-achieved group. The mean ($\pm$ SD) doses of insulin glargine in the target-achieved group at baseline and weeks 4, 8, 12, 16, 20, and 24 were 6.2 ± 3.3 , 7.2 ± 3.8 , 7.7 ± 4.2 , 7.8 ± 4.5 , 7.9 ± 4.5 , 7.9 ± 4.5 , and 7.8 ± 4.5 units, respectively. Insulin glargine doses in this group leveled off after 12 weeks. On the other hand, doses in the target-not-achieved group rose continuously throughout the observation period, with mean ($\pm$ SD) doses of 6.4 ± 3.2 , 7.7 ± 3.8 , 8.8 ± 4.4 , 9.5 ± 5.0 , 10.0 ± 5.4 , 10.4 ± 5.6 , and 10.9 ± 5.9 units at the respective 4-week intervals.

Predictive factors associated with HbA1c <7.0 % at final evaluation

All potential predictors were simultaneously included in the model, and consequently, the results of logistic regression analysis were obtained based on 452 patients whose information on all potential predictors was complete. Results indicated that patients with shorter diabetes duration, one pre-study OAD administered, absence of diabetic neuropathy, and lower baseline levels of HbA1c were more likely to have achieved HbA1c <7.0 % at the final evaluation point, after adjusting for other factors (Table 2). The likelihood of achieving HbA1c <7.0 % was over five times and approximately 3.8 times as great in patients with diabetes duration of <1 year and between ≥ 1 and <2 years, respectively, as in patients with a duration of ≥ 15 years (OR: 5.27, 95 % CI 1.13–24.51, $p = 0.0340$; OR: 3.77, 95 % CI 1.19–11.93, $p = 0.0242$, respectively). Those on only one pre-study OAD were over twice as likely to achieve HbA1c <7.0 % as those with four or more pre-study OADs (OR: 2.42, 95 % CI 1.12–5.22, $p = 0.0247$). Patients with absence of diabetic neuropathy were 2.5 times as likely to achieve HbA1c <7.0 % as those with neuropathy (OR: 2.54, 95 % CI 1.12–5.76, $p = 0.0259$). The likelihood of achieving HbA1c <7.0 % increased by approximately 20 % for each 1 % lower HbA1c level at baseline.

With regard to model fit, results of the Hosmer–Lemeshow test showed that observed achievement of HbA1c <7.0 % was not significantly different from model predictions, and that the overall model fit was good ($p = 0.1031$). The model was found to account for 11 to 15 % of the variance in achievement (Cox & Snell R^2 : 0.1090; Nagelkerke R^2 : 0.1548). In addition, after the exclusion of patients with baseline HbA1c <7.0 % from the target-achieved group, factors associated with the achievement of HbA1c <7.0 % at the final evaluation point were assessed using logistic regression analysis. Results are shown as supplementary material (Supplementary Table 1).

Further analysis on predictive factors

Additional analysis was conducted based on the results obtained from logistic regression analysis. The proportion of target-achieved patients was stratified by factors found to be significant in the logistic regression results. The proportion of target-achieved patients decreased when diabetes duration exceeded 1 year (Fig. 2). More than 30 % of patients with diabetes less than 4 years achieved HbA1c <7.0 %, whereas that level was achieved in only 18–23 % of patients with diabetes 10 years or longer.

Table 1 Baseline characteristics according to achievement of HbA1c <7.0 % (overall, target-achieved group, and target-not-achieved group)

	Overall (n = 1520)		Target-achieved group (n = 400)		Target-not-achieved group (n = 1120)		p value ^a
Sex							
Men	947	62.3 %	269	67.3 %	678	60.5 %	0.0190*
Women	573	37.7 %	131	32.8 %	442	39.5 %	
Age (years)		61.8 ± 12.6		62.9 ± 12.7		61.4 ± 12.5	0.0908
Duration of diabetes (years)		11.7 ± 8.4		10.5 ± 8.6		12.1 ± 8.3	0.0004***
Number of concomitant OADs							
1	431	28.4 %	140	35.0 %	291	26.0 %	0.0071**
2	535	35.2 %	131	32.8 %	404	36.1 %	
3	412	27.1 %	95	23.8 %	317	28.3 %	
≥4	142	9.3 %	34	8.5 %	108	9.6 %	
BMI (kg/m ²)	1289	25.0 ± 4.7	339	24.3 ± 4.4	950	25.3 ± 4.8	0.0025**
HbA1c (%)	1520	9.6 ± 1.8	400	9.4 ± 2.1	1120	9.6 ± 1.6	0.0003***
FPG (mg/dL)	570	201.0 ± 73.7	168	202.3 ± 80.5	402	200.5 ± 70.7	0.8072
2-h PPG (mg/dL)	391	269.6 ± 92.8	95	273.8 ± 102.0	296	268.3 ± 89.8	0.7302
Diabetic retinopathy	225	14.8 %	57	14.3 %	168	15.0 %	0.7436
Diabetic neuropathy	226	14.9 %	53	13.3 %	173	15.5 %	0.3259
Diabetic nephropathy	344	22.6 %	72	18.0 %	272	24.3 %	0.0100**
Renal dysfunction	354	23.3 %	75	18.8 %	279	24.9 %	0.0130*
Ischemic heart disease	83	5.5 %	18	4.5 %	65	5.8 %	0.3707
Ischemic cerebrovascular disorder	68	4.5 %	26	6.5 %	42	3.8 %	0.0334*

Data are frequency and mean ± standard deviation or percentages. Totals may not sum to 100 % due to rounding

OAD orally administered antidiabetic agent, BMI body mass index, HbA1c glycosylated hemoglobin, FPG fasting plasma glucose, 2-h PPG 2-h postprandial plasma glucose

^a Fisher's exact test for nominal variables and Wilcoxon rank-sum test for continuous variables were used

* <0.05, ** <0.01, *** <0.001

In general, patients with good glycemic control at baseline tended to maintain good control through the final evaluation point (Fig. 3a). The achievement rate among patients with baseline HbA1c levels <7.0 % was approximately 80 %; the rates in patients with baseline HbA1c levels ≥7.0 % were substantially decreased, particularly for those with HbA1c of ≥7.0 to <10.0 % at baseline, with slight increases in patients with baseline HbA1c ≥10.0 %. Higher HbA1c levels at baseline were also observed in patients with shorter diabetes duration, with the exception of HbA1c <6.5 %, the shortest diabetes duration (Fig. 3b).

More target-achieved patients were observed among those on only one pre-study OAD than those on two or more OADs prior to the ALOHA2 study (Fig. 4a). Over 30 % of the patients with only one pre-study OAD achieved HbA1c <7.0 %, whereas the proportions of target-achieved patients with two, three, and four or more OADs were between approximately 22 and 25 %. The change in HbA1c level was also calculated according to the number of pre-study OADs. HbA1c levels improved

by −1.84 % in patients taking one OAD, followed by −1.54, −1.31, and −1.15 % in those taking two, three, and four or more OADs, respectively (Fig. 4b). We further explored baseline characteristics, including diabetes duration, HbA1c level, and FPG level, in relation to the number of pre-study OADs. Statistical significance, using the Kruskal–Wallis test, was observed in diabetes duration (1 OAD: 10.4 ± 9.1 years, 2 OADs: 12.0 ± 8.6 years, 3 OADs: 12.2 ± 7.7 years, ≥4 OADs: 13.3 ± 7.9 years; $p < 0.0001$). Similarly, a statistically significant difference was found in the FPG level in relation to the number of pre-study OADs (1 OAD: 220.7 ± 76.0 mg/dL, 2 OADs: 197.8 ± 77.0 mg/dL, 3 OADs: 191.2 ± 61.9 mg/dL, ≥4 OADs: 181.2 ± 62.2 mg/dL; $p = 0.0004$), while no significant difference was observed in HbA1c level at baseline (1 OAD: 9.62 ± 1.93 %, 2 OADs: 9.56 ± 1.63 %, 3 OADs: 9.31 ± 1.39 %, ≥4 OADs: 9.19 ± 1.50 %; $p = 0.0542$). The highest FPG value was observed in patients with only one pre-study OAD.

Table 2 Logistic regression results of achievement of HbA1c <7.0 % ($n = 452$) according to baseline characteristics

	OR	95% CI	<i>p</i> value
Age (1 year increment)	1.01	0.99–1.03	0.4577
Women (reference: men)	0.68	0.41–1.11	0.1206
Duration of diabetes (reference: ≥ 15 years)			
<1 year	5.27	1.13–24.51	0.0340*
$\geq 1, <2$ years	3.77	1.19–11.93	0.0242*
$\geq 2, <3$ years	0.23	0.03–1.99	0.1831
$\geq 3, <4$ years	2.01	0.62–6.55	0.2457
$\geq 4, <5$ years	1.45	0.42–4.98	0.5571
$\geq 5, <6$ years	1.71	0.54–5.44	0.3653
$\geq 6, <7$ years	1.02	0.29–3.53	0.9819
$\geq 7, <8$ years	0.69	0.20–2.35	0.5514
$\geq 8, <9$ years	1.78	0.57–5.57	0.3258
$\geq 9, <10$ years	0.57	0.11–2.84	0.4918
$\geq 10, <11$ years	1.41	0.55–3.59	0.4720
$\geq 11, <12$ years	0.84	0.16–4.34	0.8308
$\geq 12, <13$ years	1.11	0.37–3.33	0.8498
$\geq 13, <14$ years	0.87	0.16–4.71	0.8717
$\geq 14, <15$ years	2.74	0.82–9.10	0.1004
Unknown	1.55	0.81–2.95	0.1832
Number of pre-study OADs (reference: ≥ 4 OADs)			
1 OAD	2.42	1.12–5.22	0.0247*
2 OADs	0.95	0.46–1.96	0.8848
3 OADs	1.21	0.58–2.51	0.6093
Diabetic retinopathy (reference: yes)	0.69	0.35–1.34	0.2713
Diabetic neuropathy (reference: yes)	2.54	1.12–5.76	0.0259*
Diabetic nephropathy (reference: yes)	0.79	0.44–1.42	0.4380
HbA1c (1% decrease)	1.19	1.00–1.42	0.0499*
FPG (10mg/dL increment)	1.02	0.98–1.06	0.3731
BMI (1kg/m ² increment)	0.96	0.91–1.02	0.1542

OR odds ratio, CI confidence interval, HbA1c glycosylated hemoglobin, OAD orally administered antidiabetic agents, FPG fasting plasma glucose, BMI body mass index, * <0.05 (logistic regression analysis)

Fig. 2 Percentages of target-achieved (HbA1c <7.0 %) and target-not-achieved (HbA1c ≥ 7.0 %) patients by duration of diabetes at baseline. yr year, yrs years, $n = 1193$

Fig. 3 Percentages of target-achieved (HbA1c <7.0 %) and target-not-achieved (HbA1c ≥7.0 %) patients **a** and diabetes duration **b** by HbA1c at baseline. *HbA1c* glycosylated hemoglobin. **a**, **b** HbA1c levels recorded as Japan Diabetes Society (JDS) values and International Federation of Clinical Chemistry (IFCC) values were converted into the National Glycohemoglobin Standardization Program (NGSP) values utilizing the following formula: NGSP (%) = $1.02 \times \text{JDS} (\%) + 0.25$ %; or NGSP (%) = $1.02 \times [\text{IFCC} (\%) - 0.4 \text{ \%}] + 0.25 \text{ \%}$ [19]. **a** $n = 1520$, **b** the converted NGSP values were not rounded up; therefore, HbA1c levels close to 6.5 % in four patients were categorized in the HbA1c <6.5 % group, although their HbA1c levels met the inclusion criteria, $n = 1629$

Incidence of hypoglycemia in the target-achieved and target-not-achieved groups

With regard to the incidence of hypoglycemia, no statistically significant differences in rates were found between the target-achieved and target-not-achieved groups ($p = 0.16$). Hypoglycemia incidence rates were 7.00 % in the target-achieved group and 5.09 % in the target-not-achieved group (Table 3).

Discussion

The present sub-analysis was conducted to identify diabetes-related factors associated with achieving HbA1c <7.0 % among 1520 insulin-naïve patients with type 2 diabetes who had previously received therapy with OADs and had started BOT with insulin glargine. The findings demonstrated that shorter duration of diabetes, a pre-study regimen of one OAD, the absence of neuropathy, and lower

Fig. 4 Percentages of target-achieved (HbA1c <7.0 %) and target-not-achieved (HbA1c ≥7.0 %) patients **a** and change in HbA1c between baseline and final evaluation point, and **b** by number of pre-study OADs. OAD orally administered antidiabetic agent. (**a**, **b**) $n = 1411$

Table 3 Incidence of hypoglycemia according to achievement of HbA1c <7.0 % (overall, target-achieved group, and target-not-achieved group)

Parameter	Overall ($n = 1520$)		Target-achieved group ($n = 400$)		Target-not-achieved group ($n = 1120$)	
	All	Severe	All	Severe	All	Severe
Number of patients with hypoglycemia (%)	85 (5.59)	7 (0.46)	28 (7.00)	4 (1.00)	57 (5.09)	3 (0.27)
Patient-years	660.44	660.44	175.24	175.24	485.19	485.19
Number of episodes	154	8	54	5	100	3
Incidence rate (episodes/patient-year)	0.2332	0.0121	0.3081	0.0285	0.2061	0.0062

No statistically significant difference was found between the target-achieved and target-not-achieved groups in the number of patients with hypoglycemia ($p = 0.16135$, Fisher's exact test)

baseline level of HbA1c were associated with good glycemic control, suggesting that earlier initiation of BOT in patients with inadequate glycemic control can result in the achievement of optimal blood sugar control of HbA1c <7.0 %. In addition, the rates of hypoglycemia were not especially high in either the target-achieved or target-not-achieved groups. This finding among patients receiving insulin glargine was consistent with the results of the ORIGIN study [20].

Our earlier sub-analysis of the ALOHA study revealed that shorter duration of diabetes, no presence of retinopathy, and lower baseline HbA1c level were major predictive factors of better HbA1c control [13]. The duration of diabetes and HbA1c level at baseline were the common factors affecting the achievement of HbA1c <7.0 % in the ALOHA2 and ALOHA studies. Unlike previous findings on retinopathy, the present sub-analysis indicated that the absence of neuropathy at baseline was a statistically significant predictor for achieving HbA1c <7.0 %. Although these two complications are different, they are both well-acknowledged in the progression of diabetes, implying perhaps that the duration of diabetes in such patients was sufficient for the development of such complications. The findings on the number of pre-study OADs were new observations in the ALOHA2 study. In the present sub-analysis, patients with a greater number of OADs tended to have dealt with diabetes for a longer period (i.e., 1 OAD, 10.4 ± 9.1 years; 2 OADs, 12.0 ± 8.6 years; 3 OADs, 12.2 ± 7.7 years; and 4 OADs, 13.3 ± 7.9 years). This may imply that further progression of diabetes had not yet developed in patients requiring fewer OADs. However, these results must be interpreted with care, as not only the number of OADs but also the types that patients took may have affected achievement of the target HbA1c level.

Consistent with the ALOHA study, findings from ALOHA2 suggest that early initiation of insulin therapy using insulin glargine in addition to OADs can help patients achieve HbA1c <7.0 %. Despite its effectiveness in comparison to the addition of other OADs, the introduction of insulin tends to be delayed as a result of the psychological barriers among not only patients, but healthcare providers as well [21, 22]. Basal insulin utilized in BOT often requires once-daily administration. Therefore, both patients and healthcare providers might be less reluctant to introduce insulin therapy compared to other types of insulin requiring frequent administration. It is essential, however, that healthcare providers educate patients concerning the benefits of initiating insulin therapy at an early stage and to remove psychological barriers in patients.

More patients in the ALOHA2 study achieved HbA1c <7.0 % than in the earlier ALOHA study (26.3 vs. 15.5 %) [13]. This higher rate could reflect a greater

Table 4 Duration of diabetes by presence of microvascular complication(s) in patients

	No complications (<i>n</i> = 775)	Microvascular complications				
		Retinopathy (<i>n</i> = 49)	Neuropathy (<i>n</i> = 65)	Nephropathy (<i>n</i> = 139)	Retinopathy + Neuropathy (<i>n</i> = 27)	Retinopathy + Nephropathy (<i>n</i> = 44)
Duration of diabetes (SD) (years)	10.7 (7.8)	14.1 (10.8)	14.8 (8.7)	11.6 (7.7)	17.4 (11.4)	16.3 (8.4)
SD standard deviation					11.9 (7.4)	13.2 (9.9)

percentage of patients with shorter diabetes duration and less progressive diabetic symptoms included in the ALOHA2 study. Indeed, the efficacy analysis set of the ALOHA2 study included fewer patients with microvascular complications (diabetic retinopathy: 15.8 vs. 25.9 %; diabetic neuropathy: 16.5 vs. 24.7 %, diabetic nephropathy: 24.0 vs. 25.5 %) [14, 18]. It was also observed in both studies that the duration of diabetes was generally shorter in patients with no microvascular complications than those with complications (Table 4) [23]. From these points, we considered that a greater number of patients with shorter diabetes duration were included in the ALOHA2 study. Beyond the ALOHA and ALOHA2 studies, treatment milieu have varied: (1) DPP-4i was newly introduced to the market, and (2) additional applications of high-dose metformin became available. These changes may partially account for the higher rate of HbA1c <7.0 % achieved. However, patients with shorter diabetes duration presumably have less progressive symptoms and are good responders, and it may be considered that treatments for diabetes have been progressing in the terms of early initiation of insulin therapy.

Another finding of note is the variation in patterns of insulin glargine doses administered over the observation period between the target-achieved and target-not-achieved groups. The insulin glargine doses in the target-achieved group increased moderately until week 12 and stabilized between weeks 12 and 24, while doses in the target-not-achieved group increased steadily throughout the observation period. Based on the baseline characteristics presented in Table 1, the duration and progression of the disease were greater in the target-not-achieved group, implying lower beta cell function. This may imply that dose titration was not sufficient to achieve glycemic control, and the target-not-achieved group therefore may require higher insulin glargine doses.

Several points of caution must be considered in interpreting the results of the present analysis. The ALOHA2 study was conducted as post-marketing surveillance in a real-life clinical setting after the drug was marketed, and was limited to diabetes patients who had started BOT with insulin glargine, and where hypoglycemia was not strictly defined and measured compared to clinical trials. For this reason, the possibility of underestimating the frequency of hypoglycemia is worth mentioning. In addition, the present sub-analysis was exploratory, using data from the ALOHA2 study, which was not designed to assess predictors of good glycemic control. Although our results indicated significant associations between particular patient characteristics and good glycemic control, such characteristics cannot be interpreted as comprehensive prognostic factors representing all patients receiving insulin therapy.

Conclusions

In conclusion, our results suggest that earlier initiation of BOT leads to good control of HbA1c levels in insulin-naïve patients with type 2 diabetes who were previously on OADs and who started BOT with insulin glargine, which is similar to our earlier findings in the ALOHA study. Further research can be conducted integrating the ALOHA2 into the ALOHA data, since both data target patients were identical.

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Sanofi K.K. had responsibility for the study design, statistical analysis plan, and drafting and approval of the manuscript. YI and ST drafted the manuscript. TK and MO made significant suggestions regarding analysis and interpretation of the data, and reviewed and revised the draft manuscript. All authors have reviewed and approved the final version of this manuscript.

Compliance with ethical standards

This study was conducted as a special drug use surveillance and complied with the Pharmaceutical Affairs Law enacted by the Japanese Health Authority and the ministerial ordinance, “Good Post-Marketing Study Practice (GPSP)”, and was conducted after a contract was signed with each medical institution participating in the survey.

Conflict of interest YI and ST are employees of Sanofi K.K., Tokyo, Japan. Insulin glargine is marketed by Sanofi K.K. under the name Lantus®. TK has served on advisory panels for Boehringer Ingelheim, Daiichi-Sankyo, Novo Nordisk, Taisho, Takeda and Tanabe-Mitsubishi, and has served as a consultant for Boehringer Ingelheim and MSD (Merck), and has received research support from AstraZeneca, Chugai, Daiichi-Sankyo, MSD, Ono, Sanofi, Takeda and Tanabe-Mitsubishi, and has served on speakers’ bureaus for Astellas, AstraZeneca, Boehringer Ingelheim, Daiichi-Sankyo, Daiippon Sumitomo, Eli Lilly, Kowa, Kyowahakko Kirin, MSD, Novartis, Ono, Sanofi, Sanwa, Taisho, Takeda and Tanabe-Mitsubishi. MO has served on advisory panels for AstraZeneca, Boehringer Ingelheim, Novo Nordisk, Sanofi and Taisho, has received research support from Astellas Pharma, AstraZeneca, Boehringer Ingelheim, Daiichi-Sankyo, Daiippon Sumitomo, Eli Lilly, Kowa, Kyowa Hakko Kirin, MSD, Novartis, Ono, Sanofi, Taisho, Takeda and Tanabe-Mitsubishi, and has served on speakers’ bureaus for Astellas, AstraZeneca, Boehringer Ingelheim, Daiichi-Sankyo, Daiippon Sumitomo, Eli Lilly, Kowa, Kyowahakko Kirin, MSD, Novartis, Ono, Sanofi, Taisho, Takeda and Tanabe-Mitsubishi.

Informed consent Informed consent or substituted consent was obtained from all patients included in the ALOHA2 study.

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