Efficacy and safety of patient-directed titration of once-daily pre-dinner premixed biphasic insulin aspart 70/30 injection in Japanese type 2 diabetic patients with oral antidiabetic drug failure: STEP-AKITA study

Takuma Narita[1]*, Takashi Goto[2], Yumi Suganuma[1,2], Mihoko Hosoba[1,3], Tsukasa Morii[1], Takehiro Sato[1], Hiroki Fujita[1], Takeshi Miura[1,3], Takashi Shimotomai[4,5], Yuichiro Yamada[1], Masafumi Kakei[1,6]

ABSTRACT

Aims/Introduction: To clarify clinical characteristics related to optimal glycemic control achieved after adding once-daily pre-dinner biphasic insulin aspart 70/30 (BIAsp 30) in Japanese type 2 diabetic (T2D) patients with oral antidiabetic drug (OAD) failure.

Materials and Methods: Under this regimen, we evaluated changes in HbA_{1c} levels and daily self-monitoring blood glucose (BG) profiles, as well as the incidences of hypoglycemia and retinopathy progression. The patients adjusted BIAsp 30 dosages themselves every 3–4 days according to a pre-determined algorithm to achieve fasting BG levels of 101–120 mg/dL. HbA_{1c} levels were expressed as Japan Diabetes Society values.

Results: Of 29 enrolled patients, 22 (HbA_{1c} levels, 8.5 ± 1.5% [mean ± SD]) and 20 patients completed the 16- and 24-week follow-up, respectively. At 16 weeks 68.2 and 45.5%, and at 24 weeks 80.0 and 35% of patients had achieved HbA_{1c} levels of <7.0 and <6.5%, respectively. The patients who had achieved optimal glycemic control, including daytime postprandial BG profiles after treatment, had lower post-breakfast BG excursions at baseline, shorter diabetes durations and younger age. No severe hypoglycemic episodes were recorded. Progression of retinopathy was observed in 3 of the 29 enrolled patients.

Conclusions: Lower post-breakfast BG excursions, shorter diabetes duration and younger age in Japanese T2D patients with OAD failure might warrant optimal glycemic control with safety after adding once-daily pre-dinner BIAsp 30 initiating regimen. (J Diabetes Invest, doi: 10.1111/j.2040-1124.2010.00062.x, 2010)

KEY WORDS: Biphasic insulin aspart 70/30, Insulin initiation, Self-adjusted treatment algorithm

INTRODUCTION

To reduce the risk of diabetic chronic complications, it is crucial to achieve ideal glycemic control as early as possible in diabetic patients[1–4]. In clinical practice, under recent guidelines, a HbA_{1c} level of <6.5–7.0% is recommended as the target for glycemic control in diabetic patients[5,6].

The progressive decline in β-cell function in type 2 diabetic (T2D) patients has been reported, despite lifestyle modifications and pharmacological interventions using oral antidiabetic agents (OAD)[7,8]. Therefore, at present, the initiation of insulin therapy is generally thought to be inevitable in a certain proportion of T2D patients. However, how and when to initiate insulin therapy in T2D patients remains controversial.

In recent reports, once or twice daily use of basal insulin analogues as an add-on therapy to OAD (so-called basal-supported oral therapy [BOT]) in insulin-naïve T2D patients has shown that glargine or detemir can achieve clinically important improvements in glycemic control, similar to those achievable with neutral protamine Hagedorn insulin, but with less risk of hypoglycemia[9–14]. On the basis of these results, the recent guidelines from Western countries have recommended that insulin should be initiated with basal insulin[6]. However, in a report of Japanese T2D patients, approximately half of the patients could not achieve a HbA_{1c} level of <7.0%[15]. In that study, no clear explanatory characteristics distinguished patients who could achieve good glycemic control from those who did not.

In contrast to basal analogue insulin, premixed analogue insulin, such as biphasic insulin aspart 70/30 (BIAsp 30), can improve postprandial glucose levels and provide basal insulin

[1]Department of Endocrinology, Diabetes and Geriatric Medicine, Akita University Graduate School of Medicine, Hondo, [2]Akita Red Cross Hospital, Saruta, Kamikitate, [3]Akita City Hospital, Kawamoto, [4]Yokote Municipal Hospital, Yokote, [5]Akita Kumiai General Hospital, Ijima, Akita, and [6]Department of Medicine, Saitama Medical Center, Jichi Medical University, Omiya, Saitama, Japan
*Corresponding author. Takuma Narita Tel.: +81-18-884-6040 Fax: +81-18-884-6449
E-mail address: narita@med.akita-u.ac.jp
Received 13 January 2010; revised 18 June 2010; accepted 30 July 2010

coverage by one injection at mealtime. The ability of BIAsp 30 to improve postprandial glucose levels is superior to human premixed insulin 70/30[16,17]. In the recent 'The 1-2-3 study', insulin therapy was initiated with once-daily pre-dinner BIAsp 30, titrated to a target fasting blood glucose (FBG) level of 80–110 mg/dL by add-on OAD therapies (phase 1), followed by the addition of pre-breakfast BIAsp 30 (phase 2) and pre-lunch BIAsp 30 (phase 3), with OAD withdrawal in patients showing a HbA_{1c} level ≥6.5% at the end of phase 1 or 2. Just after phase 1, 2 and 3 of this regimen 41, 70 and 77%, respectively, of patients had a HbA_{1c} level of <7.0% [18]. A recent study that used a similar step-up regimen with BIAsp 30 in Japanese T2D patients[19] confirmed the efficacy and usefulness of the method.

Quite recently, the regimen of adding a once-daily pre-dinner injection of BIAsp 30 has been reported to have equal or a slightly superior efficacy in improving glycemic control than those of basal insulin analogues as add-on OAD therapies[20]. However, the efficacy and safety of this method in Japanese T2D patients has not yet been sufficiently tested. In particular, the differences in the clinical characteristics of patients who can or cannot achieve optimal glycemic control, including postprandial glycemic control, after this regimen need to be elucidated.

In an outpatient setting, patient-directed insulin dosage titration, according to a predetermined dosage-escalation algorithm, reportedly shows the same levels of improvement in glycemic control and safety as physician-led dosage titration[21,22].

We, therefore, investigated the extent to which a regimen with once-daily pre-dinner BIAsp 30 as an add-on OAD therapy would improve HbA_{1c} levels and daily profiles of blood glucose (BG) in Japanese T2D patients under OAD failure. In the present study, we used patient-directed insulin titration method on the basis of self-monitoring BG (SMBG) levels according to a predetermined algorithm. Furthermore, we attempted to identify differences in clinical characteristics between patients with and without optimal glycemic control after undergoing this regimen.

MATERIALS AND METHODS

Patients

Eligible patients were as follows: diagnosed with T2D for ≥1 year, ≥20 years-of-age, not pregnant, insulin naïve and HbA_{1c} levels of >7.0% or fasting plasma glucose levels of ≥140 mg/dL on a standard regimen[5] for ≥3 months with OAD. Sulfonylurea (SU) dosages were to be at least equivalent to a daily dose of 5 mg of glibenclamide, 80 mg of gliclazide or 3 mg of glimepiride with or without metformin (MET), thiazolidinedione (TZD) and/or alpha-glucosidase inhibitors (AGI). In addition, SMBG was introduced to eligible patients during the 4 weeks before initiation of BIAsp 30. Patients were instructed to monitor their FBG levels every day. Patients with FBG of ≥140 mg/dL (mean of the last 3 days during the 4-week SMBG period) were confirmed as final eligible patients. Enrolled patients did not have hepatic insufficiency (alanine transaminase or aspirate transaminase is ≥2-fold of the upper reference limit of each institute), renal insufficiency (serum creatinine ≥1.4 mg/dL), severe diabetic complications (overt proteinuria with renal failure, unstable proliferative retinopathy or symptomatic orthostatic hypotension), malignant tumors or dementia. We carried out this 24-week, open-label, interventional, multicenter (five hospitals in Akita Prefecture, Japan: Akita University Hospital, Akita Red Cross Hospital, Akita City Hospital, Akita Kumiai General Hospital and Yokote Municipal Hospital) study in accordance with the Declaration of Helsinki. All the patients provided written informed consent.

Medication and BIAsp 30 Titration

Eligible patients were instructed to add a once-daily BIAsp 30 injection within 15 min pre-dinner to their OAD regimens. Dosages of SU were reduced to the allowed minimum dosages for Japan (2.5 mg of glibenclamide, 40 mg of gliclazide or 1 mg of glimepiride) to avoid hypoglycemia, particularly during the night. MET, TZD and AGI were taken as baseline treatment in each patient. The initial dosage of BIAsp 30 was 3 U, followed by self-adjustment of the pre-dinner BIAsp 30 dosage every 3–4 days on the basis of an average of 3–4 previous FBG values. The dosage-titration algorithm was as follows:

Mean fasting SMBG (mg/dL)	≤80	81–100	101–120	121–140	141–160	160<
Adjustment of insulin dosage (U)	−3	−1	0	+1	+2	+3

On the basis of this method, the present study was named the 'STEP-AKITA study', abbreviated from SMBG based management of type 2 diabetes under oral antidiabetic drugs failure with evening premixed biphasic insulin aspart 70/30 injection in AKITA.

Patients were encouraged to visit an outpatient clinic every 2–4 weeks. If necessary, patients were allowed to consult their physicians about the adjustment of insulin dosages by phone or fax. BIAsp 30 was given with the prefilled (3 mL, 100 U/mL) Novorapid 30 mix FlexPen delivery system (Novo Nordisk, Bagsvaerd, Denmark).

Assessments

Blood samples for the assessment of HbA_{1c} levels were obtained every 4 weeks along with a routine examination of hepatic and renal function. HbA_{1c} levels and the proportion of patients achieving those of <7.0% or <6.5% at 16 and 24 weeks after the initiation of BIAsp 30 were assessed, as it is unclear how long an observation period needs to be for sufficient evaluation of the effect on HbA_{1c} levels in insulin therapies added to OAD. Patients were encouraged to record 8-point SMBG profiles (including pre- and post-breakfast, -lunch and -dinner profiles; bedtime and 03.00 h, where 'post' times were 2 h later) at least once a week. Because sufficient 8-point SMBG profiles were obtained in more patients around the time BIAsp 30 titration finished than at 16 or 24 weeks, 8-point SMBG profiles

recorded just before the initiation of BIAsp 30 (baseline) and just after BIAsp 30 titration was judged to be finished were used for evaluation. Bodyweight (BW) was recorded in the outpatient clinic once a month.

Patients were re-taught how to recognize the symptoms of hypoglycemia and were instructed to obtain and record their SMBG level whenever a hypoglycemic event was suspected. Hypoglycemic episodes were classified as mild when SMBG levels were <70 mg/dL, regardless of hypoglycemic symptoms, and when patients could manage themselves. Events were classified as severe when BG levels were <70 mg/dL and when patients were unable to manage themselves.

To detect any worsening of retinopathy, all patients were required to consult ophthalmologists before initiation of BIAsp 30 and after titration.

Laboratory Procedures

SMBG was carried out with provided BG (capillary) meters (One Touch Ultra, LifeScan, Milpitas, CA, USA). HbA_{1c} level was measured by high performance liquid chromatography using an automated analyzer at each hospital and values were calibrated with standard substances recommended by Japan Diabetes Society (JDS Lot 2). The reference range of HbA_{1c} levels is 4.3–5.8%. HbA_{1c} values were expressed as JDS values.

Statistical Analysis

Values are expressed as mean ± SD. The Friedman test was used to identify global differences in values throughout the study period. Furthermore, values at each time after the initiation of BIAsp 30 were compared with the value at baseline using Dunn's multiple comparison test (non-parametric). The Wilcoxon signed-ranks test was used for paired comparisons between values before and after treatment. The Mann–Whitney *U*-test and Pearson's χ^2-test were used to calculate the significance of differences in values between groups. Pearson's correlation analysis was carried out to explore relationships between corresponding values. All calculations were made using StatFlex Version 5.0 (Artec, Osaka, Japan). Two tailed *P*-values of <0.05 were considered statistically significant.

RESULTS

Participants

A total of 29 patients, with a mean fasting SMBG ≥140 mg/dL, even in the last 3 days during the 4-week SMBG period, initiated BIAsp 30 according to the protocol. Of those, seven patients did not complete the study. Reasons for withdrawal were adverse events in two patients, (progression of diabetic retinopathy and skin allergy at injection site) and non-compliance of insulin injection or SMBG recording in five patients. Finally, 22 and 20 patients completed 16- and 24-week follow up of HbA_{1c} levels, respectively. The clinical characteristics of 22 patients are shown in Table 1. No patient had been treated with SU monotherapy. More than 80% of patients had been treated with MET or TZD.

Table 1 | Clinical characteristics of type 2 diabetic patients

Male/female (*n*)	10/12
Age (years)	62.1 ± 10.8
Body mass index (kg/m^2)	25.1 ± 5.0
Duration of diabetes (years)	13 ± 9.4
Retinopathy (nil/simple/proliferative)	(15/7/0)
Albuminuria (normo/micro/macro)	(13/3/6)
HbA_{1c} at baseline (%)	8.5 ± 1.5
No. OAD (%)	
Monotherapy	0 (0)
Combination therapy	
SU + MET	3 (13.6)
SU + TZD	3 (13.6)
SU + MET + TZD	11 (50.0)
SU + TZD + AGI	1 (4.5)
SU + MET + TZD + AGI	4 (18.2)
Use of MET	18 (81.8)
Use of TZD	19 (86.4)

Data are expressed as mean ± SD or otherwise indicated.
AGI, alpha-glucosidase inhibitor; MET, metformin; OAD, oral anti-diabetic agents; SU, sulfonylurea; TZD, thiazolidinedione.

Glycemic Control

Efficacy Achieved as Per HbA_{1c} Levels

Achieved HbA_{1c} levels are shown in Figure 1a. At 8 weeks after the initiation of BIAsp 30, mean HbA_{1c} level was significantly decreased (7.4 ± 1.2, *vs* 8.5 ± 1.5% at baseline; $P < 0.05$). At 16 weeks, mean HbA_{1c} level had stabilized to 6.8 ± 1.0% ($P < 0.01$ *vs* baseline) and showed a tendency toward a slight decrease until 24 weeks (at 24 weeks, 6.6 ± 0.7%, $P < 0.01$ *vs* baseline). At 16 weeks, the rates of patients who achieved HbA_{1c} levels of <7.0 and <6.5% were 68.2% (15/22) and 45.5% (10/22), respectively. At 24 weeks, 16 of 20 (80.0%) and 7 of 20 (35.0%) patients had achieved HbA_{1c} levels of <7.0 and <6.5%, respectively. Reduction of the rate of patients achieving a HbA_{1c} level of <6.5% at 24 weeks was a result of worsening of HbA_{1c} level to ≥6.5% in two patients and a patient dropping out before 24-week follow up, among 10 patients who achieved a HbA_{1c} level of <6.5% at 16 weeks. When the patients were stratified according to baseline HbA_{1c} levels of <8.0 or ≥8.0%, 87.5% (7/8) and 75.0% (9/12) of patients, respectively, had achieved HbA_{1c} levels of <7.0% at 24 weeks. Further, 37.5% (3/8) and 33.3% (4/12) of patients with respective baseline HbA_{1c} levels of <8.0 and ≥8.0% had achieved HbA_{1c} levels of <6.5% at 24 weeks. The rates of patients who had achieved HbA_{1c} levels of <7.0 and <6.5% as the final evaluations at 24 weeks were not influenced by baseline HbA_{1c} levels. Figure 2b shows a strong linear correlation between baseline HbA_{1c} levels and change in HbA_{1c} levels from the baseline (ΔHbA_{1c}) at 24 weeks in 20 patients (Figure 2b), showing that an even higher HbA_{1c} level at baseline can be lowered sufficiently by the regimen of the present study.

Efficacy Achieved as Per Daily Profiles of SMBG

Figure 1b shows the improvement in 8-point SMBG profiles in 21 patients whose daily 8-point SMBG profiles at baseline and

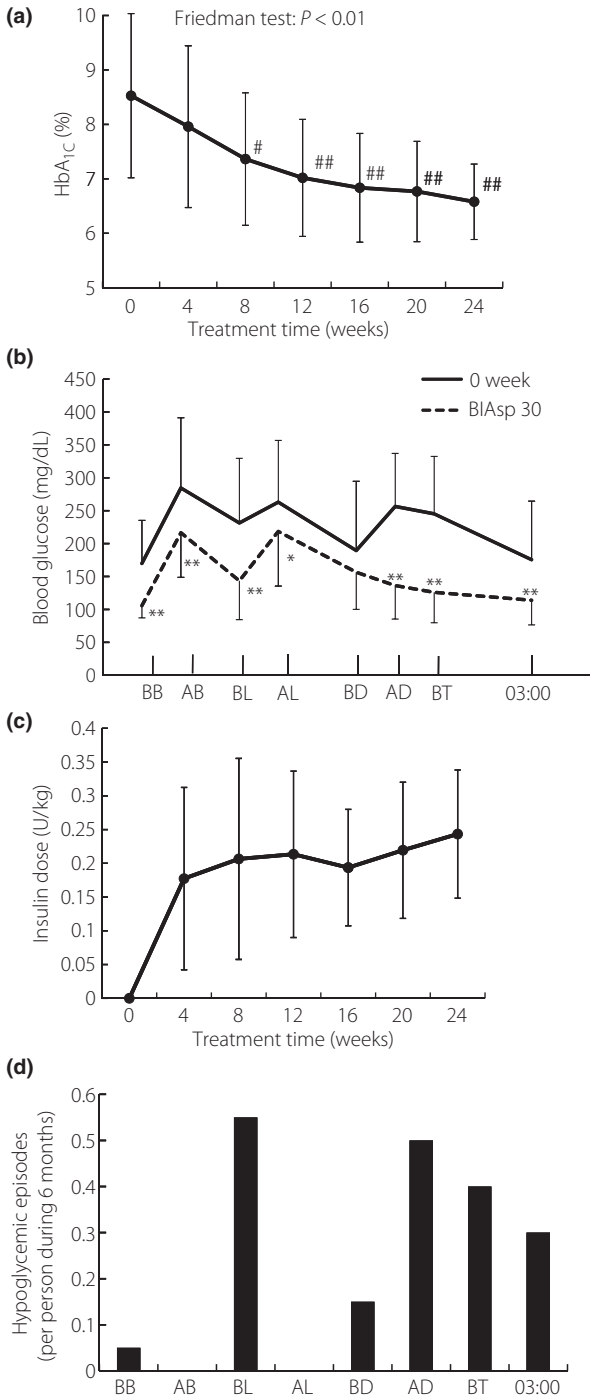

Figure 1 | Clinical parameters during the treatment with pre-dinner biphasic insulin aspart 70/30. (a) Changes in HbA_{1c}. (b) Mean 8-point self-monitored blood glucose profiles at baseline and just after BIAsp 30 titration. (c) Changes in self-titrated insulin dose. (d) Incidences of hypoglycemic episodes. Data are expressed as mean ± SD in a, b and c. AB, 2 h post-breakfast; AD, 2 h post-dinner; AL, 2 h post-lunch; BB, pre-breakfast; BD, pre-dinner; BL, pre-lunch; BT, bed time. $^{\#}P < 0.05$; $^{\#\#}P < 0.01$ versus values at 0 week revealed by Dunn's multiple comparison test. $^{*}P < 0.05$; $^{**}P < 0.01$ versus values at 0 week revealed by the Wilcoxon signed-ranks test.

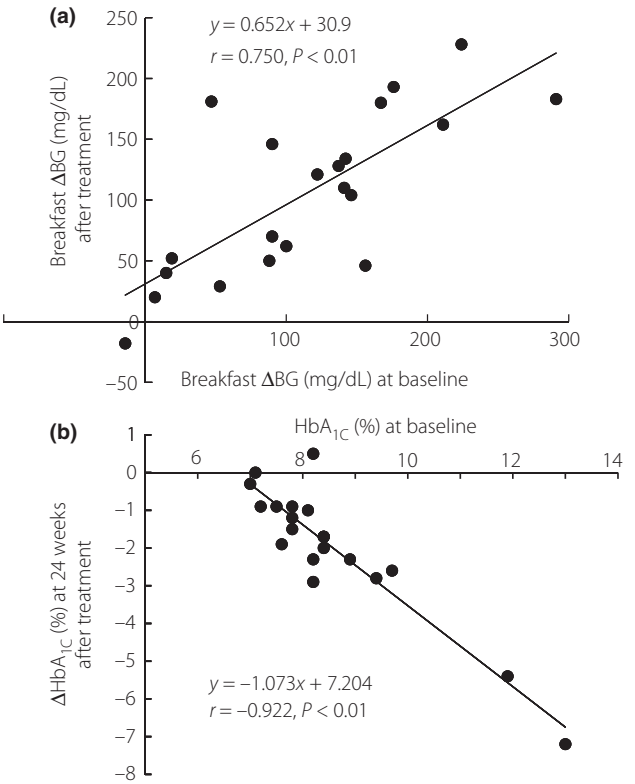

Figure 2 | Relationships (a) between post-breakfast blood glucose excursion (ΔBG) at baseline and that just after titration of pre-dinner biphasic insulin aspart 70/30 and (b) between baseline HbA_{1c} levels (%) and changes in HbA_{1c} levels (ΔHbA_{1C}, %) at 24 weeks from baseline.

just after BIAsp 30 titration (after titration) were sufficiently obtained. All the points of BG measured were significantly decreased, except for pre-dinner BG. In particular, the decreases in BG at pre- and post-breakfast, pre-lunch, post-dinner, at bedtime and at 03.00 h were remarkable ($P < 0.01$). As shown in Figure 1b, the BG profiles from post-dinner to pre-breakfast were well stabilized without post-dinner BG excursion (ΔBG) after titration (67.1 ± 85.4 mg/dL at baseline and −23.6 ± 67.4 mg/dL after titration; $P < 0.01$), whereas post-breakfast ΔBG after BIAsp 30 titration remained comparable to that at baseline (114.7 ± 77.9 mg/dL at baseline and 105.8 ± 67.7 mg/dL after titration).

Clinical Characteristics of Patients With or Without Optimal Post-breakfast ΔBG Pattern After Treatment

The patients in the present study showed widely divergent post-breakfast ΔBG (from −18 to 228 mg/dL) even after nearly ideal FBG levels had been established by BIAsp 30 titration (Fig. 2a). Therefore, clinical characteristics with or without optimal post-breakfast ΔBG after titration were explored. Individual post-breakfast ΔBG at baseline and after BIAsp 30 titration showed a strong correlation (Fig. 2a), indicating that the treatment might scarcely influence the individual post-breakfast ΔBG pattern. Therefore, we divided the patients into two groups according to

Table 2 | Clinical characteristics of type 2 diabetic patients divided according to 2-h post-breakfast blood glucose levels after biphasic insulin aspart 70/30 titration

	Blood glucose at 2 h after breakfast		
	<200 mg/dL $n = 10$ (Group A)	≥200 mg/dL $n = 11$ (Group B)	*P*-value
Male/female (*n*)	8/2	4/7	<0.05
Age (years)	55.3 ± 5.7	66.8 ± 10.5	<0.05
Body mass index (kg/m^2)	25.3 ± 4.1	24.6 ± 6.4	NS
Duration of diabetes (years)	8.7 ± 7.0	18.9 ± 11.7	<0.05
AGI use (*n*, %)	3, 30.0	2, 18.1	NS
HbA_{1c} levels at 0 week (%)	8.9 ± 1.8	8.7 ± 2.0	NS
HbA_{1c} levels at 16 weeks (%)	6.7 ± 0.62	6.8 ± 0.96	NS
ΔHbA_{1c} 0–16 weeks (%)	−2.2 ± 1.9	−1.9 ± 1.4	NS
FBG at 0 week (mg/dL)	173.8 ± 80.0	166.3 ± 52.8	NS
2h-BG-M at 0 week (mg/dL)	239.3 ± 119.3	325.6 ± 71.6	NS
ΔBG-M at 0 week (mg/dL)	65.5 ± 58.5	159.4 ± 66.6	<0.01
FBG after BIAsp 30 titration (mg/dL)	106.7 ± 14.5	109.9 ± 19.8	NS
2h-BG-M after BIAsp 30 titration (mg/dL)	152.8 ± 29.5	269.9 ± 36.9	<0.01
ΔBG-M after BIAsp 30 titration (mg/dL)	46.2 ± 33.5	160.0 ± 36.9	<0.01
Insulin dosage after BIAsp 30 titration (U/kg)	0.21 ± 0.14	0.23 ± 0.15	NS

Data are expressed as mean ± SD or otherwise indicated. The Mann–Whitney *U*-test and Pearson's χ^2-test was used to calculate statistically significant differences of the values between groups. 2h-BG-M, blood glucose 2 h after breakfast; ΔHbA_{1c} 0–16 weeks, changes in HbA_{1c} levels from baseline to 16 weeks; AGI, alpha-glucosidase inhibitor; FBG, fasting blood glucose; ΔBG-M, blood glucose excursion for 2 h after breakfast; NS, not significant.

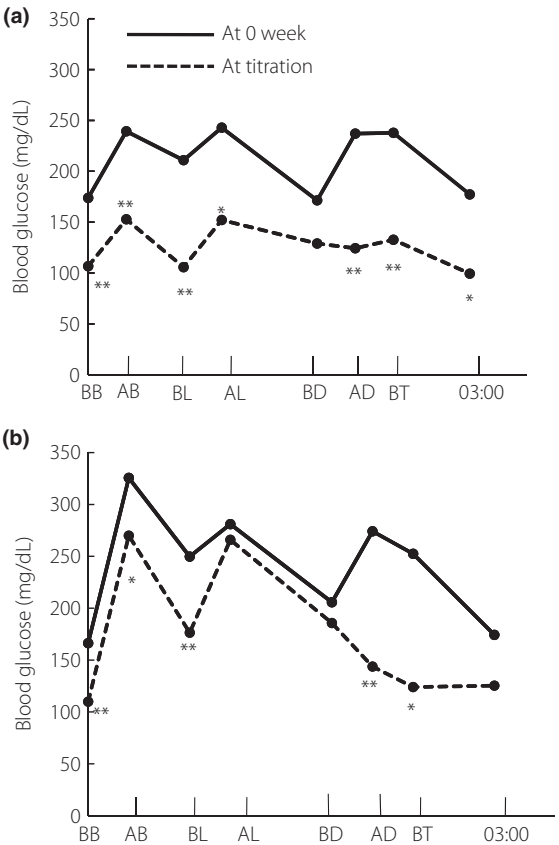

Figure 3 | Mean 8-point self-monitored blood glucose (BG) profiles at 0 week and just after pre-dinner biphasic insulin aspart 70/30 (BIASp 30) titration (a) in patients with 2 h post-breakfast BG after BIAsp 30 titration <200 mg/dL and (b) in patients with 2 h post-breakfast BG after BIAsp 30 titration ≥200 mg/dL. AB, 2 hours post-breakfast; AD, 2 h post-dinner; AL, 2 h post-lunch; BB, pre-breakfast; BD, pre-dinner; BL, pre-lunch; BT, bed time. *$P < 0.05$; **$P < 0.01$ versus values at 0 week revealed by the Wilcoxon signed-ranks test.

post-breakfast SMBG levels after BIAsp 30 titration: Group A, <200 mg/dL; and Group B, ≥200 mg/dL (Table 2). Figure 3 shows the daily 8-point SMBG profiles at baseline and after BIAsp 30 titration, indicating relatively flat BG profiles in Group A and ruggedness in Group B. Table 2 shows the clinical characteristics of both groups. Patients in Group B had a greater proportion of women, older age, longer duration of diabetes and higher post-breakfast ΔBG both before and after BIAsp 30 titration. Despite the rugged daytime BG profiles, even after BIAsp 30 titration, HbA_{1c} levels after BIAsp 30 treatment in Group B were not significantly higher compared with that in Group A (Table 2).

Insulin Dosages

Insulin dosage (U/kg) was titrated to 0.18 ± 0.14 at 4 weeks, 0.19 ± 0.09 at 16 weeks, 0.22 ± 0.10 at 20 weeks and 0.24 ± 0.09 at 24 weeks (Figure 1c).

BW Changes

BW changes from 0 week (kg) were −0.12 ± 1.0, 0.23 ± 1.8, 0.59 ± 2.3, 1.1 ± 2.2, 1.9 ± 2.8 and 2.5 ± 2.7 at 4, 8, 12, 16, 20 and 24 weeks, respectively. The Friedman test showed significant BW changes throughout the study period ($P < 0.01$). BW at 20 and 24 weeks were significantly increased compared with baseline ($P < 0.05$ by Dunn's multiple comparison test).

Hypoglycemic Episodes and Adverse Events

No severe hypoglycemic episodes were reported. Mild hypoglycemic episodes were reported by 13 of 29 patients (including 7 patients who withdrew from the study) during the study at a low rate of 1.95 events per patient over the course of 6 months (Figure 1d). Principally, patients had experienced hypoglycemic episodes pre-lunch, post-dinner, at bedtime and at 03.00 h.

One woman withdrew because of a progression of diabetic retinopathy (progression from no clinical lesions at baseline to proliferative retinopathy requiring photocoagulation and surgical procedure by an ophthalmologist 6 weeks after initiation of

BIAsp 30). Another woman withdrew because of skin allergy at the injection site. The patient with a marked retinopathy progression mentioned previously had a long estimated duration of diabetes (23 years) and marked poor glycemic control (HbA_{1c} level at baseline of 13.8%, ΔHbA_{1c} at 4, 8 and 12 weeks of −2.7, −3.8 and −4.5%, respectively). Retinopathy progression was reported in another two patients who were able to complete the study. In one woman, simple retinopathy before the initiation of BIAsp 30 had progressed to proliferative retinopathy 1 month after the end of this study (HbA_{1c} levels at baseline and at 24 weeks were 7.8, 6.9%, respectively. ΔHbA_{1c} at 4, 8 and 12 weeks were −0.5, −0.6 and −0.7%, respectively). In another patient, a man without retinopathy at baseline, simple retinopathy was found 24 months after the end of the present study (HbA_{1c} levels at baseline and at 24 weeks were 7.2 and 6.3%, respectively. ΔHbA_{1c} at 4, 8 and 12 weeks were −0.3, −1.1 and −1.6%, respectively).

DISCUSSION

This study showed that in Japanese T2D patients with failed OAD therapies, patients who had achieved optimal glycemic control, including daytime postprandial BG profiles after an addition of appropriate dosage of once-daily pre-dinner BIAsp 30 (Group A), had lower post-breakfast BG excursions at baseline, shorter diabetes durations and younger age. The other patients with opposite clinical characteristics (Group B) had still shown higher daytime postprandial BG excursions, even after achievement of ideal BG profiles from post-dinner to pre-breakfast, by the regimen used in the present study.

In Group A patients, the ranges of daily BG profiles before and after BIAsp 30 titration were relatively flat (Figure 3) and resembled those of T2D patients from Western countries, who used BOT or pre-dinner BIAsp 30 as an add-on to OAD[9–14,18,20]. Additionally, daily BG profiles after titration were ideal and didn't seem to require additional insulin supplementation at breakfast or lunch. In contrast, Group B patients had higher daytime postprandial glucose excursions both before and after BIAsp 30 titration and higher baseline post-breakfast ΔBG levels were preserved even after treatment (Figure 3), requiring bolus dosages at breakfast and/or lunch time to achieve ideal daily BG profiles. Collectively, higher post-breakfast ΔBG levels with OAD failure might predict a need for two or more bolus supplements of insulin after the establishment of ideal BG profiles from post-dinner to pre-breakfast by pre-dinner BIAsp 30 titration.

Group B patients had relatively higher age and longer durations of diabetes (Table 2), indicating that they had the characteristics of more declined β-cell function reported in long-standing T2D patients[7,8]. The main characteristics of Asian T2D patients have been thought to include declined β-cell function[23–25] and a loss of early-phase insulin response[26]. Taking these findings together, Japanese T2D patients with OAD failure can be divided into two groups: one characterized with relatively declined β-cell function with higher postprandial glucose excursions requiring appropriate basal and multiple bolus insulin supplements; and the other with relatively preserved β-cell function with lower postprandial glucose excursions requiring only appropriate FBG correction that might be achieved with the addition of once-daily injections to OAD therapies, such as pre-dinner BIAsp 30 or basal insulin analogues.

Table 2 shows that there is no difference in HbA_{1c} levels at 16 weeks between Group A and B, despite the markedly different patterns of daytime BG excursion (Figure 3). It is difficult to explain this phenomenon. Daily SMBG profiles had been well preserved during the study (the post-breakfast ΔBG last recorded during the study in Group A and B were 57.6 ± 55.5 and 141.7 ± 55.5 mg/dL [$P < 0.01$], respectively). Postprandial glucose spikes of relatively short duration might have minor effects on HbA_{1c} levels. Because glycated albumin (GA) is reported to be a more sensitive marker than HbA_{1c} for glucose excursions[27], we would have measured GA levels in the present study.

The results that 80 and 35% of participants were able to achieve HbA_{1c} levels of <7.0 and <6.5%, respectively, at 24 weeks confirmed the satisfactory results of phase 1 in 'The 1-2-3 study' (in which HbA_{1c} level was <7.0% in 41% and <6.5% in 21% of patients)[18]. Recently, it was reported that HbA_{1c} levels of 7.0 and 6.5% in the USA are equivalent to those of 6.6 and 6.1% in Japan (JDS values)[28]. Considering the methodological differences used to determine HbA_{1c} levels between Japan and the USA, the result that 35% of the patients in the present study achieved HbA_{1c} levels of <6.5% (equivalent to 6.9% in the USA) is comparable to the result of 'The 1-2-3 study'. Recent guidelines from Western countries recommend that insulin should be initiated with basal insulin analogues as add-on OAD therapies[6]. However, the satisfactory results of 'The 1-2-3 study', the study of Strojek *et al.*[20] and the present study show that adding a once-daily pre-dinner injection of BIAsp 30 in T2D patients with OAD failure might represent an alternative regimen at the initiation of insulin therapy.

The present study used an insulin titration method managed by patients themselves on the basis of SMBG levels according to a predetermined algorithm[21,22]. The satisfactory effects of the present study on HbA_{1c} levels with a minimal incidence of hypoglycemia also confirmed the usefulness of this insulin titration method in Japanese T2D patients. Dosage-adjustment levels at each correction were designed to be approximately one-third of those applied in Western countries[18,21,22], where the body mass index (BMI) of patients is approximately 30. The BMI of our patients was approximately 25, suggesting a less insulin-resistant feature of Japanese T2D patients and the need for a finer insulin titration regimen.

In the present study, no severe hypoglycemic episodes were recorded and the frequency of mild hypoglycemic episodes was considered acceptable. Recording SMBG, especially pre-breakfast everyday and self-adjustment of pre-dinner BIAsp 30 dosage, according to SMBG levels might be related to this level of safety. The reduced dosages of SU at the initiation of BIAsp 30 in the

present study might be a reason for the lack of severe hypoglycemic episodes.

Progression of retinopathy was observed in three patients. Aggressive reduction of BG levels in patients with long-term poor glycemic control has been reported to be a factor contributing to early retinopathy progression after glycemic control[29–31] and a slow reduction rate of HbA_{1c} levels (slower than −0.5% per month) is recommended for such patients[32]. The patient in the present study who withdrew because of marked retinopathy progression had a long-term poor glycemic state; longer insulin titration intervals than those used in the present study might be desirable for such patients. However, progression of retinopathy was reported in another two patients, whose baseline HbA_{1c} levels and reduction rates were not as high and not as aggressive, respectively (from 7.8 to 6.9% and from 7.2 to 6.3% during 6 months), indicating that the fast reduction rate of HbA_{1c} levels is only a definitive cause of early retinopathy worsening after aggressive glycemic control. Although causes for retinopathy progression in our patients are not clear, patients who undergo intensified glycemic control regimens should be followed up with careful and regular observation of retinopathy to prevent or to take an appropriate action against its worsening.

The present study was limited by low numbers of patients. Accordingly, the aforementioned results must be interpreted as those of a limited pilot study. A large number of participants is necessary to conclude that the regimen of the present study is a suitable method for the initiation of insulin therapy in Japanese T2D patients.

In summary, an addition of a once-daily pre-dinner injection of BIAsp 30 using a patient-directed insulin titration method on the basis of SMBG levels according to a predetermined algorithm can provide satisfactory reduction of HbA_{1c} levels and flat BG profiles from post-dinner to pre-breakfast in Japanese T2D patients with failure of OAD therapies. Lower post-breakfast BG excursions at baseline, shorter diabetes duration and younger age might warrant optimal glycemic control, including daytime postprandial BG profiles, with safety after this simple insulin initiating regimen.

ACKNOWLEDGEMENT

The authors declare no conflict of interest.

REFERENCES

1. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications of insulin-dependent diabetes mellitus. *N Engl J Med* 1993; 329: 977–986.
2. Ohkubo Y, Kishikawa H, Araki E, *et al.* Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. *Diabetes Res Clin Pract* 1995; 28: 103–117.
3. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998; 352: 837–853.
4. Holman RR, Paul S, Bethel MA, *et al.* 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med*, 2008; 359: 1577–1589.
5. Japan Diabetes Society. *Treatment Guide for Diabetes*. Tokyo: Bunkodo, 2007.
6. Nathan DM, Buse JB, Davidson MB, *et al.* Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2009; 32: 193–203.
7. UK Prospective Diabetes Study Group. UK Prospective Diabetes Study 16: overview of 6 year's therapy of type 2 diabetes: a progressive disease. *Diabetes* 1995; 44: 1249–1258.
8. Kahn SE, Haffner SM, Heise MA, *et al.* Glycemic durability of rosiglitazone, metformin, or glyburide monotherpay. *N Engl J Med* 2006; 355: 2427–2443.
9. Riddle MC, Rosenstock J, Gerich J, *et al.* The treat-to-target trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. *Diabetes Care* 2003; 26: 3080–3086.
10. Eliaschewitz FG, Calvo C, Valbuena H, *et al.* Therapy in type 2 diabetes: insulin glargine vs. NPH insulin both in combination with glimepiride. *Arch Med Res* 2006; 37: 495–501.
11. Hermansen K, Davies M, Derezinski T, *et al.* A 26-week, randomized, parallel, treat-to-target trial comparing insulin detemir with NPH insulin as add-on therapy to oral glucose-lowering drugs in insulin-naïve people with type 2 diabetes. *Diabetes Care* 2006; 29: 1269–1274.
12. Philis-Tsimikas A, Charpentier G, Clauson P, *et al.* Comparison of once-daily insulin detemir with NPH insulin added to a regimen of oral antidiabetic drugs in poorly controlled type 2 diabetes. *Clin Ther* 2006; 28: 1569–1581.
13. Yki-Järvinen H, Kauppinen-Mäkelin R, Tiikkainen M, *et al.* Insulin glargine or NPH combined with metformin in type 2 diabetes: the LANMET study. *Diabetologia* 2006; 49: 442–451.
14. Rosenstock J, Davies M, Home PD, *et al.* A randomised, 52-week, treat-to-target trial comparing insulin detemir with insulin glargine when administered as add-on to glucose-lowering drugs in insulin-naive people with type 2 diabetes. *Diabetologia* 2008; 51: 408–416.
15. Goto H, Hirose T, Shimizu T, *et al.* Effectiveness of combination therapy with a sulfonylurea and once-daily insulin glargine in Japanese type 2 diabetic patients. Evaluation of the long-term (18 months) results of the combination therapy. *J Japan Diab Soc* 2007; 50: 591–597.
16. Hermansen K, Colombo M, Storgaard H, *et al.* Improved postprandial glycemic control with biphasic insulin aspart relative to biphasic insulin lispro and biphasic human insulin

in patients with type 2 diabetes. *Diabetes Care* 2002; 25: 883–888.
17. McSorley PT, Bell PM, Jacobsen LV, *et al.* Twice-daily biphasic insulin aspart 30 versus biphasic human insulin 30: a double-blind crossover study in adults with type 2 diabetes mellitus. *Clin Ther* 2002; 24: 530–539.
18. Garber AJ, Wahlen J, Wahl T, *et al.* Attainment of glycaemic goals in type 2 diabetes with once-, twice-, or thrice-daily dosing with biphasic insulin aspart 70/30 (The 1-2-3 study). *Diabetes Obes Metab* 2006; 8: 58–66.
19. Yoshioka N, Kurihara Y, Manda N, *et al.* Step-up therapy with biphasic insulin aspart-70/30; -Sapporo 1-2-3 study. *Diabetes Res Clin Pract* 2009; 85: 47–52.
20. Strojek K, Bebakar WMW, Khutsoane DT, *et al.* Once-daily initiation with biphasic insulin aspart 30 versus insulin glargine in patients with type 2 diabetes inadequately controlled with oral drugs: an open-label, multinational RCT. *Curr Med Res Opin* 2009; 25: 2887–2894.
21. Davies M, Storms F, Shutler S, *et al.* Improvement of glycemic control in subjects with poorly controlled type 2 diabetes. Comparison of two treatment algorithms using insulin glargine. *Diabetes Care* 2005; 28: 1282–1288.
22. Meneghini L, Koenen C, Weng W, *et al.* The usage of a simplified self-titration dosing guideline (303 Algorithm) for insulin detemir in patients with type 2 diabetes. Results of the randomized, controlled PREDICTIVE 303 study. *Diabetes Obes Metab* 2007; 9: 902–913.
23. Kosaka K, Hagura R, Kuzuya T. Insulin responses in equivocal and definite diabetes, with special reference to subjects who had mild glucose intolerance but later developed definite diabetes. *Diabetes* 1977; 26: 944–952.
24. Mitsui R, Fukushima M, Nishi Y, *et al.* Factors responsible for deteriorating glucose tolerance in newly diagnosed type 2 diabetes in Japanese men. *Metabolism* 2006; 55: 53–58.
25. Jensen CC, Cnop M, Hull RL, *et al.* B-Cell Function is a major contributor to oral glucose tolerance in high-risk relatives of four ethnic groups in the US. *Diabetes* 2002; 51: 2170–2178.
26. Kadowaki T, Miyake Y, Hagura R, *et al.* Risk factors for worsening to diabetes in subjects with impaired glucose tolerance. *Diabetologia* 1984; 26: 44–49.
27. Yoshiuchi K, Matsuhisa M, Katakami N, *et al.* Glycated albumin is a better indicator for glucose excursion than glycated hemoglobin in type 1 and type 2 diabetes. *Endocr J* 2008; 55: 503–507.
28. Kashiwagi A, Kadowaki T, Haneda M, *et al.* Consensus and statement on international standardization of HbA1C in Japan: committee report on diabetes mellitus laboratory testing standardization. *J Japan Diab Soc* 2009; 52: 811–818.
29. Daneman D, Drash A, Lobes LA, *et al.* Progressive retinopathy with improved control in diabetic dwarfism (Mauriac's syndrome). *Diabetes Care* 1981; 4: 360–365.
30. Morita C, Hasumi S, Omori Y, *et al.* Effects of the rapid control of blood glucose to the diabetic retinopathy; from the aspect of the internist. *Diabetes Journal* 1992; 20: 7–12.
31. The Diabetes Control and Complications Trial Research Group. Early worsening of diabetic retinopathy in the diabetes control and complications trial. *Arch Ophthalmol* 1998; 116: 874–886.
32. Shichiri M. Glycemic control and diabetic retinopathy. *Folia Ophthalmol Jpn* 1996; 47: 1–6.