Step-up therapy with biphasic insulin aspart-70/30 –Sapporo 1-2-3 study–

N. Yoshioka[1)], Y. Kurihara[2)], N. Manda[3)], K. Komori[4)], M. Kato[5)], H. Kijima[6)], N. Wada[7)], K. Yanagisawa[8)], S. Aoki[9)], Y. Ono[10)], T. Koike [1)]

1) Department of Medicine Ⅱ,Hokkaido University Graduate School of Medicine
2) Kurihara Diabetic Care Clinic
3) Diabetes Center Manda Memorial Hospital
4) Odori Clinic of Int Med
5) Division of Diabetes, Endocrinology and Metabolism, Department of Internal Medicine Nishi Sapporo National Hospital
6) Division of Endocrinology and Metabolism KKR Sapporo Medical Center, Tonan Hospital
7) Division of Endocrinology and Metabolism Sapporo Social Insurance General Hospital
8) Department of Endocrinology and Diabetes , Sapporo City General Hospital
9) Aoki Clinic
10) Yuri Ono Clinic

Correspondence to Narihito Yoshioka, n-yoshi@med.hokudai.ac.jp
Department of Medicine Ⅱ,Hokkaido University Graduate School of Medicine, Kita 15 jyo, Nishi 7 cho-me, Kita-ku, Sapporo, Hokkaido, 060-8638, Japan
Phone: +81-11-706-5915, Fax: +81-11-706-7710

Abstract

The effectiveness of BIAsp 30 step-up therapy in achieving glycemic control in Japanese patients with type 2 diabetes mellitus was investigated. Study subjects were 99 patients with type 2 diabetes mellitus aged over 20 years who were judged to require insulin therapy due to poor glucose control (HbA1c level of ≥7.5%). BIAsp 30 dosage was determined by the patient's attending physician; co administration of hypotensive agents and antilipemic agents was permitted, but OAD co administration was limited to patients already receiving such drugs at the start of the study. Patients who did not achieve HbA1c <6.5% after 16±5 weeks with QD (Phase 1) were stepped up to BID (Phase 2). If patients still had not achieved HbA1c <6.5% after 16±5 weeks with BID, they were stepped up to TID (Phase 3). 55 of the 99 enrolled subjects completed the study and the rates of achievement of HbA1c<6.5% and HbA1c<7.0% were 45.5% and 74.5% respectively. Of all registered subjects, 5.1% (5/99) achieved HbA1c<6.5% in QD, 19.5% (16/82) in BID, and 20.6% (7/34) in TID. Statistically significant reductions in HbA1c levels were recorded at the conclusion of each phase, with no incidents requiring intervention, indicating that BIAsp 30 step-up therapy is a safe, simple therapy that can be useful in achieving better glycemic control for Japanese patients with type 2 diabetes mellitus.

[Keywords]
Biphasic insulin aspart-30, type 2 diabetes, step-up insulin therapy, HbA1c, clinical practice

1. Introduction

Biphasic insulin aspart (NovoRapid 30 Mix, hereafter BIAsp 30) is a product composed of 30% insulin aspart, a rapid-acting insulin analog, and 70% intermediate ingredient (insulin aspart protamine crystals) partially crystallized by adding protamine sulfate to insulin aspart. It demonstrates superior efficacy in suppressing postprandial blood glucose levels and has been reported to enable dose increase without increasing the incidence of hypoglycemic episodes.[1-5] Because it can be administered immediately before a meal, it is expected to improve patient compliance and QOL.[6-7]

When initiating insulin therapy for patients with type 2 diabetes mellitus, a regimen that mimics normal physiology and includes basal and prandial insulin is a rational choice. In daily clinical practice, however, many patients are averse to self-injection of insulin. It has therefore become common to initiate insulin therapy with once- or twice-daily injections rather than multiple daily injections. In such cases, a biphasic insulin analog product such as BIAsp 30 is appropriate because the basic etiology of type 2 diabetes mellitus is lowered initial insulin secretion and peripheral insulin resistance, which leads to postprandial hyperglycemia.

A 1-2-3 study was recently performed in the United States to investigate the usefulness of step-up therapy with BIAsp, starting the insulin therapy with one injection a day before dinner, increasing stepwise to two and three injections a day if the targeted glucose control was not achieved.[8] The results demonstrated not only the usefulness of once-daily injection of BIAsp 30, but also the usefulness of step-up therapy after initial insulin therapy of one injection a day. However, this study targeted American patients with type 2 diabetes mellitus whose mean BMI was 34.2. Considering the substantially lower mean BMI of most Japanese in comparison to Americans, as well as differences in the etiology of diabetes mellitus and national eating habits, it is therefore not clear whether the results of the U.S. study can be applied to Japanese patients with type 2 diabetes mellitus. Furthermore, the clinical study performed in the United States was based on a strict protocol that differs slightly from that typically used in actual clinical practice.

In this study, the authors therefore sought to investigate the usefulness of step-up therapy with BIAsp 30 in the routine treatment of Japanese patients with type 2 diabetes mellitus.

2. Subjects and Methods

2.1. Subjects

The study subjects were patients with type 2 diabetes mellitus aged over 20 years who were judged to require insulin therapy due to poor glucose control (HbA1c level of ≥7.5%) after three months or more of treatment with two or more oral antidiabetic drugs (OADs) in combination with diet/exercise therapy. Both male and female inpatients/outpatients were enrolled, but patients whose attending physicians deemed participation in a BIAsp 30 study to be inappropriate, as well as those with severe diabetic or other complications or a history of hypersensitivity to any of the components of this drug, were excluded. The subject registration period was from 16/6/2005 to 13/3/2007.

2.2. Study protocol

The study under discussion was an open-label observation study performed at a total of 10 sites in Japan (Hokkaido), reviewed and approved by the internal review board of Hokkaido University Hospital. The study was conducted as a "real world" study in actual clinical practice. The objectives and procedures of the study were fully explained (orally and in writing) to all patients before obtaining consent.

QD was started with a once-daily injection of BIAsp 30 immediately before dinner. The initial dose was left to the discretion of each physician, and the dosage was thereafter regulated according to the degree of glucose control achieved on a routine outpatient examination basis. Patients who achieved an HbA1c level of <6.5% within 16±5 weeks after the start of treatment completed the study at QD, whereas those who did not achieve the target value proceeded to BID. A test dosing period of 16±5 weeks was chosen so as to allow scope for physicians to schedule visits in accordance with their regular clinical practice.

During BID, BIAsp 30 was administered twice daily, once before breakfast and once before dinner. As in QD, the dosage was thereafter regulated according to the degree of glucose control achieved. Patients who achieved an HbA1c level of <6.5% within 16±5 weeks after the start of BID completed the study at BID, and those who did not achieve the target value proceeded to TID.

BIAsp 30 was administered three times daily in TID by adding an injection immediately before lunch, and the treatment was continued for 16±5 weeks while regulating the dose in the same manner as in Phases 1 and 2.

Coadministration of OADs was permitted for patients who were receiving them at the time of registration, but such coadministration was not permitted to start after registration. Coadministration of hypotensive agents and antilipemic agents was also permitted.

Insulin dosage, HbA1c levels, casual blood glucose levels, body weight, hypoglycemic episodes, and adverse events were investigated at each visit during each phase. Hypoglycemia was rated both by physicians on the basis of usual signs/symptoms with their severity and SMBG values below 60mg/dL. HbA1c levels and casual blood glucose levels were measured by HPLC and glucose-oxidase method, respectively, at each site. In this study, postprandial blood glucose was based on casual blood glucose level in consideration of the possibility of deviations in the postprandial measurement time. All patients were given instructions on self-monitoring blood glucose (SMBG) as well as precautions and countermeasures against hypoglycemia.

2.3. Data and statistical analysis

Data are expressed as mean ± standard deviation. Wilcoxon's test was performed for changes in the HbA1c level, casual blood glucose level, insulin dose, and BMI; a value of $p<0.05$ was considered statistically significant.

3. Results

3.1. Patients

Prior to the start of the study, a majority (97 out of 99) of the enrolled subjects received OAD treatment; one subject had been previously treated with an OAD + insulin and one subject had been previously treated with diet/exercise therapy only (Table 1). Fifty-five of the 99 enrolled subjects completed the study; 44 subjects did not complete the study because they objected to the increased number of injections or failed to appear at scheduled visits (Table 2). There was no discontinuation due to adverse events including hypoglycemia. Of the subjects who did not achieve the targeted HbA1c level at the end of a phase, 12 patients elected not to proceed from QD to BID, and 32 patients elected not to proceed from BID to TID.

The prevalence of complications was 33.3% for diabetic retinopathy, 41.4% for diabetic neuropathy, and 50.0% for diabetic nephropathy.

3.2. Glycemic control

Of all registered subjects, 5.1% (5/99) achieved the target of HbA1c<6.5% in QD, 19.5% (16/82) achieved it in BID, and 20.6% (7/34) achieved it in TID (Table 2 and Figure 1). In other words, 21.2% (21/99) of the 99 subjects who received a BIAsp 30 injection once or twice daily achieved HbA1c<6.5% before the completion of BID, and 28.3% (28/99) who received a BIAsp 30 injection once, twice or thrice daily did so before the completion of TID.

Of the subjects who achieved HbA1c<7.0%, 21.2% (21/99) did so in QD, 30.5% (18/59) did so in BID, and 23.1% (9/39) did so in TID. A total of 48 subjects achieved HbA1c<7.0%, resulting in an achievement rate at the completion of the study of 48.5% (48/99).

The 55 subjects who completed the study were analyzed and the rates of achievement of HbA1c<6.5% and HbA1c<7.0% were 45.5% (25/55) and 74.5% (41/55) respectively.

The HbA1c level of 8.9±1.2% at the start of the study was lowered to 7.8±1.1% at the completion of QD, to 7.4±1.0% at the completion of BID, and further to 7.2±1.2% at the completion of TID (Table 3). The amount of reduction compared to the start of the study was 1.1% at the completion of QD, 1.5% at the completion of BID, and 1.7% at the completion of TID. All reduction amounts were significant compared with the level at the start of the study.

As observed with the HbA1c level, casual blood glucose level was also significantly lowered at the completion of Phases 1, 2, and 3 in

comparison to the start of the study (Table 3). More specifically, the casual blood glucose level was 216.0±74.4mg/dL at the start of the study, 192.6±69.4 mg/dL at the completion of QD, 160.9±51.5 mg/dL at the completion of BID, and 151.7±57.5 mg/dL at the completion of TID.

3.3. BIAsp 30 dose

The daily insulin dose was 5.5±1.9U at the start of QD, 9.8±5.1U at the completion of QD, 15.2±6.4U at the start of BID, 19.3±10.1U at the completion of BID, 25.2±11.5U at the start of TID, and 26.2±11.0U at the completion of TID. A statistically significant difference was observed at the completion of each phase compared with the start of QD ($p<0.001$, Wilcoxon's test).

3.4. Body weight

BMI was 25.2±4.4kg/m^2 at the start of the study, 25.2±4.4kg/m^2 at the completion of QD, 25.6±4.2kg/m^2 at the completion of BID, and 25.7 ±3.5kg/m^2 at the completion of TID (Table 3). Although increases were slight, they were statistically significant when compared with the start of the study.

3.5. Safety

A total of 17 hypoglycemic episodes occurred in eight of the 99 subjects. Of these, three episodes were associated with injection of BIAsp 30 once daily and the rest with injection twice daily; no hypoglycemic episodes were observed with three injections daily. Only one episode, which was observed after twice-daily injection, was assessed as moderate; the rest were assessed as mild. There were no occurrences of serious hypoglycemic episodes that required assistance by a third party. There were no other adverse events (adverse drug reactions) related to the insulin injections.

4. Discussion

The recommended target levels of glycemic control are HbA1c<7.0% by the American Diabetes Association (ADA)[9], HbA1c≤6.5% by the American Association of Clinical Endocrinologists (AACE) and International Diabetes Federation (IDF)[10], and HbA1c<6.5% by the Japan Diabetes Society[11]. In any case, introduction of insulin at the appropriate time is essential if the target level is to be reached. However, a nationwide survey conducted by the Japan Diabetes Clinical Data Management Study Group (JDDM) showed that the mean HbA1c level was 8.5% at the time of insulin introduction in patients with type 2 diabetes mellitus, indicating that insulin is not being introduced at the appropriate time at present.[12] One method attracting attention is step-up therapy where the number of injections is increased incrementally. This therapy starts with a once-daily injection of a biphasic insulin analog before dinner, which is increased to a twice-daily regimen by adding an injection before breakfast if the targeted glycemic control is not achieved, and further to three times daily by adding an injection before lunch. A 1-2-3 study was performed in the United States to investigate the usefulness of step-up therapy using BIAsp 30. The subjects were 100 patients with type 2 diabetes mellitus in whom sufficient glycemic control was not achieved by administration of an OAD or by concomitant administration of an OAD and insulin to supplement basal secretion. The proportion of patients achieving the target was 21% in QD with once-daily injection, 52% in BID with twice-daily injection, and 60% in TID with thrice-daily injection, indicating the usefulness of step-up therapy.[8]

The present authors performed the Sapporo 1-2-3 study to investigate whether step-up therapy was useful for the routine treatment of Japanese patients with type 2 diabetes mellitus. The glycemic control level of HbA1c<6.5% recommended by the Japan Diabetes Society was targeted because the study subjects were Japanese patients. Given that no marked difference was observed in analysis comparing the subjects who completed the study (55 subjects) with all enrolled subjects (99 subjects), the latter were included in the analysis. Target achievement rates were 5.1% in QD, 19.5% in BID, and 20.6% in TID, which were less than half the achievement rates observed in the American 1-2-3 study. The results may have been affected by the fact that the Japanese subjects received smaller insulin doses in comparison to the American subjects because there were fewer obese Japanese subjects. Specifically, the mean BMI of the study subjects was 34.2 in the American 1-2-3 study whereas it was 25.2 in this study. In the American 1-2-3 study, the mean dose of BIAsp 30 administered to subjects who achieved the target level was 0.60U/kg

before dinner in QD, 0.51U/kg before breakfast and 0.64 U/kg before dinner in BID, and 0.58U/kg before breakfast, 0.25 U/kg before lunch, and 0.70U/kg before dinner in TID. In the current study, however, the mean dose of BIAsp 30 administered to subjects who achieved the target level was 0.10U/kg before dinner in QD, 0.10U/kg before breakfast and 0.14 U/kg before dinner in BID, and 0.15U/kg before breakfast, 0.07U/kg before lunch, and 0.15U/kg before dinner in TID. The total daily insulin doses for patients in the current study were 0.15U/kg in QD, 0.29 U/kg in BID, and 0.38U/kg in TID, which are all smaller than the daily dose of 0.4~0.5U/kg that is generally considered the required dose in Japan [11)].

When glycemic control was assessed by mean HbA1c level, levels at completion of Phases 1, 2, and 3 were all significantly lower than levels recorded at the start of the study. Recorded declines were -1.1%, -1.5%, and -1.7% respectively, which are comparable to the declines of -1.4%, -1.9%, and -1.8% recorded in the American 1-2-3 study. In addition, casual blood glucose levels were significantly lower at completion of each phase in comparison to levels recorded at the start of the study. Although the rate of target level achievement was lower than that observed in the American study, the results nonetheless indicate an improvement in routine therapy glycemic control.

Increased body weight, however, does continue to be a problem with insulin therapies. An increase in BMI of 5% was observed in the American 1-2-3 study, and although slight in comparison, a statistically significant increase in BMI was also observed in this study (0.3% at completion of QD, 1.75% at completion of BID, and 2.9% at completion of TID). As with the American 1-2-3 study, the increase became greater with prolongation of the study period. This suggests that appropriate diet and exercise therapies should be carried out to prevent body weight from increasing when intensifying glycemic control by using insulin therapy to correct postprandial hyperglycemia.

With respect to hypoglycemia, no occurrences of a clinically serious nature were observed during the current study, and the incidence of mild to moderate episodes did not increase in proportion to step-ups in the regimen. In addition, the few episodes that were recorded may simply be attributable to the slightly lower insulin dosages used. Although it is always necessary to exercise care when adjusting the insulin dose, and to pay attention to possible interactions with coadministered drugs, the characteristics of BIAsp 30 suggest that it may be possible to increase the dose slightly, and reduce HbA1c levels further without increasing the incidence of hypoglycemic episodes. Since several previous studies[13-18)] , some of them were conducted in Japanese patients, have shown that

BIAsp 30 improved HbA1c/daily glycemic profiles equally versus multiple insulin injection therapy or better than previous OAD therapy in insulin-naïve patients. Hypoglycemic episodes were not increased versus these regimens. All these studies concluded that treatment satisfaction was improved by the convenience-oriented regimen. In the UK, the 4-T study[19)] showed that in patients previously receiving OAD BIAsp 30 BID as well as prandial insulin TID significantly reduced HbA1c versus basal insulin 1-2 times daily. These results suggests that in insulin naive patients initiation on once-daily BIAsp 30 with subsequent recourse to further injections dependent on glycemic improvement is an acceptable insulin regimen in type 2 diabetic patients.

When selecting the most appropriate insulin therapy from the various choices available, consideration must be given to the patient's condition and glycemic control status, as well as the degree to which the patient understands and accepts insulin therapy. When a general clinician initiates insulin therapy for a patient with type 2 diabetes mellitus in routine treatment, a step-up therapy using a biphasic insulin analog product such as BIAsp 30 is an option worthy of consideration because it allows the patient to begin with a once-daily injection before dinner, and proceed thereafter to a twice-daily or thrice-daily schedule as needed. The results of this study suggest that this is a safe and simple method requiring only one type of insulin product and a single insulin device, and because it initially requires only one injection per day it is likely to be accepted even by patients who have resisted undergoing insulin therapy in the past. A simple method would also be much welcomed by busy physicians and healthcare professionals. This step-up method is an effective and maintainable method which can be performed not only by diabetes specialists but also by general clinicians.

This study contains some limitations; it was an observational study conducted in real-world clinical practice and did not follow a randomized trial design. Furthermore, since it was not a treat-to-target study, more aggressive treatment with higher insulin doses was not encouraged. The drop-out rate was also rather high, particularly among those who discontinued at the transition from BID to TID. On the other hand, this study provides some useful data. Although the most cited reason for dropping out given by patients was reluctance to take more daily injections, those who dropped out nonetheless achieved marked reductions of HbA1c (patients who discontinued at end of QD, from 8.8% to 7.8%; completed BID, from 9.2% to 7.7%). Therefore it seems that the 1-2-3 treatment method using BIAsp 30 might be a suitable, simple,

and acceptable option for Japanese as well as other Asian diabetic patients, and BiAsp 30 is a useful formulation for patients starting insulin therapy.

In summary, the step-up method with BIAsp 30 is a simple and safe insulin therapy that can be performed during routine clinical practice, and that achieves better glycemic control in Japanese patients with type 2 diabetes mellitus.

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N.Yoshioka, T.Atsumi, H.Miyoshi, T.Kondo, Y.Hida, J.Takeuchi, H.Kamoshima, M.Yoshida,T.Sawada, F. Honma (Department of Medicine Ⅱ,Hokkaido University Graduate School of Medicine)
Y.Kurihara (Kurihara Diabetic Care Clinic)
N.Manda, S.Taneda, K.Misawa, K.Tsuchida (Diabetes Center Manda Memorial Hospital)
K.Komori (Odori Clinic of Int Med)
M.Kato, H.Niwa, (Division of Diabetes, Endocrinology and Metabolism, Department of Internal Medicine Nishi Sapporo National Hospital)
H.Kijima, T. Okamoto (Division of Endocrinology and Metabolism KKR Sapporo Medical Center, Tonan Hospital)
N.Wada (Division of Endocrinology and Metabolism Sapporo Social Insurance General Hospital)
K.Yanagisawa, S.Obara, (Department of Endocrinology and Diabetes, Sapporo City General Hospital)
S.Aoki (Aoki Clinic)
Y.Ono (Yuri Ono Clinic)

6. Conflict of interest
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Table 1 Baseline characteristics of patients

Parameter	Value
No. of patients (n)	99
Age (years)	58.0±10.6
Male/Female (n)	66/33
Duration of diabetes (years)	13.7±9.1
Baseline BMI (kg/m^2)	25.2±4.4
Baseline HbA1c (%)	8.9±1.2
Previous treatment (n)	
OAD	97
OAD+glargine	1
Diet/exercise only	1

OAD: Oral antidiabetic drug

Table 2 Enrolment status and cumulative percentage of patients who achieved target HbA1c

Investigation	Phase		
	QD	BID	TID
No. of patients (n)	99	82	34
Improved glycemic control (achieved **target** HbA1c<6.5%) (n)	5.1% (5/99)	21.2% (21/99)	28.3% (28/99)
Improved glycemic control (achieved goal of HbA1c<7.0% (n)	21.2% (21/99)	39.4% (39/99)	48.5% (48/99)
Dropped out	12	32	–
Step-up patients (n)	82	34	–

Table 3 Change of HbA1c, casual blood glucose and BMI

	-4 weeks	Baseline	QD	BID	TID
HbA1c (%)	8.7±1.3	8.9±1.2	7.8± 1.1***	7.4± 1.0***	7.2± 1.2***
Casual blood glucose (mg/dL)	217.6± 74.5	216.0± 74.4	192.6± 69.4**	160.9± 51.5***	151.7± 57.5***
BMI (kg/m^2)	24.8±3.9	25.2±4.4	25.2± 4.4**	25.6± 4.2***	25.7± 3.5***

Values are mean±SD. ***p<0.001, **p<0.01 vs. baseline.

Figure legend

Fig. 1 Cumulative percentage of patients who achieved target HbA1c <6.5% in phases QD, BID, and TID.

Figure 1