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Safety and effectiveness of biphasic insulin aspart 30 in type 2 diabetes patients switched from biphasic human insulin 30: Results from the Filipino cohort of the A_1chieve study

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ABSTRACT

Aim: To evaluate the safety and effectiveness of biphasic insulin aspart 30 (BIAsp 30) in Filipino patients with type 2 diabetes previously treated with biphasic human insulin 30 (BHI 30).

Methods: Safety and effectiveness outcomes were measured in all patients switching from BHI 30 to BIAsp 30 in the Filipino cohort of the 24-week, multinational, prospective, non-interventional A_1chieve study.

Results: A total of 111 Filipino patients (mean age ± SD, 57.4±12.8 years; BMI, 25.8±5.6 kg/m^2) with mean diabetes duration of 9.9±7.1 years switched therapy from BHI 30 to BIAsp 30. The mean pre-study BHI 30 dose was 0.65±0.28 IU/kg and the baseline BIAsp 30 dose was 0.65±0.26 U/kg titrated up to 0.70±0.26 U/kg by Week 24. No serious adverse drug reactions were reported. Overall hypoglycaemia was reduced from 5.62 to 1.98 events/patient-year. Minor and nocturnal hypoglycaemia decreased and no major hypoglycaemia was reported at Week 24. Glucose control improved from baseline to Week 24 (HbA_{1c}, −2.2±2.1% [24±23 mmol/mol]; FPG, −72.0±71.8 mg/dL; PPPG, −145.5±125.4 mg/dL). A total of 24 patients achieved HbA_{1c} levels <7.0% at Week 24 compared to 6 patients reporting this target at baseline. Quality of life was positively impacted at Week 24 (change in visual analogue scores, 15.3±16.9 points).

Conclusion: Switching from BHI 30 to BIAsp 30 improved glycaemic control without increasing the risk of hypoglycaemia.

1. Introduction

In 2012, Philippines reported a diabetes prevalence of 8.2% according to a recent report released by the International Diabetes Federation. This figure also places Philippines among the top 10 countries by diabetes cases in the Western Pacific region [1]. By the year 2030, more than 7.4 million Filipinos are expected to be living with diabetes [2]. A 9-year cohort study in the Philippines provided evidence for an alarming increase in the pre-diabetes indicators, impaired fasting glucose levels and impaired glucose tolerance, thus implying a critical need for early aggressive interventions for diabetes prevention and control [3]. In the Philippines, incomplete or incorrect self-medication and selective

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compliance to medical advice is highly prevalent, acting as a potential barrier to adequate T2D management [4].

The American Diabetes Association recommends an HbA_{1c} target level <7.0% (53 mmol/mol) that is achieved by maintaining fasting plasma glucose (FPG) at 130 mg/dL and postprandial plasma glucose at 180 mg/dL (PPPG) [5]. However, it has been observed in several large observational studies that baseline glycaemic control is poor among people with type 2 diabetes (T2D) [6–8]. Early intensification of insulin is strongly recommended for this chronic debilitating condition but negative perceptions of hypoglycaemia, weight gain and impaired quality of life (QoL) often govern non-compliance to insulin therapy [9]. Furthermore, the variability in the pharmacological profile of human insulin preparations, such as biphasic human insulin 30 (BHI 30) results in unpredictable effects on glycaemic control [10]. Biphasic insulin aspart 30 (BIAsp 30) is a new generation insulin analogue that was designed to provide a more stable glycaemic control pattern. BIAsp 30 is a dual release formulation containing 30% soluble and 70% protamine-crystallized insulin aspart that offers the convenience of both prandial and basal coverage in a single injection [11,12]. Previously, a number of trials have established the superiority of glycaemic control with BIAsp 30 when compared to BHI 30 [13–16]. The glycaemic objectives were met with BIAsp 30 therapy resulting in similar or improved incidence of hypoglycaemia or weight gain [13–16]. Observational studies, PRESENT and IMPROVE, have also provided similar data in heterogeneous cohorts worldwide that switched therapy from BHI 30 to BIAsp 30 [7,8].

A recent evaluation of diabetes management in Philippines indicated that diabetes care is restricted to specialized centers with loopholes in the referral systems and diagnostic tools. Patient adherence to treatment was also affected due to lack of drug availability as well as patient education [17]. Also, public health insurance schemes and decentralized health systems did not encourage access to diabetes care [4]. Furthermore, due to a scarcity in regional study data, the clinical practice guidelines are based on North American standards that do not reflect the local standards [18]. The multinational A_1chieve study [6] was conducted primarily to throw light on local diabetes management and address the clinical benefits of insulin analogues in routine clinical practice. The overall study results are available online under www.A1chieve.com. In this sub-analysis, the clinical safety and effectiveness of BIAsp 30 was evaluated in a Filipino cohort of the A_1chieve study that switched treatment from BHI 30.

2. Methods

2.1. Study design

A_1chieve [6] was a 24-week, international, prospective, multicentre, non-interventional study to evaluate the safety and effectiveness of BIAsp 30 (NovoMix 30®, Novo Nordisk), insulin detemir (Levemir®, Novo Nordisk) and insulin aspart (NovoRapid®, Novo Nordisk), alone or in combination with oral glucose-lowering drugs (OGLDs) in T2D patients from developing countries. This sub-analysis was conducted to evaluate the clinical benefits of BIAsp 30 in T2D patients from Philippines who were previously on BHI 30 therapy. Patients were recruited between January 2010 and December 2010 at 255 sites across the Philippines. The switch from BHI 30 to BIAsp 30 and subsequent changes in dose or frequency of administration was mutually agreed upon by the patients and their respective consulting physicians. Due to the observational study design, there were no defined study procedures. All assessments were made by the physicians as a part of routine clinical care. The study drug was commercially available and administered in accordance with local regulations.

2.2. Patients

All T2D patients recruited from Philippines that switched therapy from BHI 30 to BIAsp 30 were included in the sub-analysis. The concurrent use of OGLDs was permitted in all patients during the course of the study at the discretion of the physician. Patients who were administered any of the study insulin analogues up to 4 weeks prior to enrollment were excluded. Pregnant women and women who were breast-feeding or had the intention of becoming pregnant were not eligible for study participation. All patients signed informed consent to participate in the study and this study was approved by the local ethics committee of Philippines.

2.3. Outcome measures and assessments

The primary safety outcome was the incidence of serious adverse drug reactions (SADRs), including major hypoglycaemia related to BIAsp 30, from baseline to final visit. Secondary safety assessments included changes in number of hypoglycaemic events in the last 4 weeks prior to baseline and final visit, changes in nocturnal hypoglycaemia during this period and the number of adverse drug reactions and serious adverse events (SAEs). The effectiveness outcomes included the change from baseline to final visit in HbA_{1c}, FPG, PPPG, body weight, lipid profile and systolic blood pressure (SBP). Health-related quality of life (QoL) was evaluated using the EQ-5D questionnaire that assesses mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Subsequently, the current QoL was measured using a standard 20 cm visual analogue scale (VAS, 0–100). All laboratory parameters were subject to local standardization and were National Glycohemoglobin Standardization Program-certified.

2.4. Statistical analyses

Continuous and discrete variables were summarized using descriptive statistics and frequency tables (n [%]), respectively. Due to the small sample size, all comparisons are presented descriptively. All data were analyzed by Novo Nordisk using SAS Version 9.1.3.

3. Results

3.1. Patient characteristics

A total of 111 T2D patients in Philippines switched from BHI 30 to BIAsp 30 therapy. The demographic and baseline characteristics of this cohort are reported in Table 1. The average T2D duration in this cohort was 9.9±7.1 years and the duration on prior insulin therapy was 2.7±3.5 years. In 93.7% patients, the physicians decided to switch to BIAsp 30 in order to improve glycaemic control. Other common reasons for initiating BIAsp 30 were to reduce the risk of hypoglycaemia in 42.3% patients and to reduce plasma glucose variability in 39.6% patients.

Table 1 – Baseline demographics and characteristics

Parameters	Entire cohort (n = 111)
Gender (male/female), %	43.2/56.8
Age, years	57.4 (12.8)
Body weight, kg	65.4 (13.9)
BMI, kg/m^2	25.8 (5.6)
Diabetes duration, years	9.9 (7.1)
Duration on prior insulin therapy, years	2.7 (3.5)
HbA_{1c}, %	9.4 (2.4)
HbA_{1c}, mmol/mol	79 (26)
Prior OGLDs, n (%)	
Metformin	72 (91.1)
Sulfonylureas	23 (29.1)
Thiazolidinediones	13 (16.5)
1 OGLD	47 (59.5)
2 OGLDs	26 (32.9)
>2 OGLDs	6 (7.6)

BMI, body mass index; HbA_{1c}, glycated haemoglobin A_{1c}; OGLD(s), oral glucose-lowering drug(s).
Data are mean (SD) unless specified otherwise.

3.2. Insulin dose

The insulin dose and frequency of administration are reported in Table 2. The pre-study BHI 30 dose was 0.65±0.28 IU/kg and the baseline BIAsp 30 dose was 0.65±0.26 U/kg titrated up to 0.70±0.26 U/kg at Week 24. The majority of patients received insulin twice-daily (*bid*) pre-study (92.8% patients), at baseline (88.3% patients) and at Week 24 (88.0% patients).

3.3. SADRs and SAEs

No SADRs or SAEs were reported throughout the study duration in patients that switched to BIAsp 30 therapy.

3.4. Hypoglycaemia

Overall hypoglycaemia decreased from 5.62 to 1.98 events/patient-year with a corresponding decrease from 14.4% to 8.7% in the proportion of patients affected. No major hypoglycaemia was reported at Week 24. From baseline to Week 24, minor hypoglycaemia decreased from 4.33 to 1.98 events/patient-year and nocturnal hypoglycaemia decreased from 2.23 to 0.85 events/patient-year (Table 3).

Table 2 – Insulin dose and frequency

Parameter		Entire cohort
Insulin dose per day	n = 111	
	Pre-study, IU/day[a]	41.4 (17.2)
	Baseline, U/day	41.8 (17.1)
	Week 24, U/day	43.7 (18.1)
Insulin dose by body weight	n = 106	
	Pre-study, IU/kg[a]	0.65 (0.28)
	Baseline, U/kg	0.65 (0.26)
	Week 24, U/kg	0.70 (0.26)
Dose frequency, n (%)	Pre-study	n = 111
	Once daily	6 (5.4)
	Twice daily	103 (92.8)
	Thrice daily	2 (1.8)
	Baseline	n = 111
	Once daily	6 (5.4)
	Twice daily	98 (88.3)
	Thrice daily	7 (6.3)
	Week 24	n = 92
	Once daily	5 (5.4)
	Twice daily	81 (88.0)
	Thrice daily	5 (5.4)
	>Thrice daily	1 (1.1)

Data are presented as mean (SD) unless specified otherwise.
[a] The unit of measurement for biphasic human insulin 30 pre-study was IU/day or IU/kg.

Table 3 – Baseline and 24-week data for hypoglycaemia

Hypoglycaemia	Events per patient-year / Percent with at least one event	
Overall	Baseline	5.62 / 14.4
	Week 24	1.98 / 8.7
Minor	Baseline	4.33 / 14.4
	Week 24	1.98 / 8.7
Nocturnal	Baseline	2.23 / 9.0
	Week 24	0.85 / 4.3
Major	Baseline	1.29 / 3.6
	Week 24	0.0 / 0.0

3.5. Glucose lowering, body weight and SBP

BIAsp 30 therapy improved HbA_{1c} (–2.2±2.1%, 24±23 mmol/mol), FPG (–72.0±71.8 mg/dL) and PPPG (–145.5±125.4 mg/dL) over 24 weeks (Table 4). Also, the number of patients with HbA_{1c} <7.0% (<53 mmol/mol) increased from 6 (7.0%) at baseline to 24 (43.6%) at Week 24.

Total cholesterol and triglycerides decreased while HDL levels increased and LDL levels remained unchanged (Table 5). The mean body weight increased from 63.4±12.8 kg at baseline to 63.8±13.5 kg at Week 24. The average SBP decreased by 1.7±20.3 mmHg from baseline (126.7±21.1 mmHg) to Week 24 (124.9±18.4 mmHg) (Table 5).

Table 4 – Baseline and 24-week data for glucose control parameters

Parameter		All patients
HbA_{1c}, %	n	52
	Baseline	9.4 (2.4)
	Week 24	7.1 (1.0)
	Change	−2.2 (2.1)
HbA_{1c}, mmol/mol	n	52
	Baseline	79 (26)
	Week 24	54 (11)
	Change	−24 (23)
FPG, mg/dL	n	68
	Baseline	188.5 (68.8)
	Week 24	116.5 (26.8)
	Change	−72.0 (71.8)
PPPG, mg/dL	n	11
	Baseline	283.8 (119.9)
	Week 24	138.3 (24.4)
	Change	−145.5 (125.4)

FPG, fasting plasma glucose; HbA_{1c}, glycated haemoglobin; PPPG, postprandial plasma glucose.

Table 5 – Lipid profile, systolic blood pressure and body weight

Parameter		Mean (SD)
Total cholesterol, mmol/L	n	20
	Baseline	5.3 (2.5)
	Week 24	4.7 (0.9)
	Change	−0.7 (2.3)
HDL cholesterol, mmol/L	n	9
	Baseline	1.1 (0.4)
	Week 24	1.4 (0.3)
	Change	0.3 (0.4)
LDL cholesterol, mmol/L	n	10
	Baseline	2.9 (1.8)
	Week 24	2.9 (0.8)
	Change	0.0 (1.4)
Triglycerides, mmol/L	n	16
	Baseline	1.7 (0.9)
	Week 24	1.4 (0.5)
	Change	−0.3 (0.9)
SBP, mmHg	n	79
	Baseline	126.7 (21.1)
	Week 24	124.9 (18.4)
	Change	−1.7 (20.3)
Body weight, kg	n	79
	Baseline	63.4 (12.8)
	Week 24	63.8 (13.5)
	Change	0.4 (5.7)

HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure.

3.6. Quality of life

The EQ-5D VAS scores improved from 68.1±18.3 points at baseline to 83.4±11.0 points at Week 24 (mean change = 15.3±16.9 points) for the entire cohort.

4. Discussion

This sub-analysis demonstrated the clinical safety and effectiveness of BIAsp 30 in Filipino patients that switched from BHI 30 therapy. As observed in the A_1chieve data [6] from other less well-resourced countries worldwide, Filipinos with T2D also presented with poor glycaemic control at baseline. The average baseline HbA_{1c} level was 9.4% (79 mmol/mol) and only 6 patients had HbA_{1c} <7.0% (<53 mmol/mol). Despite the evident need for therapy intensification, there was a significant delay in insulin initiation. The average diabetes duration in the cohort was 9.9 years but patients had received insulin for a mean duration of 2.7 years. This data suggests an urgent need to revisit clinical practice guidelines and seek measures for active implementation.

BIAsp 30 therapy could be a useful tool to achieve adequate glycaemic control as shown in this Filipino cohort that switched from BHI 30. The improvements in the glucose control parameters, HbA_{1c}, FPG and PPPG, were associated with a low incidence of hypoglycaemia and modest weight gain. Overall hypoglycaemia decreased from 5.62 to 1.98 events/patient-year from baseline to Week 24, while nocturnal hypoglycaemia decreased from 2.23 to 0.85 events/patient-year. At Week 24, no major hypoglycaemia was reported as opposed to the incidence of 1.29 events/patient-year at baseline. These notable improvements with BIAsp 30 in patients who previously received BHI 30 were also evidenced in the overall A_1chieve data as well as the PRESENT and IMPROVE studies [7,8,19]. Also, a meta-analysis of clinical trials comparing BIAsp 30 to BHI 30 validated that the former therapy is associated with a decreased risk of nocturnal hypoglycaemia [20]. A cross-over study employing continuous glucose monitoring to examine the frequency of low interstitial glucose levels demonstrated an increased incidence of low nocturnal glucose resulting in higher rates of hypoglycaemia with BHI 30 as compared to BIAsp 30 [21]. No SAEs or SADRs were reported during the study, thus reinforcing the safety of switching therapy to BIAsp 30. Additionally, the effectiveness of BIAsp 30 was visible with a small dose increase from 0.65 U/kg at baseline to 0.70 U/kg at Week 24. It has been noted that improved T2D control often acts as a stimulus to lifestyle changes and can benefit longevity. BIAsp 30 therapy positively impacted the QoL which could augment compliance and amend self-care behaviors amongst people affected with T2D.

The A_1chieve study results could be subject to limitations arising from the observational study design. These include the lack of a control arm, retrospective data collection and non-standardization of reported data. Additionally, parameters such as hypoglycaemia depended solely on the patients' ability to recall the event. This potential for recall bias may have led to an underestimation of the real incidence of hypoglycaemia. Nevertheless, the study provides an opportunity to access treatment in a heterogeneous real-life local setting. Also, observational studies are proven tools to identify safety concerns in a larger population that are often masked in a controlled trial due to the limited scope and selected population [22]. In

conclusion, the results of this sub-analysis were reflective of T2D management in routine clinical care in the Philippines. Switching from BHI 30 to BIAsp 30 resulted in improved glycaemic control with a reduction in the occurrence of hypoglycaemia and improved QoL. The clinical benefits of BIAsp 30 in this population indicate its therapeutic potential in T2D management without associated concerns of safety and tolerability.

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Conflict of interest statement

Dr. Anand B. Jain is employed by Novo Nordisk Pharma Malaysia. Mary Anne Lim-Abrahan received honorarium for conduct of research from Novo Nordisk, and has served as a consultant (Advisory Board) for sanofi aventis, Merck, and Novo Nordisk. No other author has any conflict of interest to report. This study was sponsored by Novo Nordisk A/S, Denmark. The sponsor took part in the development of the protocol, the process of data collection and analysis, funding of medical writing services, and in reviewing the manuscript, but not in participant selection, choice of therapies (study or otherwise), provision of therapies including insulin or continuing clinical management of the participants.

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