Original Article

Clinical experience of switching from biphasic human insulin to biphasic insulin aspart 30 in Indian patients with type 2 diabetes in the A_1chieve study

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ABSTRACT

Aim: The aim of the following study is to evaluate the safety and effectiveness of switching from biphasic human insulin (BHI) to biphasic insulin aspart 30 (BIAsp 30) in Indian patients with type 2 diabetes as a sub-analysis of the 24-week, non-interventional A_1chieve study. **Materials and Methods:** Indian patients switching from BHI to BIAsp 30 based on the physicians' decisions were included. The primary outcome was the incidence of serious adverse drug reactions (SADRs), including major hypoglycemic events; secondary outcomes included changes in hypoglycemia in the 4 weeks preceding baseline and week 24 and changes from baseline to week 24 in glycated hemoglobin A_{1c} (HbA_{1c}), fasting plasma glucose (FPG), postprandial plasma glucose (PPPG), body weight and quality of life (QoL). **Results:** Overall, 1976 patients (mean ± standard deviation age, 55.1 ± 10.6 years and diabetes duration, 10.1 ± 5.3 years) on a mean pre-study BHI dose of 0.44 ± 0.18 U/kg were included. The mean BIAsp 30 dose was 0.43 ± 0.17 U/kg at baseline and 0.44 ± 0.17 U/kg at week 24. No SADRs were reported. The proportion of patients reporting overall hypoglycemic events reduced significantly from baseline to week 24 (15.0% vs. 2.9%, $P < 0.0001$). The mean HbA_{1c} level improved significantly from 9.1 ± 1.4% at baseline to 7.5 ± 1.0% at week 24, along with improvements in FPG, post-breakfast PPPG and QoL ($P < 0.001$). The mean body weight decreased from 69.3 ± 10.8 kg at baseline to 69.1 ± 10.4 kg at week 24 ($P = 0.003$). **Conclusion:** Switching from BHI to BIAsp 30 therapy was well-tolerated and was associated with improved glycemic control.

Key words: Biphasic human insulin, biphasic insulin aspart 30, India, type 2 diabetes

Introduction

Type 2 diabetes (T2D) is a major health predicament in the Indian subcontinent. According to the International Diabetes Federation, India had approximately 61.3 million adults with diabetes in 2011 and is predicted to have 101.2 million diabetes patients by 2030.[1] This estimate implies that around 2 million new cases of diabetes would be diagnosed every year in India.[1] A difference in T2D prevalence has also been noted between the urban and rural populations in India (11.6% and 2.4%, respectively).[2]

Alleviating the T2D burden is of paramount importance as diabetes causes many severe long-term complications including kidney failure, cardiovascular disease and retinal complications. It is imperative to effectively intensify treatment strategies for T2D in the primary care setting;[3] however, patient compliance to intensified therapy, including insulin, is often compromised due to fears of hypoglycemia, weight gain and the perceived inability to lead a normal life.

Biphasic insulin formulations combine rapid-acting insulin with a longer-acting protaminated variant, thereby

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providing both mealtime and post-meal control of blood glucose levels.[4] Such preparations also have the benefit of requiring fewer injections compared with a traditional basal-bolus insulin regimen and therefore offer more convenient and simpler options for dosing.

Biphasic insulin aspart 30 (BIAsp 30) is an insulin analogue preparation consisting of insulin aspart and protaminated insulin aspart in a 30:70 ratio.[4] Studies have reported that BIAsp 30, in comparison to biphasic human insulin (BHI), lowers glycated hemoglobin A_{1c} (HbA_{1c}) to a similar or greater extent and is associated with better control of postprandial plasma glucose (PPPG) levels.[5-7] Lowering PPPG levels is known to have important effects on improving general cardiovascular health and minimizing vascular risks.[8] Improved patient outcomes in the long-term could therefore well be contingent upon an insulin regimen that can deliver effective PPPG control. The risks of major hypoglycemia (hypoglycemic events associated with a blood glucose level of <56 mg/dL that the patient is unable to self-treat) and nocturnal hypoglycemia are also reported to be lower with BIAsp 30 than with BHI.[9]

In the multinational A_1chieve study, the use of insulin analogues to treat T2D patients was examined across 28 countries.[10] Results from the overall A_1chieve cohort that switched from BHI therapy to BIAsp 30 have been published previously,[11] as have the results from the entire Indian cohort initiating or switching to BIAsp 30.[12] This sub-analysis of the Indian cohort aimed to determine whether patients with poorly controlled T2D on BHI could be benefitted by changing therapy to BIAsp 30.

Materials and Methods

Study design

A_1chieve was a 24-week, prospective, open-label, non-interventional study conducted across four continents to examine the safety and effectiveness of BIAsp 30 (NovoMix® 30, Novo Nordisk A/S), insulin detemir (Levemir®, Novo Nordisk A/S) and insulin aspart (NovoRapid®, Novo Nordisk A/S), alone or in combination with basal insulin, in clinical practice.[10] This subgroup analysis was performed in Indian patients with T2D who changed therapy to BIAsp 30 from BHI.

Patients were recruited from 621 centers in India between May 2009 and December 2010. The decision to switch from BHI to BIAsp 30 therapy was made by the consulting physicians who also decided the dose and dosing frequency throughout the study. BIAsp 30 was available locally and was used in accordance with the locally approved label. Concomitant oral glucose-lowering drugs (OGLDs) were also permitted at the discretion of the physician.

Data were recorded in the standard case report forms from the physicians' notes and the patients' diaries and blood glucose meters.

Selection criteria

Patients who had changed therapy from BHI to BIAsp 30 within 4 weeks prior to starting the study were included in this subgroup analysis.

Any patient with known allergies or hypersensitivity to the study drug or any of the excipients was excluded. Pregnant or lactating women and those who planned to become pregnant within 6 months of starting the study were also excluded. The study was approved by the Local Ethics Committee in India and all patients provided informed consent for study participation.

Study assessments and endpoints

There were no special investigative procedures in this study; all assessments were carried out by the consulting physicians at routine visits (baseline, week 12 and week 24) to the local clinics.

The primary endpoint was the occurrence of serious adverse drug reactions (SADRs), including major hypoglycemia, over 24 weeks. Secondary safety endpoints included the occurrence of serious adverse events (SAEs) over 24 weeks and the change in the frequency of hypoglycemic events in the 4 weeks preceding baseline and week 24.

Efficacy endpoints comprised the change from baseline to week 24 in HbA_{1c}, fasting plasma glucose (FPG), PPPG, total cholesterol, triglycerides, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, systolic blood pressure (SBP) and body weight. Laboratory parameters were subject to local standardization and quality control.

In addition, quality of life (QoL) was assessed using the EuroQoL-5 dimension (EQ-5D) questionnaire and the EuroQoL visual analog scale (EQ-VAS). The EQ-5D questionnaire covers five health dimensions (anxiety/depression, mobility, pain/discomfort, self-care and usual activity), whereas the EQ-VAS rates a patient's current health state from 0 (worst score) to 100 (best score).

Statistical analysis

Statistical analyzes were performed for the subgroup of Indian patients switching from pre-study BHI therapy to BIAsp 30. Continuous variables were summarized using descriptive statistics (mean, median, standard deviation [SD]) and discrete variables were summarized using frequency tables (*n*, %).

The change from baseline to week 24 in HbA_{1c}, FPG, PPPG, lipids, body weight, SBP and QoL was analyzed using a paired *t*-test. The difference from baseline to week 24 in the proportion of patients reporting at least one hypoglycemic event was analyzed using McNemar's test. Two-sided tests were used and statistical significance was pre-defined at the 5% level.

All analyzes were performed by Novo Nordisk using SAS® Version 9.1.3.

Results

General characteristics

A total of 1976 patients switched therapy from pre-study BHI to BIAsp 30 in the Indian cohort [Table 1]. These patients had a mean ± SD age of 55.1 ± 10.6 years, body mass index of 25.9 ± 3.7 kg/m^2 and had T2D for 10.1 ± 5.3 years. The average duration on insulin was 3.0 ± 2.6 years for these patients.

The most frequently reported physicians' reasons for changing therapy were to improve glycemic control (95.5% of patients) and to reduce the risk of hypoglycemia (40.3% of patients).

At baseline, 83.8% of patients were taking metformin and 59.1% were taking sulfonylureas concomitantly with BIAsp 30 therapy [Table 1].

Daily insulin dose and frequency of dosing

The mean total BHI dose by weight was 0.44 ± 0.18 U/kg at pre-study [Table 2]. Patients started on a mean total BIAsp 30 dose of 0.43 ± 0.17 U/kg at baseline and had a mean dose of 0.44 ± 0.17 U/kg by the end of the study. The mean total daily insulin doses at pre-study, baseline and week 24 are presented in Table 2.

At pre-study, 83.3% of patients were taking BHI twice daily (bid). At baseline and week 24, 87.4% and 90.3% of patients, respectively, dosed BIAsp 30 bid.

SADRs and SAEs

No SADRs were reported in this subgroup during the study.

Four SAEs were reported (abdominal pain, vomiting, diarrhea and angioplasty), all considered unlikely to be related to BIAsp 30 therapy.

Hypoglycemia

The incidence of overall hypoglycemia was 4.15 events per patient-year at baseline and 0.56 events per patient-year at week 24 [Table 3]. The proportion of patients reporting at least one event of overall hypoglycemia significantly decreased from baseline to week 24 (15.0% vs. 2.9%, $P < 0.0001$).

Table 1: Demographic and baseline characteristics of patients switching from BHI to BIAsp 30

	All patients
N	1976
Male, %	66.9
Female, %	33.1
Age*, years	55.1 (10.6)
Body weight*, kg	69.8 (11.1)
Body mass index*, kg/m^2	25.9 (3.7)
Duration of diabetes*, years	10.1 (5.3)
Duration on insulin*, years	3.0 (2.6)
OGLDs at baseline, *n* (%)	
Metformin	1146 (83.8)
Sulfonylureas	808 (59.1)
Thiazolidinediones	164 (12.0)
One OGLD	560 (41.0)
Two OGLDs	606 (44.3)
>Two OGLDs	201 (14.7)

*Data are mean (SD). BHI: Biphasic human insulin, BIAsp 30: Biphasic insulin aspart 30, OGLDs: Oral glucose-lowering drugs, SD: Standard deviation

Table 2: Insulin dose and dosing frequency at pre-study, baseline and week 24

	All patients
Insulin dose, U/kg	
n	1898
Pre-study*	0.44 (0.18)
Baseline*	0.43 (0.17)
Week 24*	0.44 (0.17)
Insulin dose, U/day	
n	1976
Pre-study*	30.0 (11.8)
Baseline*	29.5 (10.9)
Week 24*	29.6 (11.1)
Daily dose frequency	
Pre-study, *n*	1976
Once, *n* (%)	168 (8.5)
Twice, *n* (%)	1646 (83.3)
Thrice, *n* (%)	162 (8.2)
>Thrice, *n* (%)	-
Baseline, *n*	1976
Once, *n* (%)	169 (8.6)
Twice, *n* (%)	1727 (87.4)
Thrice, *n* (%)	79 (4.0)
>Thrice, *n* (%)	1 (0.1)
Week 24, *n*	1556
Once, *n* (%)	127 (8.2)
Twice, *n* (%)	1405 (90.3)
Thrice, *n* (%)	22 (1.4)
>Thrice, *n* (%)	2 (0.1)

*Pre-study, baseline and week 24 values are mean (SD). SD: Standard deviation

Table 3: Baseline and week 24 data for hypoglycemia

Hypoglycemia (event per patient-year/percent with at least one event)	Baseline	Week 24	*P* value
Overall	4.15/15.0	0.56/2.9	<0.0001
Major	0.49/3.2	0.0/0.0	<0.0001
Minor	3.66/14.3	0.56/2.9	<0.0001
Nocturnal	1.21/7.0	0.12/0.6	<0.0001

P value is from McNemar's test on paired proportions of patients experiencing at least one event

No major hypoglycemic events were reported at week 24 compared with incidence of 0.49 events per patient-year at decreased from baseline to week 24 (15.0% vs. 2.9%, P < 0.0001).

No major hypoglycemic events were reported at week 24 compared with incidence of 0.49 events per patient-year at baseline [Table 3]. The difference from baseline to week 24 in the proportion of patients reporting at least one event of major hypoglycemia was significant ($P < 0.0001$).

Significant decreases from baseline to week 24 were also noted in the proportions of patients reporting at least one event of minor hypoglycemia (14.3-2.9%) and nocturnal hypoglycemia [7.0-0.6%, both $P < 0.0001$, Table 3].

Glycemic parameters

From baseline to week 24, the mean HbA_{1c} level reduced significantly from 9.1 ± 1.4% to 7.5 ± 1.0% [$P < 0.001$, Table 4]. At week 24, 394 patients had HbA_{1c} levels of <7.0% compared with 52 patients at baseline.

The mean FPG level significantly reduced from 186.3 ± 54.4 mg/dL at baseline to 127.5 ± 36.9 mg/dL at week 24 and the mean post-breakfast PPPG significantly reduced from 274.0 ± 74.2 mg/dL to 200.7 ± 60.0 mg/dL during the same time [both $P < 0.001$, Table 4].

Lipids

Significant reductions were observed in the mean total cholesterol, triglyceride and LDL cholesterol levels over 24 weeks [all $P < 0.001$, Table 5]. There was no statistically significant change in the mean HDL cholesterol level from baseline to week 24.

Table 4: Baseline and 24-weeks data for glucose control parameters

	n	Baseline	Week 24	Change	*P* value
HbA_{1c}, %	1434	9.1 (1.4)	7.5 (1.0)	−1.6 (1.3)	<0.001
FPG, mg/dL	1352	186.3 (54.4)	127.5 (36.9)	−58.8 (54.2)	<0.001
PPPG, mg/dL	844	274.0 (74.2)	200.7 (60.0)	−73.3 (73.7)	<0.001

Baseline, week 24 and change values are mean (SD). FPG: Fasting plasma glucose, HbA_{1c}: Glycated hemoglobin A_{1c}, PPPG: Postprandial plasma glucose, SD: Standard deviation

Body weight and SBP

The mean body weight was 69.3 ± 10.8 kg at baseline and 69.1 ± 10.4 kg at week 24 [$P = 0.003$, Table 5].

The mean SBP also reduced significantly from 135.6 ± 16.0 kg at baseline to 128.4 ± 11.8 kg at week 24 [$P < 0.001$, Table 5].

QoL

Patient-reported QoL increased significantly from 55.0 ± 9.8 points at baseline to 72.8 ± 9.3 points at week 24 as measured by the EQ-VAS ($P < 0.001$).

From baseline to week 24, the proportion of patients reporting no problems in the five dimensions of the EQ-5D questionnaire also appeared to increase (anxiety/depression: 43.3% vs. 81.5%; mobility: 41.2% to 86.9%; pain/discomfort: 36.2% vs. 76.2%; self-care: 40.2% vs. 68.4%; usual activity: 36.1% to 73.5%).

Discussion

This subgroup analysis demonstrated that switching from pre-study BHI to BIAsp 30 therapy was well-tolerated and resulted in improvements in glycemic parameters for T2D patients in local clinical practice in India. No SADRs were reported in this subgroup. Furthermore, there was a significant decline from baseline to week 24 in the proportion of patients reporting at least one event of overall hypoglycemia.

Poor glycemic control was apparent in this subgroup at baseline. Patients had been taking insulin for an average of 3 years, with or without OGLDs; however, the mean baseline HbA_{1c} level was 9.1%, well above the international clinical recommendation of <7.0%.[13] Following the therapy switch from BHI to BIAsp 30, the mean HbA_{1c} improved significantly, along with significant reductions in the mean FPG and post-breakfast PPPG levels and a low incidence of overall hypoglycemia at week 24 (0.56 events/patient-year). El Naggar *et al.*[11] have also reported improved glycemic control and low incidences of hypoglycemia in the overall A_1chieve cohort that switched to BIAsp 30 therapy from BHI. Sub-analyzes from the improve and present

Table 5: Baseline and 24-week data for lipids, body weight and SBP

	n	Baseline	Week 24	Change	*P* value
Total cholesterol, mmol/L	230	5.2 (0.8)	4.8 (0.7)	−0.4 (0.5)	<0.001
Triglycerides, mmol/L	427	2.0 (0.8)	1.8 (0.6)	−0.2 (0.5)	<0.001
HDL cholesterol, mmol/L	437	1.0 (0.2)	1.0 (0.3)	−0.0 (0.2)	0.125
LDL cholesterol, mmol/L	430	2.9 (0.9)	2.7 (0.7)	−0.3 (0.7)	<0.001
Body weight, kg	1409	69.3 (10.8)	69.1 (10.4)	−0.2 (2.2)	0.003
SBP, mmHg	1092	135.6 (16.0)	128.4 (11.8)	−7.2 (13.2)	<0.001

Baseline, week 24 and change values are mean (SD). *P* values are not presented when the number of patients analyzed was <100. HDL: High-density lipoprotein, LDL: Low-density lipoprotein, SBP: Systolic blood pressure, SD: Standard deviation

observational studies also demonstrated that switching to BIAsp 30 therapy from BHI was associated with significantly ameliorated glycemic control as well as a reduced risk of hypoglycemia in T2D patients.[14,15] Significant improvements in mean HbA_{1c} were also noted in patients who switched from BHI 30 or 50 to BIAsp 30, 50 or 70 in routine clinical practice in another 26 weeks observational study.[16]

The improvements in glycemic parameters were obtained without a substantial increase in the mean BIAsp 30 dose levels from baseline to week 24. A retrospective study in the United Kingdom found that effective reductions in HbA_{1c} could be obtained with lower doses of BIAsp 30 compared with BHI 30 in patients with T2D.[17] These results could potentially have important implications for developing countries such as India where medication costs would also be a key factor in the choice of treatment. The majority of patients followed bid dosing of BIAsp 30 and 394 patients achieved the HbA_{1c} target at the end of the study. Further, BIAsp 30 tid dosing can also be effective for patients who are unable to attain glycemic targets with bid dosing, as demonstrated in the 1-2-3 study.[18]

Significantly lower total cholesterol, triglyceride and LDL cholesterol levels were noted at week 24 compared with baseline, along with significant improvements in SBP levels in this subgroup. A retrospective review of data from patients with T2D previously treated with BHI noted that lipid levels and blood pressure (systolic and diastolic) improved over 6 months after switching to BIAsp 30 therapy.[19] Ohira *et al*.[20] have reported improvements in arterial stiffness, which is known to be associated with coronary atherosclerosis, in a group of 26 T2D patients 3 months after switching from BHI 30 to BIAsp 30. High PPPG levels are known to be correlated with increased cardiovascular dysfunction; hence, it is feasible that the improvements in PPPG obtained with BIAsp 30 therapy could also positively impact cardiovascular outcomes.

There was a small reduction in mean body weight from 69.3 ± 10.8 kg at baseline to 69.1 ± 10.4 kg at week 24 in this subgroup ($P = 0.003$) in contrast to findings from a 12-month comparative study, which indicated that BIAsp 30 and BHI therapy displayed similar effects on weight increase.[21] It is possible that enrolment in the A_1chieve study may have prompted patients to embrace positive life-style changes, which in turn could have led to the lower mean body weight seen at week 24 in the Indian subgroup.

Hypoglycemia and the other co-morbidities associated with T2D are known to deteriorate QoL.[22,23] In this sub-analysis, significant improvements in QoL after 24 weeks were noted based on the EQ-VAS ratings. Furthermore, patients appeared to have fewer problems with anxiety/depression, mobility, pain/discomfort, self-care and usual activity at week 24 compared with baseline as measured by the EQ-5D questionnaire.

The absence of a control group could potentially have introduced bias in this study. It is possible that the findings could be attributed to a study effect as most of the safety and effectiveness parameters were based on patient recall, diaries or self-reported information. Data for hypoglycemia were recorded based on the patient's recall of the hypoglycemic events that occurred in the 4 weeks prior to the study visits. Furthermore, no information was collected on the patients' diet and concomitant medication during the study. However, despite these limitations, glycemic control improved in this subgroup following the switch to BIAsp 30 therapy from pre-study BHI. Importantly, BIAsp 30 therapy was not associated with any SADRs during the study.

Conclusion

The results from this sub-analysis suggest that patients poorly controlled on BHI could be benefitted by switching to a BIAsp 30 regimen with or without OGLDs.

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