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Biphasic Insulin Aspart 30 (BIAsp 30) is Safe and Improves Glycaemic Control in Insulin Naïve Patients with Type 2 Diabetes

Alireza Esteghamati[1], Manouchehr Nakhjavani[1], Ashraf Aminorroaya[2], Robabeh Aboutorabi[3], Mitra Niafar[4], Mohammad Mohammadi[5] and Ehsan Parvaresh[6]*

[1]Tehran University of Medical Sciences, Tehran, Iran
[2]Isfahan University of Medical Sciences, Tehran, Iran
[3]Mashad University of Medical Sciences, Tehran, Iran
[4]Tabriz University of Medical Sciences, Tehran, Iran
[5]Yazd University of Medical Sciences, Tehran, Iran
[6]Novo Nordisk Pars, Medical & Clinical Research, Tehran, Iran

Introduction

Type 2 diabetes mellitus (T2DM) is a progressive disease characterized by gradual decline in beta-cell function and insulin resistance [1]. The recommendations for initial treatment of T2DM include lifestyle adjustments and oral anti-diabetic medications [2]. The United Kingdom Prospective Diabetes Study (UKPDS) and other studies have shown that intensive glycaemic control in type 2 diabetes significantly reduces the risk of development and/or deterioration of microvascular complications [1,3]. The incidence and progression of microvascular complications correlate with the glycaemic control and lower glycated haemoglobin (HbA_{1c}) levels are associated with the reduction of cardiovascular risks [3]. Both fasting blood glucose (FBG) and post-prandial blood glucose (PPBG) contributes to the level of HbA1c, and current data suggest that postprandial hyperglycaemia is associated with an increased risk of macrovascular disease [4]. Therefore, it seems reasonable to target postprandial hyperglycaemia in addition to FBG levels to achieve maximum benefits [5,6].

Biphasic insulin aspart 30 (BIAsp 30) (NovoMix®30) is an insulin analogue mixture which contains 30% unbound rapid-acting insulin aspart and 70% intermediate-acting protaminated insulin aspart. This premix formulation aims at postprandial hyperglycaemia and also provides basal insulin coverage [7]. In patients with type 2 diabetes inadequately controlled with OADs, insulin therapy is frequently started by adding basal to existing OADs [8]. BIAsp 30 provides both postprandial plasma glucose and fasting plasma glucose control [9]. In a treat-to-target trial, 41% of subjects with type 2 diabetes achieved the target of HbA1c < 7% on once-daily treatment with BIAsp 30 [10]. In addition, more patients could safely achieve the goals for optimal glycaemic control when the number of daily injections of BIAsp30 increased from one to two, and then if not meeting the HbA_{1c} target, from two to three daily injections [11,12].

In Iran, quality of care of patients with type 2 diabetes is poor. It has been reported that only 6.4% of Iranian patients had HbA_{1c} measurements at least once in a year and majority of them had poor glycaemic control according to their most recent HbA_{1c} levels [13].

The aim of the IMPROVE™ study was to evaluate the clinical safety profile and efficacy while using BIAsp 30 (NovoMix®30) under normal clinical practice conditions. Data from a subgroup of insulin naïve patients with type 2 diabetes in Iran are reported. Beneficial information on safety, efficacy and pattern of use of a drug in an extensive patient population can be gained from this observational study.

Patients and Methods

Study design

IMPROVE™ was a 26-week, open-label, non-randomized, multi-centre observational study of patients with type 2 diabetes conducted in 11 countries (Canada, China, Greece, Persian Gulf region countries, India, Iran, Italy, Japan, Poland, Russia and South Korea) [14,15]. BIAsp 30 (100 IU/ml) was prescribed by the physician in routine clinical evaluations. The starting dose and frequency of injection, as well as subsequent dose adjustments were individualised and were at the discretion of the physician. No study-specific investigations were performed except the collection of data at baseline, follow-up visit (approximately 13 weeks after enrolment), and final visit (approximately 26 weeks after enrolment). Study procedures complied with local regulations and practice governing observational studies. Health authority approval and ethics committee approval were achieved. This is a subgroup analysis from the IMPROVE study. Results from the insulin naïve Iranian patients with T2DM are reported in this paper.

Patients

Written informed consent was obtained for all patients before any trial-related activity. The study was performed in accordance with the Declaration of Helsinki [16] and International Conference on Harmonisation Good Clinical Practice [17]. Patients recruited in the IMPROVE study were 18 years and older treated with BIAsp 30 in routine clinical practice. Patients were excluded if they had known or suspected allergy to BIAsp 30. Females who were pregnant, breast-feeding or intending to become pregnant were also excluded. This subgroup included insulin naive patients with T2DM who were previously treated with oral anti-diabetic medications only in Iran. The majority of these patients (69.2%) were on a combination of Biguanides and Sulphonylureas, while 8.8%, 9.4% of patients were on Biguanides only and Sulphonylureas only, respectively. The dose of insulin was not specifically adjusted for OADs but at the physician's discretion.

Endpoints

The primary endpoint was the incidence of major hypoglycaemic episodes reported as serious adverse drug reactions (SADRs). Major hypoglycaemic episode was defined as an episode with severe central

***Corresponding author:** Ehsan Parvaresh, Medical Manager, Novo Nordisk Pars, Medical & Clinical Research, 11th floor, Kian Tower, No. 2551, Vali-e-Asr Ave., Tehran, Iran (Islamic Republic of), Fax: +982188645230; E-mail: ehpa@novonordisk.com

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nervous system symptoms consistent with hypoglycaemia in which the patient was unable to treat himself/herself and had one of blood glucose <50 mg/dl (2.8 mmol/l) or reversal of symptoms after either food intake or glucagon or intravenous glucose administration.

The secondary endpoints included the number of minor hypoglycaemic episodes, changes in body weight and body mass index (BMI), HbA_{1c}, FBG, the variability in FBG, PPBG after all main meals and treatment satisfaction as assessed by the Diabetes Medication Satisfaction (DiabMedSat) questionnaire (0 to 100-point scale with higher scores indicating higher quality of life) [18]. Minor hypoglycaemic episode was defined as an episode with symptoms of hypoglycaemia with the confirmation of blood glucose measurement <56 mg/dL (3.1 mmol/l) and which was handled by the patient or any asymptomatic blood glucose measurement <56 mg/dL (3.1 mmol/l).

Statistical analyses

In this predefined subgroup, data were collected at baseline (159 patients), follow-up visit (approximately 13 weeks, 154 patients), and final visit (approximately 26 weeks, 149 patients). The summary of the baseline characteristics and safety data were based on Full Analysis Set (FAS), which consisted of all patients with a baseline visit, had been prescribed BIAsp 30 at least once and did not use BIAsp 30 prior to the start of the study. The analysis of the efficacy outcome variables were based on Efficacy Analysis Set (EAS), which was defined as all patients from FAS who had the final visit, at least one measurement concerning FBG, PPBG, most recent HbA_{1c}, weight or hypoglycaemic episodes at baseline and final visit, with the final visit within 18 to 31 weeks from baseline. FBG and PPBG Variability were defined as the standard deviation of the most recent 3 values obtained by the investigator. The analysis of the quality of life (QoL) data was based on Quality of Life Analysis Set (QLAS, 132 patients), which was defined as all patients from FAS who were treated before the study with either OAD or insulin and who had completed at least one item of the DiabMedSat questionnaire at baseline and final visit.

Statistical comparisons of BIAsp 30 outcome measures at baseline and final visit were performed using Wilcoxon signed rank test for discrete variables (hypoglycaemic episodes) and using paired t-test for continuous variables (HbA_{1c}, mean FBG and FBG variability, mean PPBG and PPBG variability). All testing used two-sided tests with significance level $\alpha = 0.05$ and were performed using SAS, Version 9.1 (SAS Institute, Cary, NC).

Descriptive statistics were used to summarise hypoglycaemic episodes expressed as both absolute number of episodes and the number of episodes per patient years. The Wilcoxon signed rank test was used to compare the number of hypoglycaemic episodes at baseline and final visit. Descriptive statistics were used to summarise HbA_{1c}, mean FBG and FBG variability, mean PPBG and PPBG variability. Paired t-test was used to compare HbA_{1c}, mean FBG and FBG variability values at baseline and final visit. The test was performed only if values at both visits were present. Discrete variables were displayed in frequency tables. All testing used two-sided tests with significance level $\alpha = 0.05$ and were performed using SAS, Version 9.1 (SAS Institute, Cary, NC).

Results

Baseline demographics

Of the 478 patients enrolled in Iran, 159 (33.3%) were previously treated with oral anti-diabetic medications only and 151 of them completed the study. A total of 8 (5.0%) patients discontinued from the study, due to "lost contact" (3.1%) or "other reasons" (1.9%). The demographic characteristics of all patients are summarised in Table 1. The patients had mean age of 54.9±11.1 years, with a slightly lower rate of males to females (48/52 %). Mean BMI was 27.1±4.7 kg/m^2 and mean diabetes duration was 12.6±7.0 years. Microvascular complications (60%) were more commonly reported than macrovascular complications (34%) by the patients. The majority of the patients (73%) were previously treated with two oral anti-diabetic medications, 9% patients with more than two oral anti-diabetic medications, and 18% patients with one oral anti-diabetic medication.

The most common reason for starting a new therapy was to improve FBG (76%) and for an easy start of insulin therapy (76%) (Table 2). The mean daily dose of BIAsp 30 after entering into the study (baseline) was 18.3 IU (0.26 IU/kg) and increased to 48.4 IU (0.60 IU/kg) at final visit. A majority of patients were injected BIAsp 30 twice daily throughout the study period (56.6% at baseline and 67.5% at final visit) (Table 3). Patients were exposed to BIAsp 30 for approximately 27.3 weeks.

Safety

Hypoglycaemic episodes: Major hypoglycaemic episodes

Total number of patients	159
Mean age±SD (years)	54.9±11.1
Gender, M/F (%)	48/52
Mean weight±SD (kg)	73.3±14.9
Mean BMI±SD (kg/m2)	27.1±4.7
Mean diabetes duration±SD (yrs)	12.6±7.0
Mean HbA_{1c}±SD (%)	9.3±2.0
Macrovascular Complications (%)	34
Peripheral vascular disease	1
Coronary heart disease	32
Stroke	2.9
Microvascular Complications (%)	60.4
Retinopathy	29.6
Diabetic nephropathy	23.3
Peripheral neuropathy	31.4
Autonomic neuropathy	5.7

Table 1: Baseline characteristics.

Reason(s) for starting a new therapy, n (%)	**Total**
Easy Start of Insulin Therapy	121 (76.1)
Easy Intensification of Insulin Therapy	22 (13.8)
Improve HbA_{1c}	106 (66.7)
Improve FBG	121 (76.1)
Improve PPG	113 (71.1)
Reduce Risk of Hypoglycaemia	27 (17.0)
Patient Dissatisfaction with Previous Therapy	64 (40.3)
Side Effects from Previous Therapy	12 (7.5)
Change Due To Insulin Pen	29 (18.2)
Allow For Mealtime Administration	50 (31.4)

Percentages are based on the number of patients with non-missing values
A patient may have findings in more than one category in Reason(s) for starting a new therapy

Table 2: Reason (s) for starting a new therapy.

Injection times	**Baseline, n (%)**	**Final visit, n (%)**
1 time per day	67(42.1%)	7(4.6%)
2 times per day	90(56.6%)	102(67.5%)
3 times per day	2(1.3%)	41(27.2%)
4 times per day	0	1(0.7%)

Table 3: Total number of BIAsp 30 injections.

Parameter (SD)		Baseline	Final visit	Absolute change
Mean HbA_{1c}, %Hb		9.26 (1.96)	7.49 (1.26)	-1.77 (1.85)*
Mean FBG, mg/dL		222 (62)	138 (35)	-84 (68)*
Mean PPBG, mg/dL	At breakfast	306 (81)	193 (52)	-114 (86)*
	At lunch	226 (100)	151 (38)	-75 (97)
	At dinner	266 (111)	165 (52)	-101 (109)
Body weight, kg		73.70 (14.90)	76.39 (14.72)	+2.69 (5.21)*
BMI, kg/m^2		27.24 (4.69)	28.30 (4.89)	+1.06 (1.97)*
DiabMedSat	Overall score	59.20 (12.56)	75.56 (11.50)	+16.37 (15.78)*
	Relief of burden	71.26 (14.85)	82.90 (11.85)	+11.64 (17.72)*
	Relief of symptoms	68.10 (15.19)	70.43 (17.85)	+2.33 (20.77)
	Effectiveness	38.47 (18.51)	73.31 (15.98)	+34.84 (24.11)*

FBG: fasting blood glucose
PPG: post prandial glucose
NS: not significant
* p<0.001

Table 4: Change from baseline in efficacy parameters.

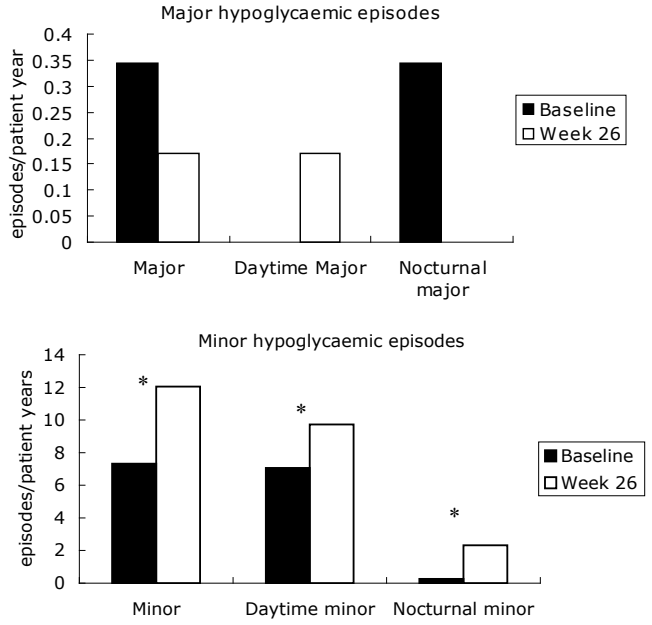

Figure 1: Number of hypoglycaemic episodes (episodes/patient years).

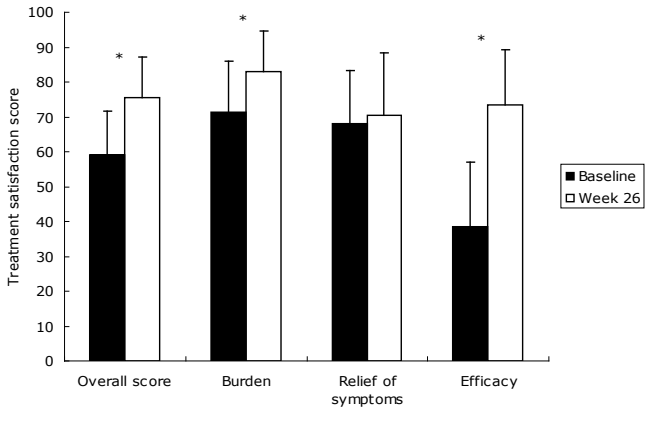

Figure 2: Patient treatment satisfaction among insulin naive patients (Diab-MedSat).

decreased from 0.344 episodes/patient year at baseline to 0.172 episodes/patient year at final visit, though this decrease was not statistically significant ($p > 0.05$). From baseline to end of the study, daytime major events were increased by 0.172 episodes per patient year while nocturnal major events were decreased by 0.344 episodes per patient year. Neither of these changes were statistically significant ($p > 0.05$) Minor hypoglycaemic episodes increased from 7.318 episodes/patient year at baseline to 12.053 episodes/patient year at final visit ($p < 0.05$). Similar trends were observed for daytime minor episodes (7.060 episodes/patient year at baseline to 9.728 episodes/patient year at final visit) as well as nocturnal minor events (0.258 episodes/patient years at baseline to 2.325 episodes/patient year at final visit) ($p < 0.05$ for both cases; Figure 1).

Adverse events: In the total Iranian cohort (N=478), 22 adverse events (AEs) were reported and the diagnosis included angina unstable, cardiac arrest, familial tremor, hypoglycaemia, diabetic amyotrophy, haemarthrosis, optic nerve infarction, etc. Among all those reported AEs, 14 events were categorized as serious adverse events (SAEs). A total of 5 AEs (2 SAEs) were categorized as probable, 4 AEs (3 SAEs) were reported as possible and 13 AEs (9 SAEs) were considered as unlikely to be associated with the study medication by study investigators. In Iranian patients, 9 adverse drug reactions (ADRs) were reported and there were 5 serious adverse drug reactions (SADRs) among them. A total of 5 ADRs (2 SADRs) were categorized as probable to be related to the study drug, 4 ADRs (3 SADRs) were possible to be due to the study medication. In Iranian insulin naive subgroup (N=159), 8 AEs were reported in 8 patients and there were 5 reports of SAEs in 5 patients. Four ADRs were reported in 4 patients and there were 3 reports of SADRs in 3 patients in Iranian insulin naive subgroup. In the current study, two major hypoglycaemic episodes were reported by two patients as SADRs.

Body weight

Compared with baseline, body weight was increased at final visit by 2.69±5.21 kg. Accordingly, BMI was increased at final visit by 1.06±1.97 kg/m^2 (Table 4).

From baseline to final visit, small increases in body weight were observed in different BMI groups (BMI<25 group: 4.0±5.2kg, 25≤BMI<30 group: 2.0±4.4kg, 30≤BMI<35 group: 2.3±6.2kg, in BMI≥35group: 2.5±5.9kg).

Effectiveness

HbA_{1c} was 9.26±1.69% at baseline and 7.49±1.26% at final visit. There was a mean reduction in HbA_{1c} of 1.77±1.85% from baseline to final visit.

FBG was reduced from baseline to final visit by 84±68 mg/dl. Meanwhile, FBG variability was reduced by 16±17 mg/dl.

Breakfast PPBG was reduced from baseline to final visit by 114±86 mg/dl. Meanwhile, lunch PPBG was reduced by 75±97 mg/dl and dinner PPBG was reduced by 101±109 mg/dl.

Patient treatment satisfaction

The Diabetes Medication Satisfaction questionnaire evaluated relief of burden, relief of symptoms and effectiveness before and after treatment with BIAsp 30. The overall treatment satisfaction was increased from baseline to final visit (on a 100-point scale, baseline vs. final visit: 59.2 point score vs. 75.6 point score). All three domains showed an improvement in scores from baseline to final visit, while the largest improvement was observed in the efficacy domain (baseline vs.

final visit: 38.5 point score vs.73.3 point score). A small increase was also observed in the relief of burden (baseline vs. final visit: 71.3 point score vs.82.9 point score) (Figure 2).

Discussion

IMPROVE™ is a 26-week, open-label, non-randomized, multi-centre observational study to evaluate the safety and efficacy of BIAsp 30 in type 2 diabetic patients under the routine clinical practice. The results from the Iranian cohort of insulin naïve patients with type 2 diabetes show that insulin initiation with BIAsp 30 is a safe and effective method of insulin therapy. Glycaemic control and treatment satisfaction was improved without an increased risk of major hypoglycaemic episodes. These results in the Iranian cohort are in concordance with the findings of the global IMPROVE™ study [19-22].

After 26 weeks of treatment with BIAsp 30, there was no increase in risk of major hypoglycaemic episodes in insulin naïve Iranian patients with type 2 diabetes and this is consistent with the global IMPROVE™ study [20]. However, there was an increased risk of minor hypoglycaemic episodes in insulin naïve Iranian patients with type 2 diabetes, which was also consistent with both the Iranian and global cohort of insulin naïve patients [20].

Body weight in Iranian patients previously treated with OADs only was increased by 2.7kg after 26 weeks of treatment, which was slightly higher than the increase of 1.7kg in the overall Iranian cohort [23]. It is consistent with the UKPDS data where insulin treatment is associated with a weight gain [3]. Furthermore, small increases in body weight were observed in all different BMI groups in this study.

In this study, BIAsp 30 improved the glycaemic control in insulin naïve Iranian patients with type 2 diabetes. Mean HbA_{1c} was significantly reduced after 26 weeks of treatment. This result is consistent with that of the overall Iranian cohort and the global cohort [20]. These patients had long diabetes duration, poor glycaemic control, and most were treated with two or more OADs. Furthermore, 60% of patients reported microvascular complications, while 34% of recruited patients reported macrovascular complications in their past medical history. All these findings imply that insulin treatment should have been initiated earlier. The incidence of clinical complications is significantly associated with glycaemic level. In UKPDS study it has been shown that each 1% reduction in mean HbA1c was associated with reduction of 14% in incidence of myocardial infarction, 21% for deaths related to diabetes, 37% for microvascular complications and 43% in peripheral vascular disease [24].

In this trial, the clear benefits with BIAsp 30 regimen were the larger reductions in FBG, FBG variability and PPBG. Therefore, BIAsp 30 not only provides basal insulin coverage but also effectively controls the postprandial component of glycaemic parameters, consistent with the finding in other clinical trials [25].

The overall treatment satisfaction was improved after treatment with BIAsp 30, which is consistent with the finding in the overall Iranian cohort and the global study [20]. The largest improvement was observed in the efficacy domain and this is not unexpected since the most cited reason for starting a new therapy was to improve glycaemic control An improvement in treatment satisfaction may enhance treatment and self-management. A small increase was also observed in the relief of burden. It should be emphasized that BIAsp 30 treatment led to beneficial effect on relief burden of the treatment despite the start of a difficult therapy such as insulin. The patients who were previously insulin naïve started insulin injection once daily or majority twice daily. However, they had increased relief of burden after BIAsp 30 treatment.

The improved glycaemic control in the present observational study is consistent with the fact that most physicians decide to initiate treatment with BIAsp 30 in order to improve FBG and for an easy start of insulin therapy. A study effect could also contribute partially to this improvement. Heterogeneity of real-life populations and the absence of a control group in observational studies may limit the conclusions we can draw from them.

There are also limitations with the current study. The lack of randomization and the lack of other treatment arms added confounding factors to the study. In addition, other parameters regarding lipids metabolism and insulin resistance may be informative; however, we did not investigate into detail.

In summary, initiating BIAsp 30 in insulin naïve Iranian patients with type 2 diabetes was safe and effective. Treatment with BIAsp 30 improved glycaemic control and patient treatment satisfaction without an increased risk of major hypoglycaemia. Furthermore, the results in Iranian patients are consistent with the global IMPROVE™ study cohort.

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