Glycaemic control, safety and treatment satisfaction in Romanian subjects with type 2 diabetes treated with biphasic insulin aspart 30

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Abstract

This 6-month, prospective, open-labelled, uncontrolled, observational study involving 28 centres across Romania evaluated the utility of biphasic insulin aspart 30 (BIAsp30; NovoMix® 30) in routine clinical practice. Subjects with type 2 diabetes inadequately controlled on their previous therapy were enrolled into the study and prescribed with BIAsp30 as monotherapy, or in combination with oral hypoglycaemic agents. Among 912 subjects available for analysis, treatment with BIAsp30 was associated with baseline reductions in HbA_{1c} of 1.78 ± 1.38% and 2.64 ± 1.81% at 3 and 6 months, respectively. Reductions in other glycaemic parameters (FPG and PPPG) from baseline were also observed at 3 and 6 months of BIAsp30 treatment. The proportion of subjects reporting hypoglycaemic episodes was 24.9%, 27.2% and 22.0% at baseline, 3 and 6 months, respectively. Nonetheless, there was a reduction in the rate of major hypoglycaemic episodes between baseline and the end of the study, from 0.688 to 0.091 episodes per patient year. Only one case of an adverse drug reaction (ADR) was suspected during the course of the study, however, under-reporting of ADRs by the participating centres cannot be ruled out. The majority (>90%) of subjects were perceived as being either "very satisfied" or "satisfied" with BIAsp30 over previous treatment, and when the treating physicians were asked to rate how satisfied they were with BIAsp30 over their subject's previous treatment, the majority of responses (>90%) were also either "very satisfied" or "satisfied", at both 3 and 6 months of treatment.

Keywords: biphasic insulin aspart, pre-mixed insulin analogue, type 2 diabetes

Introduction

Since the time when Romanian physician Nicolae Paulescu reported the first isolation of insulin, the production of medical insulin has undergone radical change. Along with the advances in molecular biology techniques, it has become possible to produce insulin analogues. These compounds are designed to more closely mimic the basal and prandial components of endogenous insulin secretion, and they have several advantages over human insulin preparations, including a reduced risk of hypoglycaemia [1÷3]. Currently, a number of insulin analogues have been approved for use in Romania and these include the short-acting insulin lispro, insulin aspart and insulin

glulisine, and the long-acting insulin glargine and insulin detemir.

There is a paucity of data concerning the use of the insulin analogues within Romanian clinical practice. We hereby report our findings of the use of biphasic insulin aspart 30 (BIAsp30, marketed as NovoMix® 30; manufactured by Novo Nordisk A/S) in clinical practice among a large pool of Romanian patients. BIAsp30 is a biphasic insulin analogue formulation consisting of 30% soluble rapid-acting insulin aspart and 70% insulin aspart crystallized with protamine. The soluble fraction of BIAsp30 is absorbed more quickly, reaches a higher plasma concentration, and produces glucose-lowering actions faster than the soluble fraction of a biphasic formulation of regular human insulin (BHI 30/70) [4,5]. The protaminated insulin aspart component of BIAsp30 provides basal insulin coverage through its prolonged absorption profile.

Our study was part of a large multi-national, observational study called the PRESENT NovoMix® 30 (Physicians' Routine Evaluation of Safety & Efficacy of NovoMix® 30 Therapy) study, which involved over 34,500 subjects from 15 countries worldwide (China, India, Iraq, Jordan, Kuwait, Lebanon, Qatar, Romania, Russia, Saudi Arabia, South Africa, South Korea, Sri Lanka, Turkey and the United Arab Emirates). The objective of the study was to evaluate the efficacy, safety and treatment satisfaction with BIAsp30 in the routine clinical practice of these participating countries.

Methods

Study Design

This was a 6-month, prospective, open-labelled, uncontrolled, observational study involving 28 centres across Romania. Subjects with type 2 diabetes, who were judged by their treating physicians to be inadequately controlled on their previous therapy, were enrolled into the study and prescribed with BIAsp30 as monotherapy, or in combination with oral hypoglycaemic agents (OHA). The dosing adjustments were made at the physician's discretion, reflecting routine clinical practice.

The physicians that participated in this study were asked to document details of the subject's history, treatments prescribed, blood glucose measurements, adverse drug reactions (ADRs) and hypoglycaemic episodes, on data collection forms (DCFs), for each of their individual subjects. The DCFs also included questions that attempted to address the issue of subject and physician satisfaction towards BIAsp30 treatment, as well as questions on the reasons for starting BIAsp30 treatment, or for stopping treatment. Serious ADRs (SADRs) also had to be reported by the participating physicians on separate forms, which were to be faxed to the pharmacovigilance department of the manufacturer within 24 hours.

Data was collected at baseline, and at 3 and 6 months of therapy. No study-specific interventions were involved except the collection of data. The time elapsed from meal for PPPG measurement was not predefined and was at the discretion of the subject or physician.

Statistical Analysis

All enrolled subjects having baseline data were included in the Safety Analysis Set, which was used for the analyses of efficacy, safety and treatment satisfaction. Demographic characteristics, glycated haemoglobin A1c (HbA_{1c}), fasting plasma glucose (FPG), postprandial plasma glucose (PPPG) levels, hypoglycaemic episodes, adverse drug reactions (ADRs) and treatment satisfaction are summarised with descriptive statistics, using mean and standard deviation (s.d.) for continuous variables, and frequency and percentages for categorical variables. All statistics were calculated with SAS® version 9.1.3 (SAS Institute Inc., Cary, NC, USA).

Results

Subjects

Of 1,227 subjects that initially enrolled, 912 were included in the Safety Analysis Set, and the baseline characteristics of the subjects in the Safety Analysis Set are summarised in Table 1. The most common reasons stated by the treating physicians for starting a subject on, or transferring a subject to BIAsp30, were to 'improve postprandial glucose levels' and to 'improve fasting glucose levels', which were cited in 87.7% and 75.2% of physician responses, respectively.

Table 1: Demography and baseline characteristics

	Safety Analysis Set
n	912
Age (years)	58.1 ± 11.0
Race (C/O/U) (%)	99.6/0.3/0.1
Gender (female/male) (%)	53.9/46.1
BMI (kg/m^2)	28.2 ± 4.8
Duration of diabetes (years)	7.8 ± 6.5
HbA_{1c} (%)	10.0 ± 1.8
Previous treatment (%)	
OHA only	35.0
Insulin only	39.5
Insulin + OHA	15.0
Diet only	8.8
Unknown/missing information	1.7

Values represent mean ± s.d. or as otherwise noted. For race: C, Caucasian/White; O, others; U, unknown. OHA = oral antihyperglycaemic agents

A total of two (0.2%) and 11 (1.2%) subjects discontinued BIAsp30 treatment by the end of 3 and 6 months, respectively. The treating physicians were asked if discontinuation was due to one or more of the following reasons: (i) hypoglycaemia, (ii) ADR, (iii) unsatisfactory 24-hour glycaemic control, (iv) availability of treatment, (v) cost

of therapy, and/or (vi) other reasons. 'Other reasons' was cited as the reason for discontinuing treatment among all subjects that discontinued treatment by the end of 3 months, and among two (18.2%) subjects that discontinued treatment by the end of 6 months. At 6 months, another five subjects cited "availability of treatment" as the reason for discontinuing treatment, one subject cited "hypoglycaemia", and three others did not provide a reason. No subjects, at 3 or 6 months, cited ADR as a reason for discontinuing treatment. For subjects who discontinued due to 'other reasons', the specific reason for discontinuation was not reported.

Glycaemic Control and insulin dose

Treatment with BIAsp30 was associated with a reduction in HbA_{1c} baseline value of 1.78 ± 1.38% at 3 months and 2.64 ± 1.81% at 6 months (Figure 1). The proportion of subjects having an HbA_{1c} of <7.0% increased from 2.4% at baseline to 6.5% at 3 months and to 32.0% at 6 months. Treatment with BIAsp30 was also associated with reductions in FPG baseline value of 4.14 ± 4.51 mmol/L at 3 months and 5.18 ± 4.50 mmol/L at 6 months, as well as reductions in PPPG of 5.27 ± 4.73 mmol/L at 3 months and 6.54 ± 4.66 mmol/L at 6 months.

The mean total BIAsp30 dose was 0.47 U/kg at baseline, and 0.49 U/kg and 0.50 U/kg at 3 months and 6 months, respectively. The majority of subjects were treated with BIAsp30 twice-daily at breakfast and dinnertime (93.5%, 93.3% and 92.6% of subjects at baseline, 3 months and 6 months, respectively). The proportion of subjects receiving thrice-daily BIAsp30 administration (i.e. at breakfast, lunchtime and dinnertime) was low (0.6%, 1.9% and 1.8% of subjects at baseline, 3 months and 6 months, respectively). The proportion of subjects receiving once-daily BIAsp30 administration (either at lunch or dinner) was approximately 5% at 3 months and 6 months. All subjects used the prefilled FlexPen® insulin pen device (manufactured by Novo Nordisk A/S) to administer their BIAsp30.

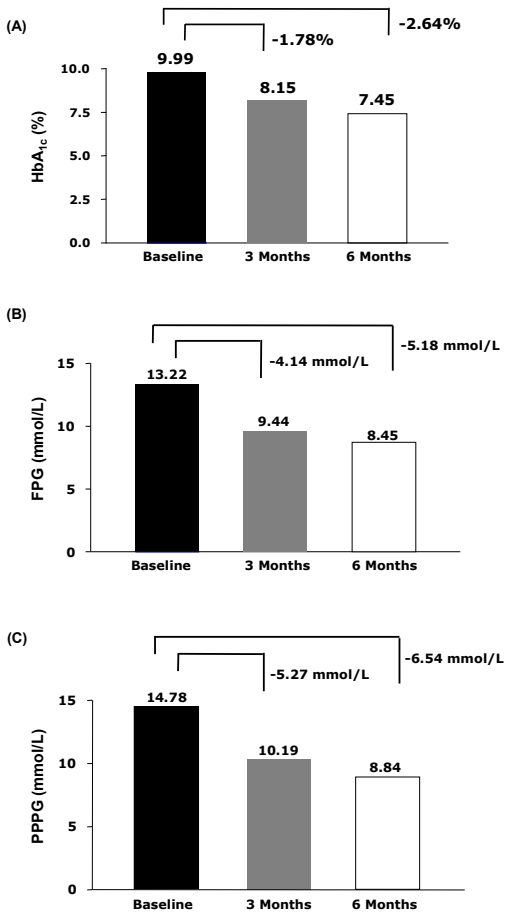

Figure 1 A-C. Mean HbA_{1c}, FPG and PPPG at baseline, and at 3 months and 6 months of BIAsp30 therapy

Hypoglycaemia and ADRs

The proportion of subjects reporting hypoglycaemic episodes rose from 24.9% at baseline to 27.2% at 3 months, then subsequently declined to 22.0% at 6 months (Table 2). The majority of hypoglycaemic episodes reported at 3 months and at 6 months were minor in nature, and only 3.8% (27 in 719) of episodes reported at 3 months, and 0.5% (2 in 394) at 6 months were major hypoglycaemic episodes. In addition, hypoglycaemic episodes tended to occur during the day, with 29.5% (212 in 719) of episodes reported at 3 months, and 30.5% (120 in 394) at 6 months occurring during the night. Overall, treatment with BIAsp30 was associated with a decline in the rate of hypoglycaemic episodes from 6.924 episodes per patient year at baseline, to 3.481 episodes per patient year at the end of the study. Notably, the rate of major hypoglycaemic episodes decreased from 0.688 episodes per patient year at baseline to 0.091 episodes per patient year at the end of the study, with BIAsp30 treatment.

Table 2 Hypoglycaemic Episodes by Classification

	N (%)	E
Overall		
Baseline	227 (24.9%)	1504
3 months	176 (27.2%)	719
6 months	134 (22.0%)	394
Severity		
Baseline		
Major	42 (4.6%)	143
Minor	222 (24.3%)	1361
3 Months		
Major	14 (2.2%)	27
Minor	173 (26.7%)	692
6 Months		
Major	2 (0.3%)	2
Minor	133 (21.8%)	392
Timing of Episode		
Baseline		
Daytime	182 (20.0%)	862
Nocturnal	153 (16.8%)	642
3 Months		
Daytime	159 (24.6%)	507
Nocturnal	95 (14.7%)	212
6 Months		
Daytime	119 (19.5%)	274
Nocturnal	70 (11.5%)	120

N, number of subjects with hypoglycaemic episodes; %, percentage of subjects exposed in the given period having hypoglycaemic episodes; E, absolute number of hypoglycaemic episodes

One case of an ADR was suspected in a single subject at 6 months, but the treating physician did not report further details of the ADR, presumably because of uncertainty that

the reaction had been definitely caused by BIAsp30 therapy.

Treatment Satisfaction

Subjects' satisfaction to BIAsp30 therapy was assessed by their treating physicians, through an unvalidated, close-ended questionnaire. The majority (>90%) of subjects were perceived as being either "very satisfied" or "satisfied" with BIAsp30 over previous treatment, as assessed at both 3 and 6 months of treatment (Figure 2). The treating physicians were asked to rate how satisfied they were with BIAsp30 over their subject's previous treatment, and the majority of responses (>90%) were also either "very satisfied" or "satisfied" at both 3 and 6 months of treatment.

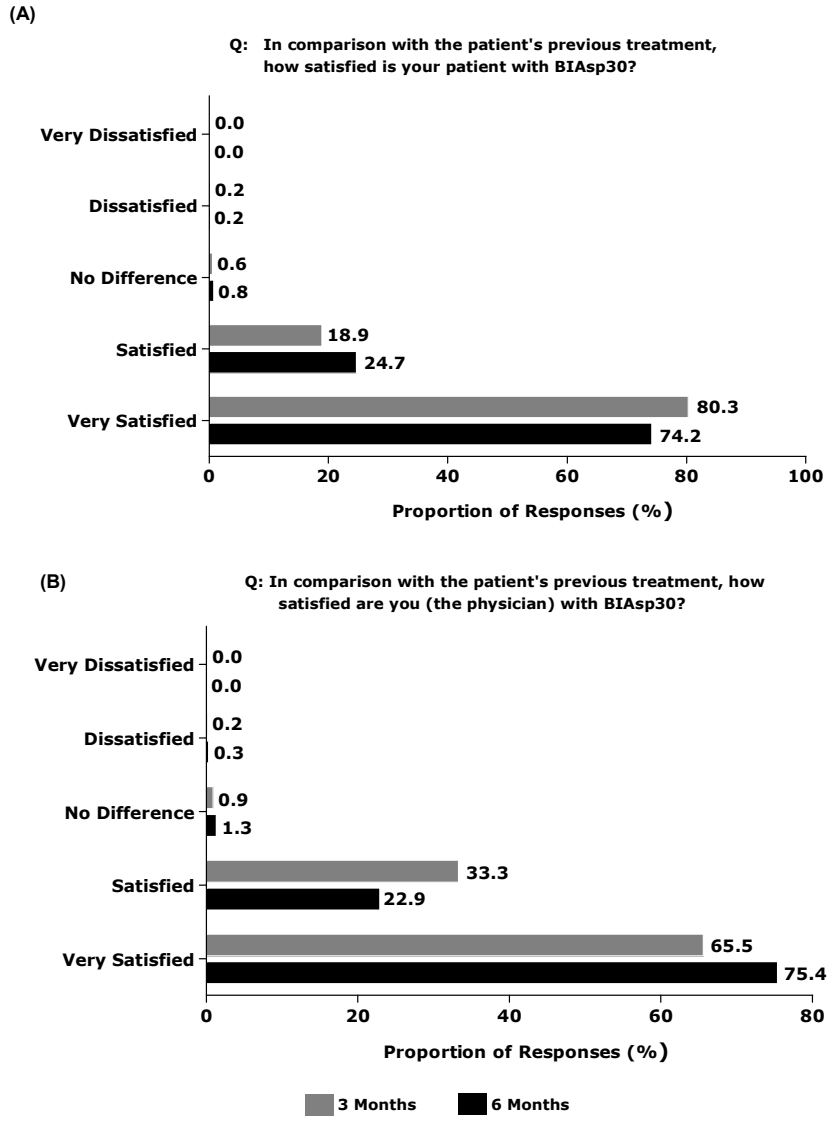

Figure 2 A-B. Treatment Satisfaction, as Assessed by the Patient and Physician, at 3 months and 6 months of BIAsp30 therapy

Discussion

There is an extensive evidence base supporting the benefits of achieving tight HbA_{1c} control among patients with diabetes. Investigators in the United Kingdom Prospective Diabetes Study (UKPDS), for instance, have shown that for every 1% reduction in HbA_{1c} there was a 37% decrease in the risk of microvascular complications, and a 21% decrease in the risk of deaths related to diabetes [6]. Similarly, an analysis of the Norfolk cohort of European Prospective Investigation into Cancer and Nutrition has shown that an increase of 1% in HbA_{1c} is associated with a 28% increase in the risk of death among men, independent of age, blood pressure, serum cholesterol, body mass index, and cigarette smoking habit [7]. Against this background, it is encouraging to find from our study, that it is possible for Romanian subjects with type 2 diabetes to achieve reductions in HbA_{1c} of approximately 2.6% at 6 months of treatment with BIAsp30 under clinical practice conditions.

The American Diabetes Association's (ADA) goal HbA_{1c} for patients with diabetes is <7.0% [8], and in our study, although the proportion of subjects achieving an HbA_{1c} of <7.0% did increase from 2.4% at baseline to 6.5% at 3 months and 32.0% at 6 months with BIAsp30 treatment, clearly, glycaemic control among the majority of subjects was still not optimal at the end of the study. To enable a greater proportion of subjects to achieve target HbA_{1c}, one option would have been to increase the dose and frequency of BIAsp30 administration in a stepwise manner, as has been demonstrated in the NovoMix® 30 1-2-3 study [9]. Indeed, the NovoMix® 30 1-2-3 study has shown that in subjects with type 2 diabetes failing oral agent therapy, the addition of once-daily BIAsp30 enables 41% of subjects to achieve HbA_{1c} <7.0%; with two daily injections of BIAsp30, this glycaemic target could be achieved by 70% of subjects, and when the number of daily administrations of BIAsp30 is further raised to three, 77% achieved HbA_{1c} <7.0%.

Given that only a single case of ADR was reported during our entire study, under-reporting of ADRs in our study by the participating centres cannot be ruled out. Under-reporting of ADRs is a common problem in general practice [10÷16]. Many reasons have been given as to why health care professionals do not report ADRs, and these include reluctance to send reports based on mere suspicion, lack of time, and ignorance of reporting requirements [10]. That said, some of these reasons may be applicable in the context of our study.

Nonetheless, the findings of our study with respect to ADRs are consistent with two prior studies that also investigated the use of BIAsp30 in routine clinical practice (Joshi *et al* [17] and Sridhar *et al* [18]). The study period for both these studies were 12 weeks in duration, and in both studies, no ADRs were reported throughout the study. Hence, although the possibility of under-reporting in our study as well as in the two prior studies exists, overall, our studies may suggest that the true frequency of ADRs with BIAsp30 treatment in patients with type 2 diabetes appears to be low. Moreover, in our study, data on treatment discontinuation and data on ADRs were collected separately, and consistent with the low frequency of ADRs observed, the data that was collected on treatment discontinuation

showed that there were no subjects that discontinued treatment due to ADRs.

Hypoglycemia is the main limiting factor in the glycaemic management of insulin-treated diabetic subjects [19]. Although the proportion of subjects reporting hypoglycaemic episodes rose from 24.9% to 27.2% between baseline and 3 months, at 6 months, it subsequently declined to a level below baseline (22.0%), and one reason for this decline may be stabilisation of dose, after the initial period of insulin titration. Importantly, most hypoglycaemic episodes reported were minor in nature, and the rate of major hypoglycaemia did not rise along with the improvements in glycaemic control. Indeed a reduction in the rate of major hypoglycaemia was observed instead and one reason for this may be due to the fact that close to half of subjects were converted from another insulin to BIAsp30 at baseline. Previous studies have shown BIAsp30 to be associated with a reduced risk of major hypoglycaemia compared with biphasic human insulin [20,21].

Treatment satisfaction issues have become steadily more important in healthcare practice. Our study attempted to investigate patient and physician satisfaction with BIAsp30 treatment through an unvalidated questionnaire that was completed by the physician. The results suggest an improvement in treatment satisfaction with BIAsp30 therapy over the patients' previous insulin treatment among the majority of patients and physicians. This finding is consistent with a 6-month follow-up study in a mixed group of type 1 and type 2 diabetic patients, which showed that individuals receiving BIAsp30 had significantly higher treatment satisfaction as compared to those receiving biphasic human insulin 30 [22]. In our study, all subjects were using the prefilled FlexPen® insulin pen device to administer their BIAsp30, and an added reason to account for the improved treatment satisfaction among our study subjects may be due to the increased convenience and flexibility associated with the delivery system [23].

In summary, the findings from this large cohort of Romanian subjects suggest that BIAsp30 improves glycaemic control and treatment satisfaction in patients with type 2 diabetes who are inadequately controlled on their previous therapy. Treatment with BIAsp30 was associated with a reduction in the rate of major hypoglycaemia, and this study did not provide evidence of a concern relating to ADRs. However, under-reporting of ADRs by the participating centres cannot be ruled out.

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