Safety and effectiveness of biphasic insulin aspart 30 (BIAsp 30) in people with type 2 diabetes mellitus in the Pakistani population: Results from the A1chieve study

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Abstract

Objective: To explore the safety and effectiveness of treatment with the insulin analogue, biphasic insulin aspart 30 (BIAsp 30), in people with type 2 diabetes mellitus (T2DM) in a subgroup of a Pakistani population from the A1chieve study.

Methods: A1chieve was a 24-week, international, prospective, multicentre, open label, observational, non-interventional study designed to evaluate the safety and clinical effectiveness of 66,726 people with T2DM who were initiated with basal insulin detemir, fast acting insulin aspart, and BIAsp 30 (30% soluble insulin aspart, 70% protamine-crystallized insulin aspart). The study was conducted in 28 countries across Asia, Africa, Latin America, and Europe. Here, we report data from a subgroup of 762 people with T2DM from the Pakistani cohort (insulin naïve and insulin users) who were treated with premix insulin (BIAsp 30)±oral antidiabetic drugs (OADs).

Results: The decrease in HbA1c at week 24 was statistically significant in the entire cohort, the insulin naïve, and insulin users (1.7±1.1%, 1.8±1.3% and 1.7 ±0.9%, respectively, p<0.001 for all). There was a statistically significant decrease in the mean fasting plasma glucose (FPG) and postprandial plasma glucose (PPG) from baseline to week 24 in the entire cohort, in the insulin naïve and in the insulin users with BIAsp 30 treatment (p<0.001 for all). No major hypoglycaemic events were reported during the entire study period. There was a statistically significant decrease in the systolic blood pressure (SBP) in all groups (p<0.001). The improvement in the quality of life score (QoL) was statistically significant in all groups (p<0.001 for all).

Conclusion: BIAsp 30 treatment appeared to be well tolerated and effective as indicated by improved glycaemic control and QoL in people with T2DM in the Pakistani population after 24 weeks.

Keywords: Biphasic insulin aspart 30, Type 2 diabetes mellitus, Pakistani population, Oral antidiabetic drugs. (JPMA 62: 929; 2012)

Introduction

Type 2 diabetes mellitus (T2DM) is a chronic progressive disorder characterised by insulin resistance and inadequate insulin secretory response because of the gradual decline in beta-cell function.1 Due to the progressive nature of T2DM, the majority of people are unable to sustain glycaemic control and maintain haemoglobin A1c (HbA1c) targets with lifestyle modifications and oral glucose lowering therapies. Introduction and optimization of exogenous insulin is, therefore, required to achieve better glycaemic control.2-4

The UK Prospective Diabetes Study (UKPDS) and other studies have shown that intensive glycaemic control in T2DM significantly reduces the risk of microvascular complications5,6 and may improve cardiovascular outcomes.6 In a prospective observational study, Stratton et al.7 have estimated that a 1% reduction in HbA1c was associated with a 37% reduction in microvascular complications and a 16% reduction in heart failure with an overall 43% reduction in the risk of amputation or death from peripheral vascular disease.
American Diabetes Association (ADA) recommends HbA1c level of <7.0% for people with T2DM. According to the International Diabetes Federation (IDF), diabetes mellitus is affecting 366 million people worldwide. Pakistan is among the top 10 countries in the world with an estimated 11.4 million people with diabetes mellitus by 2030. IDF treatment guidelines recommend to initiate treatment with insulin when lifestyle modification and combination of two or more Oral antidiabetic drugs (OADs) fail to achieve glycaemic targets and if HbA1c is above 7.5%. Simple basal insulin regimen is commonly initiated to achieve glycaemic targets. Basal insulin is efficient in achieving the target for Fasting Plasma Glucose (FPG) control; however it fails to achieve the target of Post Prandial Glucose (PPG) control that significantly contributes to hyperglycaemia in people with T2DM. Achieving target HbA1c is frequently impossible without addressing PPG. As HbA1c approaches normal values, the contribution of PPG increases. Treatment of both PPG and FPG parameters is required at all times for optimal glycaemic control. The closer HbA1c approaches target, the more emphasis is needed on PPG.

Premix insulin products comprise rapid-acting and intermediate-acting components that are effective in achieving better FPG and PPG control with only one injection. Biphasic insulin aspart 30 (BIAsp 30, Novomix® 30), a premixed insulin analogue, consists of a mixture of rapid-acting insulin aspart and intermediate-acting protamine crystallised insulin aspart in a 30:70 ratio. As demonstrated by large-scale observational studies, switching from basal insulin to a premix analogue (BIAsp 30) was well tolerated and significantly improved glycaemic control.

The Achieve study assessed the clinical safety and effectiveness of insulin analogues in a large and diverse population from a globally broad variety of clinical care. In the current study which was conducted on the Pakistani population, patients with T2DM were either put on basal insulin detemir (Levemir®, Novo Nordisk A/S, Denmark) and bolus insulin aspart (NovoRapid®, Novo Nordisk A/S, Denmark) or biphasic insulin aspart 30 (Novomix® 30, NovoNordisk A/S, Denmark), alone or in combination, to evaluate their clinical safety and effectiveness in the routine clinical use. In this manuscript, we present the data on safety and effectiveness of insulin analogue BIAsp 30 in this Pakistani sub population from the Achieve study.

Patients and Methods

Study Design:

Achieve was a 24-week, international, prospective, multicentre, observational, non-interventional study in people with T2DM who were initiated with basal insulin detemir (Levemir®, Novo Nordisk A/S, Denmark), fast-acting insulin aspart (NovoRapid®, Novo Nordisk A/S, Denmark) and biphasic insulin aspart 30 (NovoMix30®, Novo Nordisk A/S, Denmark) to evaluate their clinical safety and effectiveness in routine clinical practice. The study was performed in 28 countries across Asia, Africa, Latin America, and Europe. Details of the methods and results of the Achieve study have been published previously.

This paper presents data on a subgroup of people with T2DM from the Pakistani cohort who was treated with premix insulin (BIAsp 30) ± OADs by their treating physician (Figure-1). In this paper, results are presented in following three groups: entire cohort, 'insulin naïve' and 'insulin users'. The STROBE (strengthening the reporting of observational studies in epidemiology) guidelines were followed while writing the paper.

There were 57 study sites in Pakistan (Karachi and Hyderabad in Sindh province, Lahore, Rawalpindi/Islamabad, Multan, Faisalabad, Bhawalpur and Gujranwala in Punjab province and Peshawar in Pukhtunkhaw province). Treating physician made decision on the starting dose and administration frequency, as well as the later changes to either dose or frequency, if any on an individual basis. Physician also decided on concomitant medication. Extensive inclusion exclusion criteria were not applied to this observational study. After the physician had taken the decision to use BIAsp 30 (alone or in combination), any subject with T2DM who was not treated with BIAsp 30 or who had started BIAsp 30 within the last 4 weeks before inclusion in this study, was eligible. Subjects who were previously enrolled in this study, subjects with a hypersensitivity to BIAsp 30, or to any of the excipients and women who were pregnant, breast feeding or had the intention of becoming pregnant within the next 6 months were excluded from the study. Participants were free to withdraw from the study at any time. Data were taken at visit 1, with an interim visit 12 weeks after baseline and a final visit following 24 weeks of participation in the study. Information was to be gathered from the physician's usual clinical notes, and the participants' recall and self-monitoring glucose diary.
at each visit as available.

The study was approved by local and national ethics and regulatory agencies and was implemented in accordance with the provisions of the Declaration of Helsinki.

Assessments and Outcome Measures:

The study aimed to evaluate the clinical safety of the BIAsp 30 by the incidence of serious adverse drug reactions (SADRs), including change in major hypoglycaemic events from baseline to the end of study. Safety assessments were the change in number of hypoglycaemic events in the last 4 weeks before interim and final visits, compared with the last 4 weeks before the baseline visit, the change in number of nocturnal hypoglycaemic events during these periods, and the number of adverse drug reactions (ADRs) from baseline to final visit. Major hypoglycaemic events were defined as events with severe central nervous system symptoms, consistent with hypoglycaemia, for which the person was unable to self-treat, and accompanied by plasma glucose <56 mg/dL, or reversal of symptoms after either food intake or glucagon or intravenous glucose administration. Minor hypoglycaemia was any event, with or without symptoms of hypoglycaemia, with a plasma glucose reading below 56 mg/dL that the participant being able to self-treat. Nocturnal hypoglycaemia was defined as a symptomatic event consistent with hypoglycaemia that occurred during sleep between bedtime after the evening insulin injection and before getting up in the morning.

In this subgroup analysis the safety of BIAsp 30 was assessed by the incidence of SADRs and efficacy assessments including change in HbA1c, FPG and PPG from baseline to the final visit. All laboratory measurements were performed in local laboratories and were thus subject to local standardisation and quality control procedures.

Statistical Methods:

Analysis were performed for the entire cohort (all participants), for the insulin naïve and insulin users for BIAsp 30 in the Pakistani subgroup. Continuous variables were summarised using descriptive statistics and discrete variables were summarised using frequency tables (n, %). For hypoglycaemia the percentage of people reporting at least one event was analysed using Fisher's exact test. Change from baseline HbA1c, FPG, PPG, and blood lipids were analysed using paired t-test. The percentage of patients having HbA1c <7.0% at 24 weeks was summarised. Health-related quality of life (QoL) was measured using the EQ-5D questionnaire at baseline and after 24 weeks of treatment. This EQ-5D score ranges from 0 (worst imaginable health) to 100 (best imaginable health).

Analysis was performed for people who completed the EQ-5D questionnaire at both baseline and week 24. Change from baseline inQoL with the EQ-5D score as a continuous variable was analysed using the paired t-test.

The full analysis set (FAS) was defined as all subjects with a baseline visit and who used BIAsp at least once (BIAsp dosage at baseline, interim or final visit >0 units (U)). The efficacy analysis set (EAS) comprised patients who had a final visit, at least one measurement concerning FPG, PPG, most recent HbA1c, weight or hypoglycaemic events (Yes, No) at baseline and final visit.

Results

A total of 762 patients were recruited for the...
study under BIAsp 30 treatment group from Pakistan which included study groups of insulin naïve (495 patients) and insulin users (267 patients) (Figure-1). Of these 703 (92.3%) patients completed the study. Patient demographics and clinical characteristics at baseline were stratified by pre-study insulin treatment and for the overall population. In the entire cohort, 52.9% patients were males and 47.1% patients were females. Average age of patients was 51.6 ± 9.5 years with 76.7 ± 14.0 kg of mean body weight and 28.5 ± 5.5 kg/m$^2$ BMI. Average duration of T2DM was 8.8 ± 4.5 years in these patients. The HbA$_1c$ at baseline was 9.2 ± 1.3%. Prior to enrolment in the study, 488 (64%) patients were being treated with OADs alone, 267 (35%) patients received insulin + OADs and 7 (1%) patients were not on any medication for diabetes mellitus. Metformin was the most common OAD taken and was received by 605 (93.9%) patients. There were 114 (17.7%) patients taking sulfonylurea, and thiazolidinediones were taken by 105 (16.3%). There were 196 (30.4%) patients who were taking more than two OADs. There were no notable differences between the insulin-naïve and prior insulin groups.

The reasons for change in therapy by the treating physicians were to improve glycaemic control 746 (97.9%), unstable diabetes mellitus 275 (36.1%), reduce the
risk of hypoglycaemia 264 (34.6%), and reduce plasma glucose variability 240 (31.5%) in the entire cohort. Of the 762 patients, all were exposed and constituted the FAS population, whereas 694 (91.1%) constituted the EAS population. A total of 59 (7.7%) patients withdrew from the study. The commonest reason for withdrawal was failure to maintain contact with their physician n= 34, (4.5%), no patient withdrew due to an ADR, and the remaining withdrew n=25, (3.3%) for other reasons.

The change in HbA1c, FPG, and PPG from baseline to week 24 are summarised in Figure-2. Blood glucose control improved statistically significantly during 24 weeks treatment period in the entire cohort with BIAsp 30 treatment. The mean change in HbA1c in the entire cohort was -1.7±1.1% (p<0.001). The decrease in HbA1c at week 24 was statistically significant in both insulin naïve and insulin users (1.8±1.3% and 1.7 ±0.9%, p< 0.001 for both). The ADA target achievers (HbA1c <7%) were analysed for the entire cohort. A total of 1.4% patients were at target at baseline. However the number of target achievers increased to 20.4% at week 24.

The analysis of FPG and PPG in the entire cohort showed a significant decrease in the mean values from baseline to week 24 with the BIAsp 30 treatment (66.1 ± 50.5mg/dL and 104.9 ± 62.7 mg/dL, p<0.001 for both).

When the analysis of FPG and PPG was performed for insulin naïve and insulin users there was significant decrease in both FPG (69.3 ± 53.3 mg/dL and 60.7 ± 45.0 mg/dL) and PPG (111.1 mg/dL ± 70.3 and 95.8 ± 48.7 mg/dL) at week 24 (p<0.001 for both).

Average BIAsp 30 dose in the entire cohort at baseline was 0.51±0.21 U/kg with 33 (4.3%) patients taking once daily, 686 (90%) patients taking twice daily, and 43 (5.6%) patients taking thrice daily injections. After 24 weeks, the average daily dose had increased to 0.72±0.22 U/kg with 11 (1.6%) patients on once daily, 598 (85.5%) on twice daily, and 94 (13.4%) patients on thrice daily injections.

Similarly in the insulin naïve group the majority of patients n=45, (91.3%) started with twice daily BIAsp 30 injection. This number decreased to 384 (86.3%) at the end of the study. The number of patients on twice daily BIAsp 30 injection in the insulin users group also changed from 234 (87.6%) at baseline to 214 (82.9%) at the end of study.

No major hypoglycaemic events were reported during the study period. However, a statistically significant increase (p<0.0001) in the percentage of patients with at least one minor hypoglycaemic event was observed in the insulin naïve group and this is also true for nocturnal hypoglycaemia (Table-1).

Body weight, blood lipids and blood pressure control:

There was a statistically significant increase in the mean body weight over 24 weeks with the BIAsp 30 treatment for the entire cohort, the insulin naïve and the insulin user population. The mean increase from baseline was 1.2 ± 3.5 kg, 1.1 ± 3.5 kg, and 1.4 ± 3.5 kg for the entire cohort, the insulin naïve and insulin user groups consecutively, (all p<0.001).

Total cholesterol levels were statistically significantly reduced in the entire cohort from baseline to 24 weeks with BIAsp 30 treatment (Table-2). The reduction in the total cholesterol levels from baseline was almost similar among insulin naïve and insulin user groups (Table-2).

There was a statistically significant fall in the levels of low-density lipoprotein (LDL) cholesterol and triglyceride levels in the entire cohort with BIAsp 30 treatment (Table 2).

A similar significant fall in the levels of LDL cholesterol and triglyceride from baseline was also observed in the insulin naïve and insulin user groups.

Systolic blood pressure decreased significantly in the entire cohort by9.6 ± 18.5 mmHg after 24 weeks of treatment with BIAsp 30 (p<0.001). Similarly there was statistically significant reduction in SBP both in insulin naïve and insulin users (8.6 ± 20.0 mm Hg and 11.3± 15.6 mmHg, respectively; p<0.001 for both).

The Quality of life (QoL) scores improved statistically significantly with BIAsp 30 in all three groups from baseline to week 24 (all p<0.001) (Table-3).

Discussion

The current analysis explored the safety and effectiveness of treatment with the insulin analogue, BIAsp 30 in people with T2DM in a subgroup of the Pakistani population from the A achieve study.

The results showed that after 24 weeks of BIAsp 30 treatment there were statistically significant reductions in HbA1c, FPG, and PPG levels in the entire cohort, insulin naïve, and insulin users. These results are consistent with the results from the studies that investigated BIAsp 30 initiation in people with T2DM who were inadequately controlled with OADs. The decrease in HbA1c, FPG, and PPG levels was greater in insulin naïve compared to the insulin users. The reason for this may be that insulin naïve patients have shorter mean duration of diabetes mellitus and that
Insulin is initiated at an early stage in the course of T2DM. However, statistical comparisons between the groups were not performed because such comparisons were not part of the analysis plan due to the observational nature of the study.

Intensification of treatment by adding insulin to improve the glycaemic control can be constrained by the reluctance from patients and health care providers due to the concern of hypoglycaemia. No major hypoglycaemic was reported during the entire study period. However, the overall rate of minor hypoglycaemic events increased significantly from baseline to week 24 in the insulin naïve cohort. As expected differences in the hypoglycaemia rate among groups were influenced by the prior insulin use. These findings were similar to other reported studies. No major hypoglycaemic episodes were also reported in patients using BIAsp 30 treatment in both the INITIATE and PRESENT studies.

As glycaemic control improves following the initiation of insulin therapy, an increase in weight is often observed. As expected, in the current analysis, the mean body weight was slightly increased in all groups after 24 weeks of BIAsp 30 administration but was not clinically relevant. In the 26-week, multicentre, open-labelled randomised trial there was a significant weight gain of 1.53 kg (p<0.005) with BIAsp 30 treatment at the end of 26 weeks. In the 28-week parallel-group INITIATE study there was statistically significant weight gain of 5.4 ± 4.8 kg (p<0.001) with BIAsp 30 treatment. In the current analysis, the mean increase in body weight from baseline to week 24 was less than that observed in the above studies. The reason for this may be that these patients have received dietary advice from their physicians during the course of the study. However, since dietary advice to patients was not standardised, but left to physicians' discretion, this remains speculative. In addition, changes in patients' OAD therapy during the course of the study were not recorded, so any potential effects such changes may have had on glycaemic control and weight remain unclear.

ADA and American Association of Clinical Endocrinologists (AACE) guidelines on management of diabetes mellitus emphasize control of blood pressure, dyslipidaemia and obesity in addition to glycaemic control which has the potential to substantially improve long-term cardiovascular outcomes. Several studies have shown that insulin plays a very important role in regulation of carbohydrate and lipid metabolism. It stimulates the uptake of glucose by cells, promotes the synthesis of lipids, and inhibits lipid degradation. The insulin resistance observed in T2DMs characterized by derangement in the metabolism of lipids and carbohydrates. Adipose tissue has a special role in insulin resistance. In many insulin-resistant states circulating free fatty acids derived from adipocytes are elevated and have been suggested to contribute to the insulin resistance of diabetes mellitus by inhibiting glucose uptake, glycogen synthesis and glucose oxidation, and by increasing hepatic glucose output. Insulin is also known to exert cardioprotective effects via glucose-dependent and glucose-independent mechanisms. It brings cardioprotective effect by reducing glucose toxicity, exerting positive inotropic action on heart; reducing oxidative stress, inflammation, and apoptosis; and by regulation of blood flow. In the current analysis total cholesterol, LDL cholesterol, and triglyceride levels were reduced significantly across all the three groups. Also there was significant reduction in the SBP. This would indicate improvement in the metabolic status of patients and also cardiovascular disease risk reduction and reduction in the microvascular complications.

Assessment of QoL is an important aspect of clinical practice. An increasing number of studies suggest that specific aspects of diabetes mellitus and its treatment influence on patient perceptions of QoL. Decisions of the patient and physician may be influenced by factors such as the effect of a specific treatment on the QoL. Thus, therapeutic options are affected by the personal opinions as patients consider their own well-being in guiding their treatment choices. The QoL score improved significantly with BIAsp 30 in all three groups from baseline to week 24. This indicates that BIAsp 30 treatment significantly improved patient satisfaction and their QoL irrespective of their prior insulin use, and it is known that improvements in glycaemic control are associated with improvements in QoL. This is consistent with the results from the previous studies.

There are a number of limitations to this study that should be considered while evaluating the findings. As this was an observational study with no control group it is not possible to categorically state that the observed outcomes were directly related to the study medication.

As shown by one of the observational study conducted in Pakistan the management of T2DM is dependent on various factors like patient compliance, physician's preference and cost of treatment and usage pattern of insulin. There is a need for improvement in the management of patients with diabetes.
background of increasing awareness of the need for better glycaemic control in patients with T2DM, this study provides several pieces of new information. The average HbA1c level at which insulin is initiated in Pakistan is 9.2%, a level far above optimal value. As suboptimal glycaemic control has been shown to increase the risk of long-term morbidity and mortality, there is an urgent need to initiate insulin early in the treatment of T2DM. This study provides important data that may be used to support individualisation of antidiabetic therapy to accommodate both patient expectations and the clinical desire to attain therapeutic goal.

In conclusion, initiating BIAsp 30 treatment in people with T2DM in the Pakistani population was well tolerated and effective. BIAsp 30 treatment improved glycaemic control and there was no increased risk of major hypoglycaemia. In addition, improved QoL scores may enhance patient adherence to therapy and self-management. Furthermore, the results in the Pakistani population are consistent with the global A1chieve study cohort.

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References


APPENDIX-1

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