

Clinical Experience with Biphasic Insulin Aspart 30 Treatment in Patients with Type 2 Diabetes Poorly Controlled on Oral Antidiabetic Drugs: The Turkish PRESENT Study.

Oral Antidiyabetik İlaçlarla Kontrol Altına Alınmayan Tip 2 Diyabetli Hastalarda Bifazik İnsülin Aspart Tedavisi ile Klinik Deneyim: PRESENT Türkiye Çalışması

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Abstract

Objective: PRESENT is the largest, completed, six-month, multi-national, open-labelled, uncontrolled, observational study of the efficacy and safety of biphasic insulin aspart 30 (BIAsp 30) treatment in clinical practice. We present results from Turkish patients poorly controlled on oral antidiabetic treatment (OADs).

Material and Methods: Only data from type 2 diabetes mellitus patients consistently prescribed BIAsp 30+OADs (n=270) or BIAsp 30 only (n=573) are presented.

Result: At six months, mean HbA_{1c} was reduced from baseline in the BIAsp 30+OADs (-2.35±1.82%) and BIAsp 30-only groups (-2.05±1.85%) (p<0.001). More patients achieved HbA_{1c} < 7% in the BIAsp 30+OADs (33.8%) and BIAsp 30-only groups (24.6%), compared with baseline. Mean FPG and PPPG were reduced in the BIAsp 30+OADs (-85.4±72.4mg/dl; -106.8±80.2mg/dl) and BIAsp 30-only groups (-125.6±83.6 mg/dl; -153.3±87.6mg/dl), respectively (p<0.001). The majority of the hypoglycaemic episodes reported were minor and diurnal. Fifteen non-serious adverse drug reactions (ADRs) were reported in the BIAsp 30+OADs group.

Conclusions: Treatment with BIAsp 30 alone or in combination with OADs effectively and safely improved glycaemic control with no major and few minor hypoglycaemic episodes among patients inadequately controlled on OADs. *Turk Jem 2008; 12: 4-9*

Key words: Biphasic insulin aspart, oral antidiabetic drugs, type 2 diabetes mellitus, insulin analogue, combination therapy, clinical experience

Özet

Amaç: PRESENT klinik uygulamada bifazik insülin aspartın (BIAsp 30) etkinlik ve güvenilirliğini göstermeyi amaçlayan altı ay süreli, çok uluslu, kontrolsüz, açık etiketli, tamamlanmış, en büyük gözlemsel çalışmadır. Burada oral antidiyabetik (OAD) tedavilerle kontrol altına alınamayan Türkiye'deki hastaların sonuçlarını sunmaktayız.

Yöntem: Sadece düzenli biçimde BIAsp 30+OADler (n=270) veya sadece BIAsp 30 (n=573) kullanan tip 2 diabetes mellituslu hastalara ait veriler sunulmuştur.

Bulgular: OADler ile kontrol altına alınamayan hastalarda, BIAsp 30 tek başına veya OADler ile birlikte majör hipoglisemi olmaksızın ve çok az minör hipoglisemik atak ile etkin ve güvenilir biçimde glisemik kontrolü iyileştirmektedir.

Sonuç: Altıncı ayda, BIAsp 30+OADler (-2.35±1.82%) ve sadece BIAsp 30 gruplarında (-2.05±1.85%) ortalama HbA_{1c} başlangıca göre düşmüştür (p<0.001). Başlangıca göre BIAsp 30+OADler grubunda (33.8%) ve sadece BIAsp 30 kullanan grupta (24.6%) daha çok hasta HbA_{1c} < %7 hedefine ulaşmıştır. Ortalama APG ve PPPG sırasıyla BIAsp 30+OADler grubunda (-85.4±72.4mg/dl; -106.8±80.2mg/dl) ve sadece BIAsp 30 kullanan grupta (-125.6±83.6mg/dl; -153.3±87.6mg/dl) düşmüştür, (p<0.001). Çoğu hipoglisemik olay minör ve diüurnal özellikte idi. BIAsp 30+OAD'ler grubunda ciddi olmayan 15 Advers ilaç Reaksiyonu (AİR) rapor edildi. *Turk Jem 2008; 12: 4-9*

Anahtar kelimeler: Bifazik insülin aspart, oral antidiyabetik ilaçlar, tip 2 diyabetes mellitus, insülin analogu, kombinasyon tedavisi, klinik deneyim

Introduction

Due to the progressive nature of type 2 diabetes mellitus, the majority of patients need multiple therapies in order to attain and maintain glycaemic targets in the longer term (1). In many cases, patients using combination therapies of insulin and oral antidiabetic drugs (OADs) also benefit from the insulin-sparing effect of some OADs, which allows a lower dose of insulin to be used, thereby reducing the potential for adverse effects, including hypoglycaemia (1) and weight gain (2). Studies have shown that combining insulin with OADs could be a safe and effective alternative to intensive insulin therapy (3). Further, the latest diabetes treatment guidelines recommend the use of combination therapy involving modern insulin and OADs, such as secretagogues (e.g. glyburide) and insulin-sensitizers (e.g. metformin) (4,5).

Biphasic insulin aspart 30 (BAsp 30), a premixed insulin analogue that contains 30% rapid-acting insulin aspart and 70% longer-acting protaminated insulin aspart, has been investigated and used successfully in combination with the majority of marketed OADs, including sulphonylureas, thiazolidinediones (6) and biguanides (7,8). These studies have shown that the addition of BAsp 30 to an OAD results in greater glycaemic improvement compared with the addition of a second OAD (7,8). Following its documented efficacy in combination therapy, BAsp 30 has been approved for use in combination with metformin in Europe (9). Combination therapy of BAsp 30 and OADs is also in line with current IDF recommendations for the treatment of type 2 diabetes patients with an HbA1c greater than 7.5% while receiving OAD therapy (5).

The efficacy and safety of BAsp 30 are well established in the current literature on controlled clinical trials (8,10-17). However, information on its use in routine clinical settings remains limited. The Physicians' Routine Evaluation of Safety and Efficacy of NovoMix® 30 Therapy (PRESENT) Study is the largest multi-national, observational study on BAsp 30 carried out in a routine clinical setting completed to date. The aim of the study was to collect data on the safety and efficacy of BAsp 30 treatment in a large number of patients with type 2 diabetes in routine clinical practice to support clinical data from smaller randomized clinical trials. In this article, we present results from a subgroup of the Turkish cohort who were poorly controlled on prior OAD treatment and who either added BAsp 30 treatment to their prior OAD treatment or who received BAsp 30 treatment without continuing their prior OAD treatment.

BAsp 30 has been available in Turkey since March of 2003. To our knowledge, there has been only one previous study of BAsp 30 conducted in Turkey (18). Turkey currently has an estimated 2.89 million patients with diagnosed type 2 diabetes (19), although it is possible that many others remain undiagnosed. Our study provides valuable data on the efficacy and safety of BAsp 30 treatment, with practical implications for this patient population in Turkey.

Materials and Methods

Study design

This observational study was designed to evaluate the efficacy and safety of using BAsp 30, either as a monotherapy or in combination with OADs, for type 2 diabetes management in routine clinical prac-

tice. This was a multi-national, multi-centre, six-month, prospective, open-labeled, uncontrolled, clinical experience evaluation study. Adding BAsp 30 treatment to existing OAD treatment and discontinuation of OADs was entirely at the discretion of the attending physicians. No special investigational procedures outside the normal clinical practice were planned. A total of 126 centres participated in the Turkish study. As this was an observational study, the only selection criteria were that patients had type 2 diabetes mellitus, were inadequately controlled on their current therapy and were prescribed BAsp 30, as a monotherapy or in combination with OADs, in accordance with the approved labeling.

Data collection and study endpoints

The efficacy and safety endpoints were evaluated at three and six months of BAsp 30 treatment. The efficacy endpoints were the change in HbA1c, fasting plasma glucose (FPG) and postprandial plasma glucose (PPPG) at the end of treatment compared with baseline. The safety endpoints were the occurrence of hypoglycaemic episodes and adverse drug reactions (ADRs). Patient data were collected at baseline, three months and six months using standardized forms. Data collected included patient demographic data at baseline (such as weight, duration of diabetes, current diabetes therapy), HbA1c measurements within one month prior to visit, FPG and PPPG measurements within one week prior to visit, number of hypoglycaemic episodes and ADRs. The number of hypoglycaemic episodes and ADRs at baseline was based on patient recollection and clinical records from three months prior to the baseline visit. For the three- and six-month datapoints, the number of hypoglycaemic episodes was similarly based on patient recollection and clinical records. Major hypoglycaemic episodes were defined as those where the patient needed third-party assistance to be treated.

Statistical analyses

The patients were separated into two groups: patients treated with BAsp 30 only and patients treated consistently with a combination of BAsp 30 and OADs throughout the study (BAsp 30+OADs). The safety analysis set consisted of enrolled patients with a minimum of baseline data. Baseline demographic information, diabetes therapy, and efficacy and safety outcomes were presented as descriptive statistics (% , mean \pm S.D. or 95% confidence interval). Changes in HbA1c, FPG and PPPG from baseline were analyzed using the paired t-test. Changes from baseline in the proportion of patients with an HbA1c of less than 7% (ADA guidelines) were compared using the McNemar's test. Hypoglycaemic episodes and ADRs were presented according to category and severity using summary statistics and event rates. All statistical analyses were performed using SAS® version 9.1.3 (SAS Institute, NC, USA).

Results

Baseline demography

The safety analysis set consisted of 270 patients in the BAsp 30+OADs group and 573 patients in the BAsp 30-only group (Table 1). The majority of patients in both groups completed the six-month study (82% in the BAsp 30+OADs group and 85% in the BAsp 30-only group). The mean body mass index (BMI) was higher in the BAsp 30+OADs group, whereas the mean duration of diabetes, mean FPG and mean PPPG were slightly higher in the BAsp 30-only group.

OAD and BIAsp 30 exposure**Prior treatment**

In the BIAsp 30+OADs group, the majority of patients were previously treated with sulphonylureas+biguanides (41.1% [111 patients]) or sulphonylureas+biguanides+alpha glucosidase inhibitors (16.3% [44 patients]), or sulphonylureas only (8.9% [24 patients]). In the BIAsp 30-only group, the majority of patients were previously treated with sulphonylureas only (29.8% [171 patients]) or sulphonylureas+biguanides (28.3% [162 patients]) or sulphonylureas+biguanides+alpha glucosidase inhibitors (11.3% [65 patients]).

Table 1. Baseline characteristics

Characteristics	BIAsp 30 + OADs	BIAsp 30 only
Safety population	270	573
Gender (male/female), (%)	42.2 / 57.8	43.3 / 56.7
Ethnicity		
White, N (%)	258 (97.0)	538 (94.4)
Other, N (%)	8 (3.0)	32 (5.6)
Mean age, years \pm S.D.	55.0 \pm 9.4	56.3 \pm 10.9
Mean diabetes duration, years \pm S.D.	8.6 \pm 6.1	9.7 \pm 6.0
Mean BMI, kg/m ² \pm S.D.	29.4 \pm 4.5	28.2 \pm 4.5
Mean HbA _{1c} , % \pm S.D.	9.9 \pm 2.0	9.7 \pm 2.0
Mean FPG, mg/dl \pm S.D.	236.0 \pm 79.3	277.4 \pm 86.5
Mean PPPG, mg/dl \pm S.D.	297.2 \pm 88.3	344.1 \pm 93.7

BMI: Body mass index; FPG: Fasting plasma glucose; PPPG: Postprandial plasma glucose

Table 2. Mean total daily dosage of OADs and BIAsp 30

	BIAsp 30 + OADs ¹	BIAsp 30 only
Safety population	270	573
Prior to study		
OADs, mg \pm S.D.		
Biguanides	1607.0 \pm 539.1	1629.0 \pm 546.8
Meglitinides	145.5 \pm 149.5	91.6 \pm 129.0
Thiazolidinediones	4.1 \pm 0.7	4.9 \pm 2.3
Alpha-glucosidase inhibitors	233.1 \pm 78.7	218.9 \pm 95.1
Baseline		
BIAsp 30, U/kg b.w. \pm S.D.	0.4 \pm 0.1	0.5 \pm 0.2
OADs, mg \pm S.D.		N.A. ²
Biguanides	1594.2 \pm 504.7	
Meglitinides	57.7 \pm 97.3	
Thiazolidinediones	4.4 \pm 1.3	
Alpha-glucosidase inhibitors	230.0 \pm 76.4	
Three months		
BIAsp 30, U/kg b.w. \pm S.D.	0.5 \pm 0.2	0.5 \pm 0.2
OADs, mg \pm S.D.		N.A.
Biguanides	1652.8 \pm 483.1	
Meglitinides	57.9 \pm 97.1	
Thiazolidinediones	4.2 \pm 1.3	
Alpha-glucosidase inhibitors	241.9 \pm 75.0	
Six months		
BIAsp 30, U/kg b.w. \pm S.D.	0.5 \pm 0.1	0.6 \pm 0.2
OADs, mg \pm S.D.		
Biguanides	1726.0 \pm 482.1	N.A.
Meglitinides	N.A. ³	
Thiazolidinediones	4.4 \pm 1.6	
Alpha-glucosidase inhibitors	264.5 \pm 59.4	

¹Dosage of sulphonylureas is not presented due to the wide range of sulphonylureas available. ²Not applicable because no patients took OADs. OADs: Oral antidiabetic drugs**Current treatment**

The dosage of biguanides and alpha glucosidase inhibitors concurrently prescribed with BIAsp 30 treatment generally increased from baseline to six months (Table 2) (dosage of sulphonylureas was not presented due to the wide range available). The mean total daily dosage of BIAsp 30 per body weight (b.w.) at three and six months increased slightly from baseline in both groups (Table 2). The majority of patients in both groups followed a twice-daily injection regimen: 97.4% at baseline, 96.1% at three months and 99.1% at six months in the BIAsp 30+OADs group and 98.8% at baseline, 98.6% at three months and 98.1% at six months in the BIAsp 30-only group.

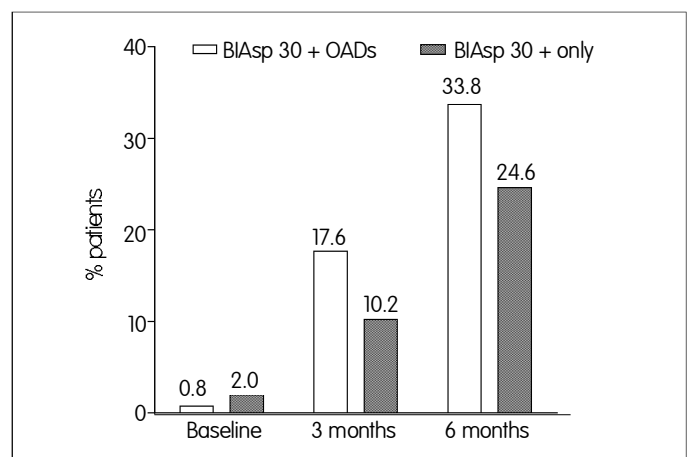
Efficacy

Glycaemic control was significantly better compared with baseline in both treatment groups at the end of three and six months ($p < 0.001$) (Table 3). Although a significantly greater reduction in mean HbA_{1c} was observed in the BIAsp 30+OADs group ($p < 0.001$ at three months, $p = 0.032$ at six months), the HbA_{1c} values at six months were comparable between the treatment groups (7.40 \pm 1.01% in the BIAsp 30+OADs group and 7.59 \pm 1.16% in the BIAsp 30-only group). Similarly, although the BIAsp 30-only group showed a significantly greater reduction in mean FPG ($p < 0.001$ at three and at six months) and mean PPPG ($p < 0.001$ at three and at six months), the mean FPG and PPPG values at six months were comparable between the groups: 145.0 \pm 39.5 mg/dl and 177.6 \pm 42.3 mg/dl in the BIAsp 30+OADs group, and 142.3 \pm 36.8 mg/dl and 181.4 \pm 48.3 mg/dl in the BIAsp 30-only group, respectively.

A higher proportion of patients in the BIAsp 30+OADs group reached target HbA_{1c}, compared with the BIAsp 30-only group (Fig. 1). Among the patients who achieved an HbA_{1c} of less than 7%, 38% in the BIAsp 30+OADs group and 85% in the BIAsp 30-only group did not report any hypoglycaemic episodes throughout the study.

Safety

The number of patients who reported hypoglycaemic episodes increased from 11.9% at baseline to 41.4% at six months in the BIAsp 30+OADs group and from 5.6% to 12.3% in the BIAsp 30-only group. Most of the hypoglycaemic episodes were reported at three months (335 events in the BIAsp 30+OADs group and 172 events in the BIAsp 30-only group), and fewer episodes were reported at six months (229 events and 143 events, respectively). Most of the hypoglycaemic episodes in both treatment groups were minor and diurnal in nature. While the rate of minor, diurnal and nocturnal hypoglycaemic episodes increased at the end of the study from baseline

**Figure 1.** Proportion of patients with an HbA_{1c} of < 7% before and after treatment

in both groups, the rate of major episodes decreased over the same period (Fig. 2). The BIAsp 30+OADs group reported a higher rate of minor, diurnal and nocturnal episodes, whereas the rate of major episodes was comparable between groups. Fifteen non-serious ADRs were reported in the BIAsp 30+OADs group and none in the BIAsp 30-only group. There were no serious ADRs reported in either treatment group. The non-serious ADRs were lipodystrophy (10 events), oedema (four events) and symptoms of local hypersensitivity (one event).

Discussion

The data from the Turkish PRESENT study serve to compare the results of two treatment options for initiating insulin treatment in

insulin-naïve patients in a clinical setting. Both regimens, BIAsp 30+OADs and BIAsp 30-only, were shown to be effective in lowering the parameters of glycaemic control. Since baseline demographic status and study design can influence the extent of improvements in the parameters of glycaemic control between studies (20), it is not appropriate to compare absolute results from our current study to other studies on BIAsp 30 treatment. Nevertheless, other studies of BIAsp 30 treatment in insulin-naïve patients have consistently reported reductions in HbA1c: BIAsp 30-only [-1.6% (7)] and BIAsp 30+OADs [-1.3% (8), -1.6% (21), -1.7% (7), -2.8% (12)].

In this study, patients treated with a combination of BIAsp 30+OADs showed a greater reduction in HbA1c levels, compared with those treated with BIAsp 30 alone. This finding is consistent with other studies of combination therapy involving insulin and OADs, particu-

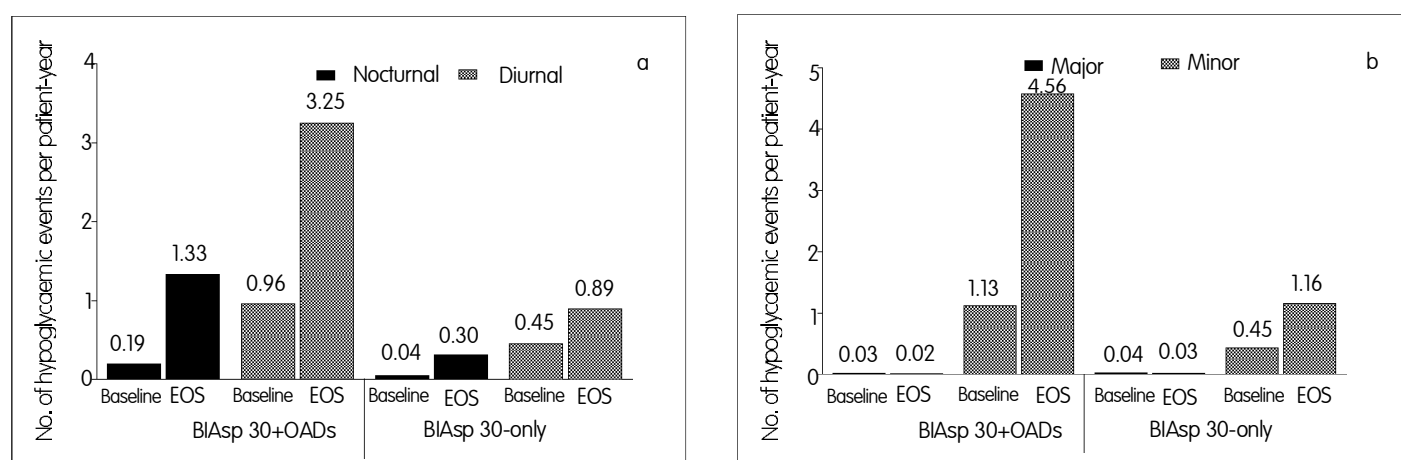


Figure 2. Hypoglycaemia at baseline and end of study (EOS) stratified according to (a) time of day and (b) severity. End of study includes data from three and six months

Table 3. Means and Standard Deviation of Concentration of FBS- 2hppBS – Hb A1C & C-peptide in Diabetic patients of L-Carnitine and placebo groups.

	BIAsp 30 + OADs	BIAsp 30 only
Safety population	270	573
Mean HbA1c, % ± S.D. (95% CI)		
At baseline	9.89±1.98	9.69±1.99
Change at three months of treatment	-1.96±1.63* (-2.18;-1.75)	-1.56±1.74* (-1.73;-1.39)
Change at six months of treatment	-2.35±1.82* (-2.60;-2.11)	-2.05 ± 1.85* (-2.23;-1.88)
Mean FPG, mg/dl ± S.D. (95% CI)		
At baseline	235.6 ± 78.9	277.2 ± 87.0
Change at three months of treatment	-70.6 ± 75.5* (-80.3;-60.9)	-110.6 ± 84.1* (-118.4;-102.7)
Change at six months of treatment	-85.4 ± 72.4* (-95.5;-75.3)	-125.6 ± 83.6* (-133.7;-117.5)
Mean PPPG, mg/dl ± S.D. (95% CI)		
At baseline	296.9 ± 88.1	344.3 ± 93.1
Change at three months of treatment	-101.2±90.4* (-113.1;-89.4)	-137.8±94.2* (-146.6;-129.2)
Change at six months of treatment	-106.8±80.2* (-118.4;-95.5)	-153.3±87.6* (-162.1;-144.5)

* p < 0.001 (change from baseline).

CI: Confidence interval; FPG: Fasting plasma glucose; PPPG: Postprandial plasma glucose

larly if the OADs used were insulin sensitizers such as thiazolidinediones or metformin (22). This combination therapy constitutes a regimen that could both replace insulin and increase insulin sensitivity, creating a synergistic drug effect (22). The only other known study on BIAsp 30 conducted in Turkey was a multi-centre, open-labeled, randomized, parallel-group trial comparing three treatment regimens in patients with type 2 diabetes: twice-daily BIAsp 30-only versus twice-daily BIAsp 30+metformin versus once-daily insulin glargine (18). After 24 weeks, mean HbA1c was reduced by 2.1% and 2.0% in patients treated with BIAsp 30+metformin and BIAsp 30-only, respectively (the mean HbA1c was reduced by 0.8% in patients treated with glargine). Similarly, in a multi-national, open-labeled, randomized, controlled trial on insulin-naïve patients (7), a twice-daily regimen of BIAsp 30+metformin was shown to reduce HbA1c by 1.7%, compared with 1.6% in a twice-daily regimen of BIAsp 30-only. A greater proportion of the patients in the BIAsp 30+OADs group achieved an HbA1c of less than 7%, compared with the BIAsp 30-only group. Similar results were reported in the previous Turkish study on BIAsp 30 (18). In a randomized, double-blind trial comparing insulin-only treatment with insulin+metformin treatment (23), 54% of patients in the insulin+metformin group achieved an HbA1c of less than 6.5%, compared with 18% in the insulin-only group. It appears that BIAsp 30+OAD combination therapy enabled more patients to reach target HbA1c, an observation that could be of interest to clinicians.

Interestingly, the reductions in FPG and PPPG were greater in the BIAsp 30-only group, compared with the BIAsp 30+OADs group.

A similar result was observed in the previous Turkish study, in which the BIAsp 30-only group showed a marginally greater reduction of 36.0 mg/dl in FPG, compared with a reduction of 34.2 mg/dl in the BIAsp 30+metformin group (18). It is likely that differences in baseline values of HbA1c, FPG and PPPG had an effect on the extent of improvement between the groups. Nevertheless, the final mean FPG and PPPG values were comparable between the groups.

The rate of hypoglycaemic episodes increased from baseline levels in both groups. This was not surprising since the rate of hypoglycaemia typically increases in patients when glycaemic control is improved (12,24). The increase was more pronounced in the BIAsp 30 + OADs group. One possible explanation is that while both treatment groups reported a similar increase in BIAsp 30 dosage from baseline to six months, the BIAsp 30+OADs group also reported increases in the dosage of OADs, particularly of the biguanides. This increase could have resulted in heightened sensitivity to insulin (22). Only minor hypoglycaemia was increased, whereas major hypoglycaemia was reduced. This important observation supports the safety profile of BIAsp 30 observed from other clinical trials (7,8,12,16,17). The majority of episodes occurred in the first three months, with fewer episodes occurring in the later part of the study. This concurs with the results of a two-year randomized, controlled, multi-national trial, which reported fewer major hypoglycaemic episodes in the second year, compared with the first year (17). This supports the hypothesis that the improved pharmacokinetic profile of biphasic insulin analogues may reduce the risk of hypoglycaemia while maintaining good control of hyperglycaemia (17). It is of interest to note that a proportion of patients who achieved target HbA1c (less than 7%) were able to do so without any reports of hypoglycaemia during the study. The more physiological profile of BIAsp 30 may be a possible explanation for this finding.

This study was observational in nature and hence had its inherent limitations. The method of data collection for hypoglycaemic episodes and ADRs was based on patient recollection, which could have resulted in inconsistent reporting from different countries. The treatment assignment to BIAsp30+OAD or BIAsp30 only was not randomized but was at the discretion of the physicians in a routine clinical setting. The study was conducted over a relatively short period of six months and was inadequate for capturing long-term trends and observations. However, given the fact that this study was carried out in a routine clinical setting, which would be a closer reflection of the "real-world", the results are a good indicator of the effects of treatment with BIAsp 30 in daily practice. The positive results from this study are in line with and support the results of previous randomized controlled trials with BIAsp 30.

Conclusions

BIAsp 30 was shown to effectively and safely improve glycaemic control in patients who were previously inadequately controlled on oral medication alone. Significant improvements were observed in both patients who were treated with BIAsp 30 alone or in combination with OADs. A combination of BIAsp 30+OADs offered slightly better improvement in HbA1c, compared with BIAsp 30 monotherapy. No major hypoglycaemic episodes were reported and both treatment options were associated with a low frequency of minor hypoglycaemia.

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