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The safety and efficacy of biphasic insulin aspart 30 (BIAsp 30) in Iranians with type 2 diabetes: an open-label, non-randomised, multi-centre observational study — the Iran subgroup of the IMPROVE™ study

Bezpieczeństwo i skuteczność dwufazowej insuliny aspart 30 (BIAsp 30) u Irańczyków chorych na cukrzycę typu 2: otwarte, nierandomizowane, wieloośrodkowe badanie — irańska podgrupa badania IMPROVE™

Alireza Esteghamati[1], Reza Rajabian[2], Masoud Amini[3], Amir Bahrami[4], Mohammad Ebrahim Khamseh[5], Mohammad Afkhami-Ardekani[6], Ehsan Parvaresh Rizi[7]

[1]*Imam Khomeini Hospital, Endocrine and Metabolism research Department, Tehran, Iran*
[2]*Mashhad University of Medical Sciences, Endocrine and Metabolism Department, Mashad, Iran*
[3]*Isfahan University of Medical Sciences, Isfahan Endocrine and Metabolism Research Centre, Isfahan, Iran*
[4]*Tabriz University of Medical Sciences, Endocrine and Metabolism Department, Tabriz, Iran*
[5]*Iran University of Medical Sciences, Endocrine and Metabolism Department, Tehran, Iran*
[6]*Shahid Sadoughi University of Medical Sciences, Yazd Diabetes Research Centre, Yazd, Iran*
[7]*Novo Nordisk Pars, Medical Department, Tehran, Iran*

Abstract

Introduction: To evaluate the clinical profile of BIAsp 30 (30% soluble insulin aspart, 70% protamine-crystallized insulin aspart) (NovoMix®30) in type 2 diabetes patients in routine clinical practice in Iran.

Material and methods: IMPROVE™ was a 26-week, multinational, open-label, non-randomized study in patients with type 2 diabetes. The safety and efficacy of BIAsp 30 were assessed at baseline and at 13 and 26 weeks. The titration of BIAsp30 was at the physician's discretion.

Results: In Iran, 478 patients (47% male) previously treated with oral antidiabetic drugs (OADs) (N = 159, 33.3%) and/or insulin other than BIAsp30 (N = 317, 66.3%) or a few who were treatment-naïve (N = 2, 0.4%) participated in the study. After 26 weeks of treatment with BIAsp 30, the rate of reported major hypoglycaemic episodes was reduced by 88.1% from baseline (baseline *v.* Week 26: 0.303 *v.* 0.037 episodes/pt-year; $p < 0.001$). No significant differences in minor hypoglycaemic episodes between baseline and Week 26 were found. Glycaemic control was significantly improved from baseline to Week 26 with a mean HbA_{1c} reduction of 1.2 ± 1.9%. Patients' quality of life as measured by the DiabMedSat questionnaire significantly improved from baseline (58.1) to the end of the study (75.4, $p < 0.001$).

Conclusions: BIAsp 30 therapy appeared safe and effective and improved quality of life in Iranian patients with type 2 diabetes after 26 weeks of treatment. **(Pol J Endocrinol 2010; 61 (4): 364–370)**

Key words: *type 2 diabetes, insulin aspart, quality of life*

Streszczenie

Wstęp: Celem badania była ocena profilu działania insuliny BIAsp 30 (30% rozpuszczalnej insuliny aspart, 70% insuliny krystalizowanej z protaminą) (NovoMix®30) u chorych na cukrzycę typu 2 w warunkach standardowej opieki zdrowotnej w Iranie.

Materiał i metody: IMPROVE™ było 26-tygodniowym, wieloośrodkowym, międzynarodowym, otwartym i nierandomizowanym badaniem z udziałem chorych na cukrzycę typu 2. Bezpieczeństwo i skuteczność insulin BIAsp 30 oceniano na początku badania oraz po 13 i 26 tygodniach. Dawkowanie insuliny BIAsp30 było zależne od zaleceń lekarskich.

Wyniki: W irańskiej części badania uczestniczyło 478 chorych (47% stanowili mężczyźni) leczonych dotychczas doustnymi lekami hipoglikemizującymi (N = 159, 33.3%) i/lub insuliną inną niż BIAsp30 (N = 317, 66,3%) oraz nieliczna grupa pacjentów niestosujących wcześniej farmakoterapii (N = 2, 0,4%). Po 26 tygodniach leczenia insuliną BIAsp 30, częstość epizodów ciężkiej hipoglikemii zmniejszyła się o 88,1% (wartości wyjściowe *v.* tydzień 26: 0,303 *v.* 0,037 epizodów/pacjenta-rok; $p < 0,001$). Dane dotyczące częstości epizodów lekkiej hipoglikemii na początku badania i po 26 tygodniach leczenia nie różniły się istotnie. Odnotowano natomiast poprawę kontroli glikemii; po 26 tygodniach odsetek HbA_{1c} obniżył się średnio o 1,2 ± 1,9% w stosunku do wartości wyjściowej. W okresie od rozpoczęcia do zakończenia badania nastąpiła istotna poprawa jakości życia chorych, oceniana przy użyciu kwestionariusza DiabMedSat; punktacja wynosiła odpowiednio 58,1 i 75,4 ($p < 0,001$).

Wnioski: Terapia insuliną BIAsp 30 stosowana przez 26 tygodni u Irańczyków chorych na cukrzycę typu 2 okazała się bezpieczna i skuteczna, a ponadto spowodowała poprawę jakości życia pacjentów. **(Endokrynol Pol 2010; 61 (4): 364–370)**

Słowa kluczowe: *cukrzyca typu 2, insulina aspart, jakość życia*

Ehsan Parvaresh Rizi M.D., Novo Nordisk Pars, 11th floor, Kian Tower, No. 2551, Sattari St., Vali-e-Asr Ave., 1968643111, Tehran, Iran, tel.: +98 91 259 743 98, e-mail: ehpa@novonordisk.com

Introduction

Therapy for type 2 diabetes has been focused on controlling fasting blood glucose (FBG) with oral antidiabetic drugs (OAD) and/or basal insulin [1]. As type 2 diabetes progresses, treatment strategies focusing on basal insulin combined with OADs are limited in their effectiveness due to the lack of provision for prandial insulin requirements. Hence, postprandial hyperglycaemia is becoming a significant contributor to overall glycaemic load. On the other hand, the relative contribution of postprandial glucose excursions is predominant in moderately controlled patients, whereas the contribution of fasting hyperglycaemia increases gradually with diabetes progression [2].

It is well established that incidence and progression of diabetic microvascular complications are correlated with the status of glycaemic control. Improved long-term glycaemic control (lower HbA_{1c}) has also been shown to be associated with a reduction in cardiovascular risks [3–8].

Metformin, in combination with diet and exercise, is recommended as a first line treatment for patients with type 2 diabetes by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Upon progression of type 2 diabetes, metformin is often combined with insulin secretagogues (e.g. sulphonylureas such as glimepiride) or peroxisome proliferator-activated receptor agonists (e.g. thiazolidinediones such as rosiglitazone). Insulin therapy, as add-on or monotherapy, is indicated for subjects who do not achieve good glycaemic control despite this OAD combination therapy. However, ADA/EASD also recommends the addition of insulin times when appropriate glycaemic control cannot be obtained with metformin mono-therapy alone in patients with type 2 diabetes [9].

Biphasic insulin aspart 30 (BIAsp 30) (NovoMix®30) is a premixed insulin analogue containing 30% unbound rapid-acting insulin aspart and 70% protaminated intermediate-acting insulin aspart. This premix formulation provides prandial and basal insulin coverage after one injection . The rapid onset of action of BIAsp 30 means that it can be injected immediately before or within 15 minutes of meal start [11], in contrast to biphasic human insulin which should be injected 30 minutes before a meal [12]. Garber et al. [13] demonstrated that the initiation of once daily treatment (and intense titration) with BIAsp 30 in combination with OADs enabled 41% of patients to achieve $HbA_{1c} \leq 7.0\%$, the ADA glycaemic target for patients with diabetes . More patients could safely achieve these goals when the number of daily injections was increased from one to two and from two to three. With three daily injections of BIAsp 30, good glycaemic control was achieved in 77% ($HbA_{1c} < 7.0\%$) of patients. In a treat-to-target study with insulin-naïve patients with type 2 diabetes poorly controlled with metformin (alone or in combination with other OADs), significantly more patients treated with BIAsp 30 twice daily than those treated once daily with insulin glargine achieved an $HbA_{1c} < 7.0\%$ (66% *v.* 40%, $p < 0.05$) [15]. The similar findings were also obtained in another study, in insulin-naïve patients with type 2 diabetes poorly controlled with OADs (twice-daily BIAsp 30 plus metformin *v.* once-daily insulin glargine plus glimepiride) [16].

Limited information about diabetes in Iran was available except recent epidemiological and cost data of diabetes in the Iranian population which indicates the prevalence of diabetes mellitus as 8.7% (age 25 to 64) with 3 times more direct costs for diabetics compared to non-diabetic patients [17–18]. Although the efficacy and safety of BIAsp 30 have been extensively documented in randomized clinical trials (RCTs) [13, 15–16, 19–22], there was no data regarding the use of BIAsp 30 in patients from Iran. Observational studies are a valuable tool for assessing the effectiveness and safety of drugs in a wide and heterogeneous population, without the confines of an RCT [23–24].

This observational study aimed to evaluate the clinical safety profile and efficacy of BIAsp 30 under normal clinical practice conditions in Iran.

Material and methods

Study design

IMPROVE™ is a 26-week, open-label, non-randomised, multi-centre observational study of patients with type 2 diabetes conducted in 11 countries (Canada, China, Greece, the Gulf region, India, Iran, Italy, Japan, Poland, Russia, and South Korea), as described in previous publications [19, 21]. The study included patients with type 2 diabetes who were 18 years old and above treated with BIAsp 30 in routine clinical practice.

Results from the Iranian subgroup are reported in this paper. 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 involved except the collection of data at baseline, follow-up visit (approximately 13 weeks), and final visit (approximately 26 weeks). The study was conducted in accordance with the Declaration of Helsinki. The procedures complied with local regulations governing observational studies, which were applicable to health authority and ethics committee approval and patient informed consent.

Measurements

The primary endpoint was the incidence of major hypoglycaemic events reported as serious adverse drug reactions (SADRs). A major hypoglycaemic episode was defined as an episode with severe central nervous system symptoms consistent with hypoglycaemia, in which the patient was unable to treat him/herself and had one measurement of blood glucose < 50 mg/dL (2.8 mmol/L) or reversal of symptoms after either food intake or glucagon or intravenous glucose administration. A 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).

The secondary endpoints included the number of SADRs, the number of minor hypoglycaemic episodes, changes in body weight and body mass index (BMI), HbA_{1c}, fasting blood glucose (FBG), the variability in FBG, post prandial glucose (PPG) 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) .This questionnaire had been translated into Farsi (Persian) and also validated in a subgroup of patients.

Statistical analyses

In this study, data were summarised by visits including baseline and Week 26. The summary of the baseline characteristics and safety data were based on a Full Analysis Set (FAS), which consisted of all patients with a baseline visit, who had been prescribed BIAsp 30 at least once and did not use BIAsp 30 before the start of the study. The analysis of the efficacy outcome variables were based on an Efficacy Analysis Set (EAS), which was defined as all patients from FAS who had the Week 26 visit, at least one measurement concerning FBG, PPG, most recent HbA_{1c}, weight, or hypoglycaemic episodes at baseline and Week 26, with the final visit within 18 to 31 weeks from baseline. The analysis of the quality of life (QoL) data was based on a Quality of Life Analysis Set (QLAS), 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 DiabMed questionnaire at baseline and Week 26.

Descriptive statistics were used to summarise the absolute number of hypoglycaemic episodes, and hypoglycaemic episodes were expressed as both the 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 Week 26. Descriptive statistics were used to summarise HbA_{1c}, mean FBG and FBG variability, and mean PPG and PPG variability. The proportion of patients who achieved $HbA_{1c} \leq 6.5\%$, $HbA_{1c} < 7.0\%$, and physician's own target recommendation for HbA_{1c} was summarised using percentages. Paired t-test was used to compare HbA_{1c}, mean FBG, and FBG variability values at baseline and Week 26. 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).

Table I. *Baseline characteristics*

Tabela I. *Charakterystyka badanych*

	Total
N	478
Mean age ± SD (years)	55.3 ± 11.8
Gender, M/F (%)	47/53
Mean weight ± SD [kg]	75.3 ± 14.3
Mean BMI ± SD [kg/m²]	28.1 ± 4.8
Mean diabetes duration ± SD (years)	13.2 ± 8.2
Mean HbA_{1c} ± SD (%)	8.6 ± 2.0
Macrovascular Complications	41.6%
Peripheral vascular disease	6.0%
Coronary heart disease	37.8%
Stroke	4.4%
Microvascular Complications	61.1%
Retinopathy	31.8%
Diabetic nephropathy	22.2%
Peripheral neuropathy	37.7%
Autonomic neuropathy	7.1%

Results

Baseline Demographics

A total of 479 patients were enrolled by 5 centres and 9 independent investigators from Tehran, Isfahan, Yazd, Tabriz, and Mashhad in Iran. One of the patients had biphasic insulin aspart treatment prior to the study and was excluded from the study. Included in the analysis were 478 patients, and 435 of them completed the study. The demographic characteristics of all patients and the reasons for initiating new therapy are summarised in Table I. The patients had a mean age of 55.2 ± 11.8 years, with a slightly higher proportion of females (male: female = 47/53%). Mean BMI was 28.1 ± 4.8 kg/m² and mean diabetes duration was 13.2 ± 8.2 years. Macrovascular complications (41.6%) and microvascular complications (61.1%) were commonly reported by the pa-

Table II. *Reason(s) for starting new therapy*
Tabela II. *Powody rozpoczęcia nowej terapii*

Reason(s) for starting new therapy, n (%)	Total
Easy Start of Insulin Therapy	190 (39.7)
Easy Intensification of Insulin Therapy	77 (16.1)
Improve HbA_{1c}	273 (57.1)
Improve FBG	309 (64.6)
Improve PPG	291 (60.9)
Reduce Risk of Hypoglycaemia	125 (26.2)
Patient Dissatisfaction with Previous Therapy	187 (39.1)
Side Effects from Previous Therapy	35 (7.3)
Change Due To Insulin Pen	250 (52.3)
Allow For Mealtime Administration	142 (29.7)

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

tients. The majority of the patients (N = 317, 66.3%) were previously treated with Insulin ± OAD, of which 34.7% were treated with insulin only and 31.6% with both insulin and OAD. Overall, 0.4% (N = 2) of patients were pharmacological intervention naive and 33.3% (N = 159) were previously treated with OAD only.

The most cited reason for starting new therapy was to improve glycaemic control (to improve FBG: 64.6%, to improve PPG: 60.9%, to improve HbA_{1c}: 57.1%) (Table II). The mean daily dose of BIAsp 30 after entering into the study (baseline) was 33.3 IU (0.44 IU/kg) and increased to 55.7 IU (0.70 IU/kg) at Week 26. The majority of patients injected BIAsp 30 on average twice daily throughout the study period (74.1% at baseline and 64.6% at Week 26). Patients were exposed to BIAsp 30 for approximately 27 weeks.

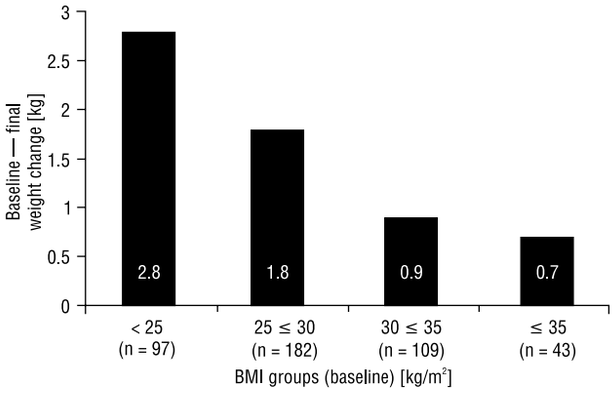

Figure 1. *Weight change by BMI groups*
Rycina 1. *Zmiana ciężaru ciała w zależności od wskaźnika BMI*

Safety

The proportion of patients with major hypoglycaemic episodes which were reported as SADRs during the study was 0.4%. The proportion of patients who reported major hypoglycaemic episodes decreased over time: from 4.4% at baseline to 0.5% at Week 26. The same trends were seen for daytime major episodes (2.9% at baseline to 0 at Week 26) and nocturnal episodes (2.1% at baseline to 0.5% at Week 26). In contrast, the proportion of patients reporting minor hypoglycaemic episodes did not change across the study period (37% at baseline and 34.7% at Week 26 visit), regardless of the time of occurrence (daytime or nocturnal episodes).

Major and minor hypoglycaemic episodes are also summarised as episodes/patient year in Figure 1. The total number of major hypoglycaemic episodes decreased from 0.303 episodes/patient year at baseline to 0.037 episodes/patient year at Week 26. Both daytime (baseline: 0.184 episodes/patient year, Week 26:

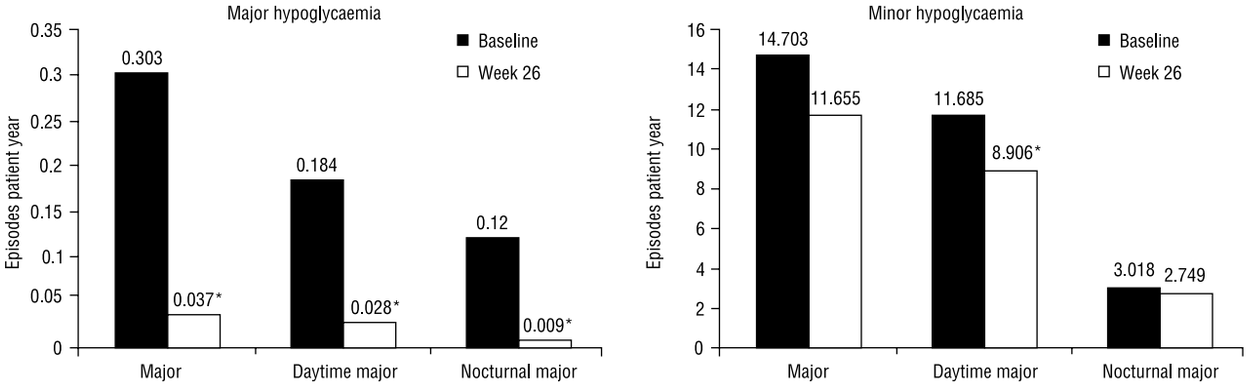

Figure 2. *Number of hypoglycaemic episodes (episodes/patient years)*
Rycina 2. *Liczba epizodów hipoglikemii (epizod/pacjent/rok)*

Table III. *Change from baseline in efficacy parameters*
Tabela III. *Zmiany parametrów skuteczności terapii w stosunku do wartości wyjściowych*

Parameter (SD)	Baseline	Week 26	Absolute change
Mean HbA_{1c}, %Hb	8.6 (2.0)	7.4 (1.2)	–1.2 (1.9)*
Mean FBG [mmol/L]	10.7 (3.8)	7.7 (2.3)	–3.0 (4.0)*
Mean PPG, mmol/L			
At breakfast	14.8 (5.1)	9.8 (2.9)	–5.0 (5.1)*
At lunch	12.4 (5.3)	9.9 (3.6)	–2.6 (5.4)*
At dinner	11.9 (4.6)	9.2 (2.3)	–2.7 (4.0)*
Body weight, kg	75.6 (14.5)	77.2 (14.3)	+1.7 (4.0)*
BMI [kg/m²]	28.2 (4.8)	28.9 (4.9)	+0.7 (.9)*
DiabMedSat			
Overall score	58.1 (12.7)	75.4 (12.0)	+17.3 (16.0)*
Relief of burden	68.9 (15.8)	83.0 (12.6)	+14.1 (18.5)*
Relief of symptoms	63.8 (15.8)	71.2 (15.9)	+7.4 (20.2)*
Effectiveness	42.1 (19.4)	72.6 (17.3)	+30.5 (25.0)*

* $p < 0.001$; FBG — fasting blood glucose; PPG — post prandial glucose; NS — not significant

0.028 episodes/patient year) and nocturnal (baseline: 0.120 episodes/patient year, Week 26: 0.009 episodes/patient year) major episodes also decreased. Daytime minor hypoglycaemic episodes decreased from 11.685 episodes/patient year at baseline to 8.906 episodes/patient year at Week 26. No differences between baseline and Week 26 were found in overall minor hypoglycaemic episodes and nocturnal minor hypoglycaemic episodes.

Efficacy

HbA_{1c} was significantly reduced by 1.24 ± 1.85% from baseline to Week 26. FBG was significantly reduced by 3.00 ± 3.95 mmol/L at Week 26. Moreover, the mean value of FBG variability was significantly reduced by 0.60 ± 1.56 mmol/L at Week 26 (Table III). A significant decrease was also observed in PPG at breakfast, lunch, and dinner (Table III).

Body weight

The mean values of body weight and BMI over time and the change from baseline to Week 26 are summarised in Table III. Body weight was significantly increased at Week 26 by 1.67 ± 4.86 kg. Accordingly, BMI was significantly increased at Week 26 by 0.66 ± ± 1.86 kg/m². The change in body weight from baseline to Week 26 by various BMI groups at baseline is shown in Figure 2. It is observed that the increase in body weight from baseline to the end of treatment appeared to be greater with decreasing baseline BMI.

Patient satisfaction

The overall total DiabMedSat score after 26 weeks was significantly higher than that of baseline (baseline *v.* Week 26: 58.1 *v.* 75.4, $p < 0.001$) (Table III). All three subscale scores of DiabMedSat, "burden", "symptoms", and "efficacy" at Week 26 were increased in contrast to that of baseline, with the greatest improvement in the 'efficacy' subscale (baseline *v.* Week 26: 42.1 *v.* 72.6, $p < 0.001$) (Table III).

Discussion

The IMPROVE™ study was a 26-week, multi-national, observational study in patients with type 2 diabetes, conducted to evaluate the clinical profile of BIAsp 30 in routine clinical practice. The safety and efficacy of BIAsp 30 were assessed at baseline and at Week 26. The results achieved in this study of the Iranian cohort of the IMPROVE™ study show that BIAsp 30 was safe, effective, and improved the quality of life in patients with type 2 diabetes. These results are in concordance with the findings in randomised clinical trials [12–13, 15–16, 26] as well as with the IMPROVE™ studies conducted in other countries [19–22].

The primary endpoint in this observational study was the incidence of major hypoglycaemic episodes reported as SADRs. The proportion of patients with major hypoglycaemic episodes which were reported as SADRs during the study was 0.4%. An association of

increased risk of hypoglycaemia and tight glycaemic control was demonstrated in previous studies. However, in this study although both fasting and post prandial glycaemic control was improved during the 26-week treatment with BIAsp 30, the number of hypoglycaemic episodes reported was significantly reduced over time, with most episodes occurring during the first 13 weeks of treatment. The safety profile observed in this study was consistent with the safety profile in the global IMPROVE™ study in which, generally, there was a lower risk of major hypoglycaemia (reduced from baseline by 89% after 26 weeks in the Iranian cohort and by 94% in global results) [22]. In line with the global IMPROVE™ study, no differences were found in minor hypoglycaemic episodes [22].

Treatment with BIAsp 30 enabled Iranian patients with type 2 diabetes to reach a mean HbA_{1c} of 7.39% after 26 weeks of treatment (mean baseline: 8.63%) with a mean reduction of 1.24%. For the global cohort, mean HbA_{1c} was decreased from 9.3% at baseline to 7.1% at Week 26 [22]. The greater mean reduction in HbA_{1c} in the global cohort could be explained by the larger portion of patients with no or OAD-only pretreatment in the global cohort. In the global cohort, 17.1% patients had received no previous treatment and 64.5% were on OAD only (*v.* 0.4% and 33%, respectively, in the Iran subgroup).

In line with the global results, FBG, the mean value of FBG variability, and PPG decreased significantly from baseline after the treatment with BIAsp 30. Therefore, BIAsp 30 not only provides basal insulin coverage but also effectively controls the postprandial component of glycaemic parameters, consistent with the finding in clinical trials [26].

An increase in body weight of 1.7 kg was observed after 26 weeks of treatment with BIAsp 30 in Iranian patients, while in the global IMPROVE™ study, weight changed very little from baseline to Week 26 (–0.1 kg) [22]. The discrepancy between the Iran cohort and global results might be due to the ethnic difference since the baseline BMI and the change in body weight varied greatly within countries in the IMPROVE™ study. It is indicated that further cross-ethnic comparisons are needed for better understanding of the relationship between BIAsp 30 and body weight.

The overall total DiabMedSat score after 26 weeks was significantly higher than at baseline (baseline *v.* Week 26: 58.1 *v.* 75.4), which is consistent with the global study (57.2 *v.* 74.5) [22]. The most cited reason for starting new therapy was to improve glycaemic control, indicating that patients were most dissatisfied with the efficacy of their previous treatments prior to the study. After 26 weeks' treatment with BIAsp 30, all three subscale scores of DiabMedSat, "burden", "symptoms", and "efficacy" were increased from baseline, with the greatest enhancement in the 'efficacy' subscale. The results indicated that treatment with BIAsp 30 significantly improved patient satisfaction and their quality of life.

Although limitations existed in this study in terms of a lack of control groups or tightly controlled populations and the potential recall bias in retrospective data collection, the better understanding of the safety and effectiveness of BIAsp 30 in routine clinical practice served as a valuable part for confirming the results from controlled clinical studies.

Conclusions

In routine clinical practice in Iran, treatment with BIAsp 30 can improve glycaemic control without increasing hypoglycaemic episodes in poorly controlled Iranian patients with type 2 diabetes. In addition, the improvement of overall treatment satisfaction may enhance patient adherence and self-management.

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Principal investigators for the IMPROVE™ — Iran Study Group

Alireza Esteghamati, Reza Rajabian, Masoud Amini, Amir Bahrami, Mohammad Ebrahim Khamseh, Mohammad Afkhami-Ardekani, Noushin Khalili, Mohammad Reza Mirzaei, Hasan Rezvaniyan, Sedighe Moradi, Fatemeh Golgiri, Iraj Heydari, Amirkamran Nikoosokhan, Lili Mahoozi, Hossein Delshad, Maryam Salami, Shahin Davalli, Amir Ziyaee, Jian Valiee, Manouchehr Nakhjavani, Mehdi Rafiee, Fatemeh Esfahanian, Peymaneh Heydariyan, Alireza Mofid, Hamidreza Zakeri, Alireza Mohajeri Tehrani, Sasan Sharghi, Mohammad Hasan Khazaei, Farzad Najafipour, Seyyed Morteza Taghavi, Omid Atoofi, Robabeh Abutorabi, Zohreh Moosavi, Mozhgan Afkhamizadeh, Mohammad Mohammadi, Naser Sartipzadeh, Mohammad Mashahiri, Akbar Aliasgarzadeh, Majid Mobasseri, Mitra Niyafar, Naser Aghamohammadzadeh, Hamidreza Aghaee meybodi, Saeideh Tavajoh, Ashraf Aminorroaya, Ali Kachooei, Mansour Siyavash, Mahmood Parham.

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