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Initiating or switching to biphasic insulin aspart 30 in type 2 diabetes patients from Algeria: a sub-analysis of the A_1chieve study

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ABSTRACT

Aim: To determine the safety and effectiveness of biphasic insulin aspart 30 (BIAsp 30) in Algerian patients with type 2 diabetes initiating insulin or switching from prior insulin therapy.
Methods: Insulin-naive and insulin-experienced patients, including prior basal insulin users, starting BIAsp 30 were evaluated in this sub-analysis of the 24-week, open-label, non-interventional A_1chieve study. Clinical safety and effectiveness was evaluated as a part of routine clinical care.
Results: A total of 134 insulin-naive patients initiating BIAsp 30 at a mean dose of 0.44±0.23 U/kg and 283 insulin-experienced patients, including 129 prior basal insulin users, switching from a mean pre-study insulin dose of 0.51±0.23 U/kg to BIAsp 30 (0.54±0.20 U/kg) were evaluated. At Week 24, the average BIAsp 30 dose was 0.60±0.25 U/kg and 0.66±0.24 U/kg in insulin-naive and insulin-experienced patients, respectively. No serious adverse drug reactions were reported. From baseline to Week 24, the proportion of patients experiencing overall hypoglycaemia increased in the insulin-naive group ($p = 0.0067$) and no significant changes were reported in the insulin-experienced group including prior basal insulin users. Glucose control improved significantly in the insulin-experienced group ($p < 0.001$) and appeared to improve in the insulin-naive patients and prior basal insulin users as well. Body weight increased significantly in all patients ($p < 0.001$). Quality of life was positively impacted after 24 weeks of BIAsp 30 therapy.
Conclusion: Initiating or switching to BIAsp 30 therapy in this Algerian cohort was well-tolerated and significantly improved glucose control.

1. Introduction

Algeria is currently facing a significant crisis to control the exponential increase of people with type 2 diabetes (T2D). A recent update from the International Diabetes Federation estimated a prevalence of 6.92% in 2012 and a projected prevalence of 7.7% by the year 2030 [1,2]. A multicentre cross-sectional study on 1005 patients assessing the status of the management of diabetes in Algeria revealed that only 18.7% of patients had HbA_{1c} <7%. Furthermore, a third of the patients had HbA_{1c} levels >9%. Among those included, 26% of patients were treated with oral

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glucose-lowering drugs (OGLDs) in combination with insulin and 19% of patients were on insulin therapy alone [3]. Despite the availability of general clinical and medical resources, diabetes management in this region is considered inadequate [4].

The amount of local clinical data available for Algeria as well as other developing countries facing the T2D epidemic is limited. In order to elucidate the existing status of T2D management and provide viable therapeutic options, the international, open-label, non-interventional A_1chieve study was conducted in 28 developing countries, including Algeria [5]. This study provides a comprehensive overview of baseline characteristics and T2D treatment strategies employed in routine clinical care. The safety and effectiveness of insulin analogues that are proven to establish glycaemic control with a reduced risk of adverse effects was evaluated in this study [5].

Premix insulin analogues, including biphasic insulin aspart 30 (BIAsp 30) offer a pharmacokinetic profile that is effective in providing both basal and post-prandial glucose control in T2D patients [6]. Randomized controlled trials have indicated that glycated haemoglobin (HbA_{1c}), fasting plasma glucose (FPG) and postprandial plasma glucose (PPPG) control with BIAsp 30 is comparable or superior when compared with biphasic human insulin 30 (BHI 30), insulin glargine or neutral protamine Hagedorn insulin in insulin-naive patients. BIAsp 30 therapy in these studies was also associated with a low risk of hypoglycaemia [7–9]. Controlling PPPG levels is vital to the prevention of macrovascular complications and cardiovascular deterioration [10–12]. Studies comparing basal insulins with BIAsp 30 indicate that the PPPG lowering effect of BIAsp 30 is superior to that of basal insulin [7,13,14]. In addition to insulin initiation, observational studies, including the A_1chieve study, also examined the safety and effectiveness of BIAsp 30 in patients switching from another insulin therapy. Complete A_1chieve study results are available online under www.A1chieve.com. Overall data indicated that glucose control improved and hypoglycaemia decreased in patients switching from basal insulins or BHI 30 [15–19]. This sub-analysis was conducted specifically to determine the safety and effectiveness of initiating or switching to BIAsp 30 in the Algerian cohort of the A_1chieve study.

2. Methods

2.1. Study design

The A_1chieve study [5] was a 24-week, international, prospective, non-interventional study to evaluate the safety and effectiveness of premixed insulin (BIAsp 30 [NovoMix 30®, Novo Nordisk]), basal insulin (insulin detemir [Levemir®, Novo Nordisk)] and prandial insulin (insulin aspart [NovoRapid®, Novo Nordisk]), alone or in combination with OGLDs in T2D patients from developing countries. This sub-analysis was conducted in Algerian patients with T2D initiating or switching to BIAsp 30 at the discretion of their consulting physicians. Patients were recruited at 90 sites in Algeria between March 2009 and September 2010. BIAsp 30 was commercially available and was administered in accordance with local regulations. As there were no defined study procedures, all assessments were made by the treating physician during routine visits in normal clinical care. Data for analysis from the physicians' clinical notes and patients' recall and self-monitoring diary/meter were collected at baseline and final visit (around 24 weeks from baseline).

2.2. Patients

Insulin-naive and insulin-experienced patients including those on pre-study basal insulins were included in this sub-analysis. Patients who had received any of the A_1chieve study insulin analogues (alone or in combination) for more than 4 weeks prior to the study were not eligible. Pregnant women and women who were breast-feeding or had the intention of becoming pregnant were also excluded. All patients signed informed consent to participate in this study and the study was approved by the ethics committee of Algeria.

2.3. Outcomes

The primary outcome was the clinical safety of BIAsp 30 based on the incidence of serious adverse drug reactions (SADRs), including major hypoglycaemia over 24 weeks. Secondary safety assessments were changes in the occurrence of hypoglycaemic events in the last 4 weeks prior to baseline and final visit, changes in nocturnal hypoglycaemia during this period and the number of serious adverse events (SAEs). Measures to assess effectiveness of therapy comprised change from baseline to Week 24 in HbA_{1c}, FPG, PPPG, body weight, lipid profile and systolic blood pressure (SBP). Health-related quality of life (QoL) was evaluated using the EQ-5D questionnaire that assesses mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Subsequently, the QoL was measured on a standard 20-cm visual analogue scale (VAS, 0–100 [worst imaginable health to best imaginable health]).

2.4. Statistical analyses

Statistical analyses were performed by pre-study therapy type, i.e., insulin-naive and insulin-experienced patients. Since a large number of insulin-experienced patients switched from pre-study basal insulin to BIAsp 30, this subgroup was also evaluated separately. As the patients were not randomized, baseline characteristics including concomitant medical conditions, choice of insulin and time of initiation were not completely elucidated. Hence, comparisons between insulin-naive and insulin-experienced patients were descriptive rather than statistical.

Continuous and discrete variables were summarized using descriptive statistics and frequency tables (n, %), respectively. Unless otherwise stated, all statistical analyses were conducted using two-sided tests at a pre-specified 5% significance level. The paired t-test was used to

Table 1 – Demographic and baseline characteristics for all patients receiving biphasic insulin aspart 30 by pre-study therapy

Parameter	Insulin-naive	Insulin-experienced	Prior basal insulin users
n	134	283	129
Gender (male/female), %	34.3/65.7	27.9/72.1	28.7/71.3
Age, years	59.2 (10.0)	61.7 (10.4)	62.7 (10.3)
Body weight, kg	70.6 (13.2)	75.6 (12.5)	76.1 (13.0)
Body mass index, kg/m^2	26.8 (5.4)	29.1 (4.8)	29.2 (4.9)
Diabetes duration, years	10.1 (6.2)	14.2 (7.3)	13.3 (7.2)
Duration on insulin, years	0.0 (0.1) [a]	4.7 (4.8)	3.5 (4.4)
Current smokers, n (%)	9 (6.7)	6 (2.1)	3 (6.5)
HbA_{1c}, mmol/mol	87 (23)	75 (20)	79 (20)
HbA_{1c}, %	10.1 (2.1)	9.0 (1.8)	9.4 (1.8)
Duration on OGLDs, years	9.8 (6.3)	11.4 (7.4)	11.6 (6.9)
Prior OGLDs, n (%)			
Metformin	103 (79.8)	153 (80.5)	90 (81.8)
Sulfonylureas	96 (74.4)	76 (40.0)	60 (54.5)
Glucosidase inhibitors	25 (19.4)	17 (8.9)	10 (9.1)
Glinides	14 (10.9)	25 (13.2)	19 (17.3)
1 OGLD	35 (27.1)	117 (61.6)	47 (42.7)
2 OGLDs	78 (60.5)	66 (34.7)	57 (51.8)
>2 OGLDs	16 (12.4)	7 (3.7)	6 (5.5)

Data are presented as mean (SD) unless specified otherwise.
[a] Some patients were on insulin for a short period in the past, but were not on insulin when they were enrolled into the study.

analyse the changes in HbA_{1c}, FPG, PPPG, SBP, blood lipids, body weight and QoL from baseline to Week 24. McNemar's test was used to analyse changes from baseline to Week 24 in the proportion of patients reporting at least one hypoglycaemic event. Detailed statistical analyses of the A_1chieve study are discussed elsewhere [4]. All analyses were performed by Novo Nordisk A/S using SAS® Version 9.1.3.

3. Results

3.1. Baseline and demographic characteristics

This sub-analysis included a total of 417 patients starting BIAsp 30 therapy. Of these, 134 patients were insulin-naive and 283 patients were insulin-experienced at baseline. Among the insulin-experienced patients, 129 were on a pre-study basal insulin therapy. Baseline and demographic characteristics for the three subgroups are presented in Table 1. Physicians decided to start BIAsp 30 in 97% of insulin-naive patients and 84.8% of insulin-experienced patients to improve glucose control. The most frequently administered OGLD pre-study was metformin in 79.8% of insulin-naive patients, 80.5% of insulin-experienced patients and 81.8% of prior basal insulin users. Pre-study, a total of 60.5% of insulin-naive patients and 51.8% of prior basal-insulin users were on 2 OGLDs, while, overall, 61.6% of insulin-experienced patients were on 1 OGLD.

3.2. Insulin dose and dosing frequency

BIAsp 30 was initiated in insulin-naive patients at a mean dose of 0.44±0.23 U/kg and titrated up to 0.60±0.25 U/kg by Week 24. Insulin-experienced patients were on a mean pre-study insulin dose of 0.51±0.23 U/kg while the mean BIAsp 30 dose at baseline was 0.54±0.20 U/kg and 0.66±0.24 U/kg by Week 24. The average pre-study basal insulin dose was 0.39±0.18 U/kg. Patients in this subgroup started BIAsp 30 therapy at a mean dose of 0.46±0.18 U/kg that was titrated to 0.62±0.25 U/kg by Week 24. The majority of patients were on a twice-daily BIAsp 30 dosing regimen at baseline and Week 24 (Table 2).

3.3. SADRs and SAEs

During the 24-week evaluation period, no SADRs were reported in any subgroup. A total of 4 SAEs (event type: 1, acute coronary syndrome; 1, gangrene; 2, hypoglycaemia) in 4 insulin-naive patients were reported. In the insulin-experienced group, 5 SAEs (event type: 1, hypoglycaemia, 1, myocardial infarction; 1, cardiogenic shock; 1, pancreatic carcinoma; 1, cholesteatoma) in 5 patients were reported. No SAEs were reported in the patients switching from prior basal insulin therapy. Of the 5 SAEs in insulin-experienced patients, 3 had fatal outcomes. The relation to BIAsp 30 was unlikely for all SAEs reported.

Table 2 – Insulin dose and frequency by pre-study therapy

		Insulin-naive	Insulin-experienced	Prior basal insulin users
Insulin dose[a], U/kg	n	134	282	128
	Pre-study	–	0.51 (0.23)	0.39 (0.18)
	Baseline	0.44 (0.23)	0.54 (0.20)	0.46 (0.18)
	Week 24	0.60 (0.25)	0.66 (0.24)	0.62 (0.25)
Dose frequency, n (%)	Pre-study (n)	–	283	129
	Once daily		97 (34.3)	93 (72.1)
	Twice daily		171 (60.4)	36 (27.9)
	Thrice daily		9 (3.2)	–
	>Thrice daily		6 (2.1)	–
	Baseline (n)	134	283	129
	Once daily	26 (19.4)	16 (5.7)	13 (10.1)
	Twice daily	104 (77.6)	255 (90.1)	113 (87.6)
	Thrice daily	4 (3.0)	12 (4.2)	3 (2.3)
	>Thrice daily	–	–	–
	Week 24 (n)	119	259	118
	Once daily	13 (10.9)	12 (4.6)	8 (6.8)
	Twice daily	94 (79.0)	207 (79.9)	91 (77.1)
	Thrice daily	10 (8.4)	33 (12.7)	18 (15.3)
	>Thrice daily	2 (1.7)	7 (2.7)	1 (0.8)

[a] Data are presented as mean (SD).

Table 3 – Baseline and 24-week hypoglycaemia data for patients receiving biphasic insulin aspart 30 by pre-study therapy

Hypoglycaemia		Insulin-naive		Insulin-experienced		Prior basal insulin users	
		Incidence[a]	%[b]	Incidence[a]	%[b]	Incidence[a]	%[b]
Overall	Baseline	2.62	6.7	8.27	25.1	6.35	20.2
	Week 24	4.26	15.1	7.13	20.8	10.03	25.4
	p	–	0.0067	–	0.163	–	0.3035
Minor	Baseline	2.43	6.0	8.04	25.1	6.15	20.2
	Week 24	4.15	14.3	6.68	20.5	9.92	25.4
	p	–	0.0046	–	0.1281	–	0.3035
Nocturnal	Baseline	0.87	3.0	4.04	13.8	2.92	10.9
	Week 24	1.42	4.2	2.56	9.7	3.64	13.6
	p	–	0.2568	–	0.1489	–	0.5316
Major	Baseline	0.19	0.7	0.23	1.4	0.20	0.8
	Week 24	0.11	0.8	0.45	0.8	0.11	0.8
	p	–	1	–	0.4142	–	1

p-values are from McNemar's test on paired proportions of patients experiencing hypoglycaemia.
[a]Events per patient-year.
[b]% of patients experiencing at least one hypoglycaemic event.

3.4. Hypoglycaemia

The proportion of insulin-naive patients experiencing overall hypoglycaemia increased significantly from 6.7% at baseline to 15.1% at Week 24 ($p = 0.0067$). The proportion of insulin-experienced patients experiencing hypoglycaemia, including those on pre-study basal insulin, did not change significantly from baseline to Week 24. The proportion of patients experiencing major and nocturnal hypoglycaemia did not change significantly between baseline and Week 24 in any group (Table 3).

3.5. Glucose control

From baseline to Week 24, HbA_{1c} levels appeared to decrease in insulin-naive patients [10.1±2.1% (87±23 mmol/mol) vs. 7.8±1.4% (62±15 mmol/mol)] and in pre-study basal insulin users [9.4±1.8% (79±20 mmol/mol) vs. 8.3±1.6% (67±18 mmol/mol)]. Overall, in the insulin-experienced patients, HbA_{1c} significantly decreased from 9.0±1.8% (75±20 mmol/mol) at baseline to 8.1±1.5% (65±16 mmol/mol) at Week 24. HbA_{1c} <7.0% (<53 mmol/mol) was observed in 34 (35.4%) insulin-naive patients at Week 24 compared to

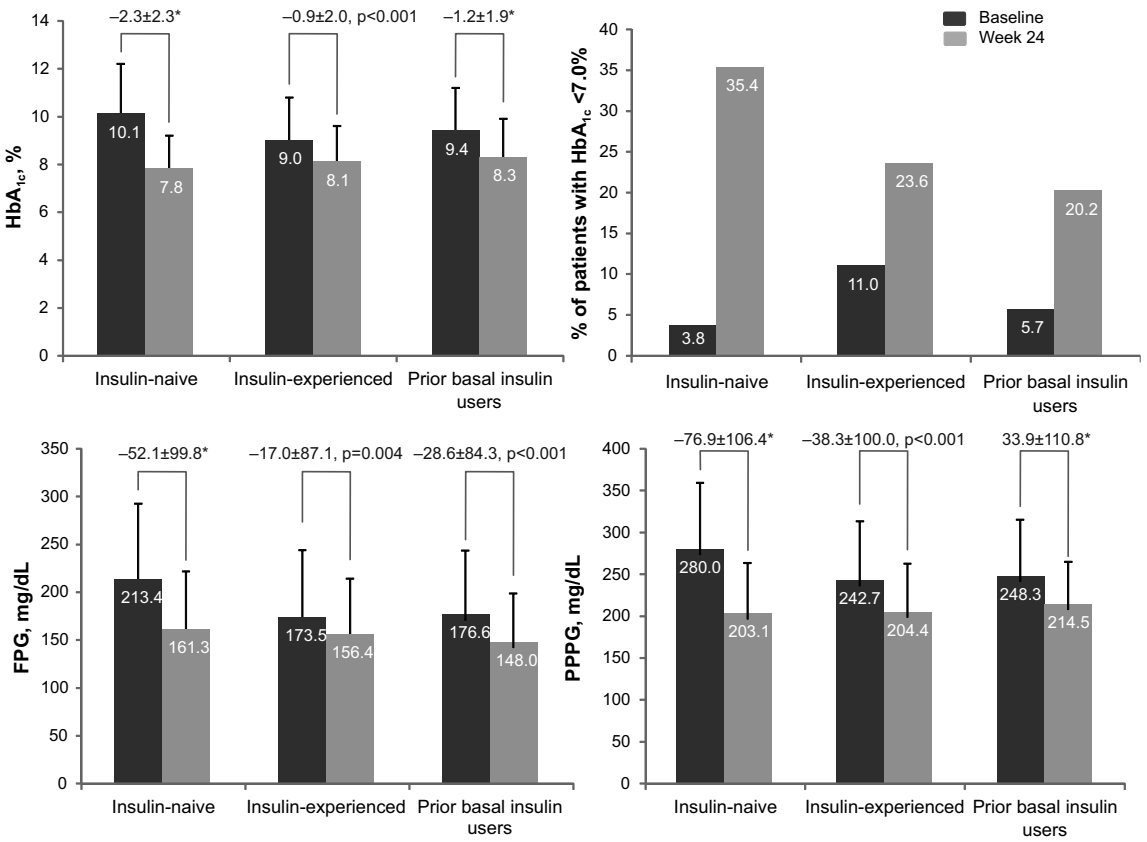

Fig. 1 – Change from baseline to Week 24 in glucose control parameters. *p-value not reported as n < 100.

4 (3.8%) patients at baseline. In the insulin-experienced group, 54 (23.6%) patients including 22 (20.2%) pre-study basal insulin users reported HbA_{1c} <7.0% (<53 mmol/mol) at Week 24 compared to 24 (11.0%) patients [6 (5.7%) pre-study basal insulin users] reporting this target at baseline (Fig. 1).

FPG levels significantly decreased in insulin-experienced patients and prior basal insulin users from 173.5±70.4 mg/dL and 176.6±67.0 mg/dL at baseline to 156.4±57.8 mg/dL and 148.0±50.6 mg/dL at Week 24, respectively ($p < 0.005$). In insulin-naive patients, the mean FPG was 161.3±60.3 mg/dL at Week 24 compared to 213.4±79.0 mg/dL at baseline. PPPG decreased significantly from 242.7±81.9 mg/dL at baseline to 204.4±70.1 mg/dL at Week 24 in insulin-experienced patients ($p < 0.001$). From baseline to Week 24, insulin-naive patients (280.0±88.9 vs. 203.1±68.4 mg/dL) and pre-study basal insulin users (248.3±85.5 vs. 214.5±81.3 mg/dL) also appeared to experience improvements in PPPG (Fig. 1).

3.6. Body weight, SBP and lipids

Body weight increased significantly from 70.6±13.2 kg at baseline to 73.8±12.8 kg at Week 24 in insulin-naive patients ($p < 0.001$). Insulin-experienced patients including pre-study basal insulin users also experienced a significant increase in weight from baseline to Week 24 ($p < 0.001$, Table 4). Changes in SBP and lipids, over 24 weeks of BIAsp 30 therapy, were not conclusive (Table 4).

3.7. Quality of life

From baseline to Week 24, VAS scores of the EQ-5D improved significantly in insulin-naive patients (59.8±16.7 vs. 72.7±13.7 points, $p < 0.001$), insulin-experienced patients (62.3±16.8 vs. 71.2±14.6 points, $p < 0.001$) and pre-study basal insulin users (59.4±16.1 vs. 70.9±14.6 points, $p < 0.001$).

4. Discussion

This sub-analysis evaluated the safety and effectiveness of BIAsp 30 therapy in insulin-naive and insulin-experienced patients with T2D in Algeria. Overall improvements in glycaemic control were associated with a well-tolerated BIAsp 30 regimen without any incidence of SADRs.

At baseline, it was observed that patients presented with poorly controlled T2D, a trend that was evidenced in several participating countries of the A_1chieve study [5]. There is evidence that early initiation and active intensification of insulin could potentially alter the progression of T2D [20]. The United Kingdom Prospective Diabetes study demonstrated that 53% of patients receiving sulphonylurea as monotherapy for diabetes management, required insulin over a period of 6 years [21]. Also, an increase in HbA_{1c} levels following the use of more than 1 OGLD is associated with a corresponding decrease in beta-cell mass and function [22]. However, despite an average diabetes duration of 10.1 years and a mean HbA_{1c} level as high as 10.1% (87 mmol/mol),

Table 4 – Baseline and 24-week data for body weight, SBP and lipid profile

		Insulin-naive	Insulin-experienced	Prior basal insulin users
Weight, kg	n	117	257	116
	Baseline	70.6 (13.2)	75.6 (12.5)	76.1 (13.0)
	Week 24	73.8 (12.8)	76.8 (12.7)	78.0 (13.9)
	Change	3.3 (4.4)	1.2 (3.9)	1.8 (3.6)
	p	<0.001	<0.001	<0.001
SBP, mmHg	n	119	256	116
	Baseline	129.6 (17.2)	128.9 (17.8)	130.5 (17.8)
	Week 24	128.8 (15.7)	127.5 (17.4)	128.7 (18.4)
	Change	–0.8 (17.3)	–1.4 (17.4)	–1.9 (17.1)
	p	0.604	0.203	0.241
Total cholesterol, mmol/L	n	78	159	75
	Baseline	4.7 (1.2)	4.5 (1.1)	4.4 (1.0)
	Week 24	4.7 (1.1)	4.5 (1.0)	4.4 (1.0)
	Change	0.0 (1.2)	0.0 (1.1)	0.0 (1.1)
	p		0.997	
Triglycerides, mmol/L	n	78	174	84
	Baseline	1.5 (0.7)	1.5 (1.0)	1.5 (1.2)
	Week 24	1.3 (0.5)	1.4 (0.6)	1.4 (0.6)
	Change	–0.1 (0.8)	–0.0 (1.0)	–0.1 (1.2)
	p		0.63	
HDL cholesterol, mmol/L	n	48	104	55
	Baseline	1.2 (0.3)	1.2 (0.6)	1.0 (0.5)
	Week 24	1.2 (0.4)	1.2 (0.3)	1.2 (0.4)
	Change	0.0 (0.5)	–0.0 (0.5)	0.1 (0.5)
	p		0.933	
LDL cholesterol, mmol/L	n	46	107	55
	Baseline	2.9 (1.1)	2.8 (1.8)	2.7 (1.9)
	Week 24	2.9 (1.0)	2.8 (1.6)	2.9 (2.2)
	Change	–0.0 (1.1)	0.0 (2.5)	0.2 (2.9)
	p		0.904	

HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure.
Data are presented as mean (SD).
p-values are not presented when n < 100.

insulin-naive patients had not initiated insulin therapy in this Algerian cohort. The alarming delay in insulin initiation and intensification suggests a clinical inertia despite the recommended guidelines. Additionally, insulin-experienced patients had higher diabetes duration of 14.2 years but they had received insulin therapy for a mean duration of only 4.7 years and their mean HbA_{1c} was 9.0% (75 mmol/mol). International evidence-based guidelines recommend a therapeutic target of HbA_{1c} <7.0% (<53 mmol/mol) to reduce the risk of long-term complications. However, HbA_{1c} <7.0% (<53 mmol/mol) was reported only in 4 of 134 insulin-naive patients and 24 of 283 insulin-experienced patients. Evidently, the pre-study treatment options failed to establish adequate glycaemic control. BIAsp 30 was prescribed by consulting physicians in the majority of patients to improve glycaemic control.

After 24 weeks of BIAsp 30 therapy, glucose control parameters appeared to improve in insulin-naive patients and those switching from basal insulin therapy and the overall insulin-experienced cohort experienced a significant improvement in HbA_{1c}, FPG and PPPG. As expected, with insulin initiation, the proportion of insulin-naive patients experiencing overall hypoglycaemia increased. Although the proportion of insulin-experienced patients reporting overall hypoglycaemia decreased from baseline to Week 24, the difference was not significant. However, prior basal insulin users evaluated separately reported a non-significant increase in the proportion of patients reporting overall hypoglycaemia. The proportion of patients affected with major hypoglycaemia was not significantly different from baseline to Week 24 in any of the groups. Previous studies have reported an increase in nocturnal hypoglycaemia with BIAsp 30 compared to basal insulin; however, the proportion of patients experiencing nocturnal hypoglycaemia in this cohort did not differ significantly from baseline to Week 24.

The increase in weight gain associated with BIAsp 30 therapy in insulin-naive patients as well as those switching from other insulins was also reiterated in this cohort [13,14]. However, the overall QoL was positively impacted in all patients. This outcome holds significance especially in T2D and its associated complications that have a physical and psychological impact on the patients' well-being.

The study data are subject to standard limitations of observational studies including non-standardisation of methods and lack of a control group. Nevertheless, this study provides the basis to guide therapeutic decisions in routine diabetes care clinics that encounter patients with varied baseline characteristics and concomitant disease states. Additionally, regional data add value to the management of diseases like T2D that are associated with a genetic predisposition and influenced by lifestyle and diet.

In conclusion, BIAsp 30 could be regarded as a simple, effective and convenient option for intensification of treatment in patients initiating insulin or switching from other insulins including basal insulin.

Conflict of interest statement

Alkassem Lezzar is a board member and speaker for Novo Nordisk; he received funding for advisory and speaker activities. Abdellah Salah-Mansour is a speaker for Novo Nordisk. Fatima Ayad and Abdesselam Yahia Berrouiguet have no conflict of interests to report. Amine Dahaoui is employed by Novo Nordisk. This study was sponsored by Novo Nordisk A/S, Denmark. The sponsor took part in the development of the protocol, the process of data collection and analysis, funding of medical writing services, and in reviewing the manuscript, but not in participant selection, choice of therapies (study or otherwise), provision of therapies including insulin or continuing clinical management of the participants.

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REFERENCES

[1] International Diabetes Federation. IDF Diabetes Atlas. 5th ed. Brussels, Belgium; 2011, updated 14 November 2012.
[2] Whiting DR, Guariguata L, Weil C, Shaw J. IDF diabetes atlas: global estimates of the prevalence of diabetes for 2011 and 2030. Diabetes Res Clin Pract 2011;94(3):311–21.
[3] Belhadj M, Malek R, Boudiba A, Lezzar E, Roula D, Sekkal F, et al. DiabCare Algérie. Médecine des maladies Métaboliques 2010;4(1):1–5.
[4] Boudiba A, Mimouni-Zerguini S. Improving care and prevention for people with diabetes in Algeria. Diabetes Voice 2008;53(2):19–21.
[5] Home P, Naggar NE, Khamseh M, Gonzalez-Galvez G, Shen C, Chakkarwar P, et al. An observational non-interventional study of patients with diabetes beginning or changed to insulin analogue therapy in non-Western countries: The A_1chieve study. Diabetes Res Clin Pract 2011;94:352–63.
[6] Liebl A, Prusty V, Valensi P, Kawamori R, Christiansen JS, Palmer AJ, et al. Ten years of experience with biphasic insulin aspart 30: from drug development to the latest clinical findings. Drugs 2012;72(11):1495–520.
[7] Raskin P, Allen E, Hollander P, Lewin A, Gabbay RA, Hu P, et al. Initiating insulin therapy in type 2 diabetes: a comparison of biphasic and basal insulin analogs. Diabetes Care 2005;28:260–5.
[8] Kilo C, Mezitis N, Jain R, Mersey J, McGill J, Raskin P. Starting patients with type 2 diabetes on insulin therapy using once-daily injections of biphasic insulin aspart 70/30, biphasic human insulin 70/30, or NPH insulin in combination with metformin. J Diabetes Complications 2003;17:307–13.
[9] Christiansen JS, Vaz JA, Metelko Z, Bogoev M, Dedov I. Twice daily biphasic insulin aspart improves postprandial glycaemic control more effectively than twice daily NPH insulin, with low risk of hypoglycaemia, in patients with type 2 diabetes. Diabetes Obes Metab 2003;5:446–54.
[10] Ceriello A, Davidson J, Hanefeld M, Leiter L, Monnier L, Owens D, et al.; International Prandial Glucose Regulation Study Group. Postprandial hyperglycaemia and cardiovascular complications of diabetes: an update. Nutr Metab Cardiovasc Dis 2006;16(7):453–6.
[11] Selvin E, Marinopoulos S, Berkenblit G, Rami T, Brancati FL, Powe NR, et al. Metaanalysis: glycosylated hemoglobin and cardiovascular disease in diabetes mellitus. Ann Intern Med 2004;141:421–31.
[12] Qiao Q, Tuomilehto J, Borch-Johnsen K. Post-challenge hyperglycaemia is associated with premature death and macrovascular complications. Diabetologia 2003;46(Suppl. 1): M17–21.
[13] Strojek K, Bebakar WM, Khutsoane DT, Pesic M, Smahelová A, Thomsen HF, et al. Once-daily initiation with biphasic insulin aspart 30 versus insulin glargine in patients with type 2 diabetes inadequately controlled with oral drugs: an open-label, multinational RCT. Curr Med Res Opin 2009;25: 2887–94.
[14] Ligthelm RJ, Gylvin T, DeLuzio T, Raskin P. A comparison of twice-daily biphasic insulin aspart 70/30 and once-daily insulin glargine in persons with type 2 diabetes mellitus inadequately controlled on basal insulin and oral therapy: a randomized, open-label study. Endocr Pract 2011;17:41–50.
[15] Gumprecht J, Benroubi M, Borzi V, Kawamori R, Shaban J, Shah S, et al.; on behalf of the IMPROVE Study Group

Expert Panel. Intensification to biphasic insulin aspart 30/70 (BIAsp 30, NovoMix 30) can improve glycaemic control in patients treated with basal insulins: a subgroup analysis of the IMPROVE observational study. Int J Clin Pract 2009;63:966–72.

[16] Shah S, Benroubi M, Borzi V, Gumprecht J, Kawamori R, Shaban J, et al.; on behalf of the IMPROVE Study Group Expert Panel. Safety and effectiveness of biphasic insulin aspart 30/70 (NovoMix 30) when switching from human premix insulin in patients with type 2 diabetes: subgroup analysis from the 6-month IMPROVE observational study. Int J Clin Pract 2009;63:574–82.

[17] Jang HC, Guler S, Shestakova M, on behalf of the PRESENT Study Group. When glycaemic targets can no longer be achieved with basal insulin in type 2 diabetes, can simple intensification with a modern premixed insulin help? Results from a subanalysis of the PRESENT study. Int J Clin Pract 2008;62:1013–8.

[18] Shestakova M, Sharma SK, Almustafa M, Min KW, Ayad N, Azar ST, et al. Transferring type 2 diabetes patients with uncontrolled glycaemia from biphasic human insulin to biphasic insulin aspart 30: experiences from the PRESENT study. Curr Med Res Opin 2007;23:3209–14.

[19] Naggar NK, Soewondo P, Khamseh ME, Chen JW, Haddad J. Switching from biphasic human insulin 30 to biphasic insulin aspart 30 in type 2 diabetes is associated with improved glycaemic control and a positive safety profile: Results from the A(1)chieve study. Diabetes Res Clin Pract 2012;98(3):408–13.

[20] Niswender K. Early and aggressive initiation of insulin therapy for type 2 diabetes: What is the evidence? Clin Diab 2009;27:60–8.

[21] Wright A, Burden ACF, Paisey RB, Cill CA, Holman RR, and the UK Prospective Diabetes Study Group. Sulphonylurea inadequacy: efficacy of addition of insulin over 6 years in patients with type 2 diabetes in the UK. Prospective Diabetes Study (UKPDS 57). Diabetes Care 2002;25:330–6.

[22] Riedel AA, Heien H, Wogen J, Plauschinat CA. Secondary failure of glycemic control for patients adding thiazolidinedione or sulphonylurea therapy to metformin regimen. Am J Manag Care 2007;13:457–63.