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Criteria influencing the choice of starting insulin regimen in patients with type 2 diabetes in routine clinical practice: baseline data from the Algerian cohort of the A_1chieve study

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ABSTRACT

Aim: To examine the criteria that may influence physicians' choice of starting insulin in type 2 diabetes patients in routine practice in Algeria as a sub-analysis of the A_1chieve study.

Methods: A_1chieve was a 24-week international, prospective, non-interventional study conducted to evaluate the safety and effectiveness of biphasic insulin aspart 30 (BIAsp 30), insulin detemir (IDet), or insulin aspart alone or in combination, in real-life clinical settings. We report an analysis of baseline data from insulin-naive patients initiating basal or premix insulin from the Algeria cohort (n = 1494). Demographic and anthropometric data, blood glucose control at inclusion, microvascular complications, and pre-study therapy was compared between the two groups.

Results: A total of 772 insulin-naive patients initiating therapy with IDet or BIAsp 30 were included in this analysis: IDet: 638 (83%), BIAsp 30: 134 (17%). Most IDet-group patients initiated once-daily therapy (n = 636; 99.7%); conversely, most BIAsp 30-group patients started twice-daily therapy (n = 104; 77.6%). Baseline factors influencing regimen choice were microvascular complications (odds ratio [95% CI], yes/no: 0.73 [0.55, 0.98]; $p = 0.034$) and HbA_{1c} at baseline (%, odds ratio [95% CI] 0.82 [0.72, 0.94]; $p = 0.004$).

Conclusions: In routine practice, physicians in Algeria are more likely to prescribe basal insulin at initiation of insulin therapy in type 2 diabetes. The prescription of a premix insulin therapy correlated with poor glycaemic control and the incidence of microvascular complications.

1. Introduction

Type 2 diabetes (T2D) is a very common condition with a high prevalence in developing countries, mostly affecting the middle-aged population (40–60 years). Currently, the Middle East and North Africa region has the highest prevalence of diabetes, and Algeria's national diabetes prevalence is 6.3%, expected to rise to 7.6% by 2030 [1].

Based on many randomised controlled trials (RCTs) [2] showing the benefits of good glycaemic control on reduction of micro- and macrovascular complications, current guidelines from the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD)

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recommend early initiation of insulin therapy in T2D [3]. However, patients in many countries often present with uncontrolled T2D. In Algeria, previous studies have showed a delay in insulin initiation [4,5].

RCTs are the gold standard for assessing the efficacy of drugs, but they need strict inclusion and exclusion criteria, and may not fully represent the general patient population. On the other hand, observational studies can play an important role in exploring treatment outcomes in large, diverse populations, and are therefore complementary to RCTs [6,7].

In countries where clinical study data are limited, observational studies compensate for the lack of data regarding the use of insulins, and help to evaluate insulin safety profiles when used widely. A_1chieve is the largest non-interventional, multicentre, international study of insulin therapy in T2D, involving 66,726 patients from 28 countries with a heterogeneous and culturally diverse population [8]. Complete study results are now available online under www.A1chieve.com.

This sub-analysis was conducted on baseline data from insulin-naive patients of the Algerian cohort starting with either basal or premix insulin (these two insulin regimens are the most commonly used for insulin initiation in Algeria). The aim of the analysis was to examine the criteria that may influence the physician's choice of regimen for starting insulin in T2D patients in local clinical care in Algeria.

2. Methods

2.1. Study design

A_1chieve was a 24-week international, prospective, multicentre, open-label, non-interventional study to evaluate the safety and effectiveness of insulin analogues in people with T2D who initiated insulin therapy with one of three insulin analogues (biphasic insulin aspart 30 [BIAsp 30, NovoMix® 30, Novo Nordisk], insulin detemir [IDet, Levemir®, Novo Nordisk], or insulin aspart [NovoRapid®, Novo Nordisk], alone or in combination) in real-life clinical settings [8]. In this sub-analysis, patients were recruited from March 2009 to September 2010 across 90 sites in Algeria. The selection of patients was at the discretion of the individual physician, in accordance with local routine clinical practice, and no strict inclusion criteria were considered. The physicians gathered information from patients' recall or notes, patients' self-monitored blood glucose diaries, available before initiating study medication, and their own patient records, on examinations at baseline, interim and final visits. Data collected at the baseline visit were:

- Eligibility, demographic data (date of birth, gender), weight, and height
- Medical history:
  - Type and duration of diabetes
  - Current insulin therapy
  - Current oral antidiabetic therapy
  - The most recent (within the last 4 weeks) fasting plasma glucose (FPG) values
  - The most recent (within the last 4 weeks) postprandial plasma glucose (PPPG) values (post-breakfast)
  - The most recent (within the last 4 weeks) glycated haemoglobin A_{1c} (HbA_{1c}) value
  - The number of hypoglycaemic events experienced over the last 4 weeks before the baseline visit and, if the study insulin is started before the baseline visit, 4 weeks before the start of study insulin (total/nocturnal and major hypoglycaemic events, see definitions below)
  - The most recent (within the last 4 weeks) measurement of lipids
  - Blood pressure
- Quality of life
- Epidemiological information as specified in the case report form (to be used for health economic modelling)

2.2. Patients

Any patient with T2D who had not previously been treated with BIAsp 30, IDet, or insulin aspart, or who had started on these insulins within the last 4 weeks before inclusion was eligible for the study. Patients who were pregnant, breast-feeding, or who intended to become pregnant within 6 months, and patients who were hypersensitive to the study insulins or any of their excipients were excluded from the study. This study was conducted in accordance with the Declaration of Helsinki and national guidelines as appropriate to Algeria, and with approval from the independent ethics committee. All patients gave their written informed consent.

2.3. Outcomes

The primary endpoint of A_1chieve® was the incidence of serious adverse drug reactions (SADRs), including major hypoglycaemic events. The secondary efficacy endpoints were HbA_{1c}, other parameters of glycaemic control (the proportion of patients reaching HbA_{1c} target <7%, FPG and PPPG), lipid profile, cardiovascular risk markers, and quality-of-life questionnaires.

The secondary safety endpoints were vital signs, adverse events, and hypoglycaemic episodes. A hypoglycaemic event is defined as an event with one of the following characteristics:

(1) Symptoms of hypoglycaemia that resolve with oral carbohydrate intake, glucagon, or intravenous glucose
(2) Any symptomatic or asymptomatic plasma glucose <3.1 mmol/L or 56 mg/dL (≈ <2.8 mmol/L or 50 mg/dL blood glucose).

Nocturnal hypoglycaemic events were defined as individualised symptomatic events, consistent with hypoglycaemia, that occurred while the patient was asleep, between bedtime after the evening insulin injection and before getting up in the morning (if relevant, before morning determination of FPG and before morning injection).

Major hypoglycaemic events were defined as events with severe central nervous system symptoms consistent with hypoglycaemia in which the patient was unable

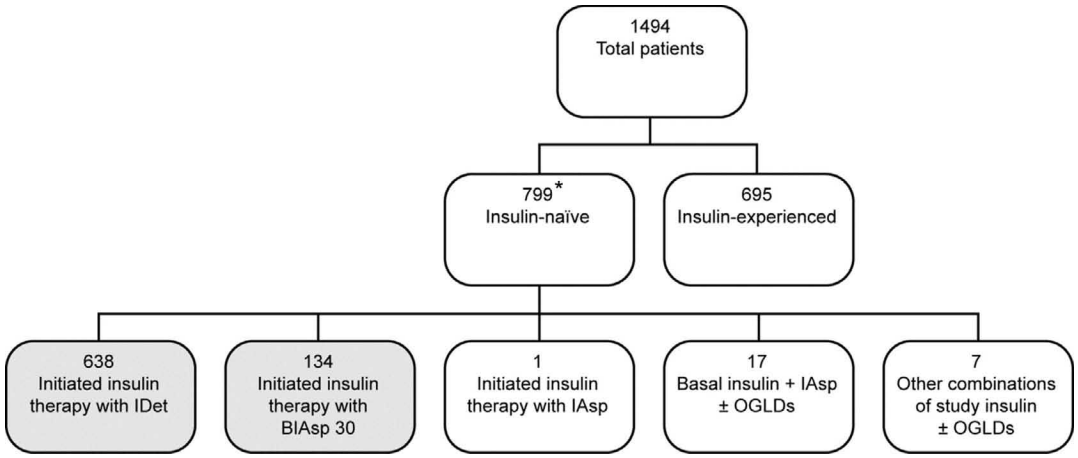

Fig. 1 – Treatment regimen of type 2 diabetes patients enrolled in the A_1chieve Algerian cohort study. *Data missing for 2 patients. BIAsp 30, biphasic insulin aspart 30; IAsp, insulin aspart; IDet, insulin detemir; OGLD, oral glucose-lowering drugs.

to treat himself/herself and had one of the following characteristics:

(1) Plasma glucose <3.1 mmol/L or 56 mg/dL (≈ <2.8 mmol/L or 50 mg/dL blood glucose) or
(2) Reversal of symptoms after either food intake or glucagon or intravenous glucose administration

This paper reports an analysis of the baseline data from the insulin-naive patient subgroup initiated on basal (Group 1) or premix (Group 2) insulin in the Algerian cohort of A_1chieve.

2.4. Statistical analysis

Data from the IDet and BIAsp 30 groups were evaluated for demographic and anthropometric data (gender, age, diabetes duration, and age at diagnosis), blood glucose control at inclusion (baseline: HbA_{1c}, FPG, and post-breakfast PPPG), microvascular complications (microalbuminuria and retinopathy), and pre-study therapy (with one, two or more oral agents for each subgroup). Insulin initiation regimen at inclusion, injection frequency, and insulin doses per day for the two groups were also evaluated.

Detailed statistical analysis for the study has been described previously [8]. In this analysis, factors influencing the choice of insulin regimen (IDet vs. BIAsp 30) were evaluated using a two-step logistic regression model. Baseline characteristics were firstly addressed in a univariate logistic regression model as independent variables with choice of insulin regimen as the dependent variables. Those significant factors were then put into a forward stepwise multivariate logistic regression. All analyses were performed by Novo Nordisk A/S using SAS® Version 9.1.3.

3. Results

3.1. Baseline demographics

The total Algerian cohort of the A_1chieve study included 1494 patients. In the subgroup of 799 insulin-naive patients, 638 (83%) initiated IDet and 134 (17%) initiated BIAsp 30 (Fig. 1). The male/female ratio was roughly similar in the insulin-naive groups that initiated IDet (39.5%/60.5%) and BIAsp 30 (34.3%/65.7%, Table 1).

Table 1 – Demographics and pre-study therapy for insulin-naive patients by study therapy

Demographic	IDet	BIAsp 30
Age, years	59.7 (9.9)	59.2 (10.0)
Gender (male/female), %	39.5/60.5	34.3/65.7
Weight, kg	74.2 (13.3)	70.6 (13.2)
BMI, kg/m^2	27.7 (4.7)	26.8 (5.4)
Duration of diabetes, years	10.3 (6.3)	10.1 (6.2)
HbA_{1c}, %	9.3 (1.7)	10.1 (2.1)
Pre-study therapy, n (%):		
1 OGLD	96 (15.1)	35 (27.1)
2 OGLDs	494 (77.7)	78 (60.5)
>2 OGLDs	46 (7.2)	16 (12.4)

BMI, body mass index; OGLD, oral glucose-lowering drug.
Data are presented as mean (SD) unless specified otherwise.

3.2. Factors influencing choice of insulin regimen

3.2.1. Univariate analysis

Prevalence of microvascular complications, HbA_{1c}, FPG, PPPG, and EQ-5D score significantly influenced the choice of insulin, while body mass index (BMI), macrovascular complications, age, gender, and duration of diabetes did not (Table 2).

3.2.2. Multivariate analysis

The significant factors were put into a forward stepwise multivariate logistic model. It was found that only microvascular complications and HbA_{1c} were significant (Table 3). Thus, the factors FPG, PPPG, BMI, and EQ-5D score were not significant and were excluded from the final model.

Table 2 – Baseline glycaemic control, quality of life, and presence of complications

	Detemir vs. BIAsp 30		
	Odds ratio (95% CI)		*P*-value
N	638/134		
Microvascular complications (yes vs. no)	0.52	(0.34, 0.80)	0.003
HbA_{1c} at baseline (%)	0.83	(0.75, 0.93)	0.001
FPG at baseline (mmol/L)	0.92	(0.88, 0.97)	0.003
PPPG at baseline (mmol/L)	0.94	(0.89, 0.98)	0.010
BMI at baseline (kg/m^2)	1.04	(0.999, 1.08)	0.060
EQ-5D score (0–100 scale)	1.02	(1.004, 1.03)	0.010
Macrovascular complications (yes vs. no)	0.82	(0.52, 1.28)	0.380
Duration of diabetes (year)	1.01	(0.98, 1.04)	0.700
Age (years)	1.01	(0.99, 1.02)	0.610
Gender (female vs. male)	0.80	(0.54, 1.18)	0.270

BMI, body mass index; BIAsp 30, biphasic insulin aspart 30; CI, confidence interval; FPG, fasting plasma glucose; PPPG, postprandial plasma glucose.
Number of OGLDs is not included in the model, due to the sparse number used.

Table 3 – Baseline factors influencing the choice of insulin regimen in the multivariate analysis

	Detemir vs. BIAsp 30		
	Odds ratio (95% CI)		*P*-value
N	638/134		
Microvascular complications (yes vs. no)	0.73	(0.55, 0.98)	0.034
HbA_{1c} at baseline (%)	0.82	(0.72, 0.94)	0.004

BIAsp 30, biphasic insulin aspart 30; CI, confidence interval.

3.3. *Dosing frequency*

In this cohort, the majority of patients initiated insulin therapy with IDet once daily (n = 636; 99.7%); one patient (0.2%) started on twice daily and one (0.2%) on thrice daily. Conversely, the majority of patients initiating treatment with BIAsp 30 started on twice daily (n = 104; 77.6%); 26 (19.4%) started with once daily and four (3.0%) with thrice daily.

4. Discussion

This is the first observational study performed in Algeria on insulin initiation with different insulin analogue regimens in T2D patients, reporting interesting data regarding baseline characteristics of insulin-naive patients and revealing prescribing trends in routine clinical practice at public sites as well as private clinics.

This analysis aimed to clarify the factors determining the choice of insulin type and regimen at initiation in T2D and their relevance compared to other cohorts in different regions from the overall A_1chieve study [8] or previous publications [9].

This analysis from the subgroup of insulin-naive T2D patients showed that the most prescribed regimen at initiation is basal insulin, used in 80% of patients, and that initiation with premix insulin is less frequent (16.8%) in routine clinical practice in Algeria.

Despite an average diabetes duration of 10 years, 799 of 1494 patients were insulin-naive at baseline. The results are concordant with the overall A_1chieve data regarding diabetes duration at initiation of insulin therapy and poor glycaemic control at inclusion into the study (mean HbA_{1c} above 9.5%) [8]. A univariate analysis suggested that no differences were found for factors such as age, duration of diabetes, weight, or BMI between the BIAsp 30 and IDet groups. However, glycaemic control indicators (HbA_{1c}, FPG, and PPPG) and microvascular complications were significant. Subsequently, these significant factors were put into a stepwise multivariate logistic model that indicated that microvascular complications and HbA_{1c} were the likely factors that influenced the choice of therapy. Patients with microvascular complications and higher HbA_{1c} are more likely to start with BIAsp 30.

At inclusion, IDet was prescribed as a once-daily injection in almost all patients (99.7% of Group 1), while BIAsp 30 was widely prescribed as twice-daily injections (77.6% of Group 2), which correlates with the profiles of the respective insulins. This could also be explained by a better acceptance of an easy and convenient once-daily injection of basal insulin, with less risk of hypoglycaemia, in out-patient care when starting insulin, compared to two or more injections of premix insulin.

The choice of basal insulin as first option for insulin initiation in Algeria probably reflects the ADA/EASD recom-

mendations, followed by physicians in their daily practice. This was also reported in the Latin American cohort of the A_1chieve study with 64% of patients starting on basal insulin, while in South Asia, 75% of patients are initiated with premix insulin. In the overall insulin-naive cohort, choice of insulin regimen was significantly influenced by baseline use of oral glucose-lowering drugs, presence of diabetes complications, HbA_{1c} levels, and BMI [10]. A similar diversity across some countries/regions was observed in people with T2D initiating BIAsp 30 [11]. This could be explained by high PPPG levels rather than FPG, a pattern of hyperglycaemia expected to determine different approaches to oral agents and insulin therapy [11]. A pooled analysis of treat-to-target trials concluded that premix analogues rather than basal insulin may be an appropriate choice to target HbA_{1c} values in older individuals and those with higher bedtime plasma glucose, while basal insulin may be more appropriate to target FPG in patients with lower BMI and higher post-breakfast PPPG [12].

Non-interventional studies like A_1chieve do not have tightly controlled populations or control groups, and there is no randomisation; this reduces the certainty with which outcomes can be ascribed to treatment, leading to potential for bias. However, data from this non-interventional study would form part of the evidence base, along with those from a comprehensive programme of controlled clinical trials. Reporting 24-week safety and efficacy results for this cohort will provide data about everyday practice and safety profiles of insulin analogues, and could help physicians in selecting the best option when starting insulin in patients with T2D according to their current disease state.

In conclusion, physicians in Algeria are more likely to prescribe basal insulin at initiation of insulin therapy in T2D in routine clinical practice. Where the choice is made to initiate with premix regimen, this appears to be associated with the existence of microvascular complications and poor glycaemic control.

Conflict of interest statement

Rachid Malek is a board member and speaker for Novo Nordisk; he has received funded for advisory and educational activities. Zakia Arbouche is a board member and speaker for Novo Nordisk. Malika Bachaoui and Abdallah Salah-Mansour are speakers for Novo Nordisk. Sakina Zinai, Amine Dahaoui, and Souror Senoussaoui are 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, 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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