Contents lists available at ScienceDirect

Primary Care Diabetes

journal homepage: http://www.elsevier.com/locate/pcd

Original research

Use of a basal-plus insulin regimen in persons with type 2 diabetes stratified by age and body mass index: A pooled analysis of four clinical trials

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ARTICLE INFO

Article history:
Received 18 November 2014
Received in revised form 8 May 2015
Accepted 28 May 2015
Available online 4 July 2015

Keywords:
Basal-plus
Insulin glulisine
Type 2 diabetes
Hypoglycemia
HbA1c

ABSTRACT

Aims: To evaluate the efficacy and safety of adding a single bolus dose of insulin glulisine to basal insulin ('basal-plus') in persons with type 2 diabetes.
Methods: Data from patients with poor glycemic control on oral antihyperglycemic drugs who were initiated on a 'basal-plus' regimen for up to 6 months were pooled from four randomized, multicenter studies. Glycated hemoglobin (HbA1c), fasting blood glucose, postprandial glucose (PPG), insulin dose and demographics were measured at baseline and end of study.
Results: 711 patients with a mean age of 59.9 years and a mean duration of diabetes of 11.0 years were included in the analysis population. A 'basal-plus' regimen was associated with significant decreases in HbA1c and PPG at 6 months, an increase in glargine and glulisine doses and small, but statistically significant, changes in body weight and BMI in all patient subsets. The proportion of patients with HbA1c < 7% also increased in all populations studied, while the prevalence of severe hypoglycemia was low and did not significantly differ across patient groups.
Conclusions: These results suggest that the use of 'basal-plus' can achieve a good therapeutic response with a low risk of hypoglycemia and weight gain, regardless of a patient's age or BMI.

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http://dx.doi.org/10.1016/j.pcd.2015.05.003
1751-9918

1. Introduction

Type 2 diabetes (T2D) is a chronic disease characterized by a progressive decline of β-cell function and/or mass in the presence of insulin resistance that requires timely treatment intensification to achieve and maintain optimum metabolic control [1]. Currently, basal insulin represents the simplest and most effective method for controlling fasting hyperglycemia [2,3]. Nonetheless, only approximately half of all patients achieve target glycated hemoglobin (HbA1c) goals despite adequate dose titration and the achievement of near normoglycemia, thus indicating a need for additional treatment to control postprandial glucose (PPG) excursions [4,5]. This can be achieved using different therapeutic modalities, including (1) a fixed combination of a rapid-acting insulin analog (RAA) and an intermediate-acting insulin, i.e., premixed insulins; (2) a combination of a basal insulin and a glucagon-like peptide-1 (GLP-1) receptor agonist; and (3) a 'basal-bolus' regimen, i.e., administration of a RAA to ongoing basal insulin before each meal. More recently, a 'basal-plus' stepwise treatment regimen, i.e., a single injection of prandial insulin prior to the meal associated with the largest PPG excursion, has been proposed. Several clinical trials have demonstrated the efficacy and safety of adding single bolus doses of insulin glulisine to basal insulin glargine [6–11]; however, the effect of individual factors such as a patient's age or BMI on the efficacy of this treatment strategy has yet to be clarified.

Therefore, a retrospective analysis of previous studies was performed to evaluate both the efficacy and safety of adding a single bolus of the 'basal-plus' regimen in patients with T2D when stratified by age and BMI.

2. Methods

2.1. Study design and patient population

Patient-level data were pooled retrospectively from four randomized, controlled, multicenter parallel-group studies designed to evaluate the efficacy and safety of a 'basal-plus' regimen in patients with T2D (OPAL [NCT00272012], ELEONOR [NCT00272064], 1-2-3 [NCT00135083], and a proof-of-concept study [NCT00360698]) [9,12–14]. Participants aged ≥ 18 years who had a diagnosis of T2D and who were poorly controlled (HbA1c ≥ 6.5% or 48 mmol/mol) using basal insulin glargine in addition to oral antidiabetic agents (OADs), with both baseline and end of study HbA1c and BMI measurements available, were deemed eligible for inclusion in this pooled study population. All included patients were initiated on a basal insulin glargine in addition to OADs, to which insulin glulisine was subsequently added once daily ('basal-plus' approach) for up to 6 months. Insulin glargine was titrated to protocol-defined fasting blood glucose (FBG) targets (with the exception of one study [13] in which no titration was undertaken), while insulin glulisine was introduced and dose titrated to protocol-defined preprandial or PPG targets [9,12–14].

2.2. Outcomes and clinical end of studies

Demographic and clinical characteristics (gender, age, weight, height, BMI, duration of diabetes and age at first diagnosis of diabetes) as well as antidiabetic drug usage (duration of prior OAD and/or insulin use, age at initiation of OAD and/or insulin use and insulin glulisine administration time) were collected and analyzed. Efficacy of the 'basal-plus' insulin regimen was determined from the insulin dose and the (1) change of HbA1c levels from baseline and proportion of patients achieving HbA1c < 7% (< 53.0 mmol/mol); (2) change of FBG level from baseline and proportion of patients at < 110 mg/dL (< 6.1 mmol/L); (3) change of PPG levels from baseline and proportion of patients at < 180 mg/dL (< 10.0 mmol/L); and (4) change of weight and BMI over the study periods.

Safety measurements comprised the frequency of episodes of severe hypoglycemia, nocturnal hypoglycemia and symptomatic hypoglycemia (as defined in each trial and determined from data collected during the respective trials [Appendix]) [9,12–14].

Efficacy and safety measurements were then analyzed following stratification by age (< 55, 55–64 and ≥ 65 years) and BMI (< 30, 30–35 and ≥ 35 kg/m^2).

2.3. Statistical analyses

Due to the requirement for HbA1c and BMI data at baseline and at end of study, the total available number of patients was reduced (hereafter referred to as the 'analysis population') (Table A1) [9,12–14]. A patient-level meta-analysis was conducted to allow for study-to-study differences. Descriptive statistics were used to measure and describe clinical characteristics and patient demographics as well as efficacy and safety outcome measurements. p values, unadjusted for study origin, were provided by χ^2 test or analysis of variance (ANOVA) when appropriate. Baseline and end of study efficacy measurements were compared with p values calculated using paired t-tests; a p value < 0.05 was used to determine the level of statistical significance, again unadjusted for study origin.

A generalized linear model was used to assess the difference between end of study and baseline measurements for HbA1c, weight and BMI while adjusting for patient age, gender, duration of diabetes and different studies. A multivariate logistic regression model was used to assess the impact of patient characteristics on the risk of hypoglycemia.

The outcomes were combined across studies using the random effects meta-analysis approach of DerSimonian and Laird [15]. All statistical analyses were carried out using SAS® version 9.3 (SAS Institute Inc., Cary, NC).

3. Results

3.1. Baseline characteristics

A total of 711 patients comprised the analysis patient population; 53.3% were male, mean age 59.9 ± 9.5 years, and the mean known duration of T2D was 11.0 ± 7.0 years (Table 1). Prior to the study periods the mean duration of OAD use was 6.5 ± 5.7 years and the mean duration of basal insulin use