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Diabetes & Metabolism xxx (2016) xxx–xxx
& Diabetes Metabolism

Original article

Factors associated with reaching or not reaching target HbA_{1c} after initiation of basal or premixed insulin in patients with type 2 diabetes☆

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Received 7 April 2016; received in revised form 18 October 2016; accepted 24 October 2016

Abstract

Aims. – To evaluate factors associated with reaching or not reaching target glycated haemoglobin (HbA_{1c}) levels by analysing the respective contributions of fasting hyperglycaemia (FHG), also referred to as basal hyperglycaemia, vs postprandial hyperglycaemia (PHG) before and after initiation of a basal or premixed insulin regimen in patients with type 2 diabetes.

Methods. – This post-hoc analysis of insulin-naïve patients in the DURABLE study randomised to receive either insulin glargine or insulin lispro mix 25 evaluated the percentages of patients achieving a target HbA_{1c} of < 7.0% (< 53 mmol/mol) per baseline HbA_{1c} quartiles, and the effect of each insulin regimen on the relative contributions of PHG and FHG to overall hyperglycaemia.

Results. – Patients had comparable demographic characteristics and similar HbA_{1c} and FHG values at baseline in each HbA_{1c} quartile regardless of whether they reached the target HbA_{1c}. The higher the HbA_{1c} quartile, the greater was the decrease in HbA_{1c}, but also the smaller the percentage of patients achieving the target HbA_{1c}. HbA_{1c} and FHG decreased more in patients reaching the target, resulting in significantly lower values at endpoint in all baseline HbA_{1c} quartiles with either insulin treatment. Patients not achieving the target HbA_{1c} had slightly higher insulin doses, but lower total hypoglycaemia rates.

Conclusion. – Smaller decreases in FHG were associated with not reaching the target HbA_{1c}, suggesting a need to increase basal or premixed insulin doses to achieve targeted fasting plasma glucose and improve patient response before introducing more intensive prandial insulin regimens.

Keywords: Basal insulin; HbA_{1c} quartiles; Premixed insulin; Target HbA_{1c}; Type 2 diabetes

1. Introduction

The 2015 position statement of the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) [1], as well as the 2016 ADA standards of medical care [2], all emphasize the need for an individualized approach to treatment of patients with type 2 diabetes (T2D). They recommend starting treatment with one injection of basal insulin for most patients and intensifying it with progressive prandial insulin injections. In patients willing to take more than one injection, twice daily premixed insulin may also be considered for initiation or intensification [1,2]. Recent meta-analyses of randomised controlled trials have shown that premixed and basal–bolus insulin regimens are equally effective in reducing

Abbreviations: ADA, American Diabetes Association; AUC, area under the curve; EASD, European Association for the Study of Diabetes; FHG, fasting hyperglycaemia; FPG, fasting plasma glucose; GLP-1, glucagon-like peptide-1; HbA_{1c}, glycated haemoglobin; OAM, oral antidiabetic medication; PHG, postprandial hyperglycaemia.

☆ This analysis was presented in part as abstracts and oral presentations at the 48th Annual Meeting of the European Association for the Study of Diabetes, 1–5 October 2012 in Berlin, Germany, and at the Congress of the French Society for Diabetes (Société Francophone du Diabète), 26–29 March 2013, in Montpellier, France.

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http://dx.doi.org/10.1016/j.diabet.2016.10.005
1262-3636/

glycated haemoglobin (HbA_{1c}) in insulin-naïve patients with T2D, with no significant differences in hypoglycaemia or weight gain, thus giving physicians the flexibility to adapt treatment to the given patient's needs and preferences [3,4].

While a patient-centred approach is recommended, few data are available to identify the parameters that influence response to insulin regimens or the characteristics of patients not reaching target HbA_{1c}, factors that could be used to tailor further intensifications of basal insulin treatment. For all antidiabetic drugs, baseline HbA_{1c} is an important determinant of efficacy: greater decreases in HbA_{1c} are frequently observed with higher baseline values, yet a smaller percentage of these patients reach their HbA_{1c} targets [5,6]. A lower baseline HbA_{1c} has also been the best predictor of patients achieving an $HbA_{1c} < 7.0\%$ (< 53 mmol/mol) with insulin glargine, but often the risk of hypoglycaemia is also increased [7].

The objective of the present analysis was to evaluate whether the reasons for reaching or not reaching a target HbA_{1c} of < 7.0% (< 53 mmol/mol) with a basal or premixed insulin regimen are related to differences in baseline glycaemic profiles. As our main interest was in the potential differences in the contributions of fasting hyperglycaemia (FHG), also referred to as basal hyperglycaemia, vs postprandial hyperglycaemia (PHG), the study therefore evaluated the relative 24-h contributions of FHG and PHG to total hyperglycaemia in patients reaching or not reaching the target HbA_{1c} after initiation of insulin therapy and according to baseline HbA_{1c} quartiles to guide further intensification of insulin regimens.

2. Methods

2.1. Study design

This was an exploratory post-hoc analysis of the initiation phase of the DURABLE study (Clinicaltrials.gov, NCT00279201), a randomised, open-label, parallel study conducted in 11 countries over a period of 30 months [8]. The trial enrolled 2091 insulin-naïve patients with T2D, aged ≥ 30 to < 80 years, who had HbA_{1c} levels > 7.0% (> 53 mmol/mol) despite taking at least two oral antidiabetic medications (OAMs). During the 24-week initiation phase [9], patients were randomised 1:1 to once daily insulin glargine ($n = 1046$) or twice daily insulin lispro mix 25 ($n = 1045$), both in combination with pre-study OAMs. Of these patients, 974 and 965, respectively, had data evaluable for this analysis. At baseline and at endpoint, their 7-point self-monitored plasma glucose profiles were obtained from the mean values of 3 days for all patients taken before each meal, at 2 h after each meal and at 0300 h.

The fasting plasma glucose (FPG) titration target was ≤ 100 mg/dL (≤ 5.6 mmol/L) for insulin glargine and < 110 mg/dL (< 6.1 mmol/L) for insulin lispro mix 25. However, no enforced insulin titration was imposed by the investigators. Daily insulin doses were recorded throughout the study, with the final analysis at the end of the 24-week period.

Hypoglycaemia was recorded whenever a patient experienced symptoms of hypoglycaemia or had a blood glucose ≤ 70 mg/dL (≤ 3.9 mmol/L), and this was deemed severe if the patient required assistance to recover.

2.2. Statistical methods

The area under the curve (AUC) for PHG (AUC_p) was estimated using the AUCs above each premeal glucose value from the 7-point glucose profiles, as suggested by Monnier et al. [10]. The AUC for FHG (AUC_f), also often referred to as basal hyperglycaemia (BHG AUC), was calculated using the AUCs between 100 mg/dL (5.6 mmol/L) and each premeal glucose value. The relative 24-h contributions of PHG and FHG to total hyperglycaemia were calculated using the following equations: $AUC_p/(AUC_f + AUC_p) \times 100\%$ for the postprandial contribution, and $AUC_f/(AUC_f + AUC_p) \times 100\%$ for the fasting contribution. Negative values were set at 0.

The AUC and relative contributions of PHG and FHG to total hyperglycaemia were calculated at baseline and at the 24-week endpoint for patients achieving the endpoint HbA_{1c} target of < 7.0% (yes/no), and by treatment group (insulin glargine or insulin lispro mix 25) and baseline HbA_{1c} category: < 8.0% (< 64 mmol/mol); ≥ 8.0% but < 9.0% (≥ 64 but < 75 mmol/mol); ≥ 9.0% but < 10.0% (≥ 75 but < 86 mmol/mol); and ≥ 10.0% (≥ 86 mmol/mol). HbA_{1c}, FPG, episodes of hypoglycaemia, insulin doses and percentages of patients achieving an $HbA_{1c} < 7.0\%$ (< 53 mmol/mol) at the end of the study period were also assessed. Continuous variables were studied using an analysis of variance (ANOVA) model with stratification variables of country, thiazolidinedione use and sulphonylurea use. Categorical variables were analysed using the Cochran–Mantel–Haenszel test stratified by country, thiazolidinedione use and sulphonylurea use. All analyses were conducted using SAS version 9.2 software (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Patients

Patients reaching or not reaching the target HbA_{1c} of < 7.0% (< 53 mmol/mol) had similar baseline characteristics as per baseline HbA_{1c} quartiles for age, gender, body mass index (BMI), HbA_{1c}, FPG (Tables 1 and 2) and FHG values (Tables 1 and 2, Figs. 1 and 2). There were no differences in oral co-medications or duration of diabetes (data not shown). However, FPG was higher at baseline in patients not reaching the target HbA_{1c}, compared with those who did, in both treatment groups (16.2 mg/dL [0.9 mmol/L] for insulin lispro mix 25, 10.8 mg/dL [0.6 mmol/L] for insulin glargine; Fig. 3), due to the higher FPG and the lower response rate with higher baseline HbA_{1c} values in those not reaching the target.

3.2. HbA_{1c} changes

Mean decreases in HbA_{1c} were greater in patients reaching the target HbA_{1c}, leading to lower endpoint values in each baseline HbA_{1c} quartile ($P < 0.05$). Indeed, there was a progressive

Please cite this article in press as: Scheen AJ, et al. Factors associated with reaching or not reaching target HbA_{1c} after initiation of basal or premixed insulin in patients with type 2 diabetes. Diabetes Metab (2016), http://dx.doi.org/10.1016/j.diabet.2016.10.005