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Original Article

Addition of once daily prandial lixisenatide to basal insulin therapy in patients with type-2 diabetes results in a reduction of HbA1c as an effect of postprandial glucose lowering☆

Holger Fleischmann[a], Rüdiger Göke[b], Peter Bramlage[c,*]

[a] Medical Department, Sanofi Aventis Deutschland GmbH, Berlin, Germany
[b] Diabetes Schwerpunktpraxis, Kirchhain, Marburg, Germany
[c] Institut für Pharmakologie und Präventive Medizin, Mahlow, Germany

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ABSTRACT

Aims: Basal insulin has been shown to effectively reduce fasting blood glucose (FBG), but postprandial plasma glucose (PPG) excursions may remain higher than normal. Glucagon-like peptide (GLP)-1 receptor agonists such as the short-acting lixisenatide are able to control such excursions by slowing gastric emptying. However, data regarding its use in a real world clinical setting are scarce.
Methods: 24 week, prospective, multicentre, non-interventional study in 1437 patients with type-2 diabetes receiving 20 μg lixisenatide once daily in combination with basal insulin. The per-protocol set (PPS) comprised 540 patients.
Results: HbA_{1c} levels were found to decrease significantly over 24 weeks of treatment in the PPS ($0.94 \pm 0.99\%$ [7.9 ± 8.5]; $p \leq 0.001$). An HbA_{1c} of <7% (53 mmol/mol) was achieved in 26.9% of patients, with 9.8% reaching <6.5% (48 mmol/mol) and 30.0% reaching their individual treatment goal. There was a slight decrease in FBG (2.84 ± 30.4 mg/dl; $p \leq 0.001$), and a significant reduction in PPG, with levels decreasing by between 35 mg/dl (1.9 mmol/l) and 38 mg/dl (2.1 mmol/l), respectively on average after all main meals in basal optimised patients (PPS; ≤140 mg/dl). Body weight decreased from 101 to 98 kg with a mean difference of 3.10 ± 4.10 kg ($p \leq 0.001$). There were few reports of hypoglycaemia and no reports of serious hypoglycaemia and need for external help. AEs were infrequent, and were in line with previous studies.
Conclusions: Lixisenatide in combination with basal insulin was shown to be an effective treatment strategy for patients with type 2 diabetes, controlling HbA_{1c} levels by reduction of PPG excursions during the whole day.

1. Introduction

The progressive nature of type 2 diabetes results in the need for gradual intensification of treatment, with a high proportion of patients ultimately requiring insulin if blood glucose levels are to be kept sufficiently low [1]. Once daily injections of basal insulin, either with or without oral antidiabetic drugs, have been shown to greatly reduce HbA_{1c} and fasting blood glucose (FBG) levels [2–4]; however, postprandial hyperglycaemic excursions may remain a problem. As these spikes in blood glucose levels have been linked to a higher risk of cardiovascular disease and mortality, reducing their occurrence especially over the whole day is essential [5–7]. To address this issue the use of GLP-1 receptor agonists might represent an option which is also recommended in the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) consensus statement [2,9]. These agents mimic the effect of the endogenous GLP-1 hormone, enhancing insulin secretion and reducing glucagon release, while retarding gastric emptying [8]. The short-acting lixisenatide primarily acts on the stomach, working via the autonomic nervous system to slow the passing of its contents to the intestine. Such a mechanism of action is ideal for regulating postprandial plasma glucose (PPG) levels (prandial acting [10]) complementing the control over FBG achieved by administration of basal insulin [10,11].

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* Corresponding author at: Institut für Pharmakologie und Präventive Medizin, Menzelstrasse 21, Mahlow, 15831, Germany.
E-mail addresses: holger.fleischmann@sanofi.com (H. Fleischmann), rbg@gmx.org (R. Göke), peter.bramlage@ippmed.de (P. Bramlage).

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A number of placebo-controlled clinical studies have demonstrated effective reductions in HbA_{1c} and blood glucose levels on treatment with lixisenatide in combination with basal insulin [3,12–14]. Riddle et al. reported a decrease in HbA_{1c} of 0.6% (42 mmol/mol) over 24 weeks of lixisenatide treatment in comparison to the 0.3% (9 mmol/mol) achieved with the placebo [12]. This was accompanied by a 3.8 mmol/l (68 mg/dl) greater decrease in PPG levels and a 1.3 kg greater decrease in body weight. Raccah et al. analysed data from 5 randomised controlled trials comparing treatments with basal insulin and the GLP-1 receptor agonist or short acting prandial insulin [15]. Both combinations resulted in similar reductions in HbA_{1c} levels, but lixisenatide treatment was associated with lower risks of hypoglycaemia and weight gain. Similarly, in the GetGoal-Duo2 trial, patients being treated with insulin glargine randomised to additionally receive lixisenatide experienced body weight reduction as well as lower incidence of hypoglycaemia in comparison to those randomised to additionally receive prandial insulin glulisine [16]. Again, reductions in HbA_{1c} were comparable.

While the evidence from the clinical trials of lixisenatide is encouraging, there are limited data available regarding real world settings. For this reason, we performed a prospective, multicentre, open-label, non-interventional study involving patients with type 2 diabetes who had been assigned to treatment with lixisenatide in combination with basal insulin. Patients were only included if they achieved a fasting blood glucose $\leq$140 mg/dl ($\leq$7.8 mmol/l) based on a prior optimization of basal insulin. Over a 24 week follow up period, we recorded changes in HbA_{1c} levels, as well as blood glucose levels, body weight, and occurrence of adverse events (AEs).

2. Methods

This was a prospective multicentre, open-label, non-interventional study conducted according to §67/6 of the German Drug Law (Arzneimittelgesetz). Patients were recruited at 526 centres across Germany between January 2013 and May 2014. All included patients provided written informed consent, and the study was carried out in accordance with the Declaration of Helsinki and its later amendments.

2.1. Patients

Patients were enrolled if they were at least 18 years old and had been diagnosed with type 2 diabetes. They were required to have a fasting blood glucose (FBG) $\leq$140 mg/dl ($\leq$7.8 mmol/l) and an $HbA_{1c} \geq$ 7.5% (58 mmol/mol). Only patients who had been receiving basal insulin treatment for at least 6 months, with or without oral antidiabetic therapy, were admitted. Furthermore, patients needed to be capable of blood glucose self-monitoring. Patients were not considered if they had type 1 diabetes, had received or were currently receiving dipeptidyl peptidase (DPP)-4 inhibitors or GLP-1 receptor agonists. Any sulfonylurea therapy needed to be discontinued prior to starting treatment with lixisenatide. Treatment with any long- or medium-acting insulin was allowed.

We initially planned to recruit approximately 7500 patients for the study. However, owing to unsuccessful financial negotiations between the developer of the drug and the agencies responsible for regulating prescription costs, lixisenatide was withdrawn from the German market. No further patients were therefore recruited after May 2014.

2.2. Treatment

The treatment strategy for each patient was left to the discretion of the physician, with patients enrolled if they received a starting dose of 10 μg lixisenatide once daily for 14 days followed by a once daily maintenance dose of 20 μg, as per label (Fig. 1). Lixisenatide was administered sub-cutaneously prior to a meal at the same time each day (as per IFU and not pre-defined). The patients were followed for approximately 24 weeks after enrolment.

2.3. Objectives

The principal objective of the current observational study was to document the change in HbA_{1c} level between baseline and the 24 week follow-up. Secondary objectives regarding glycaemic control were to determine HbA_{1c} response rates (<6.5% [48 mmol/mol], <7.0% [53 mmol/mol], <individual treatment goal), and changes in FBG, alterations in four-point diurnal glucose profile. In addition, changes in body weight and the basal insulin dose at baseline and follow-up were evaluated. Further objectives were to determine the frequency of hypoglycaemic events (blood glucose $\leq$60 mg/dl (3.33 mmol/l)), confirmed nocturnal hypoglycaemic events (between 10 pm and 6 am), severe hypoglycaemic events (blood glucose $\leq$36 mg/dl (2.0 mmol/l) with need for external help), and severe nocturnal hypoglycaemic events. Finally, we documented the frequency of AEs and adverse drug reactions (ADRs) related to lixisenatide.

2.4. Statistics

Data were documented on a paper-based case report form (CRF) and were sent back to the department managing non-interventional studies at Sanofi. After a check for completeness and AEs, the data were forwarded to a contract research organisation for data entry. They were entered in duplicate using the data management program DMSys Version 5.1 (Sigma Soft International), and then validated using a pre-defined data validation plan.

The full analysis set (FAS) included all patients that had received at least one dose of lixisenatide and for whom a CRF was available. The per-protocol set (PPS) excluded patients that did not comply with the protocol and which had a fasting blood glucose $\leq$140 mg/dl, a baseline HbA1c $\geq$7.5% (58 mmol/mol), all in- and exclusion criteria were fulfilled and confirmed by further variables in the CRF.

Statistical analyses were performed using SPSS for Windows (Release 15.0.0). Absolute frequency, relative frequency, and adjusted relative frequency were determined for categorical variables. For continuous variables, mean ± standard deviation (SD) or median with interquartile ranges (IQR) were determined. Exact 95% confidence intervals (CI) were calculated for mean changes in HbA_{1c} and FBG from baseline to end of study. For value pairs with one missing entry, no substitution was carried out (e.g. according to the last-observation-carried-forward method). Only the patients with complete value pairs were considered in the analysis (available case analysis), resulting in different sample sizes in the analysis of the longitudinal data.

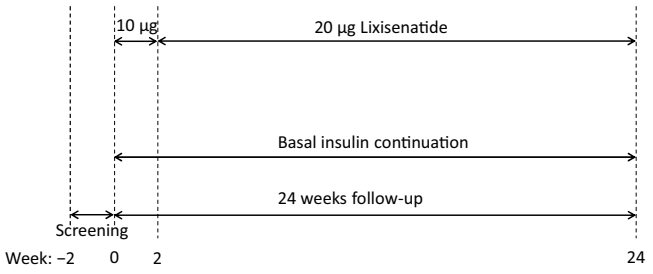

Fig. 1. Study design.

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