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Lixisenatide plus basal insulin in patients with type 2 diabetes mellitus: a meta-analysis

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ABSTRACT

Aims: The efficacy of the once-daily prandial GLP-1 receptor agonist lixisenatide plus basal insulin in T2DM was assessed by pooling results of phase III trials.
Methods: A meta-analysis was performed of results from three trials in the GetGoal clinical program concerning lixisenatide or placebo plus basal insulin with/without OADs. The primary endpoint was change in HbA_{1c} from baseline to week 24. Secondary endpoints were change in PPG, FPG, insulin dose, and weight from baseline to week 24. Hypoglycemia rates and several composite endpoints were assessed.
Results: Lixisenatide plus basal insulin was significantly more effective than basal insulin alone at reducing HbA_{1c} at 24 weeks. Composite and secondary endpoints were improved significantly with lixisenatide plus basal insulin, with the exception of FPG, which showed no significant difference between the groups. Lixisenatide plus basal insulin was associated with an increased incidence of hypoglycemia versus basal insulin alone.
Conclusions: Lixisenatide plus basal insulin resulted in significant improvement in glycemic control versus basal insulin alone, particularly in terms of controlling PPG. Prandial lixisenatide in combination with basal insulin is a suitable option for treatment intensification in patients with T2DM insufficiently controlled with basal insulin, as these agents have complementary effects on PPG and FPG, respectively.

1. Introduction

Type 2 diabetes mellitus (T2DM) is a metabolic disorder characterized by elevated blood glucose as a result of insulin resistance and β-cell dysfunction. Early T2DM can be controlled with lifestyle modifications and the use of oral antidiabetics (OADs) (Garber, Abrahamson, Barzilay, et al., 2013; Ryden, Standl, Bartnik, et al., 2007), while basal insulin as add-on to OADs is generally initiated in patients with more advanced diabetes or in patients who do not achieve glycemic control with OADs alone (American Diabetes Association, 2013). Basal insulin once daily is effective for the control of fasting plasma glucose (FPG); however, excursions in post-prandial plasma glucose (PPG) in patients with poor glycemic control are not addressed by basal insulin and may require prandial therapies. Basal–bolus and basal-plus regimens, combining once-daily basal insulin and mealtime administration of a rapid-acting insulin (RAI), or pre-mixed insulin, are commonly recommended in this regard (Inzucchi,

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Bergenstal, Buse, et al., 2012). However, insulin-based regimens, particularly those with a prandial component (Holman, Farmer, Davies, et al., 2009), are associated with weight gain and hypoglycemia, which can impact patient acceptance of treatment (Cryer, Davis, & Shamoon, 2003; Russell-Jones & Khan, 2007).

Incretin hormones secreted by the gastrointestinal tract stimulate glucose-dependent insulin secretion to ensure that PPG excursions are limited regardless of carbohydrate load (Holst, 2007; Crespo, González Matías, Lozano, et al., 2009). The incretin glucagon-like peptide-1 (GLP-1) is released post-prandially by the intestine but is rapidly degraded by dipeptidyl peptidase-4 (DPP-4). The effects of GLP-1 in the pancreas (release of insulin and suppression of glucagon release) and in the stomach (delay of gastric emptying) have made GLP-1 a focus of research for T2DM pharmacotherapies. A number of GLP-1 receptor agonists (GLP-1 RAs) have been developed to take advantage of the 'incretin effect'. These agents include liraglutide and exenatide once weekly (longer acting GLP-1 RAs with a predominant effect on FPG), exenatide twice daily and lixisenatide (GLP-1 RAs with a predominant effect on PPG). The clinical efficacy of these agents in T2DM is now established, and the advantage of significant improvements in glycemic control together with a low risk of hypoglycemia and weight gain relative to other anti-diabetic agents has made GLP-1 RAs an attractive option for treatment intensification.

Lixisenatide (Lyxumia®; Sanofi, Paris, France) is a once-daily prandial GLP-1 RA for the treatment of T2DM that is based on the exendin-4 peptide with a glycine residue at position 2, prolonging its activity as it is less readily degraded by DPP-4 (Werner, Haschke, Herling, et al., 2010). Lixisenatide, as a monotherapy, in addition to OADs or basal insulin, demonstrated significant efficacy versus placebo in reducing glycated hemoglobin (HbA_{1c}) and regulating PPG with a beneficial effect on body weight in the phase III GetGoal clinical program (Ahrén, Leguizamo, Miossec, et al., 2013; Fonseca, Alvarado-Ruiz, Raccah, et al., 2012; Riddle, Aronson, Home, et al., 2013; Riddle, Forst, Aronson, et al., 2013; Seino, Min, Niemoeller, et al., 2012). The PPG-lowering effects of prandial GLP-1 RAs, such as lixisenatide, may be of particular benefit for patients uncontrolled on optimally titrated basal insulin, for whom PPG excursions are likely to be the predominant contributor to hyperglycemia (Riddle, Umpierrez, DiGenio, et al., 2011). Lixisenatide plus basal insulin versus basal insulin alone, in patients whose T2DM was insufficiently controlled with basal insulin or OADs, was assessed in three of the GetGoal trials (GetGoal-Duo1, GetGoal-L and GetGoal-L-Asia); herein, we report a meta-analysis of these trials in order to assess the efficacy and safety of lixisenatide plus basal insulin in a large and diverse patient population. In doing so, we aim to provide information to guide clinicians using lixisenatide in combination with basal insulin.

2. Materials and methods

2.1. Analysis design

This was a meta-analysis of data from patients with T2DM in the three phase III GetGoal trials in which lixisenatide 20 μg once daily was administered as add-on to basal insulin ± OADs and compared with placebo plus basal insulin ± OADs. All medications were self-administered according to the regimens of the individual trials.

The designs of these GetGoal trials have been reported previously (Riddle, Aronson, Home, et al., 2013; Riddle, Forst, Aronson, et al., 2013; Seino et al., 2012) (Supplementary Table 1). Briefly, the methodologies of these trials were as follows: GetGoal-Duo1 (NCT00975286) investigated lixisenatide as add-on to newly initiated insulin glargine in patients whose T2DM was insufficiently controlled with metformin ± thiazolidinediones; GetGoal-L (NCT00715624) assessed lixisenatide as add-on to basal insulin in patients whose T2DM was insufficiently controlled on basal insulin (insulin glargine, insulin detemir or neutral protamine Hagedorn) ± metformin; GetGoal-L-Asia (NCT00866658) assessed lixisenatide as add-on to basal insulin in Asian patients whose T2DM was insufficiently controlled on basal insulin (insulin glargine, insulin detemir or neutral protamine Hagedorn) ± sulfonylurea. Each of the trials was of 24 weeks' duration and had change in HbA_{1c} at trial end as the primary endpoint. The trials were conducted between July 2008 and August 2011 across 25 countries (the number of countries and enrolment/completion dates varied by trial). Patients were randomized to receive lixisenatide or placebo 1:1 in GetGoal-Duo1 and GetGoal-L-Asia, and 2:1 in GetGoal-L.

2.2. Inclusion criteria

All patients had inadequately controlled T2DM ($HbA_{1c} \geq 7\%$) and were randomized to receive either lixisenatide or placebo in addition to treatment with basal insulin ± OADs in one of the phase III GetGoal trials (thus three trials were included in this meta-analysis). Included patients were from the intent-to-treat population of their respective trial and were required to have HbA_{1c} measurements at baseline and at 24 weeks.

2.3. Endpoints

The primary endpoint of this meta-analysis (and of the three GetGoal trials) was change in HbA_{1c} from baseline to week 24. Secondary endpoints included change from baseline in the proportion of patients with HbA_{1c} <7% or ≥7% at week 24. In addition, sub-analyses were performed of HbA_{1c} change from baseline to week 24 in patients who were treated concomitantly with sulfonylureas versus patients who were not and in patients who were basal-insulin naïve at the beginning of treatment in the trials versus patients already receiving basal insulin. Other secondary endpoints were the first PPG measurement after injection of lixisenatide based on patients' 7-point self-monitored blood glucose profiles (mg/dL); 2-hour PPG levels (mg/dL) after the standardized meal test; change from baseline in FPG (mg/dL) at week 24; the proportion of patients with FPG <110 mg/dL (6.1 mmol/L) or ≥110 mg/dL at week 24; and insulin dose (U/kg) change at week 24. The standardized meal test consisted of a 600 kcal liquid meal (400 mL Ensure Plus, Abbott Nutrition, Columbus, OH, USA) comprising 53.8% carbohydrate, 16.7% protein and 29.5% fat, to be consumed within a 10-minute period.

Safety endpoints in this meta-analysis were: prevalence of per-protocol-defined symptomatic hypoglycemia at week 24; the annualized rate of symptomatic hypoglycemic events; and the number and proportion of patients with severe hypoglycemia. A sub-analysis of the occurrence of hypoglycemia was also performed in patients who were being treated concomitantly with sulfonylureas versus patients who were not. In common with trials of other GLP-1 RAs, symptomatic hypoglycemia was defined as an event with clinical symptoms consistent with an hypoglycemic episode (e.g. sweating, palpitations, hunger, fatigue, restlessness, anxiety, irritability, headache, loss of concentration, somnolence, psychiatric or visual disorders, transient sensory or motor defects, confusion, convulsions or coma) with documented plasma glucose <60 mg/dL (3.3 mmol/L). Severe hypoglycemia was defined as an hypoglycemic event during which patients required assistance from another person because they could not self treat due to acute neurological impairment resulting from hypoglycemia (The Diabetes Control & Complications Trial Research Group, 1991) and where the event was associated with plasma glucose <36 mg/dL (2.0 mmol/L) or where the event was associated with prompt recovery after oral carbohydrate, or intravenous glucose/glucagon.

This meta-analysis also assessed a number of composite endpoints at week 24 that comprised both efficacy and safety parameters; these were: HbA_{1c} levels <7% and no symptomatic hypoglycemia; HbA_{1c}