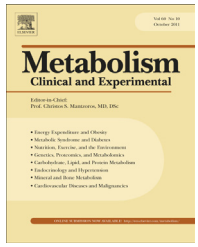
METABOLISM CLINICAL AND EXPERIMENTAL 62 (2013) 1330–1339

Available online at www.sciencedirect.com

Metabolism

www.metabolismjournal.com



Eight weeks of treatment with long-acting GLP-1 analog taspoglutide improves postprandial insulin secretion and sensitivity in metformin-treated patients with type 2 diabetes☆

Amalia Gastaldelli[a,*], *Michael A. Nauck*[b], *Raffaella Balena*[c,1]

[a] *Institute of Clinical Physiology, National Research Council, Pisa, Italy*
[b] *Diabeteszentrum, Bad Lauterberg im Harz, Germany*
[c] *F. Hoffmann-La Roche Ltd, Basel, Switzerland*

ARTICLE INFO

Article history:
Received 30 July 2012
Accepted 6 May 2013

Keywords:
GLP-1 analog pancreatic function
Mixed-meal tolerance test
Postprandial glucose
Postprandial insulin
Postprandial glucagon

ABSTRACT

Objective. Loss of pancreatic function is pivotal to the deterioration of fasting and postprandial glycemic control in type 2 diabetes (T2D). We evaluated the effects of a long-acting, human glucagon-like peptide-1 analog, taspoglutide, added to metformin, on pancreatic function and peripheral insulin sensitivity.

Materials/methods. We studied 80 T2D patients inadequately controlled [glycosylated hemoglobin (HbA_{1c}), 7.0%–9.5%] receiving stable metformin for ≥12 weeks. They were a subset of participants to a phase 2 trial that received also a 240-min mixed-meal tolerance test (MTT) at baseline and study end. Patients received once weekly (QW) sc injection of taspoglutide 5, 10, or 20 mg (n = 21, 19, or 19), or placebo (n = 21), plus metformin, for 8 weeks. We measured postprandial plasma glucose (PPG) and insulin profiles, insulin secretion rate (ISR), oral glucose insulin sensitivity (OGIS) index; β-cell glucose sensitivity, glucagon/glucose and insulin/glucagon ratios, and insulin sensitivity-to-insulin resistance (or disposition) index.

Results. After 8 weeks of treatment, taspoglutide 5, 10, and 20 mg QW doses *vs*. placebo improved mean $PPG_{0–240\ min}$ (relative change from baseline: −22.1%, −25.9%, and −22.9% *vs*. −8.1%; $P < 0.005$) and mean postprandial $ISR_{0–240\ min}$ (+14%, +18%, and +23% *vs*. +1%; $P < 0.005$ vs dose). Taspoglutide at 20 mg QW dose also resulted in improvements from baseline in OGIS, β-cell glucose sensitivity, glucagon/glucose and insulin/glucagon ratios and the disposition index during the MTT.

Conclusion. Taspoglutide QW significantly improved pancreatic function in patients with T2D treated with metformin.

Abbreviations: AUC, area under the curve; BMI, body mass index; FPG, fasting plasma glucose; GLP-1, glucagon-like peptide 1; HbA_{1c}, glycosylated hemoglobin; ISR, insulin secretion rate; MTT, mixed-meal tolerance test; OGIS, oral-glucose insulin sensitivity; PPG, postprandial plasma glucose; T2D, type 2 diabetes; QW, once-weekly; Q2W, once every 2 weeks.

☆ Clinical trial number: NCT00423501.

* *Corresponding author*. Institute of Clinical Physiology, CNR, via Moruzzi 1, 56100 Pisa, Italy. Tel.: +39 050 3152680/79; fax: +39 050 3152166.
E-mail address: amalia@ifc.cnr.it (A. Gastaldelli).

[1] R.B. is currently affiliated with Eli Lilly and Company Ltd. Erl Wood Manor Windlesham Surrey UK.

0026-0495/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.metabol.2013.05.001

1. Introduction

Taspoglutide is a long-acting glucagon-like peptide-1 (GLP-1) receptor agonist that has undergone phase 3 clinical development for the treatment of type 2 diabetes. It is an amino-isobutyric acid ($Aib^{8,35}$)-substituted analog of native human GLP-1(7–36)NH_2 that retains the structure of the native peptide, and has similarly potent activity but enhanced stability [1]. A sustained-release formulation of taspoglutide administered as a single dose to patients with type 2 diabetes not adequately controlled on metformin, demonstrated rapid antihyperglycemic effects on the first day of the injection with glucose lowering for up to 14 days [2]. In a dose-ranging, phase 2 trial taspoglutide once weekly (QW) and every two weeks (Q2 W) achieved placebo-corrected reductions in glycosylated hemoglobin (HbA_{1c}) of around 1% after only 8 weeks of treatment with significant reductions in fasting plasma glucose (FPG) and reduction in body weight at the high dose [3]. Adverse events included nausea and vomiting; hypoglycemia occurred infrequently [3]. Taspoglutide underwent Phase 3 development. The results of the seven pivotal trials have been recently published [4–10].

The first marketed GLP-1 receptor agonist (GLP-1-RA) was a short-acting twice daily (BID) formulation of exenatide approved for use in the United States in 2005 and in the European Union in 2006. Subsequent marketed GLP-1-RAs include liraglutide, a longer acting agent administered once daily (QD), and a long-acting formulation of exenatide administered once weekly (QW). Additional GLP-1 RAs are in clinical development, including another QD agent, lixisenatide, and two QW agents, albiglutide and dulaglutide [11]. GLP-1 RAs improve glycaemic control through multiple mechanisms of action including enhancement of glucose-dependent insulin secretion from pancreatic β-cells, glucose-dependent suppression of inappropriately elevated glucagon secretion, slowing the rate of gastric emptying and the absorption of meal-derived glucose, and reducing caloric intake [11–15].

Taspoglutide has similar homology to native GLP-1 (93%) and has been studied using once weekly dosing. Currently available GLP-1 receptor agonists for the treatment of type 2 diabetes, exenatide and liraglutide, are administered twice daily [16] or once daily [17] due to their short plasma half-lives. Data indicate that there is a beneficial effect from sustained GLP-1 activation, especially in the control of FPG [18,19]. Comparative studies with GLP-1 receptor agonists suggest that the longer acting agents provide more potent glucose lowering [18–21].

The aim of this analysis was to evaluate the postprandial effect of taspoglutide by analyzing multiple parameters of pancreatic endocrine function in a subset of patients who participated in a phase 2 trial and underwent a mixed-meal tolerance test (MTT). We hypothesized that due to the similarity of taspoglutide to native GLP-1, it would have similar effects on β-cell function as have been previously shown for human GLP-1 [22], and the effects would persist for at least 1 week after the last injection.

2. Methods

The study was conducted in accordance with all the institutional review boards, with the principles of the Declaration of Helsinki, as well as the laws and regulations of the countries where the research was conducted. All patients provided informed consent prior to entering the study.

2.1. Study participants

Patients enrolled into a phase 2b trial of taspoglutide QW or once every 2 weeks (Q2W) at predetermined sites were invited to participate in an MTT. Eligibility criteria of patients were previously published [3]. Briefly, men and women (postmenopausal or surgically sterile) 18 to 75 years of age with type 2 diabetes who were receiving maximum doses of metformin (≥1500 mg/d) and no other antihyperglycemic medication, including GLP-1 receptor agonists, for ≥3 months prior to screening were eligible. Their diabetes had to be inadequately controlled on metformin with an HbA_{1c} between 7.0% and 9.5% and an FPG > 7.0 mmol/l and ≤13.3 mmol/l. They were also required to have a body mass index (BMI) > 25 and ≤45 kg/m^2, with a stable weight and no exposure to weight loss medications in the 3 months prior to screening. Patients with impaired liver or kidney function, gastrointestinal disease, uncontrolled hypertension, or stroke or myocardial infarction in the prior 6 months were also excluded.

2.2. Mixed-meal tolerance test

One hundred eighteen patients met the inclusion criteria at baseline and underwent a 240-min MTT prior to randomization into the phase 2b study (week −1). Patients reported to the clinic in the morning after an overnight fast (i.e. ≥8 h after their last meal) and were instructed not to take their morning dose of metformin. The MTT was performed under post-absorptive conditions at baseline and at week 9 (one week after the 8th and final QW dose). The mixed meal (Ensure® liquid meal) consisted of 50 g carbohydrate, 13 g protein, and 11 g fat (350 kcal in total). Patients remained in a supine or semi-supine position and did not consume additional food or drink during the MTT. Following consumption of the meal, blood samples were collected at times 0 (baseline), 30, 60, 90, 120, 180, and 240 min for measurement of glucose, insulin, C-peptide, and glucagon concentrations.

Following the baseline MTT, patients entered the 8-week double-blind portion of the study and were randomized to placebo or one of the following doses of taspoglutide administered sc: 5 mg QW, 10 mg QW, 20 mg QW, 10 mg Q2W, or 20 mg Q2W. The MTT was repeated at week 9 in patients who completed the study. Fasting and postprandial glucose, insulin, C-peptide, and glucagon levels were measured by a central laboratory (Covance, Geneva, Switzerland; Harrogate UK; Indianapolis, IN, USA). The primary analysis of efficacy and tolerability of all QW and Q2W doses has been reported previously by Nauck et al. [3]. The current analysis focuses on the effects of QW doses only, since this dosing regimen was shown to be more clinically effective [3] and was selected for the phase 3 trials.

2.3. Endocrine pancreatic function and insulin sensitivity

The prehepatic insulin secretion rate (ISR) was calculated from plasma C-peptide levels by deconvolution analysis using a two-compartment model with standard parameters for C-