Long-Term Effects of Adding Exenatide to a Regimen of Metformin and/or Sulfonylurea in Type 2 Diabetes: An Uncontrolled, Open-Label Trial in Hungary

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ABSTRACT

Background: Studies of the glucagon-like peptide-1 receptor agonists (GLP-1RAs) are needed to determine the durability of metabolic response and tolerability associated with long-term treatment.

Objective: The present study was conducted to provide long-term data on glycemic control, weight changes, and tolerability of exenatide 10 μg BID treatment in patients with type 2 diabetes mellitus who have failed to achieve glycemic targets with oral antihyperglycemic medication.

Methods: In this uncontrolled, open-label trial with treatment up to 156 weeks, patients received exenatide 10 μg BID while continuing treatment with metformin and/or a sulfonylurea (SFU). Intent-to-treat (ITT), 52-, 100-, and 132-week completer populations were defined. Metabolic changes were analyzed in the completer and ITT populations; adverse events (AEs) were summarized in the ITT population. Descriptive statistics were used for absolute and change-from-baseline data. Within-treatment comparisons were conducted using the paired *t* test.

Results: Of 155 patients in the ITT population (mean [SD]: age, 59 [9] years; 56% female; duration of diabetes, 9.1 [5.9] years; weight, 88.8 [16.5] kg; body mass index, 31.9 [4.7] kg/m^2; hemoglobin [Hb] A_{1c}, 8.7% [1.2%]), 133, 111, and 103 patients completed 52, 100, and 132 weeks of treatment, respectively. In the ITT population, the mean (SE) change in HbA_{1c} from baseline to week 132 was −1.0% (0.10%) ($P < 0.0001$). In patients completing 52, 100, and 132 weeks, HbA_{1c} changes from baseline to end point were −1.3% (0.10%), −1.0% (0.12%), and −1.0 (0.13%) ($P < 0.0001$), with 40% of patients achieving HbA_{1c} <7% at 132 weeks. Patients in the ITT and completer populations experienced mean (SE) weight changes of −3.7 (0.39) kg and −3.9 (0.51) kg ($P < 0.0001$) at week 132. Improved glycemic control and weight loss occurred in 63% of patients in the completer population at week 132. In addition, 38% of completers at week 132 achieved HbA_{1c} <7% without weight gain. No relationship was found between the development of antiexenatide antibodies and change in HbA_{1c}. The most common AEs were gastrointestinal in nature, reported in 46% of patients and leading to discontinuation in 7 cases. Serious AEs were reported in 26% of patients, and 18% withdrew due to a treatment-emergent AE. Of 24% of patients in whom hypoglycemia was reported, 22% were on SFU or metformin + SFU combination, and 2% were on metformin.

Conclusions: The findings from this open-label, single-arm study characterized the response to exenatide 10 μg BID for up to 132 weeks. Significant, persistent improvements in HbA_{1c} and weight were observed in patients receiving exenatide BID, with reported AEs consistent with those from studies of shorter duration. ClinicalTrials.gov identifier: NCT00044668. (*Clin Ther.* 2012;34:1301–1313) © 2012 Elsevier HS Journals, Inc. All rights reserved.

Key words: exenatide, GLP-1 receptor agonist, glucose control, HbA_{1c}, hypoglycemia, type 2 diabetes mellitus.

INTRODUCTION

Exenatide is a glucagon-like peptide-1 receptor agonist (GLP-1RA) with several glucoregulatory actions, including glucose-dependent enhancement of insulin secretion, suppression of elevated glucagon levels, slow-

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ing of gastric emptying, and increased satiety. Exenatide is a twice-daily GLP-1RA approved for glycemic control in patients with type 2 diabetes mellitus (T2DM).[1] Treatment with exenatide BID added to a regimen of ≥1 oral antihyperglycemic medications (OAMs) in patients with T2DM who have not achieved optimal glycemic control has been evaluated in numerous randomized, placebo-controlled trials.[2–5] Randomized insulin-controlled trials have reported that treatment with exenatide BID was associated with improved overall glycemic control comparable to conventional insulin therapy.[6–10] Furthermore, treatment with exenatide BID was associated with weight loss, whereas patients on insulin formulations gained weight. In addition, treatment with exenatide BID did not increase the risk for hypoglycemia in patients not receiving a sulfonylurea (SFU).[4,8,11] The prevalence of nocturnal hypoglycemia was significantly lower with exenatide BID than with an insulin comparator.[11]

Limited data exist, however, on the maintenance of glycemic control and weight with exenatide BID over several years from a single uniform cohort. Ideally, antihyperglycemic medications should exert sustained glucose-lowering activity despite the progressive nature of T2DM.[12] So far, the longest exenatide clinical studies reported have been open-label extensions of 3 pivotal Phase III, placebo-controlled trials[13] and a 3-year, randomized, insulin glargine active-controlled trial reported by Bunck et al.[14] Those data provided evidence for sustained improvements in glycemic and weight control, with no new adverse events (AEs) observed with exenatide BID in the patients who continued therapy. The initial decrease in hemoglobin A_{1c} (HbA_{1c}) was maintained in patients on exenatide BID, progressive weight loss was continuous. However, prospective long-term studies are needed to further explore the durability of metabolic effects and the safety profile of exenatide BID treatment.

This article reports the findings from a single-arm, open-label, uncontrolled study that evaluated exenatide BID treatment for up to 156 weeks in patients with T2DM who did not achieve optimal glycemic targets despite treatment with metformin and/or an SFU in Hungary.

PATIENTS AND METHODS

This Phase III, single-arm, open-label study of treatment exposure up to 156 weeks was conducted between August 2002 and September 2005 at 3 centers in Hungary. The study protocol was reviewed by the respective local ethics committees. All of the patients provided informed consent, and the study was conducted in accordance with the principles of the Declaration of Helsinki.[15]

Inclusion and Exclusion Criteria

Patients with T2DM who were aged 20 to 75 years were included if they had suboptimal glycemic control (HbA_{1c} ≥7.5% and ≤12.0%) at screening despite ≥12 weeks of OAM treatment (metformin 1500 mg/d with or without SFU [dose as per protocol]), fasting plasma glucose (FPG) <15.5 mmol/L, stable weight for ≥12 weeks before screening, and a body mass index (BMI) of 25 to 45 kg/m^2. Patients were excluded if they had a clinically significant history of cardiovascular disease or events, including myocardial infarction, arrhythmia, unstable angina, moderate to severe congestive heart failure, and/or the need for coronary artery bypass surgery and/or angioplasty. Also, a clinically significant history or the presence of hepatic, renal, pulmonary, hematologic, or gastrointestinal disease; treatment with a thiazolidinedione, an α-glucosidase inhibitor, a meglitinide, or a systemic corticosteroid in the ≥12 weeks before screening led to exclusion.

Treatment

Patients received open-label treatment with exenatide 5 μg BID for 4 weeks, followed by an open-ended maintenance period of exenatide 10 μg BID, while continuing on their prestudy OAM regimens. Clinic visits were scheduled within 2 weeks after enrollment, followed by visits every 1 or 2 weeks during the initiation period. Clinic visits occurred at 4-week intervals (until week 24) or at 8-week intervals (until week 48 and after week 52) for the remainder of the study.

Efficacy Assessments

The primary end point was the change in HbA_{1c} from baseline to weeks 52, 100, and 132. Other end points included FPG, weight, and fasting lipid concentrations (LDL-C, HDL-C, total cholesterol [TC], and triglycerides [TG]). Laboratory values were quantitated by the central Quintiles Laboratories Europe laboratory (Scotland, United Kingdom) using standard methods.

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