Clinical Therapeutics/Volume ▮, Number ▮, 2016

Early Pharmacodynamic Effects of Exenatide Once Weekly in Type 2 Diabetes Are Independent of Weight Loss: A Pooled Analysis of Patient-Level Data

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ABSTRACT

Purpose: Exenatide once weekly, a glucagon-like peptide-1 receptor agonist (GLP-1RA), is approved as an adjunct to diet and exercise for the treatment of adults with type 2 diabetes mellitus. Exenatide acts by binding to and activating glucagon-like peptide-1 receptors, thereby stimulating glucose-dependent insulin secretion, suppressing glucose-dependent glucagon secretion, slowing gastric emptying, and increasing feelings of satiety. Gradual increases in drug level ("autotitration") after the initiation of a fixed exenatide 2-mg weekly dose achieve minimal effective (~50 pg/mL) and steady-state (~300 pg/mL) concentrations by 2 weeks and 6 to 8 weeks, respectively. The purpose of this study was to examine pharmacodynamic outcomes with exenatide once weekly and to determine whether changes are secondary to weight loss and thus delayed by the sequential nature of responses.

Methods: This post hoc analysis evaluated trials in the exenatide once-weekly development program. Outcomes included glycosylated hemoglobin (HbA_{1c}), weight, fasting serum or plasma glucose (FG), lipids, and blood pressure (BP) at weeks 2, 4, and 24. Relationships between changes from baseline in these outcomes and changes in weight were examined. The effect of nausea and vomiting (adverse events characteristic of GLP-1RAs) on weight loss was also assessed.

Findings: Pooled data were analyzed from 12 trials in which 2190 patients received exenatide once weekly. Patients had a mean HbA_{1c} level of 8.4% and weight of 87 kg at baseline. Exenatide once weekly produced significant improvements in HbA_{1c}, FG, weight, and systolic BP at weeks 2 and 4, with continuous improvements through week 24. There were no clinically meaningful correlations between weight loss and improvements in pharmacodynamic outcomes at weeks 2, 4, or 24. Patients had significant reductions in weight at weeks 2, 4, and 24 regardless of whether they experienced nausea and/or vomiting during the study, although patients with at least 1 nausea/vomiting event had greater weight loss at week 24 than those who did not.

Implications: Improvements in pharmacodynamic end points occurred early in treatment with exenatide once weekly, before steady-state plasma concentrations. These early effects did not seem to be secondary to weight loss and are likely the direct effects of exenatide. (*Clin Ther*. 2016;▮:▮▮▮–▮▮▮) © 2016 The Authors. Published by Elsevier HS Journals, Inc.

Key words: diabetes mellitus, early response, exenatide, glucagon-like peptide-1 receptor agonist, HbA_{1c}, pharmacokinetics.

INTRODUCTION

Sustained metabolic control has been shown to minimize complications in type 2 diabetes mellitus (T2DM). However, reduction in hyperglycemia early after treatment initiation is reassuring to physicians and patients, providing evidence that the chosen therapy is effective. Thus, treatment is also geared toward rapid reduction in hyperglycemia and control of cardiometabolic risk factors such as lipids and blood pressure (BP).

Although long-term glycemic control is important to prevent complications of T2DM, a rapid response to therapy is also reassuring to physicians

Accepted for publication March 30, 2016.
http://dx.doi.org/10.1016/j.clinthera.2016.03.039
0149-2918/$ - see front matter

and patients. Early response helps build patients' confidence that the medication is working, and patients' perception that the treatment is worthwhile may help empower them to continue therapy.[1] However, because T2DM is a chronic disease, the use of therapies that deliver robust responses which are sustained over the long term is of greater benefit to patients than a rapid response. Moreover, having realistic expectations about the timing of anticipated therapeutic benefits is important to prevent wrong treatment decisions such as premature switching of treatment. Exenatide once weekly has demonstrated durable long-term benefits, with glucose-lowering effects sustained for several years in long-term studies.[2,3] Compared with the time course of response to thiazolidinediones and dipeptidyl peptidase-4 inhibitors, glycemic and weight responses with exenatide once weekly have been shown to occur early after treatment initiation.[4,5] However, because exenatide once-weekly microspheres release exenatide gradually, there has been a perception that the onset of efficacy may be too slow and that the efficacy may be dependent on weight loss. Therefore, more information is needed about the rate of onset of exenatide once-weekly therapy, and establishing whether there is a correlation between weight loss and early therapeutic outcomes is of crucial interest.

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are injectable glucose-lowering medications approved as an adjunct to diet and exercise for the treatment of adults with T2DM. Agents in the GLP-1RA class bind to and activate glucagon-like peptide-1 (GLP-1) receptors, thereby producing effects similar to those of endogenous GLP-1, including stimulating glucose-dependent insulin secretion, suppressing glucose-dependent glucagon secretion, slowing gastric emptying, and increasing feelings of satiety.[6] Because these agents act by supplementing endogenous GLP-1 activity, treatment with high concentrations of GLP-1RAs can produce stronger effects compared with dipeptidyl peptidase-4 inhibitors, which act by inhibiting proteolytic cleavage of endogenous GLP-1 and produce only 2- to 3-fold increases in plasma GLP-1 concentrations.[7] GLP-1RAs offer effective glycemic control with the added benefits of weight loss, a low risk of hypoglycemia, and positive effects on cardiovascular risk factors.[1]

Exenatide is a GLP-1RA that is available for administration as a BID and a once-weekly formulation. In the once-weekly formulation, exenatide is encapsulated in poly-(D, L-lactide-co-glycolide) microspheres and released from these microspheres in a 3-stage process (initial release, diffusion release, and erosion release), resulting in continuous delivery of exenatide.[8] Due to the long release of exenatide from the microsphere depots for up to 10 weeks, drug concentrations accumulate with subsequent injections. Exenatide once weekly achieves the minimal effective concentration (~50 pg/mL) for glucose lowering with regular once-weekly dosing in 2 weeks, and steady-state plasma concentrations (~300 pg/mL) are reached in 6 to 8 weeks.[9–12] Gradual dose escalation of exenatide has been shown to improve gastrointestinal tolerability.[13] Therefore, most GLP-1RAs are initiated at a low dose, with subsequent dose increases to improve tolerability ("titration"). With exenatide once-weekly administration, the concentration of exenatide increases with autotitration and reaches steady-state plasma levels in 6 to 8 weeks, and the risk of gastrointestinal adverse events has been found to be reduced compared with BID dosing.[8] Understanding the balance between the robust and sustained effects of exenatide once weekly and tolerability during initiation of therapy is an important consideration for patients and health care providers.

In randomized controlled studies of 24 to 30 weeks and extensions up to 6 years, exenatide once weekly has been shown to improve glycemic control, reduce excess body weight, and improve cardiovascular risk markers, including BP and lipids.[2,14,15] However, the time courses of these changes may not be identical. Because glycemic control and cardiovascular risk markers can be improved by weight loss alone, the relationship of weight loss with efficacy outcomes is of interest.

The current post hoc analysis was designed to: (1) characterize the early therapeutic response to exenatide once weekly and thus inform patient and physician expectations for clinical practice; and (2) examine whether early improvements in pharmacodynamic outcomes are secondary to weight loss or are direct effects.

PATIENTS AND METHODS

This post hoc analysis considered pooled data from 11 randomized, placebo- or active comparator–controlled trials and 1 single-arm study from the exenatide once-weekly development program. Pharmacodynamic