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Five-Year Efficacy and Safety Data of Exenatide Once Weekly: Long-term Results From the DURATION-1 Randomized Clinical Trial

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Abstract

Objective: To evaluate the 5-year efficacy and safety of once weekly exenatide.

Patients and Methods: The Diabetes Therapy Utilization: Researching Changes in A1C, Weight and Other Factors Through Intervention with Exenatide Once Weekly (DURATION-1) randomized clinical trial consisted of a 30-week controlled phase (2 mg of exenatide once weekly vs 10 μg of exenatide twice daily) with an open-ended uncontrolled extension (once weekly exenatide only) in patients with type 2 diabetes mellitus on background glucose-lowering therapies (April 15, 2006, through February 21, 2012). At week 30, patients initially receiving 10 μg of exenatide twice daily switched to 2 mg of exenatide once weekly. Study end points included changes from baseline in hemoglobin A_{1c}, fasting plasma glucose, weight, lipids, and blood pressure. Long-term safety data included adverse events, liver and renal function, and heart rate.

Results: Of 258 extension-phase patients, 153 (59.3%) completed 5 years of treatment. Hemoglobin A_{1c} levels were significantly and durably reduced from baseline (least-squares mean, −1.6%; 95% CI, −1.8% to −1.4%; vs −1.9% for exenatide once weekly at week 30), and 65 (43.9%) of 148 patients achieved hemoglobin A_{1c} levels of less than 7.0%. Significant improvements in fasting plasma glucose level (−28.8 mg/dL; 95% CI, −36.2 to −21.5 mg/dL), weight (−3.0 kg; 95% CI, −4.6 to −1.3 kg), lipids, and diastolic blood pressure were observed, with minimal heart rate increase. Frequencies of nausea and injection-site reactions or nodules were decreased vs the initial 30-week controlled phase. Minor hypoglycemia occurred predominantly with sulfonylurea use, and no major hypoglycemia or new safety signals were observed.

Conclusion: Long-term once weekly exenatide treatment was generally well tolerated with sustained glycemic improvement, weight reduction, and improved markers of cardiovascular risk in patients with type 2 diabetes.

Trial Registration: clinicaltrials.gov Identifier: NCT00308139

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Type 2 diabetes mellitus (T2DM) is a progressive disease characterized by declining β-cell function, insulin resistance, and an attenuated incretin effect.[1] As a result, patients exhibit uncontrolled hyperglycemia if inadequately treated, along with an associated increased risk of myocardial infarction, stroke, microvascular events, and premature death.[2,3] Treatment is aimed at lowering hemoglobin A_{1c} (HbA_{1c}) levels and normalizing elevated fasting plasma glucose (FPG) and postprandial glucose levels, with patients generally requiring long-term therapy for the remainder of their lives. Moreover, the progressive nature of the disease often necessitates increasingly intensive treatment regimens to maintain glycemic control.[4,5]

Initial pharmacotherapy for T2DM involves the use of single or multiple oral agents. Despite the availability of a number of oral agent classes, the progressive nature of the disease prevails and hyperglycemia becomes increasingly difficult to control.[6,7] A common next step is to add basal insulin to background oral agents. Despite being efficacious for many patients, a large meta-analysis of trials of 16 to 134 weeks' duration found that almost 60% of patients with T2DM did not achieve an HbA_{1c} level less than 7% with basal insulin–based regimens (with or without other antidiabetes agents), and a basal-bolus regimen failed in

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nearly 50%.[8] Furthermore, hypoglycemia risk increases with more intensive insulin regimens and longer duration of insulin therapy. In a post hoc analysis of 2251 patients with T2DM enrolled in 11 prospective randomized clinical trials of insulin glargine, severe hypoglycemia occurred in 1.5% of patients,[9] whereas a clinical trial comparing basal bolus to prandial premixed insulin revealed incidences of 2.1% and 3.2%, respectively.[10] A retrospective study of 215 patients with T2DM found increased incidence of hypoglycemia with increased insulin treatment duration (1-5 years, 10%; 6-10 years, 15%; >10 years, 35%).[11] Weight gain is another issue associated with insulin therapy. In a meta-analysis of 46 randomized studies, patients with T2DM following a basal insulin regimen gained 3.6 kg in 1 year, whereas those following a prandial insulin regimen (with or without basal insulin) gained 6.4 kg.[12]

Glucagon-like peptide 1 receptor agonist (GLP-1RA) therapy is an alternative injectable therapy option to insulin in the management of T2DM.[6,7] Because these agents act in a glucose-dependent manner, the risk of hypoglycemia is low with monotherapy or when combined with other nonhypoglycemic treatments.[13-16] In addition, GLP-1RAs suppress inadequately elevated glucagon levels, delay gastric emptying, and reduce appetite and food intake at mealtimes, with this last effect likely to be associated with the reduction in body weight also observed in GLP-1RA–treated patients with T2DM.[17,18]

Exenatide, the first US Food and Drug Administration–approved GLP-1RA for use in patients with T2DM as an adjunct to diet and exercise, was first available for administration as a twice daily subcutaneous injection before the morning and evening meals (or the 2 main meals).[19] A sustained-release exenatide formulation was later approved by the US Food and Drug Administration for once weekly administration.[13] The Diabetes Therapy Utilization: Researching Changes in A1C, Weight and Other Factors Through Intervention with Exenatide Once Weekly (DURATION-1) randomized clinical trial was designed to compare twice daily and once weekly exenatide.[20-22] The study consisted of 2 phases: a 30-week, controlled, open-label phase and an uncontrolled, open-ended, extension phase. In the controlled period, once weekly exenatide exhibited a greater reduction from baseline in HbA_{1c} levels compared with twice daily exenatide (−1.9% vs −1.5%, P=.002) and a significantly greater achievement of the HbA_{1c} target of 7.0% or less (77% vs 61%, P=.004).[21] The 1-, 2-, and 3-year results of once weekly exenatide treatment in the open-ended extension have been previously published.[20,22,23] The current analysis expands on these results by examining the safety and efficacy of once weekly exenatide treatment over 5 years, to our knowledge, the longest assessment of a GLP-1RA reported to date.

METHODS

Study Design and Patients

In the initial randomized, comparator-controlled, open-label study (April 15, 2006, through February 21, 2012), patients with T2DM were randomized to 2 mg of exenatide once weekly or 10 μg of exenatide twice daily (5 μg twice daily for the first 28 days) and followed for 30 weeks.[21] At week 30, patients who initially received exenatide twice daily were switched to exenatide once weekly; all patients received exenatide once weekly throughout the open-ended extension.[20,22] Those patients who switched from twice daily to once weekly exenatide and were concomitantly receiving a sulfonylurea were required to have their sulfonylurea dose reduced to the minimum recommended dose until week 40, after which time their sulfonylurea dose was uptitrated based on daily glucose measurements (target FPG ≤110 mg/dL [to convert to mmol/L, multiply by 0.0555]). Patients maintained on exenatide once weekly did not change their sulfonylurea treatment regimen after the controlled phase. Concomitant lipid-lowering, antihypertensive, and non-sulfonylurea glucose-lowering therapies during the 30-week controlled phase and open-ended extension generally remained stable, with changes allowed at the discretion of the study investigator or primary care physician. Only patients who completed the 30-week controlled phase were permitted to enter the open-ended extension.

The initial study protocol was approved by an institutional review board at each site, and