Once-Weekly Glucose-Lowering Therapy for Type 2 Diabetes

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Editor's note: *Exenatide once weekly (QW), which was recently approved for patients with type 2 diabetes, has great potential as a new diabetes therapy in the primary care setting. This article, and the commentary that precedes it (p. 92), offer an overview of this new therapeutic tool and important insights about its clinical utility. In the interest of transparency, however, we want to point out that the authors of both articles are affiliated with Amylin Pharmaceuticals, Inc., which manufactures exenatide QW and markets it under the trade name Bydureon.*

Patients with chronic diseases such as osteoporosis or depression have been shown to adhere to treatment better with once-weekly medications than with more frequently dosed medications, but it is not known whether patients with type 2 diabetes will respond similarly.[1,2] In an informal survey to assess patients' attitudes toward a once-weekly injectable therapy, ~40% of patients with type 2 diabetes thought that a once-weekly injectable therapy might improve their adherence.[3]

Exenatide once weekly (QW), a glucagon-like peptide-1 (GLP-1) receptor agonist, is the first and only glucose-lowering therapy indicated for once-weekly administration with diet and exercise to improve glycemic control in patients with type 2 diabetes. GLP-1 receptor agonists are a unique class of glucose-lowering therapy related to GLP-1, a hormone produced in response to food intake that regulates blood glucose.[4,5] GLP-1 is rapidly degraded by dipeptidyl peptidase-4 (DPP-4), so GLP-1 receptor agonists were developed to be resistant to DPP-4. GLP-1 receptor agonists reduce glucose by increasing the body's own insulin production and release and suppressing its release of glucagon.[4,5] GLP-1 receptor activation also slows gastric emptying and increases satiety, which may assist patients with weight loss.[4,5]

Several GLP-1 receptor agonists are available for use in the United States, including exenatide twice daily, liraglutide once daily, and exenatide QW. Recent American Diabetes Association treatment guidelines recommend a GLP-1 receptor agonist as one option for second-line therapy in patients not achieving glycemic goals after treatment with lifestyle modification and metformin, except for patients who are markedly symptomatic or have elevated fasting glucose or A1C, who should be considered for treatment with insulin and possibly concomitant therapies.[6] Recent American Association of Clinical Endocrinology guidelines state that GLP-1 receptor agonists are a useful additional therapy for patients achieving inadequate A1C control with oral monotherapy.[7]

IN BRIEF

Exenatide once weekly (QW), a glucagon-like peptide-1 receptor agonist, is the first and only glucose-lowering therapy approved for once-weekly administration to patients with type 2 diabetes. In clinical trials, significant reductions in A1C (–1.3 to –1.9%) and weight (–2 to –4 kg) were observed over 6 months with minimal risk of hypoglycemia in the absence of a sulfonylurea. Although the risk of injection-site reactions and mild to moderate gastrointestinal events increased after initiation of exenatide QW, tolerability improved over time. Reductions in A1C and weight were maintained for 3 years in patients who continued to use exenatide QW.

Exenatide QW has been shown to provide continuous glucose control by gradually releasing exenatide, the active ingredient in exenatide twice daily, from subcutaneously injected microspheres.[8] Exenatide-containing microspheres, which are about the diameter of a human hair, are made of the same material as dissolvable sutures and release exenatide by diffusion during degradation (Figure 1).[9] The microspheres are administered through a 23-gauge needle after resuspension with vigorous shaking.

Regular, weekly administration of exenatide QW has been shown to result in consistent exenatide concentrations, although peak efficacy is not attained immediately.[8] After two injections, the plasma concentration

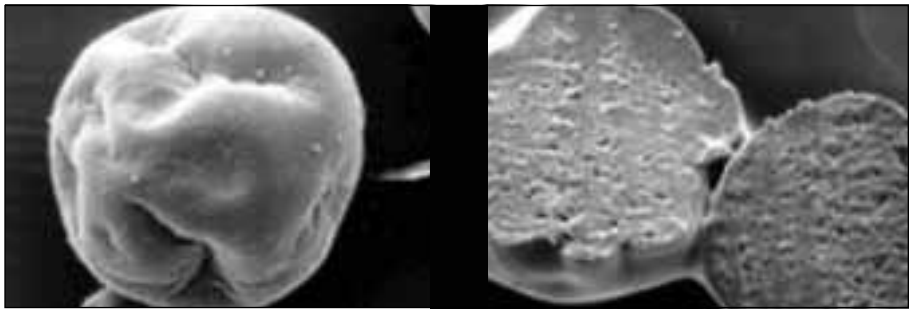

Figure 1. Electron micrograph of exenatide QW microspheres.[9]

of exenatide reaches the therapeutic range to affect fasting glucose, and steady-state plasma concentrations are reached after 6–7 weeks.[8,10–12]

Efficacy in Clinical Trials

The clinical effectiveness and tolerability of exenatide QW were demonstrated in six randomized, active-controlled trials (n = 3,223) in which mean A1C reductions over ~ 6 months ranged from –1.3 to –1.9% in patients with baseline A1C values of 8.3–8.5%. Direct comparative trials showed that A1C reductions with exenatide QW were significantly greater than A1C reductions with sitagliptin, pioglitazone, exenatide twice daily, or insulin glargine, but significantly less than with liraglutide in type 2 diabetes patients already using one or more glucose-lowering therapies.[12–16]

In pharmacological treatment–naive patients, exenatide QW was shown to be more effective in reducing A1C than sitagliptin, as effective as metformin, and not as effective as pioglitazone (Figure 2A).[17] Overall, the percentage of patients achieving an A1C of < 7% improved from none at baseline to between 52 and 77% at endpoint in patients treated with exenatide QW (Figure 2B). Decreases in both fasting and postprandial glucose were observed (Figure 2C).[12] Furthermore, treatment response to exenatide once weekly appeared to be consistent in patients of different ages, races, and durations of diabetes.[18]

Exenatide QW has been shown to reduce A1C in combination with metformin or in combination with a thiazolidinedione or sulfonylurea, but it has not been studied in combination with basal insulin.[19] In an extension trial, patients continuing on exenatide QW therapy for up to 3 years demonstrated sustained mean A1C reductions of –1.6% and weight reductions of –2.3 kg.[20]

In addition to demonstrating improved glucose control, exenatide QW therapy was associated with a mean weight loss of ~ –2 to –4 kg over ~ 6 months, which was sustained in 66% of patients at 3 years.[12–17,20] In the randomized, controlled trials, weight loss with exenatide QW treatment was similar to that of exenatide twice daily or metformin; significantly greater than that of sitagliptin, pioglitazone, or insulin glargine; and slightly but significantly less than that of liraglutide (Figure 2D).[12–17]

Exenatide QW has been demonstrated to improve blood pressure and lipids in addition to A1C and body weight. Average systolic blood pressure reductions of –6.2 mmHg were demonstrated in pooled extension data at 52 weeks.[21] The systolic blood pressure reductions correlated weakly with weight loss, and the greatest reductions (–11.4 mmHg) were observed in patients with a baseline systolic blood pressure of ≥ 130 mmHg. Patients who continued exenatide QW therapy for 3 years (n = 194) exhibited sustained reductions in systolic blood pressure (–2 mmHg), triglycerides (–12%), total cholesterol (–9.9%), and LDL cholesterol (–7.0%).[20]

Adverse Events in Clinical Trials

Analysis of the safety of exenatide QW in 4,328 patients demonstrated no overall increase in risk compared to exenatide twice daily or other glucose-lowering therapies. The incidence of adverse events leading to withdrawal from exenatide QW therapy ranged from 2.4 to 6.9%.[12–17]

The most frequent adverse events observed with exenatide QW were transient gastrointestinal (GI) events such as mild to moderate nausea. In two studies that compared exenatide QW and exenatide twice daily, the incidence of spontaneously reported nausea was 14.0 and 26.4% for exenatide QW versus 35.0 and 35.4% for exenatide twice daily.[12,14] Most nausea occurred within the first 2 weeks of treatment; only 1.4% of patients discontinued the drug because of GI events (data on file, Amylin Pharmaceuticals, Inc.).

GI events associated with exenatide QW may be less frequent than with exenatide twice daily because the gradual increase in exenatide concentration approximates a dose titration.[22]

Previous studies demonstrated that exenatide does not stimulate insulin secretion at normal glucose concentrations (Figure 3A),[23] suggesting that hypoglycemia might occur infrequently with this medication. In trials of exenatide QW, no events of major hypoglycemia (defined as requiring assistance because of severe impairment in behavior with blood glucose concentration < 54 mg/dl) were observed. Minor hypoglycemia rates were low and comparable to those of oral therapies in patients not treated

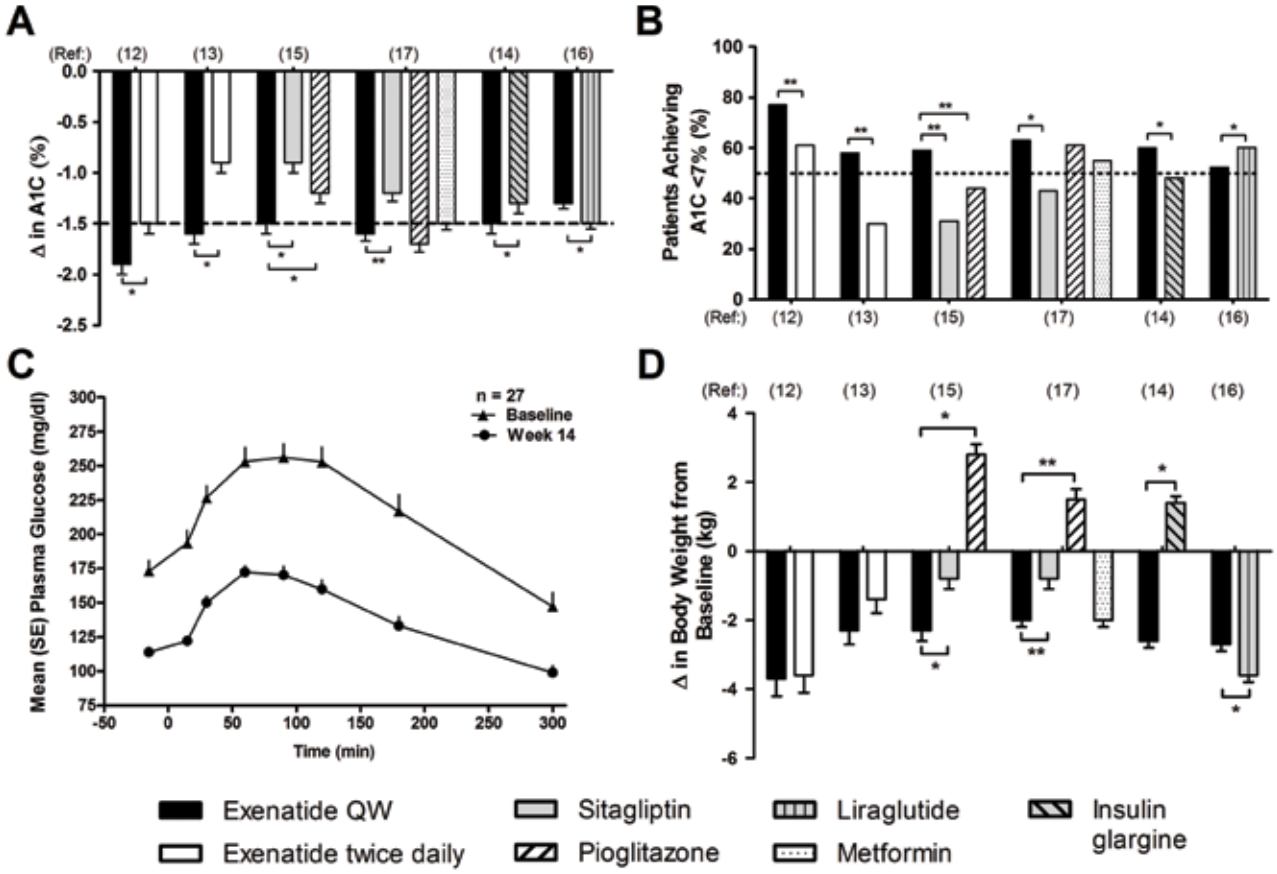

*Figure 2. Change in A1C (A), percentage of patients achieving a target A1C of < 7% (B), and body weight (D) in the clinical trials of exenatide QW.[12–14,16–17,29] (C) The time course of postprandial plasma glucose concentrations in patients treated with exenatide QW (*n = *27) at baseline (triangles) and after 14 weeks treatment (circles).[12] Data are mean ± SE.* *P < *0.05; **P < *0.001. (C) reprinted with permission from The Lancet Publishing Group.*

with a concomitant sulfonylurea (Figure 3B).

Injection-site reactions were observed more frequently with exenatide QW than with exenatide twice daily (7.1 vs. 2.6%) (data on file, Amylin Pharmaceuticals, Inc.). Common injection-site reactions included pruritus and indurations. Palpable bumps or nodules may be observed at injection sites for exenatide QW for ~ 1 month, although they are seldom categorized as adverse events in the clinical trials.[9] They result from a foreign body reaction to the exenatide microspheres that subsides as the microspheres dissolve.[9]

Several adverse events of potential interest have been investigated for exenatide QW. Heart rate increased with exenatide QW therapy (by 1–4 bpm), but no increased cardiovascular risk has been observed (data on file, Amylin Pharmaceutical, Inc.).[14,24] Exenatide QW is renally excreted, so it is contraindicated in patients with severe renal impairment. Post-marketing cases of pancreatitis were reported in patients treated with exenatide twice daily. Although no causal association has been demonstrated, exenatide QW is not indicated for use in patients with a current diagnosis or history of pancreatitis and should be discontinued in patients suspected of having pancreatitis. Extended exposure to exenatide was associated with thyroid C-cell tumors in rats. It is not known whether these data pertain to humans, but exenatide QW is contraindicated for patients with a personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2.[25] The Exenatide Study of Cardiovascular Event Lowering Trial, a randomized, double-blinded, placebo-controlled trial, will enroll 9,500 patients and study them prospectively for > 5 years to provide data on cardiovascular outcomes and mortality in patients treated with exenatide QW.

Practical Aspects of Therapy

The weekly dosing schedule of exenatide QW may be beneficial for many

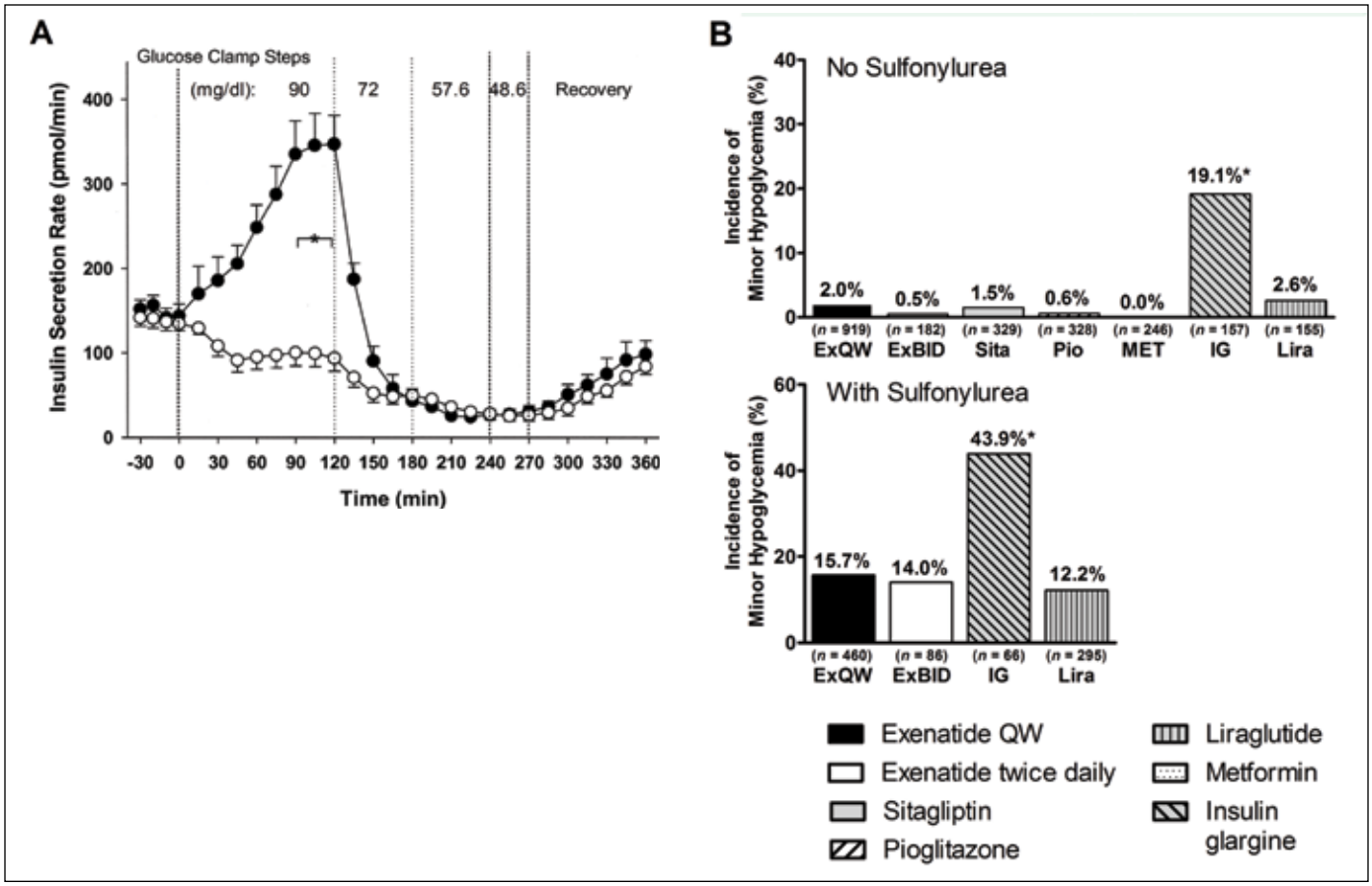

Figure 3. (A) Despite the continued presence of exenatide, insulin secretion decreased when glucose decreased to physiological concentrations. Filled circles, exenatide; open circles, placebo.[23] (B) Incidences of minor hypoglycemia in trials with (top) or without (bottom) concomitant sulfonylurea. (A) reprinted with permission from the American Diabetes Association.

patients. Exenatide QW administration does not need to be associated with a meal or a certain time of day, and dose adjustment is not necessary. Missed doses can be taken up to 4 days late. Although improvements in fasting glucose are observed within weeks of initiating exenatide QW, the A1C benefits develop over time (Figure 4). Significant improvements in diabetes treatment satisfaction and health- or weight-related quality of life were observed during exenatide QW treatment.[26,27]

Exenatide QW is delivered using a single-dose tray that requires patients to combine the microsphere powder with diluent, shake, and inject. Instructions for administration were developed using adult learning principles and were tested in 102 patients.[28] All patients but one had at least a high school degree, and the majority were injection-naive. The results showed that the instructions effectively guided a simulated injection in 88% of patients, with 73% of patients requiring only written instructions and 15% also using call center support. Results were similar in the 30 patients > 60 years of age, with 87% of patients completing all of the fundamental steps. In a subset of 24 patients with hand-dexterity issues, the success rate was 72% , with 50% of patients following the instructions alone and 22% also using the call center.[28] The most common reason for failure was skipping written instruction pages or steps, so patients should be encouraged to follow instructions carefully.

Conclusions

Exenatide QW is the first and only glucose-lowering therapy indicated for once-weekly administration in patients with type 2 diabetes. Exenatide QW, like all GLP-1 receptor agonists, has been recommended as second-line therapy after metformin for patients with inadequate glycemic control.[6,7]

In clinical trials, exenatide QW reduced A1C, fasting glucose, body weight, systolic blood pressure, LDL cholesterol, and triglycerides for up to 3 years in patients continuing therapy. These patients were at low risk for hypoglycemia when not also using a sulfonylurea.

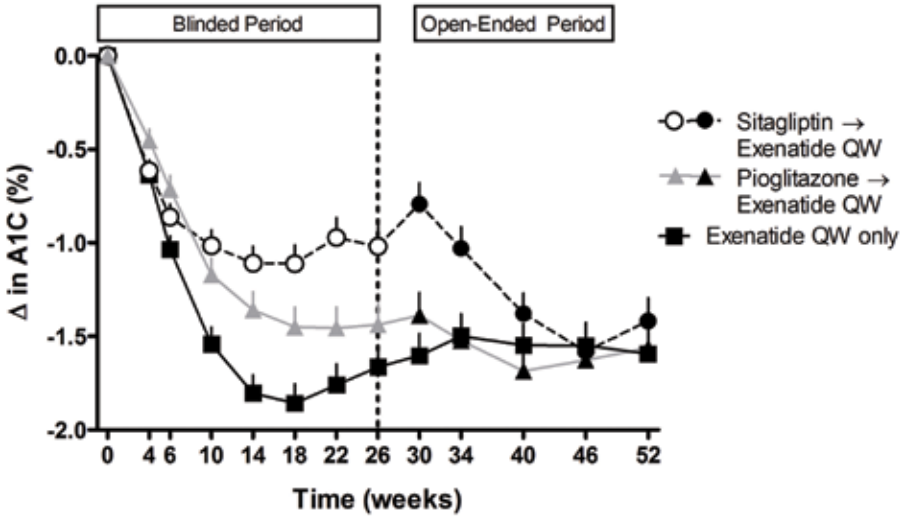

Figure 4. Change in glycemic control in evaluable patients treated with exenatide QW (black squares) over 52 weeks or treated with sitagliptin (open → filled circles) or pioglitazone (open → filled triangles) over 26 weeks and then switched to exenatide QW.[30] Reprinted with permission from John Wiley and Sons.

Exenatide QW in combination with one or more oral glucose-lowering therapies produced significantly greater reductions in A1C and weight than sitagliptin, pioglitazone, or insulin glargine and greater reductions in A1C but not weight than exenatide twice daily.[12–15] Exenatide QW in combination with one or more oral therapies demonstrated somewhat smaller reductions in A1C and weight than liraglutide.[16] In treatment-naive patients, exenatide QW reduced both A1C and weight significantly more than sitagliptin, reduced A1C and weight similarly to metformin, and resulted in less A1C reduction but more weight loss than pioglitazone.[17]

The overall tolerability of exenatide QW was comparable to that of the other GLP-1 receptor agonists, with better GI tolerability than exenatide twice daily and liraglutide once daily; few patients discontinued treatment because of GI events. It will be interesting to see how patients react to having the option of a once-weekly injectable therapy for glucose control.

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