

Exenatide Once Weekly for Management of Type 2 Diabetes: A Review

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Abstract: Exenatide is one of the exendin-based glucagon-like peptide 1 receptor agonists (GLP-1RAs) and is currently available in two formulations, ie, exenatide twice daily (BID), a short-acting GLP-1RA, and exenatide once weekly (QW), a long-acting GLP-1RA. Clinical efficacy and safety of exenatide 2 mg QW in patients with type 2 diabetes (T2DM) has been demonstrated in the DURATION study program. Exenatide QW has been shown to achieve greater HbA1c reduction compared with exenatide BID, with less injection frequency and greater treatment satisfaction. However, exenatide QW failed to show a significant cardiovascular risk reduction in a cardiovascular outcome trial (CVOT), the EXSCEL trial, while other GLP-1RAs have shown positive CV outcomes. Furthermore, exenatide QW has been shown to be inferior to liraglutide and semaglutide with respect to HbA1c or body weight reduction in the head-to-head trials. Thus, although the long-term efficacy and safety of exenatide QW have been demonstrated, exenatide QW might be selected with lower priority within the class of GLP-1RAs for the management of T2DM, especially for patients at high CV risk. On the other hand, exenatide QW is now expected to be a treatment option for children with T2DM or patients with Parkinson's disease. This review provides an overview of the current evidence regarding the clinical efficacy and safety of exenatide QW and discusses the current perspectives on exenatide QW for treatment of T2DM.

Keywords: exenatide once weekly, GLP-1 receptor agonist, type 2 diabetes, cardiovascular outcome

Introduction

In the past two decades, new anti-diabetic medications for diabetes have been developed and marketed, including incretin-based therapy, which consists of two different classes: dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists (GLP-1 RAs). DPP-4 inhibitors enhance the plasma levels of native GLP-1 and glucose-dependent insulinotropic polypeptide by preventing their proteolytic degradations, while GLP-1 RAs display structural similarities to native GLP-1 and activate the GLP-1 receptor at a supra-physiological level.¹ Both agents can be used to manage the blood glucose with low risk of hypoglycemia by suppressing glucagon secretion and enhancing insulin secretion in a glucose-dependent manner.² GLP-1RAs also suppress gastric emptying and satiety, resulting in the induction of weight reduction.² Furthermore, GLP-1RAs were reported to reduce cardiovascular disease (CVD) events, ie, 3-point MACE (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke), in several trials³⁻⁷ performed to verify their cardiovascular safety, as well as in a meta-analysis.^{8,9} In light of these evidences, the American Diabetes Association recommends that patients with type 2 diabetes (T2DM) and established atherosclerotic cardiovascular disease (ASCVD), indicators of high risk for ASCVD, or chronic kidney disease are considered for treatment with GLP-1RAs.¹⁰ However, the heterogeneity of the efficacy or safety for patients with T2DM among GLP-1RAs remains unclear. Exenatide, one of the GLP-1RAs, is a synthetic GLP-1RA derived from exendin-4.¹¹ Treatment with exenatide 2 mg once weekly (QW) as a long-acting formulation was shown to achieve a significant reduction in fasting plasma glucose.¹² In this review, we outline the current evidence regarding the clinical efficacy and safety of exenatide QW in patients with T2DM, and discuss the current perspectives on the use of exenatide QW.

Search Strategy

This mini-review performed a search using PubMed with the search terms “exenatide”, “exenatide once weekly”, “incretin”, “GLP-1”, “GLP-1 receptor agonist”, “cardiovascular outcome”, “renal outcome”, and “type 2 diabetes”. In addition, relevant articles were collected from the personal databases of the authors.

Pharmacokinetics of Exenatide QW

Exendin-4 was discovered in a search for biologically active peptides in the venom of the Gila monster.¹³ This reptilian protein shares about 50% amino acid sequence identity with mammalian GLP-1 and is resistant to DPP-4-mediated degradation. Exenatide, lixisenatide and efpeglenatide have all been developed based on exendin-4. Although liraglutide, semaglutide, dulaglutide and albiglutide were based on human GLP-1, it is unclear whether there is any difference in the effects deriving from the structural basis of the GLP-1RAs used for management of T2DM. Exenatide QW was developed as a long-acting formulation with once-weekly administration and consists of microspheres composed of a biodegradable poly (lactide-co-glycolide) polymeric matrix containing the peptide exenatide.¹⁴ Exenatide is slowly released from the microspheres through diffusion and microsphere breakdown following once-weekly subcutaneous injection,¹⁵ and a steady-state plasma concentration is reached after 6–8 weeks of treatment.

Clinical Efficacy of Exenatide QW

The efficacy and safety of exenatide QW have been evaluated in the DURATION trials (The Diabetes Therapy Utilization: Researching Changes in A1C, Weight and Other Factors Through Intervention with Exenatide Once Weekly).^{16–25} The efficacy outcomes of exenatide QW in the DURATION trials are shown in Table 1. The DURATION trials (excluding DURATION 7 due to the presence of a titration phase with insulin glargine) reported reductions in fasting blood glucose (FBG), HbA1c and body weight from the baseline in the range of 32–46 mg/dl, 1.3–1.6% and 2.0–3.7 kg, respectively, throughout 24–30 weeks of treatment with exenatide QW. DURATION 1 and 5 assessed the clinical effects of exenatide QW compared to exenatide twice daily (BID), and found that treatment with exenatide QW was superior to exenatide BID in reducing HbA1c and FBG.^{16,17,22} DURATION 2 and 4 reported treatment with exenatide QW was superior to sitagliptin for reductions in HbA1c, FBG and body weight, and equivalent or superior to pioglitazone for reductions in HbA1c and FBG in addition to clear benefits for body weight.^{18,21} DURATION 4 also reported that treatment with exenatide QW was equivalent to metformin for reductions in HbA1c, FBG and body weight.²¹ DURATION 3 demonstrated the superiority of treatment with exenatide QW for reductions in HbA1c and body weight compared with insulin glargine, in spite of the inferiority of FBG.²⁰ DURATION 7 showed reductions in FBG, HbA1c and body weight of 12 mg/dl, 1.0% and 1.0 kg from baseline, respectively, in patients treated with exenatide QW after an 8-week titration phase with insulin glargine.²⁴ DURATION 8 reported that treatment with exenatide QW plus dapagliflozin was superior to either drug alone for reductions in HbA1c, FBG and body weight, demonstrating an additive effect between these two agents.²⁵ Both treatment with exenatide QW and treatment with daily liraglutide 1.8 mg led to reductions in FBG, HbA1c and body weight in DURATION 6, and greater reductions were noted with liraglutide.²³ Thus, exenatide QW has been reported to reduce body weight, but is not approved for treatment of obesity, while liraglutide (3.0 mg once-daily) has been approved for treatment of obesity by the US Food and Drug Administration (FDA). In the DURATION trials, treatments for T2DM with exenatide QW showed the clinical efficacy though not as effective as liraglutide 1.8 mg, suggesting that exenatide QW is an option for the treatment of T2DM, but it might be used with lower priority compared to liraglutide.

Safety Concerns

The most common adverse events of GLP-1RAs are nausea, vomiting and diarrhea, and these adverse events associated with exenatide QW were also most frequently observed in the DURATION trials.^{12,26} Gastrointestinal adverse events caused by GLP-1RAs often occur within the first month of treatment and tend to diminish within a couple of weeks.^{27,28} In an integrated analysis of 4328 patients in eight trials including the DURATION1-6 studies to assess the safety and tolerability of exenatide QW,²⁸ the percentage of patients experiencing nausea and vomiting was smaller among those administered exenatide QW (14.4% and 6.7%, respectively) than those treated with exenatide BID (29.9% and 13.0%),

Table I Efficacy Outcomes of Exenatide QW in the DURATION Trials

Study	Subjects	Background	Intervention and Comparators	Duration (Weeks)	Endpoints, Changes from the Baselines (Baseline Data)		
					FBG (mg/dl)	HbA1c (%)	Weight (kg)
DURATION-1 ¹⁶ Drucker et al, 2008	295	Lifestyle modification and oral antihyperglycemic drugs, age≥16 years, HbA1c 7.1–11.0%, FBG≤288mg/dl, BMI 25–45 kg/m ²	<u>Exenatide QW</u>	30	-41 (173)	-1.9 (8.3)	-3.7 (102)
			Exenatide BID		-25* (166)	-1.5* (8.3)	-3.6 (102)
DURATION-2 ¹⁸ Bergenstal et al, 2010	491	Metformin, age≥18 years, HbA1c 7.1–11.0%, BMI 25–45 kg/m ²	<u>Exenatide QW</u>	26	-32 (166)	-1.5 (8.6)	-2.3 (89)
			Sitagliptin 100 mg/day		-16* (164)	-0.9* (8.5)	-0.8* (87)
			Pioglitazone 45 mg/day		-27 (164)	-1.2* (8.5)	+2.8* (88)
DURATION-3 ²⁰ Diamant et al, 2010	456	Metformin and/or sulphonylurea, age≥18 years, HbA1c 7.1–11.0%, BMI 25–45kg/m ²	<u>Exenatide QW</u>	26	-38 (178)	-1.5 (8.3)	-2.6 (91.2)
			Insulin glargine		-50* (175)	-1.3* (8.3)	+1.4* (90.6)
DURATION-4 ²¹ Russell-Jones et al, 2012	820	Lifestyle modification, HbA1c 7.1–11.0%, BMI 23–45kg/m ²	<u>Exenatide QW</u>	26	-41 (178)	-1.5 (8.5)	-2.0 (87.5)
			Metformin 2000 mg/day		-36 (180)	-1.5 (8.6)	-2.0 (85.9)
			Pioglitazone 45mg/day		-47 (176)	-1.6 (8.5)	+1.5* (86.1)
			Sitagliptin 100mg/day		-20* (175)	-1.2* (8.5)	-0.8* (88.7)
DURATION-5 ²² Blevins et al, 2011	252	Lifestyle modification and oral antihyperglycemic drugs, age≥18 years, HbA1c 7.1–11.0%, FBG≤280mg/dl, BMI 25–45 kg/m ²	<u>Exenatide QW</u>	24	-35 (173)	-1.6 (8.5)	-2.3 (97.0)
			Exenatide BID		-12* (168)	-0.9* (8.4)	-1.4 (94.3)
DURATION-6 ²³ Buse et al, 2013	911	Lifestyle modification and oral antihyperglycemic drugs, age≥18 years, HbA1c 7.1–11.0%, BMI≤45 kg/m ²	<u>Exenatide QW</u>	26	-32 (173)	-1.3 (8.5)	-2.7 (90.9)
			Liraglutide 1.8 mg/day		-40* (176)	-1.5* (8.4)	-3.6* (91.1)
DURATION-7 ²⁴ Guja et al, 2018	464	Lifestyle modification and metformin and/or sulphonylurea, age≥18 years, HbA1c 7.0–10.5% at randomization after an 8-week titration phase	<u>Exenatide QW + insulin glargine±metformin</u>	28	-12 (148)	-1.0 (8.5)	-1.0 (94.2)
			Placebo + insulin glargine ±metformin		-2* (144)	-0.2* (8.5)	+0.5* (94.1)
DURATION-8 ²⁵ Frias et al, 2016	685	Metformin, age≥18 years, HbA1c 8.0–12.0%	<u>Exenatide QW</u>	28	-46 (189)	-1.6 (9.3)	-1.6 (89.1)
			Dapagliflozin 10 mg/day		-49 (188)	-1.4 (9.3)	-2.2 (90.9)
			Exenatide QW + dapagliflozin 10 mg/day		-66* (195)	-2.0* (9.3)	-3.6* (92.1)

Notes: *p<0.05, versus comparators. The underlines in Table 1 show comparators.

Abbreviations: T2DM, type 2 diabetes; QW, once-weekly formulation; BID, twice-daily formulation; FBG, fasting blood glucose.

but they were larger among patients given exenatide QW compared to patients treated without GLP-1RAs (4.9% and 2.5%). In this analysis, diarrhea was experienced by a higher percentage of patients administered exenatide QW (10.5%) than patients administered exenatide BID (8.4%) or comparators without GLP-1RAs (7.4%). DURATION 6 reported that nausea, vomiting, and diarrhea occurred in a smaller percentage of patients treated with exenatide QW (9.3%, 3.7%, and 6.1%, respectively) than patients treated with liraglutide 1.8 mg/day (20.7%, 10.7%, and 13.1%).^{23,28} On the other hand, adverse events related to injection-site reactions—which were mainly induration, nodule and pruritus—were observed in

a greater percentage of patients treated with exenatide QW (16–20%) compared to those administered exenatide BID and liraglutide. However, cases of discontinuation due to adverse events related to injection-site reactions seemed to be limited, occurring in only 0.2–0.8% of patients treated with exenatide QW.²⁸ Adverse events related to pancreatitis, renal failure, gallbladder disease, and thyroid cancer were rarely reported in patients treated with exenatide QW.²⁸ Thus, treatments with exenatide QW were shown to be clinically safe, and gastrointestinal adverse events such as nausea and vomiting were less frequent in the treatment with exenatide QW compared to those with exenatide BID or liraglutide.

Effects of Switching from Exenatide BID to Exenatide QW

According to the pharmacokinetic/pharmacodynamic profiles, GLP-1RAs are categorized as either short-acting compounds, which predominantly suppress postprandial glucose levels by delaying gastric emptying, or as long-acting compounds, which predominantly reduce fasting plasma glucose levels by stimulating insulin secretion and suppressing glucagon secretion.¹ Exenatide has two formulations: a short-acting BID formulation and a long-acting QW formulation. The effects of switching from exenatide BID to exenatide QW were elucidated in a previous study by our group²⁹ as well as in studies by other authors,^{30,31} switching from short- to long-acting formulations induces reductions in HbA1c and FBG, and increases of postprandial hyperglycemia. Weights after switching were reported to be unchanged in two of the studies.^{29,31} We reported an improvement in treatment satisfaction in patients assessed by the Diabetes Treatment Satisfaction Questionnaire, and a reduced incidence of hypoglycemia after switching.²⁹ We also recently reported that despite the increase in postprandial glucose associated with accelerated gastric emptying after switching from exenatide BID to QW, change in glycemic variability assessed by continuous glucose monitoring was modest, and no significant deterioration in vascular endothelial function was observed after switching.³² These findings suggest that treatment with exenatide QW is more useful than treatment with exenatide BID in clinical practice.

Cardiovascular Outcome

The Exenatide Study of Cardiovascular Event Lowering (EXSCEL) was a randomized, double-blind and placebo-controlled trial to investigate the cardiovascular effects of treatment with exenatide QW in patients with T2DM.³³ This trial enrolled 14,752 patients, 10,782 (73%) of whom had CVD, and followed them for a median of 3.2 years. The primary outcome was evaluated as a composite endpoint of 3-point MACE, and occurred in 839 patients (11.4%) with exenatide QW compared to 905 patients (12.2%) in the placebo group. As a result, treatment with exenatide QW was shown to be noninferior to placebo ($P < 0.001$), but failed to reduce the 3-point MACE composite compared with placebo (hazard ratio (HR) 0.91; 95% CI 0.83–1.00, $P = 0.06$ for superiority). While some GLP-1RAs such as lixisenatide and oral semaglutide also achieved no significant reduction in CVD outcomes,^{34,35} other GLP-1RAs such as liraglutide, semaglutide, albiglutide and dulaglutide achieved 13% (HR 0.87, 95% CI 0.78–0.97),³ 26% (HR 0.74, 95% CI 0.58–0.95),⁴ 22% (HR 0.78, 95% CI 0.68–0.90)⁵ and 12% (HR 0.88, 95% CI 0.79–0.99)⁶ reductions in the 3-point MACE composite in their respective trials.³⁶ Efglenatide, which consists of a modified exendin-4 molecule conjugated to an IgG4 Fc fragment,³⁷ is one of the long-acting GLP-1RAs. In the recent AMPLITUDE-O trial, treatment with efglenatide 4 or 6 mg QW was reported to reduce the incidence of MACE (HR 0.73, 95% CI 0.58–0.92) and renal endpoint, as assessed by the composite of macroalbuminuria or a decrease in kidney function (HR 0.68, 95% CI 0.57–0.79), compared to placebo.⁷ Of note, the reduction in MACE in this trial was observed regardless of using metformin or SGLT2 inhibitor at baseline, while previous trials included limited persons treated with an SGLT2 inhibitor. A recent meta-analysis of AMPLITUDE-O and seven other trials, which was designed to evaluate the cardiovascular benefits and risks of GLP-1RAs, reported that human and exendin-4-based agents have similar benefits for MACE regardless of the structural basis of the GLP-1RAs.⁹ Treatment with efglenatide 4 mg QW was shown to reduce HbA1c and body weight comparable to those by liraglutide 1.8 mg/day.³⁸ In the head-to-head trial of exenatide QW and semaglutide 1.0 mg QW (SUSTAIN 3), treatment with semaglutide was superior to exenatide QW in reducing HbA1c (–1.5% vs –0.9%), FBG (–50 mg/dl vs –36 mg/dl) and body weight (–5.6 kg vs –1.9 kg) after 56 weeks of treatment.³⁹ Moreover, a retrospective cohort study employing an electronic medical record database reported that treatment with exenatide QW achieved an HbA1c reduction equivalent to that by dulaglutide 1.5 mg, but a smaller reduction in body weight compared to dulaglutide.⁴⁰ Although the reasons for the heterogeneity of effects on CVD among GLP-1RAs remain unclear,⁸ the greater efficacy for glycemic control or body weight achieved by liraglutide (DURATION 6),²³ semaglutide (SUSTAIN 3)⁴ and dulaglutide⁴⁰ compared to exenatide QW might affect the incidence of

CVD. Indeed, a meta-analysis of 12 trials evaluating the risk of MACE for treatment with the newer glucose-lowering drugs, including GLP-1RAs, suggested a relation between the reduction of HbA1c and the lower HR of MACE.⁴¹

Renal Outcome

GLP-1RAs reduced the incidence of composite renal outcomes in several trials.^{3,4,7,42} However, this effect was driven mainly by the reduction in albuminuria. It remains unclear whether GLP-1RAs are able to improve renal outcomes such as worsening of kidney function.⁹ A significant reduction in renal outcomes, as assessed by the composite of 40% estimated glomerular filtration rate (eGFR) decline, renal death, renal replacement and new macroalbuminuria, was reported with exenatide QW in an adjusted analysis (HR 0.85, 95% CI 0.73–0.98).⁴³ Finally, in the post hoc EXSCEL analysis, treatments with exenatide QW improved both the urinary albumin excretion and eGFR decline in subjects with elevated baseline urinary albumin compared to placebo, suggesting that exenatide QW reduces urinary albumin and improves the eGFR slope specifically in subjects with an elevated baseline urinary albumin: creatinine ratio.⁴⁴

Possible Mechanisms of Cardiovascular Outcome

The separation of the Kaplan–Meier curves for CVD events among treatments in the trials of GLP-1RAs appeared to occur gradually compared to the trials of sodium-glucose cotransporter 2 (SGLT2) inhibitors such as EMPA-REG OUTCOME trial.⁴⁵ These results suggest that GLP-1RAs achieve a reduction in CVD events through their anti-atherosclerotic effects, in contrast to the hemodynamic effects associated with SGLT2 inhibitors.⁴⁶ A recent study demonstrated no significant difference in carotid plaque progression for 18 months between treatment with exenatide QW and placebo,⁴⁷ suggesting that longer duration of treatment with exenatide QW may be needed to exert anti-atherosclerotic effects. Other possible mechanisms of cardiorenal protection by GLP-1RAs, such as anti-inflammatory, anti-fibrotic, anti-oxidative or vasodilatory effects, have been noted in other studies.^{36,48,49}

Current Perspectives

Treatments with exenatide QW showed clinical efficacy and safety and achieved borderline reductions in CVD for patients with T2DM in the above trials. The five- or seven-year follow-up studies in the DURATION-1 trial reported sustained improvements in glycemic control and no unexpected safety findings by treatment with exenatide QW,^{50,51} demonstrating the long-term usefulness of exenatide QW in clinical practice. In addition, once-weekly GLP-1RAs, including exenatide QW, are more convenient, and are therefore preferred by patients and more likely to encourage treatment adherence compared to agents which need daily injection.^{52–54} However, taking the results from the trials of other GLP-1RAs together, exenatide QW might be considered less preferable than other GLP-1RAs for the management of T2DM, especially for patients with high CV risk. Table 2 shows the outcomes of trials using GLP-1RAs based on exendin-4 (exenatide QW, lixisenatide and efpeglenatide). The results indicate that, among the GLP-1RAs based on exendin-4, efpeglenatide may be the first choice if it becomes available. On the other hand, from the perspective of price and utility, treatment with exenatide QW may be continued in patients with optimal glycemic control without adverse events. Additionally, the FDA approved exenatide QW for pediatric use in children aged 10 to 17 years with T2DM based on the positive Phase 3 data.⁵⁵ Exenatide QW was also reported to cause weight loss in subjects aged 10 to 18 years with obesity,⁵⁶ and thus this agent is expected to be effective for the management of glycemia and body weight, and to provide a new option as the first once-weekly injectable GLP-1RA approved for children and adolescents. Furthermore, exenatide QW as well as BID was reported to exhibit positive effects on motor scores in patients with Parkinson's disease compared to the placebo.^{57,58} Although it is unclear how to improve motor symptoms for patients with Parkinson's disease, exenatide is expected to have neuroprotective effects in this disease and other neurodegenerative disorders.⁵⁹ Thus, further verification of the effects of exenatide QW on children and adults with T2DM or obesity, as well as patients with neurodegenerative disorders, will be needed in the future.

Conclusion

This review summarized the current evidence of the clinical efficacy and safety of exenatide QW, and discussed future perspectives on the use of exenatide QW. GLP-1RAs are becoming the mainstay of therapeutic strategies for T2DM

Table 2 Summary of Cardiovascular Outcome Trials with Exendin-Based Glucagon-Like Peptide-1 Receptor Agonists

	ELIXA ^{34,60}	EXSCEL ^{33,43}	AMPLITUDE-O ⁷
Drug	Lixisenatide	Exenatide QW	Efpeglenatide
Dose	10 or 20 µg, once daily	2 mg, once weekly	4 or 6mg, once weekly
Number of participants	6068	14,752	4076
Median follow-up period, years	2.1	3.2	2.1
Mean age, years	60.3	62.0	64.5
Sex (male), %	69	62	67
Mean HbA1c at baseline, %	7.7	8.1	8.9
Mean BMI at baseline, kg/m ²	30.1	32.7	32.7
Established cardiovascular disease, %	100	73	90
3-point MACE	HR 1.02 (0.89–1.17) ^a	HR 0.91 (0.83–1.00)	HR 0.73 (0.58–0.92)
All-cause mortality	HR 0.94 (0.78–1.13)	HR 0.86 (0.77–0.97)	HR 0.78 (0.58–1.06)
Cardiovascular death	HR 0.98 (0.78–1.22)	HR 0.88 (0.76–1.02)	HR 0.72 (0.50–1.03)
Fatal or non-fatal myocardial infarction	HR 1.03 (0.87–1.22)	HR 0.97 (0.85–1.10)	HR 0.75 (0.54–1.05)
Fatal or non-fatal stroke	HR 1.12 (0.79–1.58)	HR 0.85 (0.70–1.03)	HR 0.74 (0.47–1.17)
Renal outcome ^b	HR 0.84 (0.68–1.02)	HR 0.88 (0.76–1.01)	HR 0.68 (0.57–0.79)
Worsening of kidney function	HR 1.16 (0.74–1.83)	HR 0.88 (0.74–1.05)	HR 0.35 (0.10–1.27)

Notes: ^a4-point MACE (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, hospitalization for unstable angina) was reported in ELIXA. ^bRenal outcome comprised composite kidney outcome including new-onset macroalbuminuria.

Abbreviations: 3-point MACE, major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke); HR, hazard ratio.

based on the positive evidence of CV benefits. However, within the class of GLP1-RAs, exenatide QW may not be a first choice for adult patients with T2DM, and especially for patients at high CV risk: despite its long-term efficacy and safety, exenatide QW has not been clearly shown to have CV benefits.

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Disclosure

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