

Exenatide once-weekly injection for the treatment of type 2 diabetes in Chinese patients: current perspectives

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Abstract: Glucagon-like peptide-1 (GLP-1) analogs, such as exenatide, have played an important role as antidiabetic medications in the treatment of type 2 diabetes (T2DM). Like most other hypoglycemic agents, exenatide has a number of actions, including lowering blood glucose, promoting weight loss, improving insulin resistance, and protecting islet β -cells. Although GLP-1 analogs, combined with other antidiabetic medications, have excellent performance in T2DM, some side effects and imperfections limit its use in clinical practice. Since 2012, a new generation GLP-1 agent, exenatide once weekly (QW), has been available for patients with T2DM in the USA, but not as yet in the People's Republic of China. Previous data indicate that exenatide QW achieves better fasting glucose reductions than sitagliptin or exenatide twice daily, whilst appearing non-inferior to pioglitazone and achieving less reductions than insulin glargine. Exenatide QW was better at improving average postprandial glucose than sitagliptin or titrated insulin glargine, but was inferior to exenatide twice daily. Additionally exenatide QW has a better effect in terms of weight loss than other glycemic medications. Exenatide QW can also reduce blood lipids and lower blood pressure. Accordingly, exenatide QW is cost-effective, achieves good clinical outcomes, and has acceptable side effects, indicating that it has promising prospects for future use in the People's Republic of China.

Keywords: diabetes, glycemic control, exenatide once weekly

Introduction

Diabetes is one of the most common chronic noninfectious diseases worldwide, including in the People's Republic of China. According to the China National Diabetes and Metabolic Disorder Study, the age-standardized prevalence of diabetes in people over 20 years of age was 9.7% along with 15.5% for prediabetes in 2008.¹ The most recent survey, based on the 2010 guideline of the American Diabetes Association, which integrated glycated hemoglobin (HbA1c) into the diagnostic criteria, estimated that the prevalence of diabetes and prediabetes was 11.6%–50.1%, respectively, in the People's Republic of China. This suggests that 113.9 million Chinese adults had diabetes and that 493.4 million had prediabetes in 2010.² However, various sampling, study, and analysis methods have yielded different data and results. Nonetheless, all of these findings reflect the serious public concern about diabetes in the People's Republic of China.

A variety of antidiabetic medications has been used for the treatment of diabetes in the last few decades; however, the success rate of blood glucose control remains inadequate. In one report, only 25.8% of patients with diabetes received antidiabetic treatment and only 39.7% of those treated had adequate glycemic control (HbA1c <7.0%).² The results of other studies revealed that 64% of patients still fail to achieve adequate glycemic

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control and die prematurely of a variety of complications.^{3,4} In addition to clinical efficacy, the side effects of traditional medicines also impose restrictions on selection of drugs. For example, sulfonylureas, which were the first therapies targeted to insufficient insulin secretion, can cause hypoglycemia. These compounds promote insulin secretion independent of blood glucose levels. In addition, as diabetes progresses, the ability of sulfonylureas to stimulate insulin secretion may decrease.⁵ Similarly, pioglitazone may cause bladder cancer and rosiglitazone, (which can no longer be used in the USA) may cause or worsen congestive heart failure.⁶ In addition, patient compliance with antidiabetic medication is thought to be important when evaluating a medication. These factors may include the complexity of treatment, duration of treatment, route of administration, frequency of dosing, and even cost considerations.⁴ For these reasons, there is a need to develop new drugs to treat type 2 diabetes (T2DM).

Fortunately, a number of new drugs have been developed in recent years. Some of the most popular hypoglycemic drugs include the glucagon-like peptide-1 (GLP-1) analogs and dipeptidyl peptidase (DPP)-4 inhibitors, which have already been shown to have good antidiabetic effects. However, some disadvantages are still inevitable. Exenatide is one of the GLP-1 analogs that has been used as an antidiabetic medication, and has been available since 2005. In order to improve and refine the quality of hypoglycemic drugs, one of the new generation long-term GLP-1 analogs, exenatide once weekly (QW) injection was approved by the US Food and Drug Administration in 2012. This has helped to alleviate some anti-diabetes drug shortages, but because it has been used in clinical practice for only a short time, its safety and efficacy needs further investigation. In this review, we summarize the previous findings regarding GLP-1 analogs and discuss the prospective clinical application of exenatide QW in the People's Republic of China.

GLP-1, GLP-1 analogs, and other antidiabetic agents

Overview of GLP-1 and GLP-1 analogs

In the early 20th century, researchers found that some hormones released from the intestine could stimulate insulin secretion after food intake, with an apparent glucose-lowering effect. Subsequently, McIntyre et al and Elrick et al discovered that the insulin secretion was much higher when glucose was taken orally rather than by intravenous injection.^{7,8} This additional activity was termed the "incretin effect" and was thought to account for over 50% of total insulin secretion after

a meal.⁹ In 1987, by cloning and sequencing of proglucagon genes, Drucker et al and Orskov et al identified the incretin now known as GLP-1 which could promote release of the pancreatic hormone insulin.^{10,11} Under the stimulus of food, GLP-1 could be secreted into the circulation by L-cells in the ileum and colon, inhibiting apoptosis of β -cells and improving β -cell function.¹² However, this endogenous form of GLP-1 was rapidly degraded by DPP-4 and needed to be given by continuous intravenous drip or subcutaneous injection, so its clinical application is limited.^{13,14}

In recent years, GLP-1 analogs have come onto the market; these agents not only retain the advantages of GLP-1, but also protect against degradation by DPP-4. In 2005, the first GLP-1 analog, exenatide, was approved by the US Food and Drug Administration for clinical application. This GLP-1 analog was used for T2DM and obtained widespread acceptance by the medical profession after 5 years of clinical use in the People's Republic of China.¹⁵

Basic research

Numerous data from experiments conducted in vivo and vitro have been collected to support many new therapeutic measures for controlling T2DM. Research in a mouse model demonstrated that GLP-1 can increase β -cell proliferation and reduce glucagon secretion from pancreatic α -cells.^{16,17} Similar results were observed in obese diabetic (db/db) mice that underwent prolonged administration of GLP-1, ie, improved blood glycemic excursions and more islet mass and β -cell neogenesis.¹⁸

GLP-1 also regulates a wide scope of extrapancreatic effects, including in the digestive system, locomotor system, and even the central nervous system. GLP-1 can inhibit gastric emptying and small intestinal transit by decreasing gastric smooth muscle motility.^{19,20} GLP-1 also appears to upregulate insulin sensitivity and glucose uptake in adipose tissue and skeletal muscle.^{21,22} Interestingly, rats injected with GLP-1 experienced satiety, which caused reduced caloric intake, indicating that GLP-1 was a physiological mediator of satiety.^{23,24} Meanwhile, some side effects, including increased heart rate and blood pressure, were also observed in rats treated with GLP-1.²⁵

As mentioned earlier, unlike GLP-1, GLP-1 analogs can maintain biological activity and are resistant to degradation by DPP-4 through proteolytic cleavage, which are used more often in diabetes therapy. Further, GLP-1 agonists such as exenatide enhanced postprandial insulin secretion, and as well as promoting weight loss and having a hypoglycemic effect.²⁶ The properties of GLP-1 described earlier, including glucose-dependent insulin secretion, β -cell mass expansion,

coupled with inhibition of glucagon secretion and gastric emptying. This suggests that it would greatly complement current β -cell therapies.

Clinical study of antidiabetic agents

Diabetes treatment guidelines from the American Diabetes Association and European Association for the Study of Diabetes have recommended several antihyperglycemic strategies and a number of antidiabetic medications, according to evidence-based medicine. Metformin has regained an approval on the basis of the United Kingdom Prospective Diabetes Study and has been considered the first-line treatment for T2DM since 1998.²⁷ Like metformin, GLP-1 can inhibit hepatic gluconeogenesis, and decrease fasting and postprandial blood glucose.²⁸ Additionally, GLP-1 also enhances insulin sensitivity and decreases peripheral insulin resistance.^{29,30} Both metformin and GLP-1 were shown to reduce cardiovascular morbidity and mortality, consequently extending the lifespan of T2DM patients.^{31–33} Other hypoglycemic agents like thiazolidinediones also increase insulin sensitivity in the liver and skeletal muscle and inhibit hepatic gluconeogenesis. However, thiazolidinediones can increase appetite and adipogenesis, which eventually leads to weight gain. Further, in contrast with the cardioprotection afforded by metformin and GLP-1, thiazolidinediones frequently induce or aggravate heart failure.^{34,35} Sulfonylureas can stimulate insulin secretion from β -cells, and have been used since the 1950s.³⁶ Sulfonylureas are also somewhat efficient in improving insulin levels and reducing blood glucose concentrations. Unfortunately, some studies have shown that this class of drugs results in weight gain and hypoglycemia, accelerates β -cell apoptosis, and impairs endothelial function.^{36–39} These disadvantages were not found with GLP-1.^{22,29} In recent years, DPP-4 inhibitors have been approved as a new class of antidiabetic drugs because they can inhibit the enzyme which inactivates GLP-1. This increases the effects of endogenous GLP-1, and in turn, enhances glucose-dependent insulin in order to suppress inappropriately elevated glucagon secretion as well as preserve pancreatic β -cells.^{40–42} However, head-to-head trials have demonstrated that DPP-4 inhibitors have an inferior glucose-lowering effect when compared with GLP-1.^{43,44} Moreover, DPP-4 inhibitors do not appear to have an effect on gastric emptying or weight loss, which limits their clinical application.^{16,45,46}

Side effects and disadvantages of exenatide

While GLP-1 has multiple advantages in the treatment of T2DM, some adverse effects are still unavoidable. The main

adverse reactions are gastrointestinal, including nausea, vomiting and diarrhea, however, all of them are relative to moderate.^{47,48} These side effects are mainly seen in the early treatment period.⁴⁹ Other adverse events, such as injection site reactions and hypoglycemia, are rare, but the risk of hypoglycemia may increase when exenatide is used in combination with a sulfonylurea.⁵⁰ Based on post-marketing data and several clinical studies, exenatide has been associated with both fatal and non-fatal hemorrhagic or necrotizing pancreatitis.⁵¹ It is still controversial whether there is an increased risk of pancreatic cancer with GLP-1 analogs when compared with other antidiabetic therapies.⁵² It has been reported that GLP-1 may cause thyroid C-cell adenomas in rodents.⁵³ In contrast, there are some research data indicating that the risk of developing medullary thyroid cancer is very low in patients receiving GLP-1 therapy.⁵⁴ The calcitonin was maintained at low levels and no evidence of C-cell activation was found. However, the exact relationship between GLP-1-based therapies and the risk of pancreatic or thyroid cancer remains to be clarified.⁵⁵

As mentioned earlier, GLP-1 is easily inactivated by DPP-4, which greatly limits its clinical application.⁵⁶ To avoid this problem, researchers developed GLP-1 receptor agonists, including a subcutaneous injectable formulation of exenatide, which only has a short plasma half-life of 2–4 hours and a duration of action of approximately 8 hours. Inevitably, fluctuating plasma concentrations of the drug may easily aggravate adverse effects such as diarrhea, indigestion, and nausea. The daily injection also causes pain and is inconvenient.⁵⁷ In recent years, researchers have developed exenatide QW to improve drug efficacy, safety, and patient compliance. Its superiority has been established by a series of head-to-head clinical trials.^{58–60}

Exenatide once weekly Pharmacology and pharmacodynamics

Exenatide QW is an agent combining exenatide within a microspheric technology that contains poly (lactic-co-glycolic acid), which can encase the drug molecule and enable natural hydrolysis of the ester linkages. The drug molecule is released continuously into the circulation during microspheric degradation by non-enzymatic hydrolysis under the skin,^{61,62} allowing exenatide QW to have a much longer half-life than exenatide twice daily. Moreover, previous experiments established that a single subcutaneous dose of exenatide QW could lead to a dose-related increase in concentrations of exenatide in plasma, subsequently achieving a multiple-peak profile over approximately 10 weeks.⁶³ Both exenatide QW 0.8 mg and exenatide

QW 2.0 mg can achieve effective therapeutic plasma concentrations (>50 pg/mL). However, patients dosed with 2 mg of exenatide QW can achieve both fasting plasma and postprandial glucose control, while the group dosed with 0.8 mg showed only improved fasting plasma glucose control. This indicates that 2.0 mg may be the optimal dose of exenatide QW.⁶³ Therapeutic doses and steady-state plasma concentrations of exenatide QW were achieved after approximately 2 weeks and 6–7 weeks, respectively. After discontinuation of therapy, it took 10 weeks to reduce GLP-1 analogs to a minimally detectable plasma concentration of 10 pg/mL.⁶³ As exenatide QW is eliminated by glomerular filtration, it cannot be used in patients whose creatinine clearance is less than 30 mL per minute or in patients with end-stage renal disease.

Clinical effect of exenatide QW

As with most other antidiabetic drugs used in the treatment of T2DM, a series of duration studies have revealed the safety and efficacy of exenatide QW. In general, exenatide QW achieves significantly greater reductions in HbA1c when compared with exenatide twice daily, titrated insulin glargine, sitagliptin and pioglitazone on the metformin background.^{32,49,59,64,68} Overall, there were more patients using exenatide QW to achieve the composite than using other hypoglycemic drugs. Notably, patients who switched from daily sitagliptin or pioglitazone to exenatide QW achieved improved or sustained glycemic control.⁶⁴ Regarding patients fasting glucose, treated with exenatide QW it had apparently more reductions than sitagliptin and exenatide twice daily,^{64,66,69} while appearing non-inferior to pioglitazone and with less reductions than insulin glargine.^{49,64} According to self-monitored blood glucose tests, exenatide QW improved average postprandial glucose to a greater extent than sitagliptin and titrated insulin glargine; however, exenatide QW is inferior to exenatide twice daily in improving average postprandial glucose (Table 1).^{49,64,66} The exenatide QW group achieved more weight loss (range 2–4 kg) than the sitagliptin group and similar with exenatide twice daily group, while the groups receiving pioglitazone and glargine showed weight gains up to 4–5 kg (Table 1).^{32,49,64–66,70,71} Reductions in weight and HbA1c were seen in 70%–79% of patients on exenatide QW. Although the HbA1c reduction was only significantly greater than 51%–74% of exenatide twice daily diabetics, 46% of sitagliptin diabetics, 14% of pioglitazone diabetics, and 31% of insulin glargine diabetics, the improvement in glycemic parameters was assumed to be independent of weight loss.^{32,49,64,66} Meanwhile, the study investigated other systemic effects in patients treated with exenatide QW,

including mean systolic blood pressure, which decreased by 3–5 mmHg. In patients treated with exenatide QW, mean total cholesterol and low-density lipoprotein cholesterol levels were significantly improved, but there was no significant effect on high-density lipoprotein cholesterol. In contrast, the improvement in total cholesterol was less for exenatide twice daily, compared with exenatide WQ (Table 2). However, no meaningful differences in fasting lipids were found between patients treated with exenatide QW, those treated with sitagliptin, and those treated with insulin glargine.^{32,49,64,66,67} The insulin-to-glucose ratio after 14 weeks of treatment indicated that patients on exenatide QW had a significant increase in β -cell sensitivity.⁷¹ Moreover, B-type natriuretic peptide was reduced on sitagliptin, pioglitazone, and exenatide QW therapy. However, exenatide QW was the only therapy which caused a significant reduction in the albumin-to-creatinine ratio.⁶⁴ Exenatide QW was non-inferior to metformin in the Duration-4 study.³² The combination of exenatide QW with other antidiabetic medications appeared to be well tolerated in some studies. In a recent study, Japanese T2DM patients treated with exenatide QW and oral antidiabetic medications showed great weight loss and glycemic control through 52 weeks, indicating that exenatide QW can be used as an adjunctive treatment for T2DM in this patient population.⁷² A head-to-head trial comparing exenatide QW with liraglutide suggested that both exenatide QW and liraglutide improved glycemic control as well as weight loss. Interestingly, in one study, better improvement of HbA1c and weight loss were achieved in the liraglutide group when compared with the exenatide group.⁷³ In other studies, opposite results were found.^{49,64–67,70,74–77} The reasons for these unexpected differences are presently unknown. No major hypoglycemic events were reported and gastrointestinal side effects were mild in all treatment groups.^{32,49,64–66,68,74–76} However, withdrawals due to gastrointestinal adverse events were more frequent with liraglutide.⁷³

Side effects and safety of exenatide QW

Recent studies reported that 26.4% of patients had nausea, which was the most common adverse event in all the head-to-head trials. Other gastrointestinal side effects, such as vomiting and diarrhea, were typically less frequent than nausea.^{49,64,66,67,78,79} In most patients, these adverse reactions resolved by 3–4 weeks, whilst a small proportion of patients showed intermittent side effects, which peaked by 6–8 weeks of therapy, at which time drug levels approached steady state.⁸⁰ In general, there were fewer gastrointestinal adverse effects in patients treated with exenatide QW than

Table 1 Glucose-lowering effect and weight loss on exenatide QW versus other hypoglycemic drugs

Studies	Duration (weeks)	Interventions compared	HbA1c (%)	HbA1c ≤ 7 (%)	HbA1c ≤ 6.5 (%)	FG (mmol/L)	Bodyweight (kg)	Hypoglycemia (%)
Drucker et al ⁵⁷	30	Exenatide QW 2 mg versus exenatide 10 µg BID	-1.9 -1.5	77 61	49 21	-2.3 -1.4	-3.7 -3.6	No sulfonylurea background: major: 0 versus 0 minor: 0 versus 1 Sulfonylurea background: major: 0 versus 0 minor: 14.5 versus 15.4
Buse et al ⁶⁸	52	Exenatide QW 2 mg versus exenatide 10 µg BID→QW 2 mg	-2.0	71	54	-2.4	-4.1	N/A
Diamant et al ⁶⁷	26	Exenatide QW 2 mg versus insulin glargine 10 IU QD (starting dose)	-2.0 -1.5	71 60	53 35	-2.6 -2.1	-4.5 -2.6	N/A Minor: 8 versus 26
Bergensdal et al ⁶⁴	26	Exenatide QW 2 mg versus sitagliptin 100 mg QD, pioglitazone 45 mg QD	-1.3 -1.5 -0.9	48 60 35	23 40 20	-2.8 -1.8 -0.9	+1.4 -2.3 -0.8	Symptomatic: 13 versus 31 Minor: 1.0 versus 3.0 versus 1.0
Blevins et al ⁶⁶	24	Exenatide QW 2 mg versus exenatide 5 µg BID→10 µg BID	-1.2 -1.6 -0.9	52 41.1 16.3	30 58.1 30.1	-1.5 -1.94 -0.66	+2.8 -2.3 -1.4	No major Sulfonylurea background: minor: 6.7 versus 5.4
Inagaki et al ⁶⁵	26	Exenatide QW 2 mg versus insulin 4 IU/QD	-1.11 -0.68	42.2 21.0	20.6 4.2	-2.40 -2.39	-1.67 +0.34	Minor: 0.5 versus 1.9 Symptomatic: 9.3 versus 19 Overall hypoglycemia: 9.8 versus 20.8
Diamant et al ⁷⁰	84	Exenatide QW 2 mg versus insulin 10 IU QD	-1.2 -1.0	44.6 36.8	31.3 20.2	-2.36 -2.97	-2.1 +2.4	Metformin background: minor: 8 versus 32 symptomatic: 12 versus 40 metformin plus sulfonylurea background: minor: 24 versus 54 symptomatic: 36 versus 56
Russell-Jones et al ⁷²	26	Exenatide QW 2 mg versus metformin 2000 mg QD, sitagliptin 100 mg QD, pioglitazone 45 mg QD	-1.53 -1.48 -1.63	63 55 43	49 36 26	-2.3 -2.0 -1.1	-2.0 -2.0 -0.8	N/A N/A N/A
Ji et al ⁵⁸	26	Exenatide QW 2 mg versus Exenatide 5 µg BID→10 µg BID	-1.48 -1.43 -1.12	61 46.7 35.7	42 26.0 15.5	-2.6 -2.25 -1.33	+1.5 -1.63 -2.45	N/A Sulfonylurea background: minor: 6.8 versus 12 symptomatic: 19.7 versus 26.2
Buse et al ⁷³	26	Exenatide QW 2 mg versus liraglutide 1.8 mg QD	-1.28 -1.48	53 60	N/A N/A	-1.76 -2.12	-2.68 -3.57	No sulfonylurea background: minor: 1.3 versus 1.4 symptomatic: 5.3 versus 11.3
Diamant et al ⁴⁹	156	Exenatide QW 2 mg versus insulin 10 IU/QD (starting dose)	-1.0 -0.81	48 38	28 18	-1.73 -2.65	-2.49 +2.01	N/A N/A

Notes: All the data are shown as the least squares mean (standard error); → change one antidiabetic medication to the latter one; major indicates a major hypoglycemic event; minor indicates a minor hypoglycemic event.

Abbreviations: HbA1c, glycated hemoglobin; FG, fasting glucose; QW, once weekly; BID, twice daily; QD, once daily; IU, International Units; N/A, not available.

Table 2 Effect of exenatide QW on blood lipids and blood pressure versus effects of other hypoglycemic drugs

References	Duration (weeks)	Interventions compared	TC (mmol/L)	HDL-C (mmol/L)	LDL-C (mmol/L)	TG (mmol/L)	SBP (mmHg)	DBP (mmHg)
Drucker et al ⁵⁷	30	Exenatide QW 2 mg versus exenatide 10 µg BID	-0.31 -0.10	-0.02 -0.03	-0.13 +0.03	-0.03 -0.03	-4.7 -3.4	-1.7 -1.7
Diamant et al ⁶⁷	26	Exenatide QW 2 mg versus insulin glargine 10 IU QD (starting dose)	-0.12 -0.04	0.00 0.01	-0.05 +0.04	N/A N/A	-3 -1	-1 -1
Buse et al ⁶⁸	52	Exenatide QW 2 mg versus exenatide 10 µg BID→QW 2 mg	-0.25 -0.23	-0.02 -0.04	-0.09 -0.07	-0.27 -0.22	-6.2 -3.8	-2.8 -1.8
Bergental et al ⁶⁴	26	Exenatide QW 2 mg versus sitagliptin 100 mg QD, pioglitazone 45 mg QD	-0.02 +0.07 +0.16	+0.05 +0.05 +0.15	-0.03 +0.04 +0.04	-0.10 -0.10 -0.35	-3.75 +0.15 -1.25	No difference
Blevins et al ⁶⁶	24	Exenatide QW 2 mg versus exenatide 5 µg BID→10 µg BID	-0.40 +0.02	0.00 +0.03	-0.17 +0.07	+0.94 +0.99	-1.2 -2.9	+0.2 -0.1
Inagaki et al ⁶⁵	26	Exenatide QW 2 mg versus insulin 4 IU QD	-1.67 -1.67	-0.52 -0.51	-1.41 -1.42	1.02 1.02	N/A N/A	N/A N/A
Ji et al ⁵⁸	26	Exenatide QW 2 mg versus exenatide 5 µg BID→10 µg BID	-0.24 -0.21	-0.003 -0.012	-0.19 -0.21	+0.01 +0.01	-5.41 -5.38	-1.62 -2.26
Buse et al ⁷³	26	Exenatide QW 2 mg versus liraglutide 1.8 mg QD	-0.06 -0.15	+0.02 +0.02	-0.05 -0.09	N/A N/A	-2.48 -3.45	-0.49 -0.51
Diamant et al ⁴⁹	156	Exenatide QW 2 mg versus insulin 10 IU QD (starting dose)	-0.13 -0.01	+0.05 +0.05	-0.17 -0.13	+1.02 +0.97	-2 +2	-2 -2

Notes: All the data are shown as the least squares mean (standard error).

Abbreviations: TC, total cholesterol; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; TG, triglycerides; SBP, systolic blood pressure; DBP, diastolic blood pressure; QW, once weekly; BID, twice daily; QD, once daily; IU, International Units; N/A, not available.

in those treated with exenatide twice daily, and less than 2% of patients stopped treatment because of gastrointestinal side effects. However, injection site reactions, including pain, erythema, bruising, hemorrhage, induration, and skin nodules, appeared to be more common in patients treated with exenatide QW. Fortunately, the incidence of injection site reactions decreased over time.^{66,71} As with the traditional GLP-1 analogs, the prevalence of hypoglycemia in patients treated with exenatide QW was quite low in all the studies, unless exenatide QW was used with sulfonylureas. Additionally, the action of GLP-1 agonists potentiated glucose-dependent insulin secretion, which resulted in a low incidence of hypoglycemia (Table 1).^{32,64,66,79,80} Although some studies showed that exenatide QW was associated with an increased prevalence of thyroid C-cell tumors in rats and in female mice, no similar results have been reported in humans. As mentioned previously, pancreatitis and/or pancreatic cancer were found in a few patients in some of the clinical trials or in the post-marketing data,^{66,67} however, whether these events were caused by exenatide QW directly or whether other factors were involved is still not known.⁸¹ In the renal system, direct nephrotoxicity has not been observed with exenatide QW in the preclinical and clinical studies; however, it did appear to affect renal function by

increasing serum creatinine, renal impairment, worsened chronic renal failure and acute renal failure, which could be reversed in most cases by renal protection measures, discontinuation of exenatide, or discontinuation of other potentially causative agents.⁷⁹

Cost utility of exenatide QW

There have been several cost-effectiveness evaluations done in a cohort of patients treated with exenatide QW or other hypoglycemic drugs. The computer simulation model most commonly used to project lifetime clinical outcomes and complication costs is the IMS CORE Diabetes Model (IMS CDM). One typical study compared exenatide QW with sitagliptin or pioglitazone for over 35 years with IMS CDM. Exenatide QW showed significant superiority in several ways. For example, exenatide QW increased both life expectancy and quality-adjusted life years (QALYs) by 0.28 years more than sitagliptin. Compared with pioglitazone, life expectancy and QALYs also increased by 0.17 and 0.24 years, respectively. Further, compared with sitagliptin or pioglitazone, exenatide QW was shown to save US \$2215 and US \$933, respectively, in direct costs per patient as a result of decreasing the lifetime costs of complications caused by cardiovascular disease and neuropathy. Overall, compared with sitagliptin or

pioglitazone, exenatide QW was projected to reduce the costs of diabetes-related complications over a patient's lifetime.⁸²

In the UK and USA, the IMS CDM was also used to project clinical and economic outcomes for T2DM patients treated with exenatide QW or insulin glargine. A study creatively set exenatide QW at a price equivalent to liraglutide 1.2 mg, and exenatide QW was shown to be more effective, although more costly than insulin glargine. The cost effectiveness, in practice, will depend on the price of exenatide QW on the market and should be verified by long-term use in the future.⁸⁴ To analyze the long-term cost-utility of exenatide QW versus insulin glargine, a similar comparison with a computer simulation model was done in the USA in 2012. Based on data from the Duration-3 study, exenatide QW was associated with an incremental cost of \$3,914, but life expectancy was increased by 0.135 years, along with quality-adjusted life expectancy, which increased by 0.246 years. Researchers assumed that patients would pay a threshold of \$50,000/QALY, and that the incremental cost-effectiveness ratio would be \$15,936/QALY. This study concluded that exenatide QW was more cost-effective than insulin glargine.⁸⁴ Another important model, known as the Archimedes model, was used to assess health and economic outcomes for exenatide QW, pioglitazone, and insulin therapies in ~25,000 virtual patients with T2DM over 20 years. Assuming moderate adherence, exenatide QW increased QALYs by ~0.3 per person and costs per life-year by \$469. Meanwhile, pioglitazone or high-adherence insulin did not change QALYs, but increased the cost per life-year by \$69 and \$87, respectively.⁸⁵ US researchers have recently developed a decision model to evaluate the short-term cost-effectiveness of once-daily liraglutide and exenatide QW for the treatment of T2DM. The results indicated that it was the "chosen clinical data" that determined the cost-effectiveness of liraglutide 1.8 mg once daily versus 2 mg exenatide QW.⁸⁶

Current perspectives in the People's Republic of China

Until now, exenatide QW has not been approved by the People's Republic of China Food and Drug Administration. There have been a few clinical trials investigating the curative effect and side effects of exenatide QW in Chinese subjects. Cui et al treated 25 Chinese T2DM patients with single doses and multiple doses of exenatide QW to evaluate its pharmacokinetics, safety, and tolerability.¹⁵ These patients were treated with diet modification, exercise alone or in combination with stable metformin doses, and received weekly doses of 2 mg exenatide QW for 10 weeks. All 25 patients attained steady-state plasma exenatide

concentrations (average 299 pg/mL) within 8 weeks, and indices such as fasting plasma glucose (~3.0 mmol/L), HbA1c (~1.0%), and body weight (~3.8 kg) were decreased from baseline to 10 weeks. Compared with patients in other Asian countries, Chinese patients have similar ethnic and racial backgrounds and diet habits, and have been found to have similar pharmacokinetic profiles.^{58,72} In terms of safety and tolerability, exenatide QW showed little risk of causing hypoglycemia and the most frequently reported side effects were diarrhea and vomiting, which were mild and well tolerated.

T2DM patients are rapidly increasing in number year by year in the People's Republic of China because of the huge population base and the high incidence rate of diabetes. With improved living standards and the lifestyle changes, there has been a shift from undernutrition to overnutrition, resulting in an increasing epidemic of obesity in the People's Republic of China. Moreover, Chinese T2DM patients have fewer numbers and poorer function of islet β -cells compared with diabetics in western countries. This leads to obese Chinese patients having a poorer regulation ability of islet β -cells. As mentioned earlier, exenatide QW can enhance the function of β -cells in many ways, such as increasing their quantity, preventing their apoptosis, and improving their sensitivity, which leads to better blood glucose control.^{16,17} Additionally, patients treated with exenatide QW can lose significant amounts of weight, thus effectively reducing the risk of cardiovascular complications associated with diabetes-related high blood pressure and blood lipids.⁸⁷ Major gastrointestinal adverse reactions, including nausea, vomiting, and diarrhea, which occur predominantly during the first 6–8 weeks of therapy, are gradually reduced.^{32,49,64,66–68,73,79,80}

Although it has excellent safety and tolerability, exenatide QW is quite expensive, which may limit its application in less developed countries. Many studies, as mentioned previously, have confirmed that exenatide QW has therapeutic effects in common with most hypoglycemic drugs, and even better than other antidiabetic agents in some aspects. Computer simulation economic models show that exenatide QW has good cost-effectiveness and clinical outcomes. All in all, exenatide QW will fulfill the need for another treatment option in diabetic patients with suboptimal glycemic control and could have a promising future in the People's Republic of China.

Disclosure

The authors report no conflicts of interest in this work.

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