Patient Preference and Adherence

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REVIEW

Exenatide once weekly: clinical outcomes and patient satisfaction

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Background: Type 2 diabetes mellitus (T2DM) is a complex disorder in which interactions between environmental and genetic factors result in the development of insulin resistance (in most cases) and progressive pancreatic β-cell failure. The currently available oral anti-diabetes treatments are effective as monotherapy; however, due to the progressive decline in β-cell function, most patients will require the use of combination therapy and eventually insulin to reach glycemic targets. These therapeutic options are not without undesirable side effects such as weight gain and hypoglycemia. Furthermore, T2DM is associated with impaired quality of life (QOL) and poor compliance with treatment. Hence, there is a need for anti-diabetes agents that result in sustained improvements in glycemic control without hypoglycemia or weight gain and have a positive impact on patients QOL and thereby hopefully improve compliance. Incretin-based therapy is the latest addition to anti-diabetes treatments which addresses some of the shortcomings of older treatments.

Aims: To review the evidence for the use of exenatide once-weekly.

Methods: We have searched Medline using the terms "exenatide", "exenatide once-weekly", and "exenatide LA".

Results: Exenatide once-weekly is an incretin mimetic that is currently undergoing phase 3 clinical trials, and has been shown to improve glycemic parameters (HbA_{1c} and fasting and postprandial glucose levels), with low risk of hypoglycemia, causes weight loss, and use was associated with improvements in patient satisfaction which might have a positive impact on treatment compliance.

Conclusions: Exenatide once-weekly is effective, well tolerated in patients with T2DM and should be a useful addition to the available range of anti-diabetes treatments.

Keywords: diabetes mellitus, incretins, exenatide once-weekly, quality of life, treatment satisfaction

Introduction

Type 2 diabetes mellitus (T2DM) is a global epidemic with an estimated worldwide prevalence of 6% (246 million people) in 2007 that is forecasted to rise to 7.3% (380 million) by 2025.[1,2] The health, social, and economic burden of T2DM is great;[3–5] it continues to pose a major challenge to healthcare provision around the world.

The development of insulin resistance (IR) and pancreatic β-cell dysfunction due to various environmental and genetic factors results in onset of T2DM.[6,7] Despite obesity being the single most important contributor to IR, most obese insulin-resistant individuals do not develop T2DM[8,9] because their β-cells are capable of producing sufficient insulin to maintain euglycemia.[9–13] This suggests that the failure of β-cells to secrete sufficient insulin to overcome IR is the key step in the development and progression

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of T2DM.[6,7,9,10] Pancreatic α-cell dysfunction manifesting as non-suppressed glucagon secretion in the presence of hyperglycemia is also manifest in patients with T2DM.[14]

Several pharmacological agents have been developed to treat patients with T2DM. They either improve insulin resistance (biguanides, glitazones), stimulate insulin secretion from the β-cell (sulfonylureas, metaglinides), or decrease glucose absorption from the gut (α-glucosidase inhibitors).[15] The initial improvements in glycemic control observed with these agents as monotherapy are not sustained because of the progressive nature of the disease due to the continuing decline in β-cell function.[9,16] This often necessitates the use of combination therapy and eventually insulin. Furthermore, current agents may be associated with undesirable side effects including gastrointestinal (metformin, α-glucosidase inhibitors), weight gain (sulfonylureas, metaglinides, glitazones, and insulin), and hypoglycemia (sulfonylureas, metaglinides, and insulin).[17] These side effects may contribute to further worsen the already impaired health-related quality of life (QOL) found in patients with T2DM[18] and may contribute to poor compliance common in this group of patients.[19]

Treatment acceptability and adherence are particularly important in the management of T2DM. A systematic review showed that many patients took less than their prescribed dose of insulin and/or oral anti-diabetes medications[20] and that a substantial proportion of patients had difficulty in dealing with various elements of the chronic disease management, particularly adhering to a strict drug regimen.[21,22]

Taking the above into account, there is a need for new pharmacological agents that are well tolerated with sustainable impact on glycemic control, and with very low risk of hypoglycemia, cause weight loss (or at least no weight gain) and thereby encourage patient adherence to therapy. Incretin-based therapy is the latest class of anti-diabetes medications to become available and addresses some of the shortcomings of conventional anti-diabetes treatments. Incretin-based therapy can be given either orally (dipeptidyl peptidase-4 (DPP-4) inhibitors) or via a subcutaneous injection (glucagon-like peptide (GLP-1) analogues/mimetics). They improve glycemic control with favorable impact on weight and low risk of hypoglycemia (apart from when used with sulfonylureas).[23] In addition, animal studies have shown that some of these agents improve β-cell survival,[23] which if true in humans might result in a more sustained impact on glycemic control. GLP-1 analogs/mimetics are given in once- or twice-daily dosing regimes. However, other drugs are in development in this category that require administration once weekly or even less frequently.[23] Such a dosing regimen might be highly acceptable to patients and encourage compliance with treatment.

In this article, we aim to review the available data regarding the once-weekly use of exenatide in the management of T2DM and the potential patient considerations for the use of this drug. Further details regarding incretin-based therapies are not within the scope of this article and can be found elsewhere.[24–27]

Incretins

Incretins are hormones that are released from the gut in response to ingestion of food.[28] The incretin effect was first described in 1964, when it was observed that the insulin response to oral glucose challenge was substantially higher than to an intravenous glucose load.[29] The incretin response accounts for at least 50% of insulin secretion in healthy individuals.[30]

Glucose-dependent insulinotropic polypeptide (GIP) was the first incretin to be isolated and characterized.[31,32] It is a 42 amino acid peptide secreted in the bioactive form from the K-cells in duodenum and jejunum in response to ingestion of carbohydrates and lipids.[33] The second incretin to be isolated was GLP-1, which is cleaved from pro-glucagon and secreted from the L-cells in the distal ileum and colon.[33] GLP-1 levels are reduced in patients with T2DM, unlike GIP levels which are maintained.[34]

Both GIP and GLP-1 facilitate glucose-dependent insulin secretion through their action on pancreatic β-cells. GLP-1 increases insulin gene transcription as well as all the steps of insulin biosynthesis.[35] In addition, GLP-1 results in glucose-dependent glucagon suppression, delays gastric emptying, increases satiety, and possibly reduces insulin resistance.[36,37] There is also evidence that GLP-1 increases β-cell mass in animal studies.[38]

GLP-1 secretion is reduced in patients with T2DM.[39] Although there is a blunting of GLP-1 secretory response in these patients, their response to exogenous GLP-1 is intact.[23] A continuous 6-hour intravenous infusion of GLP-1 in the fasting state, leading to GLP-1 levels 2–3 times higher than normally seen after meals, resulted in lowering of glucose and glucagon levels, with increases in insulin secretion without any hypoglycemic events in patients with poorly controlled T2DM.[40] Subcutaneous GLP-1 was also shown to have a similar glucose-lowering effect when administered pre-meal in patients with T2DM.[41]

Incretins are rapidly metabolized by the enzyme DPP-4, and thus have extremely short half-lives (GIP $<$ 2 minutes and GLP-1 5–7 minutes).[42,43] The short half-life of these naturally occurring incretins limited their clinical use. This led

to the development of various modifications of the amino acids of GLP-1, rendering them DPP-4 resistant. Exenatide (Byetta®; Eli Lilly), a synthetic analog of exendin-4, was the first-in-class incretin mimetic. Liraglutide (Victoza®; Novo Nordisk), an analog of human GLP-1, is a fatty acid derivative of GLP-1 that has been approved for clinical use more recently. There are several long-acting once-weekly preparations currently in phase 3 clinical trials – exenatide once-weekly (Byetta®; Eli Lilly), albiglutide (GlaxoSmithKline) and taspoglutide (Ipsen and Roche), all of which show promising results. Research has also targeted developing inhibitors of the DPP-4 enzyme. The currently available DPP-4 inhibitors are sitagliptin (Januvia®; Merck & Co), vildagliptin (Galvus®; Novartis) and saxagliptin (Onglyza®; Bristol-Myers Squibb and Astra-Zeneca). Alogliptin (Takeda) and linagliptin (Ondero®; Boehringer Ingelheim) are currently undergoing phase 3 clinical trials.

Exenatide, a synthetic version of the naturally occurring salivary peptide isolated from the Gila monster (*Heloderma suspectum*), is a partial structural analog of human GLP-1 and has 53% amino acid sequence homology with human GLP-1.[44] It contains a glycine at position 2, in contrast to human GLP-1, which has an alanine at position 2, thus making the molecule DPP-4 resistant, in turn conferring a longer half-life.[44] Exenatide has a half-life of 3.3–4.0 hours and clinical effects lasting for up to 8 hours.[45–47] Exenatide treatment results in significant reductions in fasting plasma glucose (FPG) and post-prandial glucose (PPG) in patients with T2DM.[48–51] In addition, it results in slowing of gastric emptying (which contributes to the reductions in PPG),[52] appetite suppression[53] and weight loss.[54]

The AC2993 Diabetes Management for Improving Glucose Outcomes (AMIGO) trials were three 30-week randomized, triple-blind, placebo-controlled, multicenter trials that had similar design and examined the impact of exenatide treatment on glycemic control in patients with T2DM.[48,55,56] They enrolled subjects aged 16–75 years who were poorly controlled on metformin and/or sulfonylurea with HbA_{1c} 7.5%–11%. In the AMIGO trials, patients were randomized to placebo, exenatide 5 µg or exenatide 10 µg while continuing metformin and/or sulfonylurea. By week 30, exenatide 10 µg resulted in mean HbA_{1c} reduction of −0.8% ± 0.1% to −0.9 ± 0.1% compared with a −0.16% ± 0.1% to 0.08% ± 0.1% in placebo.[55] The effects of exenatide on glycemic control appeared to be sustainable as reductions achieved at 30 weeks (−1.0% ± 0.1%) were maintained at 82 weeks[57] and 3 years[58] in the open-label extensions of the AMIGO trials.

The open-label extensions of the AMIGO trial also showed that exenatide treatment promotes progressive weight loss up to 82 weeks (−2.1 ± 0.3 kg versus −4.0 ± 0.3 kg for exenatide 10 µg week 30 versus week 82 respectively).[57,59] Furthermore, a subset of patients who had 3.5 years of exenatide exposure had reductions in triglycerides of 12% ($P = 0.0003$); LDL-C decreased by 6% ($P < 0.0001$), and HDL-C increased by 24% ($P < 0.0001$).[59]

Exenatide is generally well tolerated long term, but the most commonly reported adverse events (AEs) (mostly in the first few weeks of treatment) are nausea, vomiting, diarrhea, headache, dizziness, and dyspepsia.[60] In a recent meta-analysis, exenatide was associated with a significant increase in the proportion of patients experiencing hypoglycemia in placebo-controlled trials (OR: 2.92 (1.49–5.75), $P = 0.002$). This excess, however, was only observed when exenatide was combined with sulfonylureas.[61] Concerns about acute pancreatitis have been raised in patients using exenatide. However, a 1-year follow-up study of patients who were initiated on exenatide, sitagliptin, glyburide, or metformin showed the risk of acute pancreatitis to be comparable between the cohorts.[62] Nonetheless, the FDA has changed the labeling on the drug to warn about possibility of acute pancreatitis particularly in susceptible patients, based on post-marketing analysis showing 30 reported cases of pancreatitis in 2007 and 6 cases of necrotizing hemorrhagic pancreatitis in 2008.[60] The FDA also warns that exenatide should not be used in patients with severe renal impairment (creatinine clearance < 30 mL/min) or end-stage renal failure, and should be used with caution in those with renal transplant or moderate renal impairment (creatinine clearance 30–50 mL/min).[60]

Although exenatide is relatively well tolerated and effective in improving glycemic control with favorable impact on weight and low risk of hypoglycemia, the main drawback is that it needs to be administered by twice-daily injections. As a result, the development of exenatide once-weekly is now in progress.

Exenatide once-weekly

Chemistry

Exenatide once-weekly uses a sustained release drug delivery system. Molecules of exenatide are encapsulated in injectable microspheres of poly (D, L lactic-co-glycolic acid), a biodegradable polymeric matrix commonly used in extended release preparations.[63] This poly-lactide-glycolide and exenatide microsphere suspension allows gradual drug delivery at a controlled rate by diffusion and erosion of the microspheres.[63,64]

Pharmacokinetics

Mean plasma concentration of exenatide once-weekly (0.8 or 2 mg) reached clinically significant levels (at which exenatide lowers blood glucose) by week 2 in a 15-week phase 2 study of 45 adults (60% men, 60% Caucasians) whom glycemic control was suboptimal (HbA_{1c} 8.5% ± 1.2%) with metformin and/or life-style changes.[64,65] By week 6, exenatide once-weekly attained a maximum concentration higher than that attained by a single injection of exenatide 10 µg (a steady state concentration of 232 pg/mL versus 211 pg/mL).[59] Six weeks after stopping treatment, the serum concentration of exenatide once-weekly declined steadily to insignificant levels.[64]

In a randomized, double-blind, parallel study in Japanese patients with T2DM (59% men, aged 58 ± 9 years), the AUC (0–8 hours) of exenatide once-weekly on day 1 was 187.6 (133.7–263.3) pg * h/mL and 405.6 (278.4–590.8) pg * h/mL for 0.8 mg and 2 mg respectively.[66] The Cmax on day 1 was 64.3 (38.3–107.8) pg/mL for 0.8 mg and 137.3 (74.6–252.6) pg/mL for 2 mg of exenatide once-weekly. Geometric mean (90% CI) steady-state plasma concentrations were 81.2 (68.3–96.4) pg/mL and 344.5 (256.5–462.7) pg/mL with 0.8 mg and 2.0 mg respectively (Figure 1).[66]

The diabetes therapy utilization researching changes in A_{1c}, weight, and other factors through intervention with Exenatide once-weekly (DURATION)-1 study (described below) showed that plateau concentrations of exenatide were achieved after 6–10 weeks of exenatide once-weekly with a geometric mean steady state plasma concentration of 71.7 pmol/L.[67]

Clinical efficacy

Impact on glycemic parameters

There are 3 published randomized controlled trials that assessed the impact of exenatide once-weekly on glycemic parameters (Table 1). Exenatide once-weekly produced significant reductions in HbA_{1c}, FPG, and PPG when used in drug-naïve patients or patients treated with one or more oral anti-diabetes therapy.[64,66,67]

The DURATION-1 study was a randomized, open-label, non-inferiority study that compared exenatide 2.0 mg weekly to exenatide 10 µg twice daily in patients with T2DM. 303 patients were enrolled and 295 (53% men, 78% Caucasians) were randomized.[67] All patients underwent a 3-day lead-in period with exenatide 5 µg twice daily, after which they were randomized to either exenatide 2.0 mg once-weekly or exenatide 5 µg twice daily for 28 days, followed by exenatide 10 µg twice daily. Participants had a mean age of 55 ± 10 years with a mean BMI of 35 ± 5 kg/m^2. The baseline anti-diabetes treatment included metformin (73%), sulfonylurea (37%), and thiazolidinediones (16%) alone or in combination.[67] By week 10, there were significantly greater reductions in HbA_{1c} in the once-weekly group compared

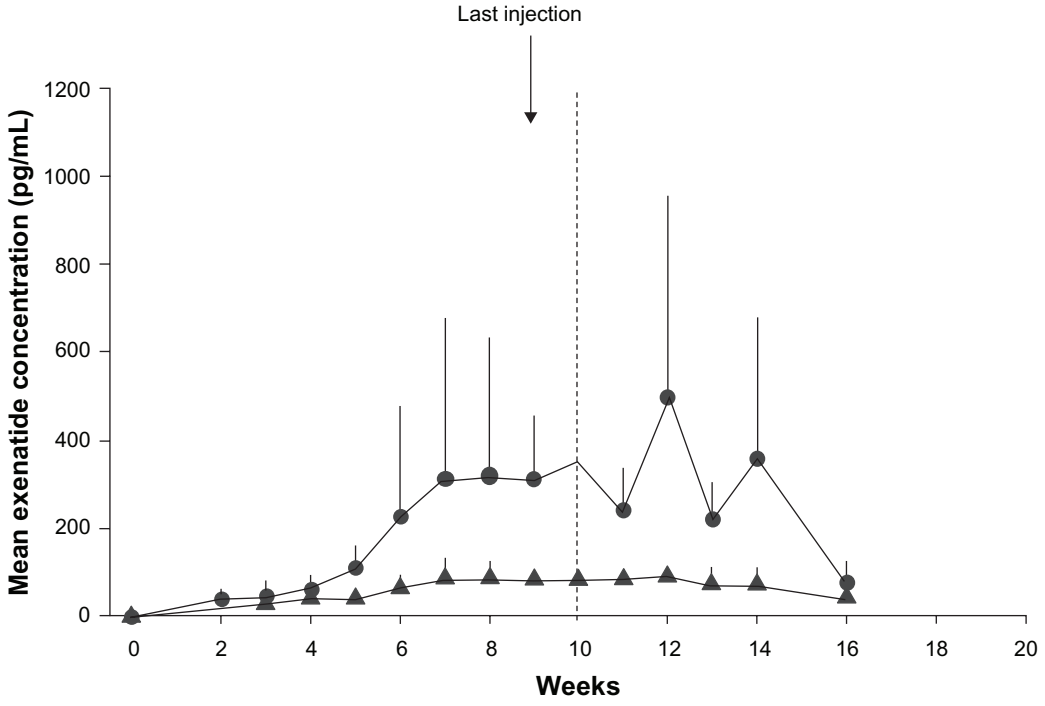

Figure 1 Mean (±SD) plasma exenatide trough concentration-versus-time profiles in pharmacokinetic evaluable patients receiving exenatide once weekly 0.8 mg (closed triangles) (n = 8) or exenatide once weekly 2.0 mg (closed circles) (n = 6). Reproduced with permission from Iwomoto K, et al. *Endocr J*. 2009;56(8):951–962.[66]

Table 1 Designs and clinical outcomes of the published exenatide once-weekly studies

Study	**Kim et al[64]**			**Drucker et al[67]**		**Iwamoto et al[66]**		
Design	Phase 2, randomized, placebo controlled			Phase 2, randomized, open-label, non-inferiority		Phase 1, randomized, placebo controlled		
Duration	15 weeks			30 weeks		10 weeks		
Baseline characteristics	Age 17–85 Men 60% Diabetes duration 5 ± 4 years FPG 9.9 ± 2.3 mmol/L			Age 55 Men 58% Diabetes duration 6.7 ± 5.0 years FPG 9 ± 2 mmol/L		Age 58 ± 9 Men 58.6% Diabetes duration 6 ± 5 years FPG 156.1 ± 29.1 mg/dL		
Study groups	**2.0 mg Ex QW**	**0.8 mg Ex QW**	**Placebo QW**	**2.0 mg Ex QW**	**10 µg Ex BD**	**2.0 mg Ex QW**	**0.8 mg Ex QW**	**Placebo QW**
Baseline treatment	Metformin-53%	Metformin-63%	Metformin-64%	Metformin-77% SU-37% TZD-15%	Metformin-69% SU-37% TZD-17%	BG-0% SU-6% TZD-11%	BG-20% SU-30% TZD-10%	BG-0% SU-50% TZD-20%
Evaluable number	15	16	12	129	130	9	10	10
Baseline HbA_{1c}	8.5 ± 1.2%			8.4%		7.4 ± 0.8%		
HbA_{1c} change (%)	−1.7 ± 0.3	−1.4 ± 0.3	+0.4 ± 0.3	−1.9 ± 0.1	−1.5 ± 0.1	−1.5 ± 0.7	−1.0 ± 0.7	−0.4 ± 0.3
P value	<0.001 vs placebo	<0.001 vs placebo		0·0023		Not reported	Not reported	Not reported
FPG change	−2.2 ± 0.5 mmol/L	−2.4 ± 0.9 mmol/L	+1.0 ± 0.7 mmol/L	−2.3 (SE 0.5) mmol/L	−1.4 (SE 0.5) mmol/L	−50.8 ± 27.8 mg/dL	−25.2 ± 10.9 mg/dL	−20.5 ± 20.4 mg/dL
P value	<0.001 vs placebo	<0.001 vs placebo		<0.001		Not reported	Not reported	Not reported
PPG change	Not reported	Not reported	–	−5.3 (SE 0.5) mmol/L **(subset n = 51)**	−6.9 (SE 0.5) mmol/L **(subset n = 51)**	−111.1 ± 48.5 mg/dL	−75.8 ± 42.9 mg/dL	−28.5 ± 38.4 mg/dL
P value	Not reported	Not reported	Not reported	Not reported		Not reported	Not reported	Not reported
Baseline weight (BMI)	106 ± 20 kg			102 (SD 20) kg (34 kg/m^2)		69.7 ± 13.4 kg (26.3 ± 2.9 kg/m^2)		
Weight change	−3.8 ± 1.4 kg	−0.04 ± 0.7 kg	−0.03 ± 0.7 kg	−3.7 (SE 0.5) kg	−3.6 (SE 0.5) kg	−0.8 ± 1.5 kg	−0.3 ± 2.2 kg	−1.6 ± 1.6 kg
P value	<0.05 vs placebo	NS vs placebo	–	0·89		Not reported	Not reported	Not reported

Abbreviations: FPG, fasting blood glucose; PPG, post prandial blood glucose; Ex, exenatide; QW, once weekly; BD, twice daily; NS, not significant; SU, sulfonylurea; TZD, thiazolidinedione; BG, biguanide.

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