R E V I E W

Role and development of GLP-1 receptor agonists in the management of diabetes

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Abstract: Glucagon-like peptide-1 (GLP-1) is a hormone secreted from enteroendocrine L cells of the intestine in response to food. Exogenous GLP-1 administration at pharmacological doses results in many effects that are beneficial for treating type 2 diabetes, these include: (1) an increase in insulin secretion from β cells; (2) a suppression of glucagon secretion from α cells in the presence of hyperglycemia but not hypoglycemia; (3) a delay in gastric emptying and gut motility which in turns delays absorption of ingested nutrients and dampens post-prandial glucose excursion; and (4) an increase in the duration of postprandial satiety therefore suppressing appetite and decreasing food intake which eventually leads to weight loss. However, GLP-1 is subject to rapid enzymatic degradation, and therefore, not suitable for long-term treatment. A synthetic enzyme-resistant GLP-1 receptor agonist that reproduces the biological effects of GLP-1 is in use and more are under development. This review aims at providing a summary of the properties of GLP-1 and the development of GLP-1-based therapies for treatment of diabetes.

Keywords: incretin, GLP-1, GLP-1R agonist, diabetes

Introduction

What are incretins?

The incretin effect describes the augmentation in insulin secretion that occurs in response to oral glucose compared to intravenous glucose.[1–3] Incretins, therefore by definition, are gut-derived factors that stimulate insulin secretion from β cells after eating. The two hormones that fulfill criteria as incretins are glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1).

GIP is a 42-amino acid peptide synthesized and released from enteroendocrine K cells mostly located in the duodenum and upper jejunum.[4] GLP-1, a product of the proglucagon gene, exists in two bioactive forms, GLP-1 (7-36) amide and GLP-1 (7–37), with GLP-1 (7–36) comprising up to 80% of the GLP-1 in circulation.[5] It is released from enteroendocrine L cells dispersed throughout the gastrointestinal tract.[6,7] Together, the insulinotropic effect of GLP-1 and GIP accounts for up to 60% of the insulin secreted after a meal in healthy humans and plays a very important role in postprandial glucose homeostasis.[8]

In patients with type 2 diabetes mellitus (T2DM), the ability of exogenous GIP and GLP-1 to stimulate insulin secretion is diminished by 54% and 29%, respectively, when compared to healthy subjects. However, the glucose lowering effect of GLP-1 is relatively preserved while that of GIP is absent.[9–11] Therefore, development of therapeutic strategies for T2DM has focused on GLP-1 and not GIP.

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Physiology of GLP-1

Fat and carbohydrate-rich meals are the primary physiological stimuli to GLP-1 secretion from enteroendocrine cells.[12] Recently, artificial sweeteners, such as sucralose, have also been shown to induce GLP-1 secretion from L cells.[13] Although GLP-1 has been found in taste buds and brain tissues, the majority of the GLP-1 measured in peripheral blood is synthesized in L cells.[7]

In healthy subjects, fasting levels of plasma GLP-1 range from 5–10 pmol/L and increase by two- to three-fold after meal ingestion.[14] GLP-1 levels peak about 20 min after oral glucose administration and about 60 to 90 min after mixed meal ingestion, and the levels gradually decline toward fasting levels thereafter.[15,16] GLP-1 stimulates insulin secretion in a glucose concentration dependent manner; its insulinotropic effect is lost at plasma glucose concentration below 4.3 mmol/L (77 mg/dL).[17]

In earlier studies, patients with long-standing T2DM and poor glycemic control (HbA$_{1c}$ ~9.2%) were noted to have deficient GLP-1 secretion.[18,19] Recent studies have shown that GLP-1 levels are similar among subjects with mild T2DM (HbA$_{1c}$ ~6.8%), impaired glucose tolerance, and normal glucose tolerance.[15,16] Therefore, GLP-1 secretion in patients with T2DM appears to depend on their glycemic status, their medication intake, and other hormonal and metabolic abnormalities associated with worsening glycemic control.[16]

GLP-1 has a short half-life of 2 min because it is rapidly degraded by dipeptidyl peptidase 4 (DPP 4) and neutral endopeptidase (NEP) 24.11.[20–22] DPP 4 cleaves the N-terminal dipeptides (His^7–Ala^8) from GLP-1 (7–36) and renders the resulting major metabolite GLP-1 (9–36) insulinotropically inactive.[20,23] NEP 24.11, a membrane-bound zinc metallopeptidase, also degrades GLP-1 at potentially six cleavage sites.[21] High levels of NEP 24.11 are found in the kidney, and GLP-1 and its metabolites are rapidly cleared through the kidneys.[24]

The action of GLP-1 is mediated through the glucagon-like peptide-1 receptor (GLP-1R), a seven-member trans-membrane G protein-coupled receptor.[25] GLP-1R is expressed in a variety of tissues including pancreatic β cells, hypothalamus, hippocampus, area postrema and various other parts of the brain, as well as stomach, heart, intestine, and kidney.[26]

GLP-1-based therapy in T2DM

Regardless of the post-prandial levels of GLP-1 in T2DM, the insulin response to GLP-1 is still defective. The response of β cells to exogenously administered GLP-1 was noted to be three to five times lower in patients with T2DM when compared to healthy subjects.[11,27] Despite the diminished response of β cells to exogenous GLP-1, overnight intravenous infusion of GLP-1 in patients with T2DM was able to lower fasting and post-prandial plasma glucose to near-normal levels, to improve β-cell function, and to restore first-phase insulin secretion.[28]

To examine the effect of long-term GLP-1 treatment in patients with T2DM, continuous subcutaneous GLP-1 infusion was given for six and 12 weeks using an infusion pump in two separate studies.[29–31] Both studies showed that GLP-1 infusion clearly improved β-cell function and improved insulin sensitivity. A subset of subjects in the 12-week infusion study had frequent blood sampling performed after six weeks of therapy and the results showed significant improvement in insulin pulse mass and pulsatile insulin secretion.[31]

Exogenous GLP-1 administration at pharmacological doses also has several noninsulinotropic effects that are beneficial for treating T2DM. With exogenous GLP-1, glucagon secretion from α cells was suppressed in the presence of hyperglycemia and euglycemia but not hypoglycemia. The suppression of glucagon leads to improved hepatic insulin resistance and glycemic control in T2DM.[17,32] Exogenous GLP-1 also delays gastric emptying and gut motility and these effects slow absorption of ingested nutrients and dampen post-prandial glucose excursion in patients with T2DM.[33] Exogenous GLP-1 also increases the duration of postprandial satiety, decreases energy intake and suppresses appetite; leading to less food being eaten and eventually weight loss in most people.[29,34,35]

Most hypoglycemic agents work by either attempting to increase insulin secretion from β cells (sulfonylureas, meglitinides) or increasing peripheral insulin sensitivity (biguanides, thiazolidinediones). None of them actually targets the root cause of T2DM; deteriorating β-cell function and mass. In addition to stimulating insulin secretion and suppressing glucagon secretion, GLP-1 has other pleiotropic effects in the pancreas. Animal studies have suggested that chronic exogenous GLP-1 administration has the ability to increase islet size, enhance β-cell proliferation, inhibit β-cell apoptosis, and regulate islet growth.[36,37] These trophic effects on β cells have not been tested in humans as there is no direct *in vivo* measure of human β-cell mass available.

Using indirect measures of β-cell function, one study showed that short-term (12 hours) GLP-1 infusion improved the ability of β cells to sense and respond to glucose in patients

with impaired glucose tolerance.[38] Overnight GLP-1 infusion also improved first- and second-phase insulin secretion in patients with T2DM.[28] Six-week infusion of GLP-1 in patients with T2DM showed improvement in insulin sensitivity and β-cell function as measured by glucose utilization and first- and second-phase C-peptide response during hyperinsulinemic euglycemic clamp.[29] If the trophic effects seen in rodents are indeed present in humans, treatment with GLP-1 will have tremendous implications in the field of T2DM as it directly addresses one of the fundamental defects in T2DM, that is, β-cell failure.

Collectively, the biological effects of exogenous GLP-1 – increasing insulin secretion from β cells, suppressing glucagon secretion from α cells, decreasing post-prandial glucose excursion through delay in gastric emptying, increasing post-prandial satiety, and possibly enhancing the trophic effects on human β cells – make GLP-1 receptor-based therapy a highly desirable treatment option for T2DM. However, the short half-life of GLP-1 (2 min) renders the native GLP-1 peptide impractical for clinical use. Two obvious options for GLP-1 receptor-based therapies are: (1) GLP-1 analogs with longer half-lives and full efficacy at the GLP-1 receptor (GLP-1R agonists); and (2) agents such as DPP 4 inhibitors that can increase plasma levels of endogenous GLP-1. In this review, we will focus on the GLP-1R agonists. So far, no headway has been made on developing drugs to specifically increase endogenous secretion of GLP-1, though a drug in common use for T2DM, metformin, does cause about a two-fold increase in GLP-1 secretion.[39]

GLP-1 R agonists

As mentioned earlier, GLP-1 has a half-life of only about 2 min because it is rapidly degraded by DPP 4 and NEP 24.11. To develop GLP-1R agonists with longer half-lives, various modifications of GLP-1 at His[7], Ala[8], or Glu[9] have been attempted so as to prevent DPP 4 from cleaving the first two N-terminal amino acids (His[7], Ala[8]) of native GLP-1.[40] Additional mid-chain modifications of the GLP-1 peptide to prevent hydrolysis by NEP 24.11 are also being studied. Other technologies that allow gradual drug delivery at a controlled rate are also being investigated. This review will summarize the GLP-1R agonists that have clinical efficacy data published in peer-reviewed journals and presented at major scientific meetings.

Exenatide

Exenatide (synthetic exendin-4) is the only GLP-1R agonist currently approved by regulatory agencies as an adjunct therapy for patients with T2DM who are not achieving satisfactory glycemic control using other hypoglycemic agents. Exendin-4 is a 39-amino acid peptide produced in the salivary glands of the Gila monster (*Heloderma suspectum*) (Figure 1). It has 53% amino acid homology to full-length GLP-1 and binds more avidly than GLP-1 to the GLP-1R.[25] There appears to be no specific exendin-4 receptor; the effects of exendin-4 are expressed through the known GLP-1 receptor. Exendin-4 has a Gly[8] in place of an Ala[8] of the N-terminus, and therefore, is not a substrate for DPP 4. In addition, it lacks some of the target bonds for NEP 24.11, and its secondary and tertiary structures may also prevent NEP 24.11 hydrolysis, thus leading to a prolonged half-life.

Pharmacology

Since exenatide is a peptide, it must be administered subcutaneously. After its subcutaneous administration, exenatide reaches a maximum plasma concentration in 2.1 hr, and the mean half-life ranges from 3.3 to 4 hrs.[41] It can be detected for up to 15 hrs in the plasma after subcutaneous injection and its biological effect remains up to at least 8 hrs after dosing.[41] In a nonclinical study, it was shown to be eliminated by the kidneys through glomerular filtration.[42]

Efficacy studies

Three randomized, placebo-controlled, double or triple-blind, 30-week clinical trials examined the efficacy of exenatide in subjects with T2DM not achieving adequate glycemic control on metformin and/or sulfonylurea (Table 1).[43–45] Patients were randomized to placebo, exenatide 5 μg twice daily, or 10 μg twice daily as adjuvant treatment to sulfonylurea, metformin, or sulfonylurea/metformin. In all three studies, exenatide significantly reduced HbA_{1c} in the treatment groups with exenatide 10 μg twice daily lowered HbA_{1c} by 0.8%–0.9%; exenatide 5 μg twice daily lowered HbA_{1c} by 0.4%–0.6%; while placebo increased HbA_{1c} by 0.1%–0.2%. In the metformin/exenatide 10 μg twice daily treatment arm, 41% of patients achieved $HbA_{1c} \leq 7\%$ and a mean weight loss of 2.8 kg. In the sulfonylurea/exenatide 10 μg twice daily treatment arm, 41% of patients achieved HbA_{1c} of $\leq 7\%$ and a mean weight loss of 1.6 kg. In the metformin/sulfonylurea/exenatide 10 μg twice daily treatment arm, 34% of patients achieved HbA_{1c} of $\leq 7\%$ and a mean weight loss of 1.6 kg.

The above three trials and their open-label extensions were folded into one open-ended, open label trial.[46] Results from this three-year follow-up study showed that after treating with exenatide 10 μg twice daily, the 1.0% reduction in $HgbA_{1c}$ was sustained; 46% of the patients maintained a
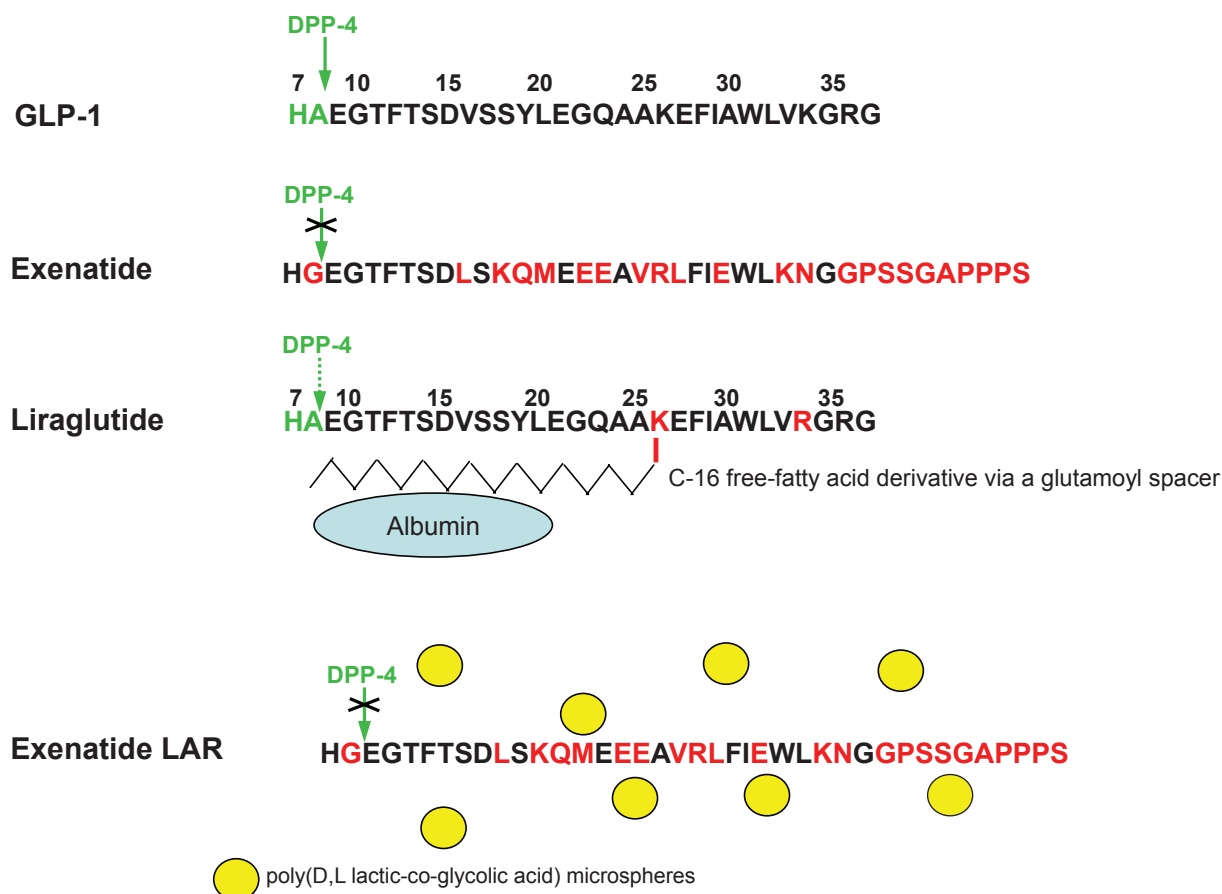
Figure 1 Structures of native GLP-1, exenatide, and liraglutide. The N-terminal dipeptide "HA" (in green letters) of GLP-1 and liraglutide is the proteolytic cleavage site for DPP 4. Red letters indicate changes introduced in derivatives or occur naturally in exendin-4 (and replicated in the synthetic version, exenatide). A crossed-out green arrow indicates absent DPP 4 activity, and a dotted green arrow indicates reduced DPP 4 activity. Exenatide long-acting release (LAR) is formulated with exenatide and poly(D,L lactic-co-glycolic acid) microspheres (yellow circles), biodegradable medical polymers commonly used in extended drug release formulation.

HbA_{1c} of $\leq 7\%$; and progressive weight loss was noted with a net-loss of 5.3 kg at the end of three years (Table 1).[46]

The efficacy of exenatide (10 µg twice daily) added to rosiglitazone (≥ 4 mg/day) alone or pioglitazone (≥ 30 mg/day) alone, or in combination with metformin was examined in a randomized, double-blind, placebo-controlled trial for 16 weeks (Table 1). When compared to placebo, addition of exenatide to thiazolidinediones (TZD) in the presence or absence of metformin reduced HbA_{1c} by 0.9%, mean fasting plasma glucose by 1.6 mmol/L, and body weight by 1.8 kg. However, only 71% of subjects given exenatide as compared with 86% of subjects in the placebo group completed the study where many (14%) discontinued the study because of gastrointestinal symptoms from exenatide.[47]

Exenatide therapy was also compared to insulin therapy as add-on to oral hypoglycemic agents. In a 26-week multicenter, open-label, randomized, controlled trial, subjects with T2DM whose glycemia was not adequately controlled by metformin and/or sulfonylurea were randomized to either adding exenatide 10 µg twice daily or insulin glargine daily (titrating to fasting blood glucose of <5.6 mmol/L). At the end of 26 weeks, both groups achieved similar improvement in glycemic control (1.1% reduction in HbA_{1c}). However, the exenatide group had better post-prandial glucose control while the glargine group had lower fasting plasma glucose levels. An average weight loss of 2.3 kg was noted with exenatide, and an average weight gain of 1.8 kg was noted with glargine. The drop out rate was 19.4% with exenatide (6% due to nausea) and 9.7% with glargine.[48]

Exenatide was also compared to biphasic insulin aspart (30% rapid-acting insulin aspart) in a 52-week, randomized, open-label trial in patients with T2DM whose glycemia was not optimally controlled with metformin and sulfonylurea.[49] The efficacy of exenatide was comparable to biphasic insulin aspart with similar reduction in HbA_{1c} (1% versus 0.9%) and comparable reduction in fasting plasma glucose (1.8 versus 1.7 mmol/L). The exenatide group had weight reduction of

Table 1 Clinical studies with exenatide

Duration Reference	Intervention	N	Baseline HbA$_{1c}$ (%)	Baseline FPG (mmol/L)	Δ HbA$_{1c}$ (%) baseline	% with HbA$_{1c}$ ≤ 7%	Δ FPG (mmol/L) baseline	Δ weight (kg) baseline
30-wk Buse et al[43]	Placebo + sulfonylurea	123	8.7	10.8	+0.1	9	+0.4	−0.6
	Exenatide 5 µg bid + sulfonylurea	125	8.5	10.0	−0.5	33	−0.3	−0.9
	Exenatide 10 µg bid + sulfonylurea	129	8.6	9.9	−0.9	41	−0.6	−1.6
30-wk DeFronzo et al[44]	Placebo + metformin	113	8.2	9.4	+0.1	13	+0.8	−0.3
	Exenatide 5 µg bid + metformin	110	8.3	9.8	−0.4	32	−0.4	−1.6
	Exenatide 10 µg bid + metformin	113	8.2	9.3	−0.8	46	−0.6	−2.8
30-wk Kendall et al[45]	Placebo + metformin/sulfonylurea	247	8.5	10.0	+0.2	9	+0.8	−0.9
	Exenatide 5 µg bid + metformin/ sulfonylurea	245	8.5	10.1	−0.6	27	−0.5	−1.6
	Exenatide 10 µg bid + metformin/ sulfonylurea	241	8.5	9.9	−0.8	34	−0.6	−1.6
16-wk Zinman et al[47]	Placebo + TZD with/without metformin	112	7.9	8.8	+0.1	16	+0.1	−0.2
	Exenatide 10 µg bid + TZD with/ without metformin	121	7.9	9.1	−0.9	62	−1.6	−1.8
26-wk Heine et al[48]	Exenatide 10 µg bid + metformin/ sulfonylurea	282	8.2	10.1	−1.1	46	−1.4	−2.3
	Glargine ~ 25 U/day + metformin/ sulfonylurea	267	8.3	10.4	−1.1	48	−2.9	+1.8
52-wk Nauck et al[77]	Exenatide 10 µg bid + metformin/ sulfonylurea	253	8.6	11.0	−1.0	32	−1.8	−2.5
	Biphasic aspart (30% insulin aspart) + metformin/sulfonylurea	248	8.6	11.3	−0.9	24	−1.7	+2.9
≥3 yrs Klonoff et al[46]	Exenatide 10 µg bid + metformin and/or sulfonylurea	527	8.2	9.6	−1.0	46	−1.3	−5.3
24-wk Moretto et al[50]	Placebo	78	7.8	8.9	−0.2	41	−0.3	−1.4
	Exenatide 5 µg bid	77	7.9	9.2	−0.7	55	−1.0	−2.8
	Exenatide 10 µg bid	78	7.8	8.6	−0.9	58	−1.0	−3.1

Abbreviations: bid, twice daily; FPG, fasting plasma glucose; TZD, thiazolidinedione.

2.5 kg while the biphasic insulin group had a weight increase of 2.9 kg.

In a 24-week, randomized, double-blind, placebo-controlled, parallel-group study, patients with T2DM naïve to hypoglycemic agents and not optimally controlled with diet and exercise, were randomized to exenatide 5 μg twice daily, exenatide 10 μg twice daily, or placebo twice daily. Significant reductions in HbA_{1c} of 0.7% and 0.9% were noted in the exenatide 5 μg and 10 μg twice daily groups, respectively, compared to reduction of 0.2% in the placebo group. A similar significant reduction in fasting serum glucose of 1.0 mmol/L was noted in the exenatide 5 μg and 10 μg twice daily groups, respectively, compared to a reduction of 0.3 mmol/L in the placebo group. Significant reduction in weight was also observed in the exenatide 5 μg and 10 μg twice daily groups; 2.8 kg and 3.1 kg, respectively, compared to 1.4 kg reduction in the placebo group.[50] The indication of using exenatide as monotherapy is currently under review by the United States Food and Drug Administration (FDA).[51]

Safety and tolerability

A meta-analysis based on randomized controlled trials was conducted to evaluate the safety and efficacy of incretin therapy in T2DM.[52] The results from this analysis showed that the most common side effects of exenatide were nausea (57%) and vomiting (17%). The amount of nausea and vomiting was dose-dependent, usually mild to moderate in nature, lessened with dose titration, and most common during the initial weeks of therapy with a decline thereafter. Overall, 4% of patients withdrew from the studies because of gastrointestinal side effects.[52] In addition, severe hypoglycemia associated with exenatide use was rare, reported in only five of 2781 patients in which all five patients also received a sulfonylurea. Mild to moderate hypoglycemia was noted in 16% of patients treated with exenatide versus 7% treated with placebo, and was again mostly occurred during co-administration with a sulfonylurea. Anti-exenatide antibodies were detected in 41%–49% of patients in the treatment arms but were not associated with glycemic control.[43–45]

The most serious (but rare) potential adverse event of exenatide is pancreatitis. In May 2008, the United Kingdom Medicines and Healthcare Products Regulatory Agency (MHRA) noted 89 post-marketing cases of pancreatitis with 87 of them occurring in the United States.[53] In August 2008, the United States FDA reported six cases of hemorrhagic or necrotizing pancreatitis in exenatide-treated patients, and two of these patients died. In the exenatide clinical trials, the incident rate of pancreatitis was 1.79/1000 subject years

for exenatide-treated patients, 1.35 for insulin comparator group, and 2.72 for placebo-treated patients.[53] The company that markets exenatide also tabulated incident data for pancreatitis in patients with T2DM (from insurance claims database) and noted a three- to four-fold greater incidence of acute pancreatitis in subjects with T2DM compared to patients without diabetes.[53] While no definite relationship has been established between exenatide and pancreatitis, the FDA has requested that information about acute pancreatitis be included in the precautions section.[53]

Exenatide and human β-cell function

Similar to GLP-1, short-term infusion of exenatide (5 hrs) has been shown to improve first- and second-phase insulin secretion in patients with T2DM.[54] Thirty weeks of exenatide use also resulted in improved β-cell function based on mathematical modeling of β cell in response to test meal in patients with T2DM who were treated with metformin and/or sulfonylurea.[55] Furthermore, when compared to insulin glargine, exenatide treatment for 52 weeks significantly improved β-cell function as assessed by arginine-stimulated hyperglycemic clamp, and the β-cell function reverted to pre-treatment levels after discontinuation of exenatide therapy.[56]

Liraglutide

Liraglutide is a GLP-1 analog with two modifications: a substitution of Arg^{34} for Lys^{34} and an attachment of a C-16 free-fatty acid derivative via a glutamoyl spacer to Lys^{26} (Figure 1). The free-fatty acid derivative is thought to promote noncovalent binding of liraglutide to albumin; therefore, the absorption rate of liraglutide is delayed from the injection site and the rate of renal clearance of liraglutide is also slowed.[57]

Pharmacology

Like GLP-1 and exenatide, liraglutide must be injected subcutaneously. Peak plasma concentrations are detected 10–14 hrs after injection, and the half-life is about 11–13 hrs.[58,59]

Efficacy studies

The LEAD® programme (Liraglutide Effect and Action in Diabetes) is the Phase 3 clinical trial of liraglutide involving five randomized, controlled, double-blind studies that included about 4,000 patients with T2DM. Results from two of the studies have recently been published in peer-reviewed journals and the results from two other studies have been presented at a scientific meeting.

The LEAD-3 Mono study is a double-blind, double-dummy, active-controlled, parallel-group study in which 746 patients with T2DM (previously treated with diet or oral hypoglycemic agent monotherapy) were randomized to receive liraglutide 1.2 mg, liraglutide 1.8 mg, or glimepiride 8mg once daily (Table 2).[60] Patients on oral hypoglycemic agent monotherapy had their treatment discontinued at randomization. At the end of 52 weeks, a significant reduction in HbA_{1c} was observed in all groups: 0.5% with glimepiride, 0.8% with liraglutide 1.2 mg, and 1.1% with liraglutide 1.8 mg. Significant reduction in fasting plasma glucose was also observed with an average reduction of 0.3 mmol/L, 0.8 mmol/L, and 1.4 mmol/L in the glimepiride 8 mg, liraglutide 1.2 mg, and liraglutide 1.8 mg groups, respectively. Furthermore, the percentage of patients who achieved a HbA_{1c} of less than 7% was 28%, 43%, and 51% in the glimepiride 8 mg, liraglutide 1.2 mg, and liraglutide 1.8mg groups, respectively. Patients on liraglutide also lost weight of about 1.9 kg and 2.3 kg in the liraglutide 1.2 mg and 1.8 mg groups, respectively, while those on glimepiride 8 mg gained about 1.2 kg.[60]

The LEAD-2 study is a 26-week, double-blind, double-dummy, placebo- and active-controlled, parallel-group clinical trial in which 1091 patients with T2DM were randomized to liraglutide once daily (either 0.6 mg, 1.2 mg, or 1.8 mg), glimepiride 4 mg once daily, or placebo, all in combination with metformin (1 gm twice daily) (Table 2).[61] All other oral hypoglycemic agents were discontinued at randomization. After 26 weeks, HbA_{1c} was reduced by 1.0% in the liraglutide 1.2 mg/metformin, the liraglutide 1.8 mg/metformin, and the glimepiride/metformin groups; decreased by 0.7% in the liraglutide 0.6 mg/metformin group; and increased by 0.1% in the placebo/metformin group. The percentage of participants who achieved HbA_{1c} of less than 7% was 28%, 35%, and 42% for the liraglutide/metformin groups (0.6 mg, 1.2 mg, 1.8 mg, respectively), 36% for the glimepiride/metformin group, and 11% for the placebo/metformin group. Fasting plasma glucose was decreased by 1.1 mmol/L, 1.6 mmol/L, 1.7 mmol/L in the liraglutide/metformin groups (0.6, 1.2, and 1.8 mg of liraglutide, respectively) compared to a reduction of 1.3 mmol/L in the glimepiride/metformin group and an increase of 0.4 mmol/L in the placebo/metformin group. Weight loss was also noted in the liraglutide/metformin groups in a dose-dependent fashion; weight reduction of 1.8 kg, 2.6 kg, and 2.8 kg for the liraglutide/metformin groups (liraglutide 0.6 mg, 1.2 mg, and 1.8 mg, respectively), which was significantly greater than the 1.5 kg weight loss noted in the placebo/metformin group. The glimepiride/metformin group had a 1.0 kg weight gain.[61]

In another 26-week, randomized, double-dummy, placebo-controlled study, 1041 subjects were randomized to five different arms: liraglutide (0.6 mg, 1.2 mg, or 1.8 mg) once daily added to glimepiride once daily, placebo/glimepiride 2–4 mg daily, or rosiglitazone 4 mg/glimepiride combination once daily (Table 2).[62] HbA_{1c} reduction of 0.6%, 1.1%, and 1.1%, were seen in the liraglutide (0.6 mg, 1.2 mg, 1.8 mg)/glimepiride groups, respectively. An HbA_{1c} reduction of 0.4% was noted in the rosiglitazone/glimepiride group, and a 0.2% HbA_{1c} increase was noted in the placebo/glimepiride group. The percentage of participants who achieved HbA_{1c} of less than 7% was 24%, 35%, and 42% in the liraglutide (0.6 mg, 1.2 mg, and 1.8 mg)/glimepiride groups, respectively, 8% in the placebo/glimepiride group, and 22% in the rosiglitazone/glimepiride group. Weight gain of 0.7 kg, 0.3 kg, and 2.1 kg was noted in the liraglutide 0.6 mg/glimepiride, liraglutide 1.2 mg/glimepiride, and the rosiglitazone/glimepiride groups, respectively, while a weight reduction of 0.2 kg and 0.1 kg was noted in the liraglutide 1.8 mg/glimepiride group and the placebo/glimepiride group, respectively. Fasting plasma glucose was reduced by 0.7 mmol/L, 1.6 mmol/L, 1.6 mmol/L in the liraglutide (0.6 mg, 1.2 mg, 1.8 mg)/glimepiride groups, respectively, reduced by 0.9 mmol/L in the rosiglitazone/glimepiride group, and increased by 1.0 mmol/L in the placebo/glimepiride group.[62]

In another 26-week randomized clinical trial, 581 subjects with T2DM were randomized to 1.8 mg liraglutide, placebo, or insulin glargine (open label) once daily as add-on to metformin 1 gm twice daily plus glimepiride 2–4 mg once daily (Table 2).[63] HbA_{1c} reduction of 1.3%, 0.2%, and 1.1% was noted in the liraglutide/metformin/glimepiride, placebo/metformin/glimepiride, and glargine/metformin/glimepiride groups, respectively. Fasting plasma glucose reduction of 1.6 mmol/L and 1.8 mmol/L were noted in the liraglutide/metformin/glimepiride and glargine/metformin/glimepiride groups while an increased of 0.5 mmol/L was noted in the placebo/metformin/glimepiride group. Furthermore, weight reduction of 1.8 kg, 0.4 kg was noted in the liraglutide/metformin/glimepiride and placebo/metformin/glimepiride groups, and weight increased of 1.6 kg was reported in the glargine/metformin/glimepiride group. The percentage of subjects who achieved HbA_{1c} of less than 6.5% was 37%, 11%, and 24% in the liraglutide/metformin/glimepiride, placebo/metformin/glimepiride, and glargine/metformin/glimepiride groups, respectively.[63]

Safety and tolerability
Similar to exenatide, the most frequently report adverse events for liraglutide were nausea and vomiting, especially

Table 2 Clinical studies with liraglutide

Duration Reference	Intervention	N	Baseline HbA$_{1c}$ (%)	Baseline FPG (mmol/L)	Δ HbA$_{1c}$ (%) baseline	% with HbA$_{1c}$ ≤ 7%	Δ FPG (mmol/L) baseline	Δ weight (kg) baseline
52-wk Garber et al[60]	Glimepiride 8 mg qd	248	8.4	9.5	−0.5	28	−0.3	+1.2
	Liraglutide 1.2 mg qd	251	8.3	9.3	−0.8	43	−0.8	−1.9
	Liraglutide 1.8 mg qd	247	8.3	9.5	−1.1	51	−1.4	−2.3
26-wk Nauck et al[61]	Placebo + Metformin 1 gm bid	122	8.4	10.0	+0.1	11	+0.4	−1.5
	Glimepiride 4 mg qd + Metformin 1 gm bid	244	8.4	10.0	−1.0	36	−1.3	+1.0
	Liraglutide 0.6 mg qd + Metformin 1 gm bid	242	8.4	10.2	−0.7	28	−1.1	−1.8
	Liraglutide 1.2 mg qd + Metformin 1 gm bid	241	8.3	9.9	−1.0	35	−1.6	−2.6
	Liraglutide 1.8 mg qd + Metformin 1 gm bid	242	8.4	10.1	−1.0	42	−1.7	−2.8
26-wk Marre et al[62]	Placebo + Glimepiride 2–4 mg qd		–	–	+0.2	8	+1.0	−0.1
	Rosiglitazone 4 mg qd + Glimepiride qd		–	–	−0.4	22	−0.9	+2.1
	Liraglutide 0.6 mg qd + Glimepiride qd	1041	–	–	−0.6	24	−0.7	+0.7
	Liraglutide 1.2 mg qd + Glimepiride qd		–	–	−1.1	35	−1.6	+0.3
	Liraglutide 1.8 mg qd + Glimepiride qd		–	–	−1.1	42	−1.6	−0.2
26-wk Russell-Jones et al[63]	Placebo + Metformin 1 gm bid/glimepiride 2–4 mg qd	581	–	–	−0.2	11[a]	+0.5	−0.4
	Glargine qd + Metformin 1 gm bid/glimepiride 2–4 mg qd		–	–	−1.1	24[a]	−1.8	+1.6
	Liraglutide 1.8 mg qd + Metformin 1 gm bid/glimepiride 2–4 mg qd		–	–	−1.3	37[a]	−1.6	−1.8

Note: [a]% with HbA$_{1c}$ < 6.5%.
Abbreviations: bid, twice daily; FPG, fasting plasma glucose; qd, once daily.

at the higher doses.[52] In the LEAD-2 study, hypoglycemia was noted in 3% of the liraglutide/metformin and placebo/metformin groups compared to 17% in the glimepiride/metformin group. Nausea was reported to occur in 11%–19% of the liraglutide/metformin groups in a dose-dependent fashion compared to 3%–4% in the placebo/metformin and glimepiride/metformin groups. Nausea was noted to decrease over the duration of the study. There were two cases of pancreatitis reported, one in the liraglutide 1.2 mg group and one in the glimepiride group, and both recovered.[61] In the LEAD-3 study, 12% and 8% of the liraglutide groups (1.2 mg and 1.8 mg, respectively) versus 24% of the glimepiride group suffered mild hypoglycemia. Nausea was reported in 28% and 29% of the subjects in the liraglutide groups (1.2 mg and 1.8 mg, respectively), and 9% of the glimepiride group. Again, the incidence of nausea decreased over time. Two participants, one each in the 1.2 mg and 1.8 mg liraglutide groups, developed pancreatitis during the study and both recovered.[60] In one of the 26-week studies, 9%–13% of the liraglutide treated subjects developed antibodies to liraglutide. Nausea was reported in 5%–11% of the liraglutide/glimepiride groups, 2% of the placebo/glimepiride group, and 3% of the rosiglitzaone/glimepiride.[62] In another 26-week study, 10% of the subjects in the liraglutide group developed liraglutide antibodies.[63] Nausea was reported in 14%, 4%, and 1% of the subjects in the liraglutide/metformin/glimepiride, placebo/metformin/glimepiride, and glargine/metformin/glimepiride groups.[63] Hypoglycemia was reported in 27%, 17%, and 29% of the subjects in the liraglutide/metformin/glimepiride, placebo/metformin/glimepiride, and glargine/metformin/glimepiride groups.[63]

Liraglutide and human β cell function

In patients with T2DM, a single dose of liraglutide was able to improve β-cell sensitivity to glucose.[64] Two different studies have demonstrated that treatment of patients with T2DM with liraglutide for seven days improved β-cell function as assessed by a model using multiple-meal tests, arginine stimulation test, and hyperglycemic clamp.[65,66]

Exenatide long-acting release (LAR)

Exenatide LAR is formulated with exenatide and poly (D,L lactic-co-glycolic acid) microspheres, a biodegradable medical polymer commonly used in extended drug release formulation.[67] Once weekly subcutaneous injection is thought to be the desired frequency, and it is currently undergoing phase 3 clinical trials.

Pharmacology

With a weekly injection of 2 mg exenatide LAR, a therapeutic plasma level of 50 pg/mL was reached after the second injection. The steady state concentration of exenatide LAR (232 pg/mL) was reached by week 6. This level is similar to the peak level reached by a single injection of 10 μg of exenatide. After 15 weeks of treatment with exenatide LAR, no more injections were given, and its concentration gradually decreased to below therapeutic level by week 21.[68]

Efficacy studies

In a randomized, placebo-controlled, phase 2 study, 45 patients with T2DM sub-optimally controlled by metformin and/or diet and exercise were randomized to exenatide LAR 0.8 mg, exenatide LAR 2.0 mg, or placebo LAR once weekly for 15 weeks (Table 3).[68] Subjects who were on metformin continued at the same dose. Exenatide LAR reduced HbA_{1c} by 1.4% and 1.7% in the exenatide LAR 0.8 mg and 2.0 mg groups, respectively, compared to an increase of 0.4% in the placebo group. The percentage of subjects who achieved HbA_{1c} of less than 7% was 36% and 86% for the exenatide LAR 0.8 mg and 2.0 mg groups, respectively, and no change in HbA_{1c} was noted for the placebo group. Fasting plasma glucose was reduced by 2.4 mmol/L and 2.2 mmol/L in the exenatide LAR 0.8 mg and 2.0 mg groups, respectively, compared to an increase of 1.0 mmol/L in the placebo group. Subjects in the exenatide LAR 2.0 mg group lost an average weight of 3.8 kg while those in the exenatide LAR 0.8 mg and placebo groups did not have any change in weight.[68]

In a 30-week, randomized, open-label, comparator-controlled, noninferiority study, exenatide LAR 2mg once weekly was compared to exenatide 10 μg twice daily in 295 patients with T2DM treated by diet, metformin, sulfonylurea, thiazolidinedione, or any combination of the two agents (Table 3).[67] Patients on exenatide LAR has HbA_{1c} reduction of 1.9% compared to 1.5% reduction in the exenatide twice daily group. Furthermore, 77% of the subjects in the exenatide LAR group achieved HbA_{1c} of less than 7% compared to 61% of the exenatide twice daily group. Weight reduction was comparable in that subjects in the exenatide LAR group lost 3.7 kg while subjects given exenatide twice daily lost 3.6 kg of weight. Fasting plasma glucose was also significantly reduced by 2.3 mmol/L in the exenatide LAR group compared to 1.4 mmol/L in the exenatide twice daily group. Fasting plasma glucagon levels were also significantly lower in the exenatide LAR-treated group compared to the placebo group.[67]

Table 3 Clinical studies with exenatide LAR

Duration Reference	Intervention	N	Baseline HbA$_{1c}$ (%)	Baseline FPG (mmol/L)	Δ HbA$_{1c}$ (%) baseline	% with HbA$_{1c}$ ≤ 7%	Δ FPG (mmol/L) baseline	Δ weight (kg) baseline
15-wk Kim et al[68]	Placebo[a]	14	8.6	10.2	+0.4	0	+1.0	0
	Exenatide LAR 0.8 mg weekly[a]	16	8.6	10.3	−1.4	36	−2.4	0
	Exenatide LAR 2.0 mg weekly[a]	15	8.3	9.3	−1.7	86	−2.2	−3.8
30-wk Drucker et al[67]	Exenatide 10 μg bid[b]	147	8.3	9.2	−1.5	61	−1.4	−3.6
	Exenatide 2 mg weekly[b]	148	8.3	9.6	−1.9	77	−2.3	−3.7

Notes: [a]Patients who were on metformin prior to randomization continued it at the same dose. [b]Patients who were also on metformin, sulfonylurea, thiazolidinedione, or any combination of the two agents.
Abbreviations: bid, twice daily; FPG, fasting plasma glucose.

Safety and tolerability

In the phase 2 study, 19% and 27% of the exenatide LAR 0.8 mg and 2.0 mg groups, respectively, experienced nausea compared to 15% in the placebo group.[68] Twenty-five percent of the subjects in the exenatide LAR 0.8 mg group experienced hypoglycemia with only one case confirmed by blood glucose concentration (3.1 mmol/L), while the exenatide LAR 2.0 mg and placebo groups did not report any hypoglycemia.[68] Sixty-seven percent of the subjects in the exenatide LAR groups developed positive anti-exenatide antibodies after 15 weeks.[68] In the 30-week randomized trial, anti-exenatide antibody levels were higher with exenatide LAR versus the exenatide twice daily group.[67] The antibody titers seems to declined progressively after 16 weeks of treatment.[67] Nausea was reported in 26% of the exenatide LAR group compared to 35% of the exenatide twice daily group, while vomiting was reported in 11% of the exenatide LAR group compared to 19% of the exenatide twice daily group. Injection site pruritus was also much more frequent (18%) in the exenatide LAR group compared to the exenatide twice daily group (1%).[67] No cases of pancreatitis were reported in either of the studies involving exenatide and exenatide LAR.[67]

Other GLP-1R agonists under development

There are other GLP-1R agonists currently under clinical development that are anticipated to have longer half-lives and presumably less gastrointestinal side effects. LY2189265 is a GLP-1 analog-Fc fusion protein, and LY2428757 is a pegylated GLP-1 analog, both can be administered just once weekly.[69] CJC-1134-PC is a recombinant human serum albumin-exendin-4 conjugated protein that has a half-life of approximately eight days and Albiglutide is an albumin-GLP-1 protein complex, both can be administered once weekly.[70–72] NN9535 is another long-acting human GLP-1 analog designed for once weekly injection using protein-acylation technology.[73] Taspoglutide and AVE0010 are two other GLP-1R agonists currently undergoing clinical trials.[74,75] An oral formulation of a GLP-1R agonist is reportedly also under development.[76] The compounds mentioned here are just a few representations of the GLP-1R agonists under clinical development, and are by no means comprehensive. Few data are publically available regarding these compounds.

Conclusions

GLP-1R agonists are a new class of hypoglycemic agents that have generated a lot of interests in the field of diabetes.

The development of GLP-1R agonists started with their potential as insulin secretagogues. Exogenous administration of GLP-1 and GLP-1R agonists at pharmacological doses showed that they not only have insulinotropic effect, but also effects on suppressing glucagon secretion in the presence of hyperglycemia, delaying post-prandial gastric emptying, inducing satiety, and promoting weight loss over prolonged administration–all of which work in synergy to normalize glucose homeostasis in patients with T2DM. Furthermore, GLP-1R agonists were noted to increase insulin synthesis, increase islet cell turnover, and decrease β cell apoptosis in animals–properties that may help slow the progression or even reverse the course of diabetes. Indirect measures of β-cell function showed that GLP-1R agonists improved β-cell responsiveness to glucose as well as first- and second-phase insulin secretion. However, the improvement in β-cell functions reverted back to pre-treatment levels after discontinuation of therapy, at least in the case of exenatide. Nausea and vomiting are the common side effects during the initial weeks of therapy, which lessen with dose titration, and generally decline with continuous use. Patients with severe gastrointestinal diseases probably should not be started on GLP-1R agonists in case of development of pancreatitis. Long-term use of exenatide (data available up to three years) has shown sustained HbA$_{1c}$ reduction and weight loss, which are very encouraging because these effects have not been shown by any other class of hypoglycemic agents. GLP-1R agonists as treatment modalities for diabetes have a promising future, especially with their potential to help reverse or prevent diabetes.

Acknowledgments

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