

Liraglutide: A Once-Daily Incretin Mimetic for the Treatment of Type 2 Diabetes Mellitus

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Diabetes mellitus currently affects an estimated 180 million people worldwide, a figure that is anticipated to double by the year 2030.¹ The Centers for Disease Control and Prevention (CDC) estimates the incidence of diabetes to be nearly 24 million in the US alone.² There currently exist several therapeutic classes available for the treatment of type 2 diabetes mellitus, yet many patients are unable to meet therapeutic goals, despite the use of combination therapy with oral agents.³ Due to this disparity, new therapeutic targets focusing on the key pathophysiologic defects seen in diabetes are currently being developed for the management of diabetes. The incretin mimetics and the dipeptidyl-peptidase 4 (DPP-4) inhibitors, for example, are relatively new categories of medications adding to the armamentarium of drugs available for the treatment of type 2 diabetes.

This article reviews publications and scientific abstracts regarding the incretin mimetic liraglutide. Liraglutide is a long-acting, synthetic analog of human glucagon-like peptide-1 (GLP-1). Endogenous GLP-1 and its analogs improve glycemic control via various mechanisms, which include stimulation of glucose-dependent insulin secretion, suppression of inappropriate hepatic glucagon secretion,

OBJECTIVE: To review the pharmacology, pharmacokinetics, efficacy, and safety of liraglutide, a glucagon-like peptide 1 (GLP-1) analog for the treatment of type 2 diabetes mellitus.

DATA SOURCES: A MEDLINE search (1966–May 2009) was conducted for English-language articles using the terms glucagon-like peptide 1, incretin mimetic, NN2211, and liraglutide. Abstracts presented at the American Diabetes Association and European Association for the Study of Diabetes annual meetings in 2006, 2007, and 2008 were also searched for relevant data.

STUDY SELECTION AND DATA EXTRACTION: Articles pertinent to the pharmacology, pharmacokinetics, efficacy, and safety of liraglutide were reviewed.

DATA SYNTHESIS: Liraglutide is a GLP-1 analog with pharmacokinetic properties suitable for once-daily administration. Clinical trial data from large, controlled studies demonstrate the effectiveness of liraglutide in terms of hemoglobin A_{1c} (A1C) reduction, reductions in body weight, and the drug's low risk for hypoglycemic events when used as monotherapy. Data also support benefits of liraglutide therapy on β -cell responsiveness to glucose, with animal and in vitro data indicating potential benefits in β -cell mass and neogenesis with liraglutide treatment. Liraglutide has been studied as monotherapy and in combination with metformin, glimepiride, and rosiglitazone for the treatment of type 2 diabetes. Additionally, comparative data with insulin glargine and exenatide therapy are available from Phase 3 trials providing practitioners valuable clinical data on which to base clinical decision making. Overall, liraglutide is well tolerated with dose-dependent nausea, vomiting, and diarrhea being the most commonly reported adverse events in clinical trials.

CONCLUSIONS: Once-daily administration may provide a therapeutic advantage for liraglutide over twice-daily exenatide, with similar improvements in A1C and body weight observed when liraglutide was compared with exenatide. The glucose-dependent mechanism of insulin release with GLP-1 agonist therapy holds potential clinical significance in the management of postprandial hyperglycemic excursions, with minimal risk of hypoglycemia.

KEY WORDS: glucagon-like peptide 1 analog, incretin mimetic, liraglutide, NN2211.

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delayed gastric emptying, and reductions in food intake. Novo Nordisk filed a New Drug Application (NDA) with the Food and Drug Administration (FDA) in May 2008, as well as a marketing authorization application to the European Medicines Agency (EMA) for approval in Europe.⁴ Action on the NDA is anticipated as early as calendar year 2009. An NDA was also submitted in July of 2008 for the approval of liraglutide in Japan.

Data Sources and Selection

A MEDLINE search (1966–May 2009) was conducted for English-language articles using the terms glucagon-like peptide 1, incretin mimetic, NN2211, and liraglutide. Abstracts presented at the American Diabetes Association and European Association for the Study of Diabetes annual meetings in 2006, 2007, and 2008 were also searched for relevant data. Articles pertinent to the pharmacology, pharmacokinetics, efficacy, and safety of liraglutide were reviewed.

Pharmacology

Diabetologists and researchers alike have been interested in the role of the gastrointestinal system in insulin secretion, dating back to the 1960s.⁵ A role for an intestinal mediator of insulin secretion was initially suggested based on the observation that oral intake of glucose resulted in a better insulin response when compared with intravenous glucose administration.^{5,6} This observation, later coined the “incretin effect,” is due to the stimulation of insulin release by the oral intake of nutrients. This effect results in insulin secretion above and beyond the insulin release induced by increased blood glucose concentrations alone. Of note, the incretin effect has been shown to be greatly impaired in patients with type 2 diabetes, which may contribute to the inability of patients to adjust their insulin secretion to meet physiological needs.⁷ The incretin effect has since been identified as being responsible for up to 60% of the insulin response to a given glucose load.⁸

The incretin effect is mainly facilitated by 2 insulinotropic gut hormones known as glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). GLP-1 is a 30 amino acid peptide released from L-cells of the intestine in response to a meal,⁹ and GIP is released by duodenal cells of the proximal small bowel.¹⁰ Circulating GLP-1 and GIP are observable within minutes following food ingestion, suggesting that both endocrine and neuronal signals play a role in the

release of these incretin hormones.¹¹ Patients with type 2 diabetes exhibit a decreased response to GIP when compared with healthy individuals, thus making GIP a poor therapeutic target in this population.^{12,13} In contrast, GLP-1 secretion is deficient in patients with type 2 diabetes,^{14,15} and GLP-1 infusion has been shown to lower glucose levels experimentally via enhanced glucose-dependent insulin secretion in subjects with type 2 diabetes, thus making GLP-1 a viable therapeutic target for the treatment of type 2 diabetes.^{16–18} Further study with GLP-1 in subjects with type 2 diabetes has demonstrated beneficial effects of GLP-1 on glucose-dependent decreases in glucagon secretion,^{19,20} increased satiety and decreased food intake,²¹ and a slowing of gastric emptying.^{22,23} Of particular interest, beneficial effects of GLP-1 on β -cell proliferation and neogenesis in animal models and in vitro studies with human pancreatic islets have been described.^{24–27} Figure 1 provides a graphical representation of the interplay between the metabolic effects attributable to GLP-1.²⁸

Despite the therapeutic promise of GLP-1 in the management of patients with type 2 diabetes, endogenous GLP-1 is rapidly degraded by the enzyme dipeptidyl peptidase-4 (DPP-4), resulting in a GLP-1 half-life of approximately 1–2 minutes.^{13,29} The development of DPP-4-resistant GLP-1 analogs and DPP-4 inhibitors has circumvented the impracticality of using GLP-1 therapeutically, due to its short half-life. Liraglutide is one agent in the incretin mimetic drug class that is an acylated GLP-1 analog suit-

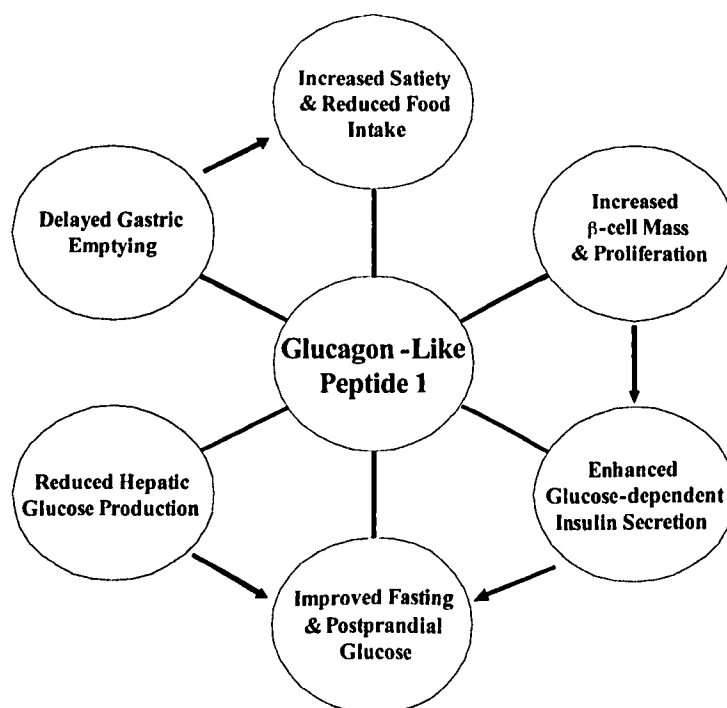


Figure 1. Metabolic actions of glucagon-like peptide 1.²⁸

able for once-daily administration.³⁰ The structure of liraglutide is based on structural modifications to human GLP-1 that include replacement of lysine with arginine at position 34 and the attachment of a C16 acyl chain to lysine at position 26 (Figure 2).³¹ In vitro studies indicate that liraglutide retains affinity for GLP-1 receptors despite these structural modifications.³¹ The addition of the C16 acyl chain allows for noncovalent binding to albumin, both hindering DPP-4 access to the molecule and contributing to a prolonged half-life and duration of action.²⁸

Pharmacokinetics

Liraglutide is an isotonic solution administered via subcutaneous injection. Upon administration, liraglutide demonstrates a relatively slow rate of absorption, with an observed time to maximum concentration of 9–14 hours.³² The half-life of liraglutide is 12.6 ± 1.1 hours, with an accumulation index of 1.4–1.5 following daily administration for 7 days. The absolute bioavailability upon subcutaneous injection is approximately 55%. Liraglutide has demonstrated sustained glucose-lowering activity at 24-hours postadministration at steady-state concentration, thus allowing for once-daily administration.³⁰

The protracted action of liraglutide appears to stem from the binding of liraglutide to serum albumin, the aggregation of liraglutide into micellar-like aggregates at the injection site, and reduced susceptibility of liraglutide to the DPP-4 enzyme.^{33–35} Liraglutide has an elimination half-life of 11–15 hours.^{28,32} In assessments of the effects of liraglutide on human liver microsomes, the drug demonstrated little to no inhibition of cytochrome P450 enzymes, thus indicating that cytochrome P450-mediated drug interactions are unlikely with liraglutide.^{28,32} Liraglutide is likely degraded slowly into small peptides, amino acids, and fatty acid fragments that are eliminated by the liver and kidney or recycled into new endogenous proteins and lipids.³⁶ No intact liraglutide and only low concentrations of its metabolites have been detected in feces or urine.³⁶ Accord-

ingly, pharmacokinetic studies in subjects with renal or hepatic impairment suggest that no dosage adjustments are required based on renal or hepatic function.^{37,38} Lastly, no effects of age or sex on the pharmacokinetic profile of liraglutide have been identified.³⁹

Clinical Studies

Liraglutide, currently approved for use in Europe and under review for approval in the US and Japan, has been studied in over 20 clinical trials evaluating its effectiveness, tolerability, safety, and pharmacokinetic profile in both healthy subjects and patients with type 2 diabetes. Table 1 provides a summary of findings from select clinical trials,^{30,32,37,38,40–55} excluding studies involved in the Liraglutide Effects and Action in Diabetes (LEAD) program, which are discussed in detail below.

LEAD STUDIES

The LEAD program is composed of 6 randomized, controlled, double-blind, Phase 3 clinical studies in participants with type 2 diabetes inadequately controlled with lifestyle and dietary interventions or oral antidiabetic therapies. Table 2 provides a summary of efficacy data gathered during the LEAD program.^{56–61} To date, data from all 6 LEAD studies have been published in peer-reviewed scientific journals or presented at scientific meetings. The following discussion presents currently known data from each of these studies.

LEAD-1 was a randomized, double-dummy trial in patients with type 2 diabetes comparing the addition of liraglutide to glimepiride therapy with glimepiride monotherapy or the addition of rosiglitazone to glimepiride.⁵⁶ Participants had a mean baseline hemoglobin A_{1c} (A1C) of 8.4% and a mean age of 56.1 years. A1C was significantly reduced with liraglutide, as well as with rosiglitazone. Glimepiride monotherapy resulted in an A1C increase of 0.23% ($p < 0.0001$). Twenty-two percent of subjects treat-

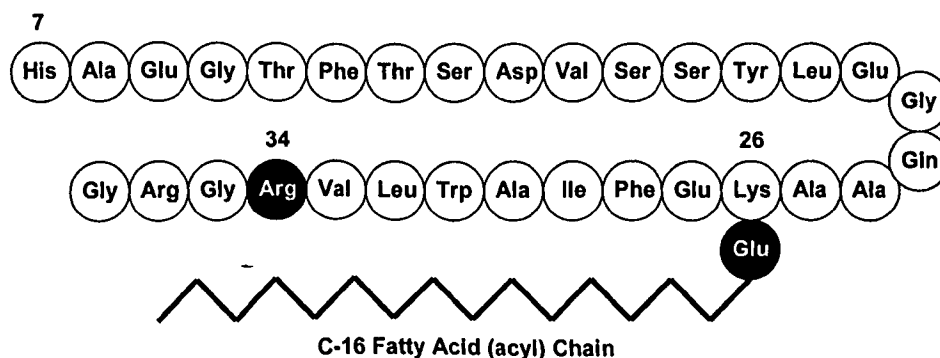


Figure 2. Structure of liraglutide.

Table 1. Select Liraglutide Clinical Trials

Reference	Pts. (N)	Purpose	Outcome Measures	Results
Irie (2008) ⁴⁰	24, type 2 diabetes, Japanese	assessment of safety, tolerability, PK/PD	AEs, PK/PD, PPG, mean plasma glucose	well tolerated, up to 25 µg/kg; dose-dependent increases in PK/PD and decreases in PPG/mean plasma glucose; no GI AEs or hypoglycemia
Seino (2008) ⁴¹	226, type 2 diabetes, Japanese	assessment of efficacy, safety	A1C, FPG, plasma glucose, plasma insulin, plasma glucagon, C-peptide	improvements in A1C, FPG, PPG, postprandial insulin secretion; no changes in BW; no development of liraglutide antibodies
Vilsboll (2008) ⁴²	39, type 2 diabetes	assess effects on β-cell function	FSIGT	improvements in first- and second-phase insulin secretion
Horowitz (2008) ⁴³	81, type 2 diabetes	evaluation of GI AEs	GSRS	tendency toward increased GI AE reporting with liraglutide treatment
Vilsboll (2007) ⁴⁴	165, type 2 diabetes	impact on glycemia, BW, and hypoglycemia risk	A1C, FPG, insulin, BW, AEs	improvements in A1C; dose-dependent decrease in BW; no hypoglycemic episodes
Flint (2007) ³⁷	24, type 2 diabetes	impact of hepatic impairment on PK	PK	no dosage adjustments required with impaired hepatic function
Jacobsen (2007) ³⁸	30, type 2 diabetes	impact of renal impairment on PK	PK	no dosage adjustments required with impaired renal function
Mari (2007) ⁴⁵	13, type 2 diabetes	assess effects on β-cell function under normal living conditions	plasma glucose, serum insulin, C-peptide	β-cell function improved due to improved glucose levels
Vilsboll (2006) ⁴⁶	165, type 2 diabetes	assess effects on BP and biomarkers of CV risk	BP, lipids, adiponectin, leptin, hsCRP, interleukin-6, TNF-α, PAI-1, BNP	decreased BP, TG, PAI-1, BNP; further study needed
Nauck (2006) ⁴⁷	144, type 2 diabetes	assessment of efficacy, AEs	FSG, A1C, BW, AEs	improvements in A1C, FSG; lower BW vs glimepiride group; transient nausea and no confirmed episodes of hypoglycemia
Damholt (2006) ⁴⁸	32, healthy	assess effects of age and sex on PK	PK	no effect of age or sex on PK
Feinglos (2005) ⁴⁹	210, type 2 diabetes	assess effects on glycemia and BW	FPG, A1C, BW	no A1C improvements with liraglutide 0.045–0.75 mg; improved BW
Degn (2004) ³⁰	13, type 2 diabetes	assess effects on glycemia and α- and β-cell function	plasma glucose, serum FFAs, serum insulin, plasma glucagon	improved 24-h glycemia; improved α- and β-cell function; reduced endogenous glucose release
Harder (2004) ⁵⁰	33, type 2 diabetes	assess effects on glycemic control, BW, body composition, 24-h energy expenditure	A1C, FSG, BW, DEXA; calorimetry	improved glycemia; no weight change detected; no influence on 24-h energy expenditure detected
Madsbad (2004) ⁵¹	193, type 2 diabetes	efficacy and safety	A1C, FSG, C-peptide, glucagon, insulin, BW, AEs	improvements in A1C, FSG, BW; mild and transient AEs
Chang (2003) ⁵²	10, type 2 diabetes	assess effects on β-cell function	ISRs, plasma insulin, plasma C-peptide	restoration of β-cell responsiveness to physiological hyperglycemia
Agerso (2003) ⁵³	8, healthy	assess effects on glucose and insulin homeostasis	plasma glucose, plasma insulin	dose proportional effect on β-cell insulin secretion
Juhl (2002) ⁵⁴	11, type 2 diabetes	assess effects on glycemia	plasma glucose, serum insulin, C-peptide, plasma glucagon, 3-OMG	improved fasting and postprandial glycemia; increased insulin secretion; delayed gastric emptying; suppressed prandial glucagon secretion
Elbrond (2002) ⁵⁵	72, healthy	safety, tolerability, PK	AEs, PK	increased incidence of headache, dizziness, nausea/vomiting; PK profile consistent with once-daily dosing
Agerso (2002) ³²	30, healthy	PK/PD, safety, tolerability	PK/PD, AEs	PK profile consistent with once-daily dosing; increased incidence of dizziness and GI AEs

3-OMG = 3-ortho-methyl-glucose; A1C = hemoglobin A_{1c}; AE = adverse event; BNP = brain natriuretic peptide; BP = blood pressure; BW = body weight; CV = cardiovascular; DEXA = dual-energy X-ray absorptiometry; FFA = free fatty acid; FPG = fasting plasma glucose; FSG = fasting serum glucose; FSIGT = insulin-modified frequently sampled intravenous glucose tolerance test; GI = gastrointestinal; GSRS = Gastrointestinal System Rating Scale; hsCRP = high sensitivity C-reactive protein; ISR = insulin secretion rate; PAI-1 = plasminogen activator inhibitor-1; PK/PD = pharmacokinetic/pharmacodynamic; PPG = postprandial glucose; TG = triglycerides; TNF-α = tumor necrosis factor-α.

ed with liraglutide 1.2 mg plus glimepiride reached an A1C less than 6.5%, with 21% reaching an A1C less than 6.5% with liraglutide 1.8 mg plus glimepiride. In contrast, 4% of those on glimepiride monotherapy and 10% of subjects treated with rosiglitazone plus glimepiride reached an A1C under 6.5% ($p < 0.0003$).

LEAD-2 was a 26-week study with liraglutide in combination with metformin in a randomized, double-blind study including participants with type 2 diabetes and a mean baseline A1C of 8.4%.⁵⁷ Significant A1C reductions were observed with all doses of liraglutide in combination with metformin. Those receiving metformin monotherapy experienced an A1C increase of 0.1%, with a decrease of 1.0% seen in those receiving glimepiride plus metformin ($p < 0.05$ vs liraglutide plus metformin vs placebo plus metformin). The percentage of patients reaching an A1C less than 6.5% was 11.3% in the liraglutide 0.6 mg plus metformin group, 19.8% in the liraglutide 1.2 mg plus metformin group, and 24.6% in the liraglutide 1.8 mg plus metformin group, compared with 4.2% of those treated with placebo plus metformin and 22.2% of those treated with glimepiride plus metformin. Weight loss was achieved in all participants receiving liraglutide, compared with a 1.0-kg weight gain observed in participants receiving glimepiride.

The LEAD-3 study enrolled patients with type 2 diabetes and a mean baseline A1C of 8.2%.⁵⁸ This Phase 3, double-blind, parallel-treatment study involved the head-to-head comparison of monotherapy with liraglutide or glimepiride. Any previous oral antidiabetic drugs (up to half the maximal dose) were discontinued at randomization prior to study drug initiation. At 52 weeks, significant A1C reductions from baseline were seen with liraglutide compared with glimepiride. Twenty-seven percent of patients on liraglutide 1.8 mg and 16% of patients on glimepiride attained an A1C less than 6.5%. Fasting and postprandial glucose levels were reduced in a dose-dependent manner with liraglutide treatment. Weight loss with liraglutide was achieved within the first 16 weeks of the study and was sustained for the duration of the trial. In contrast, participants receiving glimepiride gained weight. A 4-year LEAD-3 extension study is currently underway.

LEAD-4 was a placebo-controlled trial evaluating patients with type 2 diabetes and a mean baseline A1C of 8.3%.⁵⁹ LEAD-4 assessed the effect of adding liraglutide to metformin plus rosiglitazone in patients not adequately controlled on metformin or rosiglitazone alone. Liraglutide addition resulted in a significant A1C reduction for both liraglutide doses compared with placebo ($p = 0.0001$). An A1C less than 6.5% was achieved in 35% and 37% of pa-

Table 2. Summary of the LEAD Program

Study	Pts., N	Treatment		Treatment Period (wk)	A1C Change (%)	BW Change (kg)
		Background	Intervention			
LEAD-1 (Marre 2008) ⁵⁶	1041	glimepiride 2–4 mg/day	liraglutide 0.6 mg/day	26	–0.6 ^a	+0.7 ^b
			liraglutide 1.2 mg/day		–1.08 ^{a,b}	+0.3 ^b
			liraglutide 1.8 mg/day		–1.13 ^{a,b}	–0.2 ^b
			rosiglitazone 4 mg/day		–0.44 ^a	+2.1
			placebo		+0.23	–0.1
LEAD-2 (Nauck 2009) ⁵⁷	1091	metformin 1 g twice daily	liraglutide 0.6 mg/day	26	–0.7 ^a	–1.8 ^b
			liraglutide 1.2 mg/day		–1.0 ^{a,b}	–2.6 ^{b,c}
			liraglutide 1.8 mg/day		–1.0 ^{a,c}	–2.8 ^{b,d}
			glimepiride 4 mg/day		–1.0 ^a	+1.0
			placebo		+0.1	–1.5
LEAD-3 (Garber 2008) ⁵⁸	746	diet/exercise, 50% maximum dose of OAD monotherapy	liraglutide 1.2 mg/day	52	–0.84 ^a	–2.1 ^b
			liraglutide 1.8 mg/day		–1.14 ^b	–2.5 ^b
			glimepiride 8 mg/day		–0.51	+1.1
LEAD-4 (Zinman 2008) ⁵⁹	533	metformin 1 g twice daily, rosiglitazone 8 mg/day	liraglutide 1.2 mg/day	26	–1.48 ^a	–1.0 ^f
			liraglutide 1.8 mg/day		–1.48 ^a	–2.0 ^f
			placebo		–0.54	+0.6
LEAD-5 (Russell-Jones 2008) ⁶⁰	581	metformin 1 g twice daily, glimepiride 2–4 mg/day	liraglutide 1.8 mg/day	26	–1.33 ^{a,b}	–1.8 ^{a,b}
			insulin glargine		–1.09	+1.6
			placebo		–0.24	–0.4
LEAD-6 (Blonde 2008) ⁶¹	464	metformin, SU	liraglutide 1.8 mg/day	26	–1.12 ^b	–3.2
			exenatide 10 µg twice daily		–0.79	–2.9

A1C = hemoglobin A_{1c}; BW = body weight; LEAD = Liraglutide Effects and Action in Diabetes; OAD = oral antidiabetic drug; SU = sulfonylurea.

^a $p \leq 0.0001$ versus placebo.

^b $p < 0.0001$ versus comparator.

^cNoninferior to active comparator.

^d $p \leq 0.01$ versus placebo.

^e $p = 0.0014$ versus comparator.

^f $p < 0.05$ versus placebo.

tients receiving liraglutide 1.2 and 1.8 mg, respectively. Liraglutide 1.2 and 1.8 mg treatment resulted in reductions in fasting plasma glucose (decreased by 40 and 43 mg/dL, respectively) and postprandial glucose levels (decreased by 49 and 47 mg/dL, respectively). Patients receiving placebo experienced an increase in body weight compared with weight loss for both doses of liraglutide ($p < 0.05$ vs placebo arm for both doses).

LEAD-5 evaluated patients with type 2 diabetes and a mean baseline A1C of 8.2%.⁶⁰ This study compared liraglutide with insulin glargine as add-on therapy to metformin and glimepiride. Participants received liraglutide, liraglutide placebo, or insulin glargine in addition to metformin and glimepiride. The dose of insulin glargine was individually titrated according to a patient-driven algorithm, with an average dose of 24 units per day achieved at the end of the trial in the insulin glargine arm. A1C was decreased with the addition of liraglutide, placebo, and insulin glargine ($p < 0.05$ for liraglutide vs placebo and insulin glargine). An A1C less than 6.5% was achieved in 37.1% of patients treated with liraglutide, 10.9% of those treated with placebo, and 23.6% of patients in the insulin glargine group.

LEAD-6 included patients inadequately treated with metformin and/or a sulfonylurea with a mean baseline A1C of 8.2%.⁶¹ This trial aimed to compare liraglutide with exenatide as add-on therapy. A significant A1C reduction occurred with liraglutide. A target A1C less than 6.5% was achieved in 35% of those treated with liraglutide versus 21% for patients receiving exenatide ($p < 0.0001$). Changes in body weight were similar in both groups, with no significant differences in weight change between the treatment groups. Table 3 provides a comparison of liraglutide and exenatide based on data obtained in LEAD-6.⁶¹

EFFECTS ON BODY WEIGHT

Overall, liraglutide has demonstrated favorable effects on body weight in Phase 3 clinical trials (Table 2). In 5 of

the 6 LEAD studies (excluding LEAD-1), liraglutide treatment resulted in statistically significant reductions in body weight over 26 weeks of therapy (weight decreased by 1.0–3.2 kg depending on study and dose used)^{57,59–61} and 52 weeks of therapy (weight decreased by 2.1–2.5 kg depending on dose used) versus the comparators.⁵⁸ In the LEAD-1 study, addition of liraglutide to background glimepiride did not demonstrate decreases in body weight compared with placebo (weight loss ranging from –0.2 to +0.7 kg depending on dose used).⁵⁶

EFFECTS ON β -CELL FUNCTION

Beneficial effects of liraglutide on β -cell function have been observed in animal models. In one study, Zucker diabetic fatty rats were injected subcutaneously with either liraglutide 150 μ g/kg or vehicle twice daily for 6 weeks, at which time β -cell mass was significantly improved in liraglutide-treated animals when compared with controls.⁶² Another study in diabetic (db/db) mice demonstrated improvements in blood glucose levels and improved β -cell mass and proliferation with liraglutide treatment for 2 weeks when compared with vehicle controls.⁶³ An *in vitro* study utilizing human islets isolated from organ donors demonstrated inhibition of β -cell death by regulation of apoptosis-related gene expression when cultured with liraglutide.⁶⁴

In addition to animal and *in vitro* studies, clinical studies with liraglutide have demonstrated beneficial effects on restoring β -cell sensitivity to glucose. Chang et al.⁵² utilized a graded glucose protocol to assess the effects of a single liraglutide dose of 7.5 μ g/kg on insulin secretion. Insulin secretion increased with elevation in blood glucose in all groups; however, liraglutide treatment resulted in a more pronounced insulin response, which was similar to that observed in healthy control subjects. Additional clinical studies have shown sustained β -cell sensitivity to glucose over 12 weeks of therapy⁵¹ and improvements in glucose-induced insulin secretion, β -cell sensitivity, and suppression of 24-hour glucagon secretion following 1 week of continuous therapy with liraglutide.³⁰

EFFECTS ON THE CARDIOVASCULAR SYSTEM

Statistically significant decreases in systolic blood pressure, ranging from 2 to 7.9 mm Hg, have been observed in participants receiving liraglutide in clinical trials.^{44,57,58} The mechanism resulting in the observed reduction in systolic blood pressure is unknown, but appears to be unrelated to concomitant weight loss.⁶⁵ While the significance of the finding is unknown, small increases in pulse rates (2–3 beats/min) have been witnessed with liraglutide treatment.^{57–59}

Both *in vitro* and *in vivo* data suggest that liraglutide exerts effects on markers of endothelial cell dysfunction. One

Table 3. Comparison of Liraglutide and Exenatide^{61,a}

Parameter	Liraglutide Daily	Exenatide Twice Daily
Effects on glycemic parameters		
A1C (%)	–1.12 ^b	–0.79
FPG reduction (mg/dL)	29 ^b	11
achievement of A1C <7% (%)	54 ^c	43
Change in body weight (kg)	–3.2	–2.9
A1C = hemoglobin A _{1c} ; FPG = fasting plasma glucose.		
^a 26-week data.		
^b $p < 0.0001$ versus exenatide.		
^c $p = 0.0015$ versus exenatide.		

study performed in a human vascular endothelial cell line demonstrated inhibition of tumor necrosis factor- α - or glucose-mediated induction of plasminogen activator inhibitor type-1 (PAI-1) and vascular adhesion molecule expression.⁶⁶ Additionally, data stemming from clinical data show significant decreases in PAI-1 and B-type natriuretic peptide (BNP) in patients with type 2 diabetes.⁶⁷ While these biomarkers are associated with cardiovascular risk, large prospective trials are needed to assess whether these observed outcomes translate to clinical benefit.

Clinical Trial Limitations

Overall, liraglutide has been studied in numerous clinical trials, with the LEAD program providing high-quality efficacy and safety data to support clinical decision making. At the present, however, LEAD-2 and LEAD-3 findings have been published in peer-reviewed clinical journals, with findings from the remaining LEAD studies available only in abstract format, thus, limiting the ability of authors, peer reviewers, and clinicians to fully assess all study parameters and outcomes. Participants enrolled within the 6 Phase 3 LEAD studies ranged in age from 18 to 80 years (mean age ranging from 53 to 58 y) with an average baseline A1C of 8.2–8.4%. While the inclusion criteria for the LEAD program allowed for a wide range of ages and A1C values at baseline, participants enrolled within these studies were relatively healthy. It is unknown how elderly frail patients with multiple comorbidities and concomitant medication or patients with more modest or more pronounced A1C values will respond to liraglutide therapy in terms of both therapeutic benefit and tolerability. Additional study is also warranted regarding the effects and clinical importance, if any, of liraglutide on reductions in systolic blood pressure and other cardiac-related parameters.

Adverse Events

GASTROINTESTINAL

The most frequent adverse events associated with GLP-1 agonist therapy involve the gastrointestinal (GI) system, with nausea, vomiting, and diarrhea being the most commonly reported events. GI adverse effects are dose-dependent, with GI tolerability improved by gradual stepwise dose escalation. GI events in Phase 3 clinical trials were generally transient, with low attrition rates attributed to these effects. The transient nature of GI events was demonstrated in LEAD-2, with less than 10% of participants reporting symptoms of nausea on a weekly basis beyond the initial 4 weeks of therapy.⁵⁷ Additionally, in LEAD-4, the incidence of nausea in the liraglutide arm was similar to that observed with placebo by week 16 of the study.⁵⁹ Overall, the incidence of diarrhea with liraglutide was 15–18% compared with less than 10% reported in

comparator groups.^{57,58} In LEAD-2, the incidence of vomiting with liraglutide was 10% versus 4% in the glimepiride arm.⁵⁷ Withdrawal of participants due to GI events (including nausea, vomiting, and diarrhea) with liraglutide was 5% and 2–4% in LEAD-2 and LEAD-3, respectively.^{57,58}

A substudy was performed by Horowitz et al.⁴³ to quantify the duration and intensity of GI-related adverse events during 14 weeks of therapy with liraglutide. Duration and intensity of GI-related events was determined by self-report with a validated tool known as the Gastrointestinal System Rating Scale. Findings indicated an increased overall incidence of GI-related symptoms with liraglutide treatment, with symptoms more prominent during the first 2 weeks of therapy that tended to improve over time. Ratings of indigestion and constipation were significantly greater for participants receiving liraglutide 1.25 mg/day compared with placebo, with a dose-related effect of liraglutide on the incidence of reflux symptoms during therapy. No significant differences between liraglutide and placebo were identified in terms of rate or severity of diarrhea or abdominal pain.

HYPOGLYCEMIC EVENTS

The overall risk of hypoglycemia with incretin mimetic therapy is low due to the glucose-dependent mechanism of insulin release induced by these agents. Experimentally, GLP-1 has demonstrated a small risk of hypoglycemia in both the fasting and fed state.^{22,23,68} Consistent with these findings, monotherapy with liraglutide in LEAD-3 resulted in no major hypoglycemic events, with the incidence of minor hypoglycemic events being less than 0.5 events per patient year for liraglutide versus 2.0 events per patient year with glimepiride.^{58,65} Likewise, hypoglycemic events were rarely observed in early clinical trials with liraglutide.^{44,47,49,51} Given the inhibitory effects of liraglutide on glucagon secretion, there exists a theoretical concern regarding a potential blunting of the counterregulatory responses to hypoglycemia. Data suggest, however, that the counterregulatory response to hypoglycemia is not impaired with liraglutide treatment. Liraglutide-induced suppression of glucagon secretion is glucose-dependent, with no impairment of hypoglycemia-induced glucagon secretion observed experimentally.⁶⁸

When examining rates of hypoglycemia during the LEAD program, lower rates of hypoglycemia occurred with liraglutide when compared with subjects treated with glimepiride and exenatide.^{57,58,61} As is the case with exenatide, liraglutide use in combination with sulfonylurea therapy appears to place patients at an increased risk of hypoglycemia when compared with use of either agent alone. In LEAD-1, one participant receiving liraglutide and glimepiride combination therapy experienced a major hy-

poglycemic event.⁵⁶ Likewise, in LEAD-5, 2.2% of participants in the liraglutide arm experienced a major hypoglycemic event compared with no events in either the placebo or insulin glargine arm.⁶⁰

ANTIBODY FORMATION

The incidence of anti-liraglutide antibody formation is reported to be low and has not been correlated with loss of drug activity or efficacy.⁶⁵ Liraglutide antibodies were identified in 9.3–12.7% of liraglutide-treated subjects in LEAD-1,⁵⁶ with 9.8% of participants in LEAD-5 demonstrating antibody formation after 26 weeks of therapy.⁶⁰ It is theorized that the tendency toward anti-liraglutide antibody formation is low due to the high degree of homology between liraglutide and human GLP-1.⁶⁵

PANCREATITIS

Concerns regarding safety with the incretin mimetics arose in 2007 when the FDA issued a warning regarding pancreatitis in patients receiving exenatide, thus requiring information about the risk of pancreatitis in the exenatide product label within the US.⁶⁹ A total of 89 cases of pancreatitis in patients receiving exenatide were reported to the FDA as of September 2007, with 6 cases of hemorrhagic or necrotizing pancreatitis and 6 cases of death reported in August 2008.⁷⁰ Given the concern of pancreatitis with incretin mimetic therapy, pancreatitis has been monitored in clinical trials with liraglutide. In the LEAD-2 study, 1 subject in the liraglutide 1.2-mg/day group and 1 subject in the glimepiride group withdrew from the study due to acute pancreatitis. Both subjects were hospitalized and fully recovered.⁵⁷ In the LEAD-3 study, 2 of the 498 participants receiving liraglutide experienced pancreatitis, 1 each in the 1.2- and 1.8-mg/day groups, respectively. Both participants experienced a full recovery, with 1 discontinuing the study.⁵⁸ No cases of pancreatitis were reported during the LEAD-4 study.⁵⁹ Given postmarketing experience with exenatide in terms of pancreatitis, diligent surveillance will be important in assessing the incidence of this adverse event when liraglutide is used within a heterogeneous population.

Drug Interactions

Limited drug interaction data exist for liraglutide. Upon examination of the effects of liraglutide on human liver microsomes, little to no inhibition of cytochrome P450 enzymes was noted, thus indicating that the risk for interactions associated with these enzymes is low.²⁸ While incretin mimetics are associated with minimal risk of hypoglycemia when used as monotherapy, combination therapy with exenatide and sulfonylurea agents has been associated

with an increased risk of hypoglycemia.⁷¹ Data from the LEAD-5 study demonstrate an increased incidence of both minor and major hypoglycemic episodes when liraglutide is added to metformin and glimepiride when compared with the addition of placebo.⁶⁰ It is likely prudent to monitor for signs and symptoms of hypoglycemia when using liraglutide in combination with other medications for the treatment of diabetes. Additionally, due to the effects of liraglutide on gastric emptying, its use may reduce the rate or extent of absorption of orally administered medications. Similar to exenatide, caution should be used when using liraglutide in combination with oral drugs that require rapid absorption and a minimum threshold concentration for efficacy, such as with certain antibiotics and oral contraceptives.⁷¹

Therapeutic Considerations

The pharmacokinetic profile of liraglutide is amenable to once-daily dosing, thus creating a potential advantage when compared with exenatide, which requires twice-daily subcutaneous administration. Ease of use and maintaining drug regimen simplicity are important considerations clinically, particularly in patients receiving multiple medications for the treatment of type 2 diabetes and associated comorbidities. Patients often present with resistance to the initiation of an injectable agent; however, the potential for weight loss with the GLP-1 agonists is often a motivation for patients to consider therapy. Dose-dependent nausea, vomiting, and diarrhea often limit the utility of exenatide in practice, particularly when the dosage is titrated upward too quickly. The low attrition rates seen with liraglutide treatment in the LEAD program are encouraging, yet clinical trial participants are often very motivated and adherent to therapy. Clinical experience with liraglutide over time in the ambulatory setting will determine the impact of GI adverse events on acceptance of therapy and long-term adherence. Additional data are likewise necessary to assess the impact of liraglutide therapy on cardiovascular markers such as PAI-1 and BNP. While early data indicate that liraglutide may decrease these markers, the clinical implications, either positive or detrimental, of these findings are unknown.

Per the recent consensus algorithm released by the American Diabetes Association and the European Association for the Study of Diabetes, GLP-1 analogs are listed for consideration as tier 2 drugs, or “less well-validated therapy,” for the treatment of type 2 diabetes.⁷² The consensus guideline recommends consideration of GLP-1 agonist therapy in selected clinical situations. Of course, GLP-1 agonist therapy is not indicated for all patients and should be used with caution in those with a history of significant GI disease, such as gastroparesis, due to a possible exacerbation of such conditions with incretin mimetic ther-

apy. One situation in which GLP-1 agonist therapy could be considered is in instances where hypoglycemia is particularly undesirable, such as an elderly patient living alone without the aid of a caregiver. Additionally, GLP-1 agonist therapy could be considered if weight loss is a major consideration and the patient's A1C level is close to target (<8.0%).⁷² Because postprandial hyperglycemia affects A1C to a greater degree than fasting hyperglycemia the closer a patient is to A1C goal, GLP-1 agonists provide a viable treatment option to target postprandial glycemic excursions due to their glucose-dependent effects on insulin secretion.

Dosage and Administration

Liraglutide is an isotonic solution administered via subcutaneous injection.⁶⁵ In clinical studies, fixed doses of liraglutide ranging from 0.045 to 2 mg once daily have been used.^{47,73} During Phase 3 trials within the LEAD program, doses of liraglutide used included 0.6, 1.2, and 1.8 mg/day (Table 1). Based on efficacy and tolerability findings in LEAD-2, investigators recommend a stepwise dose titration from 0.6 mg/day up to 1.2 mg/day and then up to 1.8 mg/day based on clinical response and tolerability.⁵⁷ The EMA recently granted approval for the use of liraglutide at a starting dose of 0.6 mg/day with a dose titration to 1.2 mg/day after at least 1 week of therapy, if tolerated. A second titration to 1.8 mg/day 1 week thereafter in some patients is recommended if needed for optimal glucose control. Actual dosing recommendations for the US and Japan are pending the approval of liraglutide in these countries.

Summary

Clinical trial data from large, controlled studies demonstrate the effectiveness of liraglutide in terms of A1C reduction, beneficial effects on body weight, and a low risk for hypoglycemic events when used as monotherapy. Overall, liraglutide is well tolerated, with dose-dependent nausea, vomiting, and diarrhea being the most commonly reported adverse events in clinical trials. On April 2, 2009, the FDA reviewed data related to the approval of liraglutide. Evidence that indicated that thyroid tumors occurred in early studies of liraglutide in murine and rat models was presented. The manufacturer believes that this finding is not of concern in humans and has expressed determination to proceed with seeking approval of liraglutide. Clinical trial data in humans indicate that liraglutide may have a role in the treatment of patients with type 2 diabetes as monotherapy early in the disease process as well as in combination with metformin, glimepiride, and rosiglitazone in patients inadequately controlled on oral antidiabetic drugs. Comparative data with exenatide indicate a potential therapeutic advantage for liraglutide in terms of ease of use (once-daily administration), with similar im-

provements in A1C and body weight when compared with exenatide. Whether these modest clinical advantages over exenatide are clinically significant in practice is unknown. While promising data exist regarding the effects of liraglutide on β -cell mass and neogenesis, the clinical implications of these findings remain to be substantiated.

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Liraglutida: Un Mimético de Incretina de Uso Diario para el Tratamiento de Diabetes Mellitus Tipo 2

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EXTRACTO

OBJETIVO: Revisar la farmacología, farmacocinética, eficacia, y seguridad de liraglutida, un análogo del péptido similar a glucagón (GLP-1) para uso en el tratamiento de pacientes con diabetes mellitus tipo 2.

FUENTES DE DATOS: Se llevó a cabo una búsqueda en la literatura en el idioma inglés a través del sistema MEDLINE (1966–mayo 2009) utilizando los términos péptido 1 similar a glucagón, mimético de incretina, NN2211, y liraglutida. Los resúmenes de trabajos presentados en las reuniones anuales de 2006, 2007, y 2008 de la Asociación Americana de Diabetes y la Asociación Europea para el Estudio de Diabetes también se revisaron para obtener información relevante.

SELECCIÓN DE ESTUDIOS Y EXTRACCIÓN DE INFORMACIÓN: Los artículos en el idioma inglés relacionados con la farmacología, farmacocinética, eficacia, y seguridad de liraglutida fueron estudiados.

SÍNTESIS DE LOS DATOS: Liraglutida es un análogo de GLP-1 cuyas propiedades farmacocinéticas permiten que se administre una vez al día. Los datos obtenidos de los estudios grandes y controlados demuestran que liraglutida es un medicamento efectivo en términos de reducción de A_{1c} y peso, y que tiene un riesgo bajo de eventos hipoglucémicos cuando se usa como monoterapia. La información disponible también apoya al beneficio de liraglutida en la respuesta de las células, a glucosa. Los datos de estudios in vitro y en animales sugieren efectos beneficiosos en la masa de células, y en el proceso de neogénesis. Liraglutida se ha estudiado en monoterapia y en combinación con metformina, glimepirida y rosiglitazona para el tratamiento de diabetes tipo 2. Además, en los estudios de fase 3, se está comparando con insulina glargina y exenatida. Los datos disponibles de estos estudios pueden ayudar al proveedor de salud a tomar mejores decisiones clínicas.

CONCLUSIONES: La administración una vez al día de liraglutida puede proveer una ventaja terapéutica sobre el uso de exenatida 2 veces al día, ya que cuando se comparan ambos medicamentos, liraglutida resulta en mejoras similares en los parámetros de A_{1c} y peso. El mecanismo de estimular la secreción de insulina dependiente de glucosa que tienen los agonistas de GLP-1 provee una alternativa clínica significativa para el manejo de los aumentos postprandiales de glucosa, sin aumentar el riesgo de hipoglucemia. Liraglutida es un medicamento que se tolera bien y los efectos adversos más comunes informados en los estudios son náusea dependiente de la dosis, vómitos, y diarrea.

Traducido por Mirza Martínez

Liraglutide: Un Analogue de l'Incrétine s'Administrant une Fois par Jour Pour le Traitement du Diabète Sucré de Type 2

JJ Neumiller et RK Campbell

Ann Pharmacother 2009;43:1433-44.

RÉSUMÉ

OBJECTIF: Revoir la pharmacologie, la pharmacocinétique, l'efficacité et l'innocuité du liraglutide, un analogue du peptide à effet glucagon 1 (GLP-1) pour le traitement du diabète sucré de type 2.

PROVENANCE DES DONNÉES: Une recherche de la banque de données informatisées MEDLINE a été effectuée (1966–mai 2009) afin d'identifier les publications pertinentes de langue anglaise. Les mots clés utilisés incluaient: peptide à effet glucagon 1, analogue de l'incrétine, NN2211, et liraglutide. Les résumés des communications présentées aux réunions annuelles des années 2006, 2007, et 2008 de l'Association Américaine du Diabète et de l'Association Européenne pour l'Étude du Diabète furent aussi revus afin d'identifier les communications qui auraient pu être pertinentes.

SÉLECTION DES DONNÉES: Seules les publications de langue anglaise sur la pharmacologie, la pharmacocinétique, l'efficacité, et l'innocuité du liraglutide ont été retenues.

RÉSUMÉ: Le liraglutide est un analogue du GLP-1 avec des propriétés pharmacocinétiques permettant une administration quotidienne. L'effet clinique du liraglutide a été étudié de façon extensive au cours de plusieurs études cliniques portant sur plus de 4000 patients souffrant de diabète sucré de type 2. Dans ces études, le liraglutide était administré soit en monothérapie, soit en combinaison avec la metformine, le glimepiride ou le rosiglitazone et comparé à différentes monothérapies ou combinaisons. Toutes ces études démontrent qu'une monothérapie de liraglutide est efficace pour réduire l'HbA_{1c} et la masse corporelle tout en présentant une faible incidence d'événements hypoglycémiques. De plus, les données animales et les données in vitro démontrent que le liraglutide a un effet bénéfique sur la réponse des cellules, au glucose, sur la masse de cellules, et sur leur néogénèse. Les effets secondaires les plus fréquemment rapportés touchent le système digestif (nausées, vomissements, diarrhées) et sont reliés à la dose administrée.

CONCLUSIONS: Plusieurs études ont été effectuées avec le liraglutide, procurant ainsi aux praticiens une bonne base d'information sur laquelle fonder leurs décisions. L'administration quotidienne de liraglutide produit des améliorations de l'HbA_{1c} et de la masse corporelle similaires à une administration 2 fois par jour d'exénatide. La sécrétion d'insuline induite par le glucose, ciblée par les agonistes GLP-1, pourrait être particulièrement importante dans la gestion des épisodes hyperglycémiques postprandiaux avec un risque minime d'hypoglycémie. En général, le liraglutide est bien toléré. Des nausées, des vomissements et de la diarrhée (reliés à la dose) sont les effets secondaires les plus communément rapportés dans les études cliniques.

Traduit par Suzanne Laplante

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