

Liraglutide in the management of type 2 diabetes

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Abstract: The pathophysiology of type 2 diabetes has been attributed to the classic triad of decreased insulin secretion, increased insulin resistance, and elevated hepatic glucose production. Research has shown additional mechanisms, including incretin deficiency or resistance in the gastrointestinal tract. Liraglutide is a modified form of human glucagon-like peptide-1. Liraglutide was obtained by substitution of lysine 34 for arginine near the NH₂ terminus, and by addition of a C16 fatty acid at the ε-amino group of lysine (at position 26) using a γ-glutamic acid spacer. Liraglutide has demonstrated glucose-dependent insulin secretion, improvements in β-cell function, deceleration of gastric emptying, and promotion of early satiety leading to weight loss. Liraglutide has the potential to acquire an important role, not only in the treatment of type 2 diabetes, but also in preservation of β-cell function, weight loss, and prevention of chronic diabetic complications.

Keywords: diabetes mellitus, incretin, glucagon-like peptide, insulin resistance

Introduction

Type 2 diabetes mellitus (T2DM) is a major public health burden that poses management challenges in clinical practice.¹ The core pathophysiology of T2DM has been attributed to the classic triad of decreased insulin secretion, increased insulin resistance, and elevated hepatic glucose production. Research has shown that additional mechanisms, including those related to the fat cell (accelerated lipolysis), gastrointestinal tract (incretin deficiency/resistance), α-cell (hyperglucagonemia), kidney (increased glucose reabsorption), and the brain (insulin resistance), referred to as the “ominous octet”,² are also involved.

Overt T2DM occurs only when β-cells fail (due to decreased mass or their failure to recognize the hyperglycemic signal) and can no longer compensate for the increased insulin secretion required to maintain normoglycemia.³ Amelioration of the decline in β-cell function must be addressed to alter the progressive nature of the disease.^{4,5} Agents that may prevent deterioration of β-cell function or enhance endogenous insulin concentrations are much needed for the management of T2DM. Other pathophysiologic defects of T2DM that current therapeutic agents do not address include hyperglucagonemia, accelerated gastric emptying, and decrease or loss of the incretin effect.

It had been demonstrated that glucagon secretion in T2DM is not suppressed after a carbohydrate-rich meal.^{6,7} This results in an inability to suppress postprandial hepatic glucose production and excessive plasma glucose excursions. The rate of

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gastric emptying is a key determinant of postprandial glucose excursions and is often accelerated in people with diabetes.^{8,9}

In T2DM, glucagon-like peptide-1 (GLP-1) concentrations are reduced in response to a meal, whereas glucose-dependent insulinotropic polypeptide concentrations are normal or increased. This observation suggests resistance to the actions of glucose-dependent insulinotropic polypeptide, making GLP-1 the favored potential therapeutic target.^{10,11}

Many of the pathophysiologic disturbances that are present in T2DM can be corrected by incretin replacement with GLP-1. In response to the physiologic loss of incretin activity associated with T2DM, administration of exogenous GLP-1 has been shown to lower both fasting and postprandial plasma glucose significantly.^{12,13} The main limitation in developing GLP-1 for the treatment of T2DM is its short half-life of less than two minutes. By removing two N-terminal amino acids, dipeptidyl peptidase-4 (DPP-4) rapidly inactivates GLP-1.¹⁴ The development of the GLP-1 receptor agonists offers incretin-based therapies with built-in modifications to provide resistance to DPP-4 degradation.

Pharmacokinetics and pharmacology

Liraglutide (Victoza[®]; Novo Nordisk Inc, Bagsvaerd, Denmark) is a modified form of human GLP-1 (γ -L-glutamyl[N- α -hexadecenoyl]-Lys,₂₆ Arg₃₄-GLP-1 [7–37]). Native GLP-1 is a 30-amino acid peptide produced by cleavage of the transcription product of the preproglucagon gene.¹⁵ Liraglutide was obtained by substitution of lysine 34 to arginine near the NH₂ terminus, and by addition of a C16 fatty acid at the ϵ -amino group of lysine (at position 26) using a γ -glutamic acid spacer, which allows noncovalent binding to albumin (see Figure 1).¹⁶ The resultant molecule shares 97% (36/37 amino acids) sequence identity with native human GLP-1.¹⁷ The high degree of homology of liraglutide to GLP-1 may in part explain the relatively low levels of

antibodies produced in response to liraglutide. However, the clinical relevance of antibodies is not yet known.

Pharmacokinetic studies show that liraglutide, after subcutaneous injection, has a time to maximum plasma concentration (T_{max}) of 9–13 hours and a half-life ($T_{1/2}$) of 13 hours. The structural modifications of liraglutide are responsible for the prolonged half-life. Indeed, following subcutaneous injection, the fatty acid chain allows liraglutide to self-associate and form heptamers at the injection site depot. It is thought that the size of the heptamer and strong self-association are the most likely mechanisms by which delayed absorption of liraglutide from the subcutis is facilitated.¹⁸ Once in the bloodstream, the fatty acid chain allows reversible binding to serum albumin, providing partial stability and resistance to metabolism by DPP-4 and reduces renal clearance, giving liraglutide a protracted mechanism of action.¹⁹

Liraglutide metabolism does not depend on one single organ for its elimination. About 89%–100% of intact liraglutide is present in plasma, with only two minor metabolites and no intact liraglutide detected in urine or feces,¹⁷ suggesting slow degradation into small peptides, amino acids, and fatty acid fragments eliminated through the liver or the kidney.^{20,21}

To evaluate the effect of hepatic impairment on the pharmacokinetic properties of liraglutide, six patients with normal hepatic function and 18 patients with mild, moderate, or severe hepatic impairment received a single dose of subcutaneous liraglutide 0.75 mg.²² Liraglutide bioavailability appeared to decrease with an increasing degree of hepatic impairment, with no significant differences in the safety parameters between the two groups.

The effect of injection site (abdomen, upper arm, and thigh) on the pharmacokinetic profile of liraglutide was investigated.²³ It was found that based on the area under the concentration-time curve (AUC), the abdomen and thigh were equivalent. However, lower bioavailability was observed in the thigh compared with the abdomen. Although T_{max} and $T_{1/2}$ were similar between the injection sites, maximum concentration (C_{max}) was lower in the thigh than in the abdomen. Based on these results, the differences in bioavailability were not considered clinically relevant, and the three injection sites can be used interchangeably. Age and gender pharmacokinetic equivalence of subcutaneous liraglutide 1 mg/day demonstrated that when adjusted for body weight, similarity was confirmed between young and elderly subjects, and no significant effect of gender was observed.²⁴

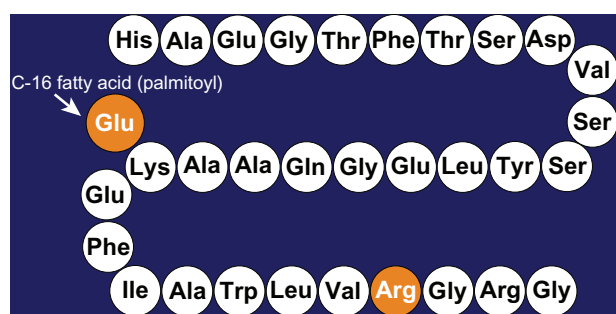


Figure 1 Liraglutide structure.

Liraglutide delays gastric emptying and could affect the absorption pattern of concomitant drugs. The effect of subcutaneous liraglutide 1.8 mg on the pharmacokinetic properties of atorvastatin 40 mg, griseofulvin 500 mg, lisinopril 20 mg, and digoxin 1 mg was evaluated in healthy subjects.²⁵ The AUCs of griseofulvin and atorvastatin were equivalent in liraglutide-treated and placebo-treated subjects. On the other hand, the AUCs of lisinopril and digoxin were decreased by 15% and 16%, respectively. The C_{\max} for atorvastatin, digoxin, and lisinopril was decreased and for griseofulvin was increased. T_{\max} for atorvastatin, digoxin, and lisinopril was also delayed, confirming a liraglutide-induced shift in absorption kinetics. A similar study assessing the effects on acetaminophen after exposure to liraglutide²³ also demonstrated lower C_{\max} and delayed T_{\max} compared with placebo.

One of the first large single-center, randomized, double-blind, sequential dose escalation (1.25 to 20.0 $\mu\text{g}/\text{kg}$ single dose) study of 64 healthy nondiabetic men confirmed that liraglutide has a pharmacokinetic profile that is consistent with once-daily administration (T_{\max} 9–12 hours after dosing and $T_{1/2}$ 11–15 hours).²⁶ Absorption of liraglutide was slow, with C_{\max} achieved between 9 and 12 hours after dosing. A frequently sampled intravenous glucose tolerance test (IVGTT) was performed and showed a statistically significant increase in insulin secretion ($P = 0.0002$), but there was no significant effect on glucagon levels. No significant effect was observed on glucose levels during the IVGTT, but there was a dose-dependent increase in the glucose disappearance constant. There were no reports of serious adverse events and all subjects completed the study. A higher number of adverse events were reported in subjects in active treatment versus placebo treatment, such as headache, dizziness, nausea, and vomiting. Whereas headache and dizziness occurred at the majority of dose levels, nausea and vomiting mainly occurred at 10–15 $\mu\text{g}/\text{kg}$. There was a tendency toward lower urine volumes at doses ≥ 12.5 $\mu\text{g}/\text{kg}$, but there was no overall significant difference in urine volumes 0–24 hours after dose administration between active and placebo treatment.

Another study in 30 healthy men with consecutive dose levels of liraglutide (1.25–12.5 $\mu\text{g}/\text{kg}$)¹⁹ showed similar results. There were dose-proportional increases in exposure (AUC and C_{\max}) with increasing doses. There were no statistically significant differences from placebo in 24-hour glucose and insulin profiles. Overall, there was a higher frequency of adverse events in the active-treated patients than in the placebo-treated subjects. Three subjects were withdrawn due to adverse events, dizziness, fever and pharyngitis, and

nausea and diarrhea. There were no serious adverse events during the study. Combined urine volume data showed a statistically significant reduction following a dose of liraglutide compared with placebo.

In a dose-finding study in 24 healthy Japanese men who received three consecutive dose levels of liraglutide (15–25 $\mu\text{g}/\text{kg}$), the daily pharmacokinetic profiles after receiving the last dose showed dose-dependent increases in the AUC at 0–24 hours, C_{\max} , and minimum concentration. Elimination rate constant, volume of distribution, and clearance were not affected by dose.²⁷ A similar profile was found when the drug was administered to T2DM patients once daily as a subcutaneous injection for one week.²⁸ Relatively high plasma concentrations of liraglutide were maintained throughout the 24-hour dosing period, demonstrating that once-daily administration of liraglutide should be sufficient.

Mode of action

Liraglutide has demonstrated glucose-dependent insulin secretion, improvements in β -cell function, deceleration of gastric emptying, and promotion of early satiety leading to weight loss.²⁹

The effects of liraglutide on β -cells in vitro and in animal models were of particular interest. When mice with diabetes mellitus (db/db mice) were exposed to liraglutide, a significantly increased β -cell mass ($P < 0.05$) and β -cell proliferation rate ($P < 0.001$) were observed versus placebo exposure.³⁰ The effect of liraglutide on β -cell mass was also noted in Zucker diabetic fatty rats.³¹ After six weeks of treatment, a higher total β -cell mass was observed in Zucker diabetic fatty rats treated with liraglutide than in those in the placebo group ($P < 0.03$). When normoglycemia was maintained in these animals, liraglutide did not cause expansion of β -cell mass. This may suggest that the influence of GLP-1 agonism on β -cell mass dynamics in vivo may depend on the glycemic state.

Liraglutide was significantly better than native GLP-1 in inhibiting apoptosis in cells treated with either agent. Particularly, liraglutide was able to inhibit cytokine-induced apoptosis in primary rat islet cells in a dose-dependent manner, and to reduce free fatty acid-induced apoptosis by approximately 50%.³²

Furthermore, a recent study investigated the efficacy of liraglutide to prevent or delay diabetes in UC Davis T2DM rats, a model of polygenic obese T2DM.³³ Liraglutide treatment delayed diabetes onset by 4.1 ± 0.8 months compared with control ($P < 0.0001$) and by 1.3 ± 0.8 months

compared with energy-restricted animals ($P < 0.05$). Energy restriction and liraglutide treatment lowered fasting plasma glucose and glycosylated hemoglobin (HbA_{1c}) compared with control. Liraglutide-treated animals demonstrated lower fasting plasma insulin, glucagon, and triglycerides compared with both control and energy-restricted animals. Additionally, energy-restricted and liraglutide-treated animals exhibited more normal islet morphology.

The effect of a single subcutaneous dose of liraglutide 10 $\mu\text{g}/\text{kg}$ on glycemic control was assessed in patients with T2DM.³⁴ Liraglutide significantly reduced fasting plasma glucose compared with placebo (6.9 ± 1.0 versus 8.1 ± 1.0 mmol/L, $P < 0.01$). In another study, subcutaneous liraglutide 0.6 mg once daily³⁵ improved fasting plasma glucose, and this effect was significant after the first week and persisted through eight weeks of treatment ($P = 0.002$ versus placebo). There was also a significant decrease in HbA_{1c} levels compared with placebo (-0.80% , $P = 0.028$). Liraglutide caused a moderate delay in the postprandial rate of gastric emptying and reduced the rate at which postprandial plasma glucose appeared in the circulation.

A study in patients with T2DM showed that liraglutide increased β -cell function in the fasting state by 30%, by homeostasis model assessment for β function (HOMA-B).²⁸ The maximum β -cell secretory capacity was significantly higher after treatment with liraglutide compared with placebo, and the proinsulin-to-insulin ratio was reduced by 40%–50%, an additional indication of improved β -cell function. This resulted in a significant reduction by approximately 20% in 24-hour glucose AUC and postprandial glucose after liraglutide injection. With liraglutide, insulin concentrations were significantly higher after an intravenous glucose bolus (first-phase insulin secretion, a 60% increase) and during steady-state hyperglycemia (second-phase insulin secretion, a 240% increase).³⁶

Patients with T2DM were randomized to treatment with liraglutide 0.65, 1.25, or 1.9 mg/day or placebo to evaluate insulin secretion.³⁷ After 14 weeks, first-phase insulin secretion (measured by IVGTT) was significantly increased at the two highest doses of liraglutide by 118% and 103%, respectively. Second-phase insulin secretion was significantly increased only in the 1.25 mg/day group versus placebo. Arginine-stimulated insulin secretion during a hyperglycemic clamp test also increased significantly at the two highest dose levels versus placebo, by 114% and 94%, respectively.

It has been demonstrated that treatment with liraglutide, at a dose of 1.8 mg daily, significantly decreased the

mean energy intake by 18% during an ad libitum meal (~ 850 kJ).³⁸ A modest effect on appetite sensation has also been reported.

Liraglutide has demonstrated some blood pressure-lowering effects. In a 14-week study, a significant 5–8 mmHg reduction in systolic blood pressure with different doses of liraglutide was seen, with no change in diastolic blood pressure.³⁹ A meta-analysis of three large pooled-data studies with liraglutide showed a significant 2.7–4.5 mmHg reduction in systolic blood pressure.⁴⁰

Finally, treatment with liraglutide may have positive effects on plasma glucagon secretion, and does not impair the counterregulatory glucagon response to hypoglycemia in patients with T2DM.⁴¹ However, other studies^{26,36,44} failed to reproduce these findings.

Efficacy and safety

Encouraging preclinical and Phase I clinical pharmacology results with liraglutide led to larger Phase II trials in patients with T2DM, demonstrating that liraglutide is effective and well tolerated, both in monotherapy and in combination with oral antidiabetic drugs.

In a 12-week, double-blind, randomized, placebo-controlled trial with an open-label sulfonylurea comparator in 190 patients with T2DM, five fixed dosage groups of liraglutide were tested (0.045, 0.225, 0.45, 0.60, or 0.75 mg).⁴² Treatment with the two highest dose of liraglutide reduced HbA_{1c} significantly more than placebo (-0.70% , $P = 0.0002$, and -0.75% , $P < 0.0001$, respectively). Fifty-nine percent of patients completing the trial in the two highest dosage groups achieved $HbA_{1c} \leq 7\%$. In the 0.45 mg liraglutide dosage group, a statistically significant decrease in body weight ($P = 0.0184$) compared with placebo was noted. Mean β -cell function (measured by HOMA) was significantly higher in the 0.75 mg liraglutide group than in the placebo group ($P = 0.0002$). The proinsulin-to-insulin ratio decrease was statistically significant after treatment with 0.75 mg of liraglutide compared with placebo ($P = 0.0244$). Of the 135 patients exposed to liraglutide, one in the 0.60 mg group experienced minor hypoglycemia. The number of patients with adverse events was comparable across the liraglutide groups and the placebo group. For gastrointestinal events (nausea), the incidence seemed to increase with increasing doses of liraglutide. Other events included diarrhea, vomiting, and constipation. Approximately two-thirds of these events were reported to resolve within 1–3 days.

Another 12-week, randomized, multicenter study compared the same five doses of liraglutide with metformin.⁴³

HbA_{1c} was maintained at a relatively stable level during treatment in the metformin group and in the 0.45 mg, 0.6 mg, and 0.75 mg liraglutide groups. The two lowest liraglutide doses were not sufficient to maintain glycemic control. After 12 weeks, patients in the metformin group had a slight weight loss of -0.61% ($P = 0.124$ versus baseline), whereas the five liraglutide groups has a weight loss ranging from -0.05% (0.045 mg, $P = 0.825$ versus baseline) to -1.87% (0.225 mg, $P = 0.006$, versus baseline). All treatment groups, except for the lowest dose, showed a decrease in total body mass and total fat mass (measured by dual-energy X-ray absorptiometry scan). The study demonstrated, except for the lowest liraglutide dose group, an increase in fasting serum insulin levels, with greater increases observed in the 0.75 mg dosage group; the same dosage group showed an increase in C-peptide levels that were significantly different from the metformin group ($P = 0.002$). The proportion of patients reporting adverse events with liraglutide treatment (52%–68%) was comparable with those treated with metformin (56%). The most frequent adverse event was injection site bruising, constipation, and diarrhea in the liraglutide group. The frequency of injection site bruising was not different between the liraglutide groups (5.7%) and the metformin group (5.9%), which only received placebo injection, indicating that bruising was most likely caused by the injection, rather than the trial medication. Five subjects (2.8%) in the liraglutide groups reported minor hypoglycemic events. There was no increase in the frequency of hypoglycemia as compared with metformin. No subjects showed a positive test for antibodies against liraglutide.

Nauck et al⁴⁴ evaluated 144 T2DM patients on metformin treatment in a five-week study where patients were randomized to receive metformin plus liraglutide, liraglutide or metformin, or metformin plus glimepiride (open-label). The dose of liraglutide in the study was increased weekly from 0.5 mg to 2 mg. Adding on liraglutide to existing metformin therapy resulted in a 3.9 mmol/L decrease in fasting plasma glucose in favor of liraglutide treatment ($P < 0.0001$), whereas switching subjects from metformin to liraglutide monotherapy gave an additional 1.4 mmol/L reduction ($P = 0.011$). HbA_{1c} lowered after treatment with metformin plus liraglutide compared with metformin alone (0.8%, $P < 0.001$). β -cell function (measured by HOMA) was significantly increased for metformin plus liraglutide versus metformin plus glimepiride (13.0%, $P = 0.014$), and for liraglutide versus metformin therapy (28.7%, $P < 0.0001$). Liraglutide monotherapy increased HOMA compared with metformin therapy (3.3%, $P = 0.0001$). After treatment, body

weight had significantly decreased from baseline by 2.2 kg and 2.1 kg in the groups receiving liraglutide combination and monotherapy, respectively, and significantly by 1.7 kg on metformin monotherapy, with a significant difference in body weight reduction between the metformin plus liraglutide group compared with metformin plus glimepiride group (-2.9 kg, $P < 0.0001$).

Vilsbøll et al³⁹ evaluated the efficacy of liraglutide as monotherapy in T2DM patients. The study was double-blind, randomized, and placebo-controlled using three doses of liraglutide (0.65, 1.25, or 1.90 mg). After 14 weeks of treatment, the HbA_{1c} changes in the liraglutide groups compared with placebo were -1.74% , $P < 0.0001$; -1.69% , $P < 0.0001$; and -1.27% , $P < 0.0001$, for the 1.90, 1.25, and 0.65 mg doses, respectively. The proportion of patients reaching HbA_{1c} $< 7\%$ was 46% (1.90 mg), 48% (1.25 mg), 38% (0.65 mg), and 5% (placebo) in the four groups. Glycemic control was associated with a decrease in body weight in all treatment groups, with a maximum estimated weight loss of 2.99 kg in the 1.90 mg liraglutide group ($P = 0.0390$). The median change from baseline in proinsulin-to-insulin ratio was significant for all three liraglutide groups versus placebo ($P = 0.0111$, $P = 0.0062$, and $P = 0.0218$ for the 1.90, 1.25, and 0.65 mg doses, respectively). In addition, there was a significant lowering in fasting glucagon concentrations in the 1.90 mg liraglutide group compared with placebo ($P = 0.0497$). Systolic blood pressure decreased significantly in all treatment groups compared with placebo (-7.9 mmHg, $P = 0.0023$; -5.2 mmHg, $P = 0.0417$; -7.4 mmHg, $P = 0.0041$ in the 1.90, 1.25, and 0.65 mg groups, respectively), but the drop of 2–3 mmHg in the diastolic blood pressure in all groups was not statistically significant. Lipid parameters were also measured, but only triglyceride levels decreased compared with placebo (-22% , $P = 0.0110$; -15% , $P = 0.0854$; -19% , $P = 0.0303$ in the 1.90, 1.25, and 0.65 mg groups, respectively). The proportions of patients reporting a gastrointestinal adverse event were 37%, 29%, 38%, and 23% of patients treated with liraglutide 1.90 mg, 1.25 mg, 0.65 mg, and placebo, respectively, with a higher event rate reported at the highest dose in the comparison with placebo ($P < 0.05$). Nausea seemed somewhat higher in the 1.90 mg and 0.65 mg groups. Only four of 123 liraglutide-treated patients withdrew from the study because of gastrointestinal adverse events. The incidence of gastrointestinal adverse events decreased over time. No major or minor hypoglycemic episodes were reported. There were no treatment-related effects on induction of antibodies and no thyroid ultrasonographic changes.

There were no clinically relevant changes reported in vital signs, electrocardiographic parameters, physical examination, or safety laboratory parameters (hematology, biochemistry, and urinalysis) in any of the above studies.^{39,42–44}

The first comparison between liraglutide and a DDP-4 inhibitor was in a parallel-group, open-label, multicenter trial, in which 658 patients with T2DM with inadequate glycemic control (HbA_{1c} 7.5%–10%) on metformin were randomized to receive 1.2 mg or 1.8 mg of subcutaneous liraglutide once daily, or 100 mg oral sitagliptin once daily for 26 weeks.⁴⁵ Mean decreases in HbA_{1c} from baseline were –1.50% for 1.8 mg liraglutide, –1.24% for 1.2 mg liraglutide, and –0.90% for sitagliptin ($P < 0.0001$ between both the liraglutide and sitagliptin groups). Mean decreases in fasting plasma glucose were –2.14 mmol/L for 1.8 mg liraglutide, –1.87 mmol/L for 1.2 mg liraglutide, and –0.83 mmol/L for sitagliptin ($P < 0.0001$ between both the liraglutide and sitagliptin groups). Mean weight loss was –3.38 kg for 1.8 mg liraglutide, –2.86 kg for 1.2 mg liraglutide, and –0.96 kg for sitagliptin ($P < 0.0001$ between both the liraglutide and sitagliptin groups). In assessment of β -cell function by HOMA, C-peptide concentration, and proinsulin-to-insulin ratio, both liraglutide doses were associated with improvement compared with sitagliptin. Changes in the lipid profile between liraglutide and sitagliptin were not significant, except for total cholesterol reduction that was greater with liraglutide 1.8 mg compared with sitagliptin ($P = 0.0332$). When comparing with sitagliptin, liraglutide 1.8 mg and 1.2 mg caused a higher proportion of nausea, but this was transient (~13 days). One patient on liraglutide 1.2 mg had a major hypoglycemic episode (3.6 mmol/L). Minor hypoglycemic episodes were reported with similar frequency in all groups. One thyroid problem (reported as a formation in the thyroid gland) in a patient on 1.2 mg liraglutide was classified as a serious adverse event, but histology showed no signs of malignancy. Changes from baseline in serum calcitonin concentrations were similar across groups. No pancreatitis was reported.

In view of a weight benefit from treatment with liraglutide compared with other antidiabetic drugs, a study in obese individuals without T2DM using higher doses of liraglutide was performed.⁴⁶ Obese subjects (body mass index 30–40 kg/m²) were randomly assigned to receive liraglutide (1.2 mg, 1.8 mg, 2.4 mg, or 3.0 mg by subcutaneous injection once a day), placebo (also subcutaneously), or orlistat (120 mg three times a day orally). The trial was therefore masked for liraglutide or placebo treatment (but not the dose), and open-label for orlistat treatment. The estimated mean weight

loss in the intention-to-treat population from randomization to week 20 was significantly greater with liraglutide at all doses than with placebo (–2.8 kg), and was dose-dependent (–4.8 kg, –5.5 kg, –6.3 kg, –7.2 kg, for 1.2 mg, 1.8 mg, 2.4 mg, and 3.0 mg doses, respectively). Sixty-one percent of individuals in the liraglutide treatment groups lost more than 5% of their baseline weight, which was significantly more than that in the placebo group ($P \leq 0.0001$). Furthermore, more individuals treated with liraglutide 3.0 mg lost more than 5% baseline weight than those treated with orlistat (76% versus 44%, $P < 0.0001$). The proportion of patients with metabolic syndrome at week 20 decreased by more than 60% in those treated with liraglutide 2.4 mg and 3.0 mg. Mean HbA_{1c} in individuals treated with liraglutide was slightly reduced compared with that in individuals on placebo and orlistat at week 20; the reduction seemed to be dose-dependent, ranging from 0.14% in the 1.2 mg group to 0.24% in the 3.0 mg dose group. Median β -cell function (as assessed by HOMA) decreased on placebo and orlistat treatment by 17% and 21%, respectively, but increased on liraglutide treatment by 5%–24%. The most common adverse events with liraglutide were nausea and vomiting, which occurred seven times more frequently with liraglutide 2.4 mg and 3.0 mg than with placebo. This was mostly transient and of mild or moderate intensity, and the frequency increased with dose. Most nausea events (80%) developed within the first four weeks of the trial during dose titration. Psychiatric disorders (insomnia, depressed mood, nervousness) were slightly more frequent in subjects treated with liraglutide 2.4 mg and 3.0 mg than in those on placebo. Serum calcitonin concentrations were measured, but no significant effect was noted.

LEAD trials

Finally, a comprehensive Phase III evaluation consisting of six randomized clinical trials was developed. The LEAD (Liraglutide Effect and Action in Diabetes) program involved 6500 subjects seen at 600 sites in 41 countries worldwide, of whom 4445 received liraglutide. The aim of these trials was to evaluate the efficacy and safety of liraglutide as monotherapy and in combination with other antidiabetic drugs and insulin (see Table 1).

LEAD 1⁴⁷ was a 26-week, five-arm randomized trial testing the effect of three doses of liraglutide (0.6, 1.2, and 1.8 mg) added to glimepiride 4 mg/day in comparison with the same dose of glimepiride in combination with placebo or rosiglitazone 4 mg/day. At the end of the study, HbA_{1c} levels were significantly more reduced in all liraglutide groups (–0.6%, –1.08%, and –1.13% for the 0.6, 1.2, and

Table 1 Liraglutide effects and actions in diabetes studies

Study	HbA _{1c} % (Δ from baseline)	% with HbA _{1c} ≤ 7%	% with HbA _{1c} ≤ 6.5%	Body weight, kg (Δ from baseline)	SBP, mmHg (Δ from baseline)	Lipids, mmol/L (Δ from baseline)
LEAD-1	-1.1	42	21	-0.2	≤-2.8	ND
LEAD-2	-1.0	42	25	-2.8	-2 to -3	ND
LEAD-3	-1.14	51	38	-2.5	-3.6	ND
LEAD-4	-1.5	54	36	-2	-5.6	TC: -0.20; LDL-C: -0.23; HDL-C: -0.04; TG: -0.32
LEAD-5	-1.3	52	37	-1.8	ND	ND
LEAD-6	-1.12	54	35	-3.2	-2.5	TC: -0.20; LDL-C: -0.44; HDL-C: -0.04; TG: -0.41

Abbreviations: LEAD, liraglutide effects and actions in diabetes; HbA_{1c}, hemoglobin A_{1c}; ND, no data reported; NS, not significant; SBP, systolic blood pressure; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides.

1.8 mg doses, respectively) than with the placebo (+0.23%) or rosiglitazone (-0.44%) groups ($P < 0.0001$). The estimated proportion of subjects treated with either liraglutide 1.2 mg or 1.8 mg reaching HbA_{1c} target was substantially greater compared with either placebo ($P < 0.0001$) or rosiglitazone ($P \leq 0.0003$), with more patients reaching HbA_{1c} < 7.0% with liraglutide 1.8 mg compared with 1.2 mg ($P = 0.018$). All doses of liraglutide decreased fasting plasma glucose more than did placebo ($P < 0.0001$), while only liraglutide 1.2 mg or 1.8 mg produced greater reductions than rosiglitazone. Changes in body weight were minor in all liraglutide and placebo groups, compared with the 2.1 kg increase in the rosiglitazone group. Reductions in the proinsulin-to-insulin ratio were greater with both liraglutide 1.2 mg and 1.8 mg compared with either rosiglitazone or placebo ($P \leq 0.02$). HOMA (β -cell function) increased with liraglutide (1.8 mg or 1.2 mg) compared with rosiglitazone ($P < 0.05$), while this increase was only different from placebo with liraglutide 1.2 mg ($P = 0.01$). Changes in blood pressure and heart rate were not significant among groups.

LEAD 2⁴⁸ was a 26-week, placebo-controlled, double-blind, five-arm, randomized trial testing the effect of three doses of liraglutide (0.6, 1.2, and 1.8 mg) added to metformin 1 g twice daily as compared with the same dose of metformin in combination with placebo or glimepiride 4 mg/day. In comparison with placebo, HbA_{1c} levels decreased significantly more with liraglutide 0.6 mg (-0.8%), 1.2 mg (-1.1%), and 1.8 mg (-1.1%). The HbA_{1c} target (7.0%) was achieved by significantly more subjects in the 1.8 mg liraglutide group than in the 1.2 mg liraglutide group (42.4% versus 35.3%, $P = 0.0265$). The decreases in fasting plasma glucose from baseline for the liraglutide groups (-1.1, -1.6, and 1.7 mmol/L for 0.6, 1.2, and 1.8 mg, respectively) were significantly greater than the increase observed for the placebo group (+0.4 mmol/L, $P < 0.0001$), but were similar to the decrease observed for the glimepiride group (-1.3 mmol/L). Weight

loss was dose-dependent in the liraglutide treatment groups (1.8 ± 0.2 , 2.6 ± 0.2 , and 2.8 ± 0.2 kg for 0.6, 1.2, and 1.8 mg, respectively) and was significantly different ($P < 0.0001$) from the weight gain in the glimepiride group (1.0 ± 0.2 kg). Weight losses in the 1.2 mg and 1.8 mg liraglutide groups were also significantly greater ($P \leq 0.01$) than the weight loss in the placebo group (1.5 ± 0.3 kg). Decreases in the proinsulin-to-insulin ratio from baseline for the liraglutide groups were comparable with those in the glimepiride group and were significantly different ($P < 0.0001$) from those in the placebo group. The liraglutide groups had improvements in HOMA (β -cell function) of 63, 70, and 71% for the 0.6, 1.2, and 1.8 mg liraglutide groups, respectively. The 1.2 mg and 1.8 mg liraglutide groups had significant reductions in systolic blood pressure of 2–3 mmHg compared with an increase of 0.4 mmHg observed in the glimepiride group (treatment difference compared with glimepiride: 1.2 mg liraglutide, -3.2 mmHg, $P = 0.0128$; 1.8 mg liraglutide, -2.7 mmHg, $P = 0.0467$).

An extension of the LEAD 2 trial with an 18-month open-label period where all patients were maintained on their randomized therapy was done to investigate treatment satisfaction obtained using a validated questionnaire.⁴⁹ All the liraglutide groups showed improved overall satisfaction from baseline, which was significantly greater than for metformin ($P < 0.05$), but comparable with glimepiride in combination with metformin. All the liraglutide groups were more satisfied with their “current treatment” and more likely to “continue” versus the metformin group after 26 and 78 weeks ($P < 0.05$). Moreover, the liraglutide 1.2 mg and 1.8 mg groups were “more likely to recommend to others” versus the metformin group ($P < 0.05$).

LEAD 3⁵⁰ was a 52-week randomized trial comparing liraglutide (0.8, 1.2, 1.8 mg) and glimepiride 8 mg/day. In comparison with glimepiride, HbA_{1c} levels decreased significantly more with liraglutide 1.2 mg (-0.33%,

$P = 0.0014$) and 1.8 mg (-0.62% , $P < 0.0001$). The reduction with liraglutide 1.8 mg was significantly greater than that with 1.2 mg (-0.29% , $P = 0.0046$). Participants previously treated with diet and exercise had greater decreases in HbA_{1c} than did those who switched from an oral antidiabetic drug to liraglutide. At the end of the study, 28% of participants treated with liraglutide 1.2 mg and 38% treated with liraglutide 1.8 mg reached the target HbA_{1c} of 6.5% or less, compared with 16% in those on glimepiride ($P = 0.0025$ and $P < 0.001$ for liraglutide 1.2 mg and 1.8 mg, respectively). Overall, compared with 28% in the glimepiride group, 43% of participants treated with liraglutide 1.2 mg ($P = 0.0007$) and 51% on liraglutide 1.8 mg ($P < 0.0001$) reached the target HbA_{1c} of less than 7%. A greater proportion of participants in the liraglutide groups achieved the fasting plasma glucose target (5.0–7.2 mmol/L) than in the glimepiride group (37.6% and 41.4% versus 22.2% for liraglutide 1.2 mg and 1.8 mg versus glimepiride group, respectively, $P \leq 0.0001$). Treatment with liraglutide was also associated with weight loss, whereas the glimepiride group presented weight gain. Insulin resistance (measured by HOMA) was reduced by 0.65% in the liraglutide 1.2 mg group and 1.35% in the 1.8 mg group, but increased in the glimepiride group ($P = 0.0249$ and $P = 0.0011$ for liraglutide 1.2 mg and 1.8 mg, respectively). The proinsulin-to-insulin ratio and β -cell function showed no significant differences between treatments.

The double-blind period was followed by an open-label, two-year extension, involving 73% of the patients who had completed the one-year follow-up. Results showed that the greater benefit of liraglutide on metabolic control and body weight as compared with glimepiride was maintained after two years, with a lower risk of hypoglycemia.⁵¹

Patient-reported outcome assessments were performed as part of the LEAD 3 trial.⁵² The battery of scales comprised 77 self-administered questions. Patient weight assessment was more favorable with liraglutide 1.8 mg ($P = 0.002$), and 52% were less likely to feel overweight. Mean weight concerns were less with liraglutide than with glimepiride ($P < 0.0001$ and $P < 0.001$ for 1.2 and 1.8 mg liraglutide, respectively). Mean mental and emotional health and general perceived health assessments improved more with liraglutide 1.8 mg than with glimepiride ($P = 0.012$ and $P = 0.033$, respectively).

LEAD 4⁵³ was a 26-week, placebo-controlled, double-blind, randomized, parallel-group trial testing the effect of two doses of liraglutide (1.2 and 1.8 mg) added to metformin 1 g twice daily and rosiglitazone 4 mg/day compared with the same dose of metformin and rosiglitazone in combination

with placebo. Mean HbA_{1c} levels decreased significantly more in the liraglutide groups than in the placebo group (-0.9% and -1.1% for liraglutide 1.2 and 1.8 mg, respectively, $P < 0.0001$). At the end of the study, 57.5% and 53.7% of subjects in the 1.2 and 1.8 mg liraglutide groups, respectively, had an HbA_{1c} $< 7\%$, compared with 28.1% in the placebo group, with 37.3% and 36.2%, respectively, reaching \leq HbA_{1c} of 6.5% compared with 14.4% on placebo. The decreases in fasting plasma glucose from baseline for the liraglutide groups (-2.2 mmol/L and -2.4 mmol/L for 1.2 mg and 1.8 mg liraglutide, respectively) were significantly greater than the decrease observed in the placebo group (-0.4 mmol/L, $P < 0.0001$). Weight loss was observed in the liraglutide-treated groups (1.0 ± 0.3 and 2.0 ± 0.3 kg from baseline for 1.2 mg and 1.8 mg liraglutide, respectively), and was significantly different ($P < 0.0001$) from the weight gain in the placebo group (0.6 ± 0.3 kg). The weight loss in the 1.8 mg liraglutide group was significantly greater than in the 1.2 mg liraglutide group ($P = 0.011$). The 1.2 and 1.8 mg liraglutide groups had significant reductions in mean systolic blood pressure compared with the placebo group (1.2 mg liraglutide $P < 0.0001$; 1.8 mg liraglutide $P = 0.0009$). Minor but statistically significant increases in pulse rate were observed in the liraglutide-treated groups versus placebo ($P = 0.0071$ and $P = 0.0001$, respectively, for 1.2 mg and 1.8 mg). The decrease in the proinsulin-to-insulin ratio and increase in C-peptide concentration from baseline for the liraglutide groups were significant ($P < 0.05$ for both) compared with the placebo group. Both liraglutide treatment groups had significant improvement in β -cell function ($P < 0.0001$ for both groups versus placebo). Insulin resistance (measured by HOMA) was reduced in all three treatment groups, but was not significantly different between groups.

LEAD 5⁵⁴ was a 26-week, randomized, placebo-controlled, double-blind, parallel-group trial testing the effect of 1.8 mg of liraglutide added to metformin 1 g twice daily plus glimepiride 2–4 mg/day in comparison with the same dose of metformin and glimepiride with placebo or insulin glargine. After 26 weeks of treatment, the HbA_{1c} reduction from baseline with liraglutide was 1.33%, 0.24% with placebo, and 1.09% with insulin glargine (treatment differences for liraglutide versus placebo -1.09% , $P < 0.0001$ and liraglutide versus insulin glargine -0.24% , $P = 0.0015$). The reduction in mean fasting plasma glucose in the liraglutide group, and the likelihood of achieving targets (5–7.2 mmol/L) was significantly superior compared with the placebo group ($P < 0.0001$) but not versus the insulin glargine group. The mean weight loss from baseline of 1.8 kg achieved in the liraglutide group was

significantly superior to that in the placebo group (weight difference of -1.39 kg, $P = 0.0001$). Weight increased by 1.6 kg with insulin glargine, resulting in a mean treatment difference of -3.43 kg, $P < 0.0001$. Overall, weight loss was independent of nausea, although in the very small number of patients with sustained nausea, there seemed to be a greater weight loss (-3.2 kg). The proinsulin-to-C-peptide ratio showed a significant improvement in the liraglutide group compared with the insulin glargine group ($P = 0.0019$) and the placebo group ($P < 0.0001$). A significant reduction in systolic blood pressure was observed with liraglutide (-4.0 mmHg) compared with insulin glargine (0.54 mmHg increase; treatment difference -4.51 mmHg, $P = 0.0001$), but not in comparison with placebo.

Blonde and Russell-Jones summarized the safety of liraglutide during LEAD 1–5 studies.⁵⁵ Throughout the trials, liraglutide was generally well tolerated; most adverse events reported were mild to moderate in severity. Gastrointestinal events were most frequently reported with liraglutide monotherapy and combination therapy and were often dose-related; 29.3% of patients receiving 1.8 mg liraglutide reported nausea. However, this symptom tended to decrease in frequency after four weeks in each trial. Serious adverse events were uncommon. In the LEAD 5 trial, patients treated with insulin glargine or placebo reported a 7% frequency of serious adverse events in comparison with 4% on liraglutide therapy. Few minor and major hypoglycemic episodes have been reported across the LEAD studies. As monotherapy, no major hypoglycemia incidents were reported, and 8% of patients treated with liraglutide 1.8 mg reported minor hypoglycemia (plasma glucose <3.1 mmol/L). Only one major hypoglycemic episode (blood glucose = 3.0 mmol/L) was reported when liraglutide was used in combination with glimepiride. No major hypoglycemia was reported when liraglutide was used in combination with metformin. The proportion of subjects experiencing minor hypoglycemia across a 26-week treatment period with liraglutide 1.8 mg in combination with glimepiride was 8.1%, significantly greater than the proportion of subjects on rosiglitazone in combination with glimepiride (4.3%, $P = 0.0065$). The incidence of minor hypoglycemia was lower when liraglutide was used in combination with metformin ($\sim 3\%$).

Antibodies to liraglutide were found in 9%–13% of subjects treated with liraglutide in the LEAD 1 study; 4.1% and 6.7% of subjects treated with 1.2 and 1.8 mg liraglutide, respectively, at the end of LEAD 4; and in 9.8% of patients in the liraglutide group in LEAD 5. No significant differences in calcitonin levels were found between the liraglutide groups

and comparators in the LEAD 2, 3, and 5 studies. There was a significant increase in calcitonin levels for the 1.2 mg liraglutide group versus placebo group ($P = 0.022$), but not with the 1.8 mg liraglutide group in the LEAD 4 study (although all levels were in the normal range).^{47,48,50,53,54}

LEAD 6 was the first study that compared two GLP-1 analogs.⁵⁶ This was a 26-week, randomized, open-label trial testing the effect of liraglutide 1.8 mg once daily versus exenatide 10 μ g twice daily in combination with metformin 1 g twice daily and/or glimepiride 2–4 mg/day. Patients treated with liraglutide showed a reduction in HbA_{1c} of 1.12%, compared with a reduction of 0.79% in the exenatide group ($P < 0.0001$), and more patients achieved an HbA_{1c} $< 7\%$ in the liraglutide group (54% versus 43%, respectively, $P = 0.0015$). Liraglutide caused a greater reduction in fasting plasma glucose (-1.61 mmol/l versus -0.60 mmol/L of exenatide, $P < 0.0001$). Weight loss was similar in the two groups, and was approximately 3 kg. Increases in fasting plasma insulin ($P = 0.0355$) and β -cell function ($P < 0.0001$) were significantly greater for the liraglutide group than for the exenatide group. Treatment differences for fasting C-peptide and proinsulin-to-insulin ratio were not significant. Fasting glucagon and blood pressure decreased with both treatments. Reduction of triglyceride ($P = 0.0485$) and free fatty acid ($P = 0.014$) values were significantly greater in the liraglutide group than in the exenatide group.

Despite an overall lower reporting of adverse events in the liraglutide group than the exenatide group, the liraglutide group had more serious (5.1% versus 2.6%) and severe (7.2% versus 4.7%) adverse events. The most frequent severe adverse events were dyspepsia in the liraglutide group and nausea in the exenatide group. Although the incidence of nausea was similar initially, it was less persistent with liraglutide. No major hypoglycemia occurred with liraglutide. The proportion of patients who had minor hypoglycemia was lower with liraglutide than with exenatide (26% versus 34%, respectively). Small decreases in calcitonin levels occurred during the trial in both groups. Heart rates increased slightly in both treatment groups, but were significantly greater for liraglutide ($P = 0.0012$).

After 26 weeks, patients continued into a nonrandomized 14-week extension;⁵⁷ all exenatide patients were switched to liraglutide 0.6 mg then escalated to 1.8 mg. Patients originally randomized to liraglutide 1.8 mg continued on this dose. Mean HbA_{1c} further decreased from 7.2% at week 26 to 6.9% at week 40 ($P < 0.0001$) after switching from exenatide to liraglutide, but remained similar with continued liraglutide (7.0%–6.9%). Further reductions in fasting plasma glucose,

body weight, and systolic blood pressure (all $P < 0.0001$) occurred, while the HOMA (β -cell function) increased ($P = 0.0001$) after switching from exenatide to liraglutide. In patients continuing liraglutide, reductions in fasting plasma glucose ($P = 0.0973$), body weight ($P = 0.0089$), and systolic blood pressure ($P = 0.0128$) occurred. Nausea and diarrhea occurred in 3.2% of patients switching from exenatide to liraglutide and in 1.5% of those continuing liraglutide. One major hypoglycemic episode occurred in a patient continuing liraglutide. Calcitonin levels remained at the lower level of the normal range and did not differ between the groups. No cases of medullary thyroid carcinoma or pancreatitis were reported during the extension.

Other safety issues

In a two-year mouse and rat carcinogenicity study, liraglutide resulted in treatment-related proliferative changes in C-cells of the thyroid gland. These changes ranged from focal hyperplasia to benign and malignant neoplasia, and were dose-dependent.⁵⁸ The clinical relevance of this finding is unknown. Moreover, five cases of papillary thyroid carcinoma have been reported in clinical trials in patients treated with liraglutide compared with one case in a comparator treatment group.⁵⁹

According to Novo Nordisk,⁶⁰ because of the uncertain relevance of the rodent C-cell tumor findings in humans, liraglutide should be prescribed only to patients for whom the potential benefits are considered to outweigh the potential risks. Liraglutide is contraindicated in patients with a personal or family history of medullary thyroid carcinoma and in patients with multiple endocrine neoplasia syndrome type 2. Based on the findings in rodents, monitoring with serum calcitonin or thyroid ultrasound was performed during clinical trials, but this may have increased the number of unnecessary thyroid surgeries. Liraglutide appears to be associated with a risk of acute pancreatitis, with seven cases in 3900 patients receiving liraglutide versus one case in a patient taking another diabetic drug.⁶¹

Conclusion

All liraglutide trials have demonstrated a consistent and sustained reduction in HbA_{1c} and fasting plasma glucose when the drug was used as monotherapy or added to other antidiabetic therapy. The advantages are its incretin effect, and the convenience of once-daily injection. The presence of antibodies was observed, but there were no indications in any of the liraglutide studies that antibody formation

compromised efficacy. Patients should be counseled regarding risk and symptoms of thyroid tumors and acute pancreatitis. Liraglutide will acquire an important role, not only in T2DM treatment, but also in preservation of β -cell function, if the data thus far are confirmed by long-term studies and post-marketing surveillance. Furthermore, the reduction in HbA_{1c} associated with the beneficial effects of liraglutide in insulin resistance, systolic blood pressure, and weight loss, as shown by the LEAD studies, could represent a significant probability of prevention of diabetic complications and may reduce atherosclerotic cardiovascular events.

Disclosure

The authors report no conflicts of interest in this work.

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