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Liraglutide

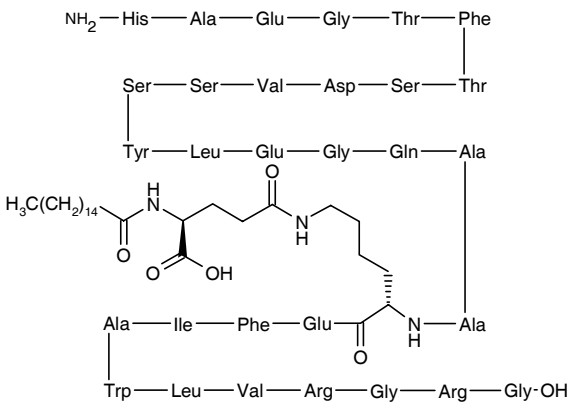
Rec INN; USAN

GLP-1 Receptor Agonist
Treatment of Type 2 Diabetes
Treatment of Obesity

NN-2211
NNC-90-1170

[*N*$^{\varepsilon}$-[(*N*$^{\alpha}$-Hexadecanoyl)-γ-L-Glu]-L-Lys^{26},L-Arg^{34}]-GLP-1(7-37)

L-Histidyl-L-alanyl-L-glutamyl-glycyl-L-threonyl-L-phenylalanyl-L-threonyl-L-seryl-L-aspartyl-L-valyl-L-seryl-L-seryl-L-tyrosyl-L-leucyl-L-glutamyl-glycyl-L-glutaminyl-L-alanyl-L-alanyl-*N*$^{\varepsilon}$-(*N*$^{\alpha}$-hexadecanoyl-γ-L-glutamyl)-L-lysyl-L-glutamyl-L-phenylalanyl-L-isoleucyl-L-alanyl-L-tryptophyl-L-leucyl-L-valyl-L-arginyl-glycyl-L-arginyl-glycine



$C_{172}H_{265}N_{43}O_{51}$
Mol wt: 3751.2037

CAS: 204656-20-2

EN: 288055

Abstract

Liraglutide (NN-2211), a novel glucagon-like peptide-1 (GLP-1) analogue for once-daily s.c. injection, is in advanced clinical phase III development for type 2 diabetes therapy. It is a GLP-1 derivative with two amino acid changes and a fatty acid side-chain. The effects of liraglutide are mediated exclusively by activation of the GLP-1 receptor. It reduces hemoglobin A1c (HbA1c), fasting and postprandial glucose by glucose-dependent stimulation of insulin secretion and inhibition of glucagon secretion, both as monotherapy and in combination with oral antidiabetic drugs. Weight loss has also been observed in obese patients and indirect measures show a possible improvement in β-cell function. Liraglutide does not cause hypoglycemia. The main adverse events are nausea and diarrhea at the beginning of treatment, which are mild to moderate and transient. The formation of anti-liraglutide antibodies has not been observed.

Background

Type 2 diabetes is a disorder of epidemic dimensions and the concomitant complications of macro- and microvascular disease are rising dramatically. Estimates indicate that the total number of people with diabetes will increase to 370 million worldwide by the year 2030 (1). Lifestyle changes with less physical activity and an overabundance of high-calorie food may lead to diabetes in subjects with a genetic predisposition to insulin resistance and other pathophysiological characteristics of type 2 diabetes (2).

Type 2 diabetes is characterized by disease progression due to a loss of islet function and regulation. Hyperglycemia, free fatty acids, cytokines, adipokines and toxic metabolic products perpetuate a loss of β-cell function and β-cell mass (3). Furthermore, type 2 diabetes is also characterized by an excessive secretion of glucagon by α-cells, worsening glucose homeostasis even further. Type 2 diabetes is therefore described as a dual defect of islet cell dysfunction (pancreatic α- and β-cells) and insulin resistance (4, 5). Obesity is another increasing problem leading to type 2 diabetes and concomitant comorbidity (6).

Current treatment options for type 2 diabetes are not satisfactory since they do not halt disease progression and do not address the entire pathophysiology. In clinical use, secondary failure of oral antidiabetic drugs is observed. On the other hand, insulin therapy can lower hyperglycemia, but at the risk of hypoglycemia and weight gain (7-9). Since hemoglobin A1c (HbA1c) goals are not reached in a significant proportion of patients, more rigorous and effective treatment strategies have to be implemented in order to prevent vascular complications (10), and there is a need for novel treatment options with a potentially superior profile.

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Glucagon-like peptide-1 (GLP-1) receptor agonists are the first agents to address the dual islet dysfunction, as well as obesity. Exenatide (Byetta®; Amylin, Lilly), a synthetic GLP-1 receptor agonist identical to the naturally occurring peptide exendin-4, has been approved for type 2 diabetes therapy in combination with metformin and/or sulfonylureas (11). Exenatide injected twice daily significantly and persistently lowers HbA1c and body weight in obese type 2 diabetic patients not sufficiently controlled with oral antidiabetic drugs (11-15).

The incretin hormones GLP-1 and gastric inhibitory polypeptide (GIP) stimulate insulin secretion under postprandial hyperglycemic conditions (4). GLP-1 has additional physiological effects that are attractive for restoring the metabolic defects present in type 2 diabetes. GLP-1 suppresses glucagon secretion, which is often found to be elevated and not suppressed under hyperglycemia. GLP-1 also slows gastric emptying and promotes satiety via central effects in hypothalamic nuclei (4, 16). Animal data and studies in isolated islets show an increase in islet cell mass and an improvement in islet cell function after treatment with GLP-1 (17). In man, exogenous GLP-1 can normalize plasma glucose in type 2 diabetes (18). Due to the action of dipeptidyl-peptidase IV (DPP IV), the biological half-life of exogenous GLP-1 is only 1-2 min, and treatment with native GLP-1 is therefore not feasible. In order to take advantage of GLP-1 effects, long-acting GLP-1 analogues, or "incretin mimetics", have been developed as an injectable therapy. The other alternative is the inhibition of the degrading enzyme DPP IV using orally active DPP IV inhibitors (18).

Preclinical Pharmacology

Liraglutide (NN-2211) is a long-acting GLP-1 analogue with full agonist activity at the human GLP-1 receptor. It has two modifications in the amino acid sequence of native GLP-1 involving an amino acid substitution (replacement of the naturally occurring lysine with an arginine in position 34) and attachment of a C16 acyl chain via a glutamoyl spacer to the lysine residue in position 26 of the peptide chain (Fig. 1). Liraglutide is stable towards enzymatic degradation by DPP IV due to the formation of micelles and binding to albumin (19).

In animal studies involving diabetic rodent models, liraglutide was shown to increase β-cell mass. Liraglutide lowers blood glucose, body weight and food intake in a broad selection of animal models (20-24).

Pharmacokinetics and Metabolism

Following once-daily s.c. injection in healthy volunteers, liraglutide is characterized by slow absorption with a time to peak plasma concentrations (t_{max}) of 10-14 h and a half-life of 11-13 h (Fig. 2) (19). Neither gender nor age influenced the pharmacokinetics of liraglutide in clinical studies (25, 26).

Clinical Studies

In patients with type 2 diabetes, liraglutide stimulates insulin secretion in a glucose-dependent manner and suppresses glucagon secretion, and it also slows gastric

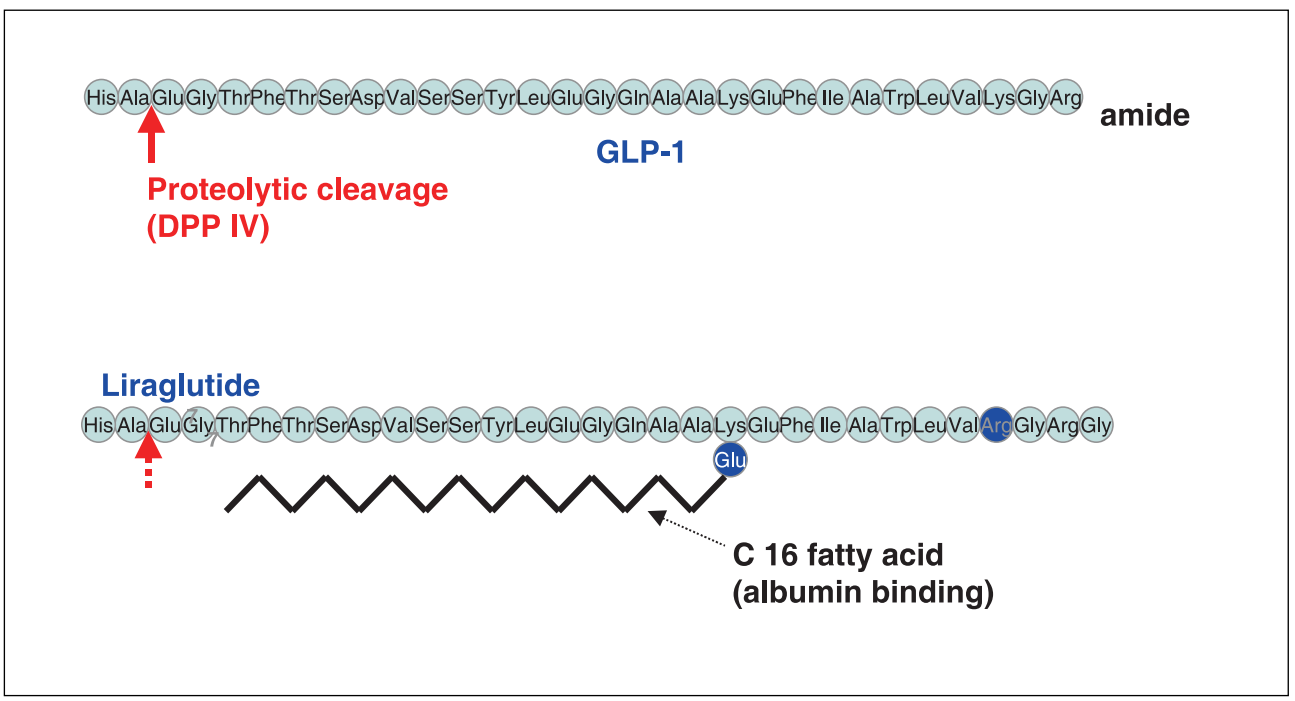

Fig. 1. Schematic structure of GLP-1 (top) and liraglutide (bottom). The amino acids are depicted as circles with the corresponding three-letter abbreviation. The changes in the amino acid sequence are highlighted in dark. The fatty acid side-chain is also depicted, as well as the cleavage site by the enzyme dipeptidyl-peptidase IV (DPP IV).

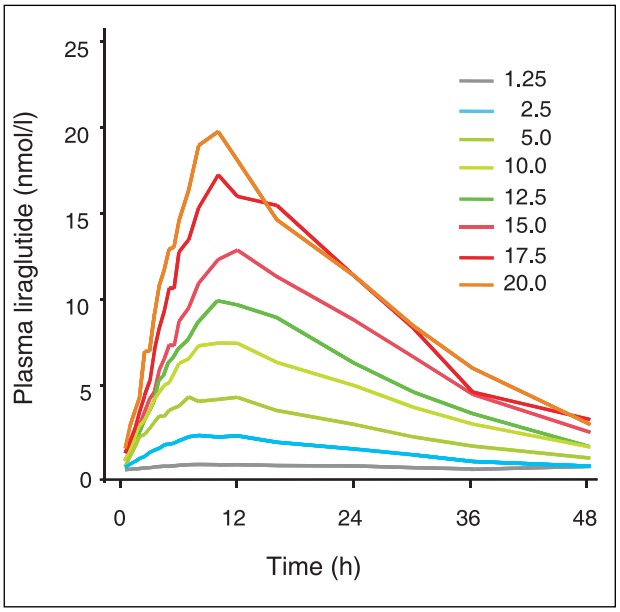

Fig. 2. Pharmacokinetic profile of liraglutide. Different doses of liraglutide (μg/kg body weight) were given as single s.c. bolus injections. The plasma concentrations of liraglutide over time are shown. Modified according to Ref. 44.

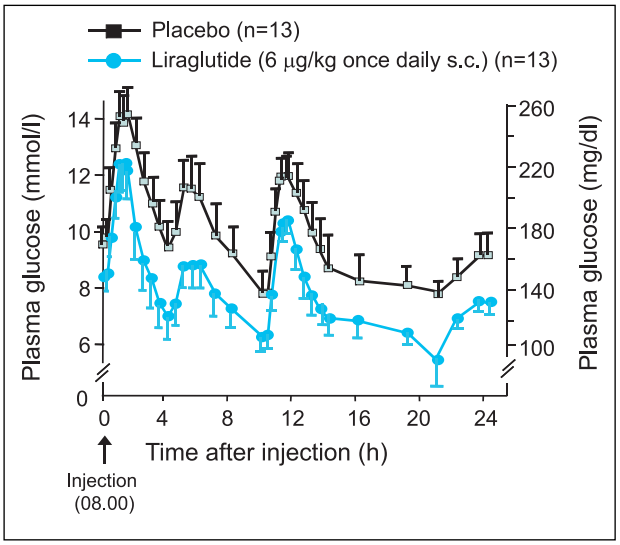

Fig. 3. Liraglutide lowers plasma glucose in type 2 diabetes after once-daily injection. Liraglutide (6 μg/kg) or placebo was given s.c. once daily in the morning in a double-blind, placebo-controlled, crossover study in 13 patients with type 2 diabetes. Plasma glucose over time is shown. Modified according to Ref. 26.

emptying. In patients on diet or oral antidiabetic treatment as monotherapy, liraglutide given once daily significantly lowered fasting plasma glucose concentrations, with a low risk for hypoglycemia, and improved parameters of β-cell function (Figs. 3 and 4) (27-31). Under hypoglycemic conditions, counterregulation by glucagon is not affected by liraglutide injections and it shows no insulinotropic action. Liraglutide treatment leads to a loss of body weight in obese type 2 diabetic subjects. No clinically significant drug interactions related to inhibition or induction of cytochrome P-450 have been observed with liraglutide (31). In patients with moderate renal insufficiency (creatinine clearance > 30-< 50 ml/min) or end-stage renal disease on dialysis, liraglutide does not seem to accumulate and does not appear to be associated with an increased risk of adverse events (32).

In a randomized, double-blind study, the dose-response relationship of liraglutide was compared to glimepiride in 190 patients with type 2 diabetes not well controlled on diet or oral antidiabetic agents. Oral antidiabetic agents were washed out at the beginning of the study and the patients were assigned to six treatment arms (fixed-dose groups of liraglutide 0.045-0.75 mg, placebo or open-label glimepiride 1-4 mg). The primary endpoint was HbA1c after 12 weeks; secondary endpoints were fasting serum glucose, fasting C-peptide, fasting glucagon, fasting insulin, β-cell function, body weight, adverse events and hypoglycemic episodes. The baseline HbA1c was 7.6% in all treatment groups and decreased maximally by 0.75% in the liraglutide 0.75 mg group ($p < 0.0001$) and fasting plasma glucose (FPG) decreased by 32 mg/dl (1.8 mM) compared to placebo. Liraglutide lowered HbA1c dose-dependently. Body weight decreased by 1.2 kg in the liraglutide 0.45 mg group compared with placebo (27).

Another randomized, double-blind, parallel-group trial including 165 patients with type 2 diabetes evaluated higher doses of liraglutide (0.65, 1.25 or 1.9 mg) over 14 weeks. In this trial, liraglutide lowered FPG concentrations by 49 mg/dl (2.7 mM) on 0.65 mg once daily and by 61 mg/dl (3.4 mM) on 1.25 and 1.90 mg liraglutide once daily compared to placebo. All three doses of liraglutide lowered fasting and postprandial blood glucose levels. Interestingly, on the two higher doses of liraglutide (1.25 and 1.9 mg), a decrease in HbA1c of up to 1.7% was observed, corresponding to almost 50% of the patients reaching the HbA1c goal of < 7% as defined by the American Diabetes Association (ADA), compared to only 5% of patients in the placebo group (Fig. 5). The highest dose of liraglutide (1.9 mg) provoked a weight loss of 2.99 kg from baseline compared to 1.77 kg with placebo (Fig. 6) (33).

Parameters of β-cell function were evaluated in a subgroup of 28 patients with an insulin-modified, frequently sampled intravenous glucose tolerance test (FSIGT) and a hyperglycemic clamp with arginine, and compared to the results in untreated control subjects. The two highest doses of liraglutide significantly increased the maximal β-cell secretory capacity compared to placebo, by 114% and 97% for 1.25 and 1.90 mg, respectively. The same doses significantly increased the first-phase insulin secretion by 124% and 107%, respectively. The second-phase insulin secretion increased at the dose of 1.25 mg, but this did not reach statistical significance on the highest dose. Additionally, a significant reduction in systolic blood pressure of 3-7 mmHg was observed in liraglutide-treated patients (31).

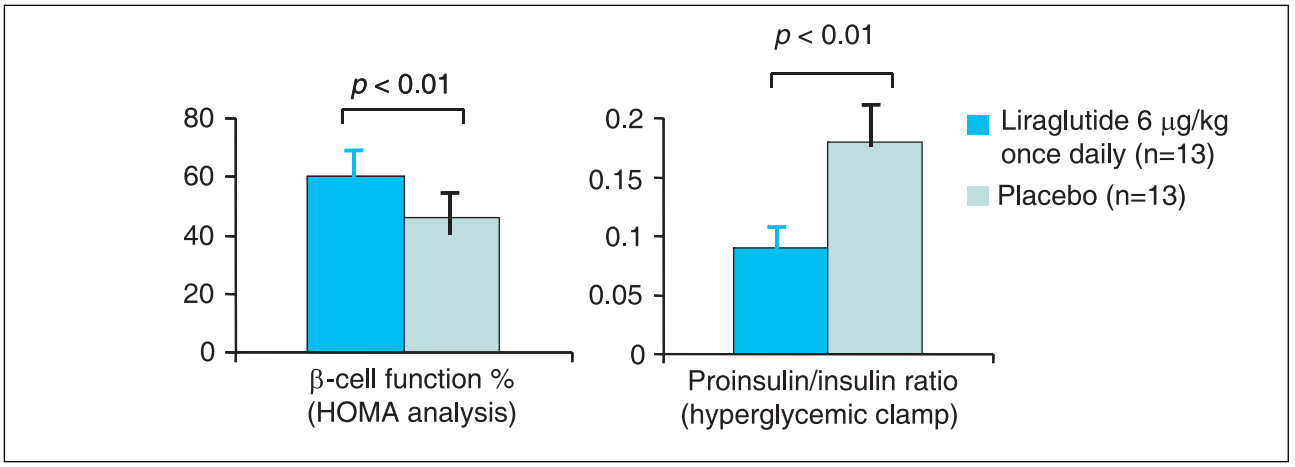

Fig. 4. Liraglutide improves β-cell function in patients with type 2 diabetes. In this study, 13 patients with type 2 diabetes received 1 week of treatment with placebo and 1 week of treatment with liraglutide in a double-blind, crossover design. Relative to placebo, liraglutide significantly increased insulin (area under the curve [AUC] and max), insulin secretion ratio (AUC and max) and disposition index, while significantly decreasing the proinsulin:insulin ratio. Thus, liraglutide treatment markedly increases β-cell function (as represented by the first- and second-phase insulin response) and enhances β-cell compensation for insulin resistance (as demonstrated by the disposition index). Data are mean ± SE. Modified according to Ref. 26.

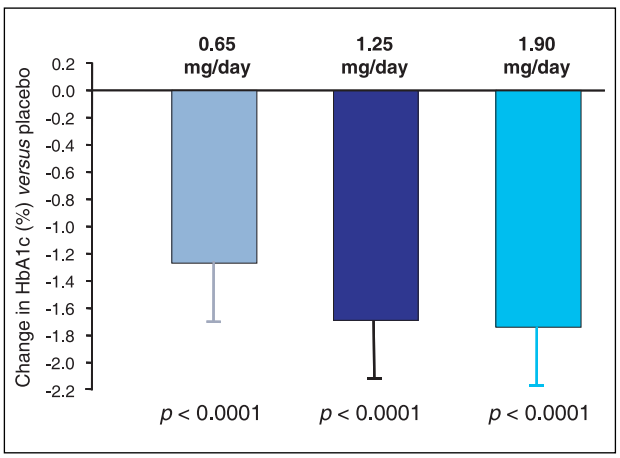

Fig. 5. Liraglutide monotherapy lowers HbA1c dose-dependently in type 2 diabetes. This study compared liraglutide monotherapy with placebo in 163 patients with type 2 diabetes. After 14 weeks of treatment, mean HbA1c increased on placebo (0.29%), but decreased in all liraglutide treatment groups. A significant improvement in HbA1c in all liraglutide groups compared with the placebo group ($p < 0.0001$) was observed. Modified according to Ref. 33.

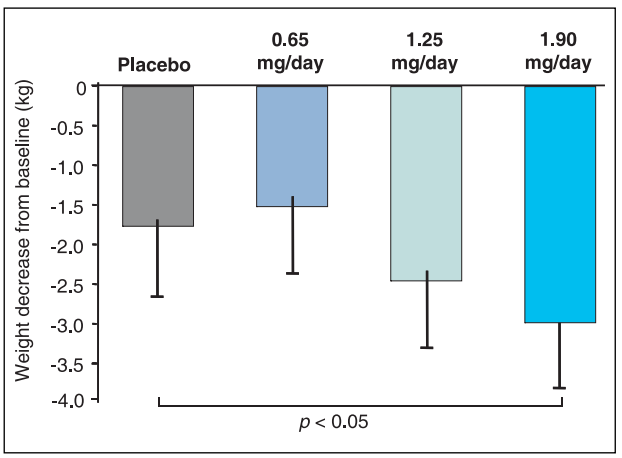

Fig. 6. Liraglutide lowers body weight dose-dependently. This 14-week study compared liraglutide monotherapy with placebo in 163 patients with type 2 diabetes. At study end, weight had decreased in all groups, but to a greater extent with liraglutide 1.9 mg/day compared to placebo. The estimated reduction in weight from baseline was 2.99 kg with 1.9 mg/day liraglutide *vs.* 1.77 kg with placebo. The difference between these groups (1.21 kg) was significant ($p < 0.05$). Modified according to Ref. 33.

Recently, data from a small phase II trial (26) were re-analyzed to investigate markers of β-cell function under normal living conditions (34). Liraglutide treatment significantly enhanced β-cell function evaluated under conditions of normal living and improvement was related to improvement in glucose levels.

The clinical efficacy and safety of liraglutide in combination with metformin were assessed and compared to a combination of metformin and glimepiride (30). A total of 144 type 2 diabetic subjects on metformin (1000 mg b.i.d.) were randomized in double-blind fashion to 5 weeks of treatment with metformin plus liraglutide, liraglutide or metformin, or in open-label fashion to metformin plus glimepiride. The dose of liraglutide was increased weekly from 0.5 to 2 mg once daily. The primary endpoints were changes in HbA1c and FPG. Liraglutide added to metformin monotherapy was associated with a significant reduction in FPG of 70 mg/dl (3.9 mM) and in HbA1c of 0.8%. The combination of metformin and liraglutide was significantly more effective than the traditional combination of metformin plus glimepiride (Fig. 7). In addition, the body weight reduction (2.9 kg) was significantly better in the metformin plus liraglutide group compared to the metformin plus glimepiride group.

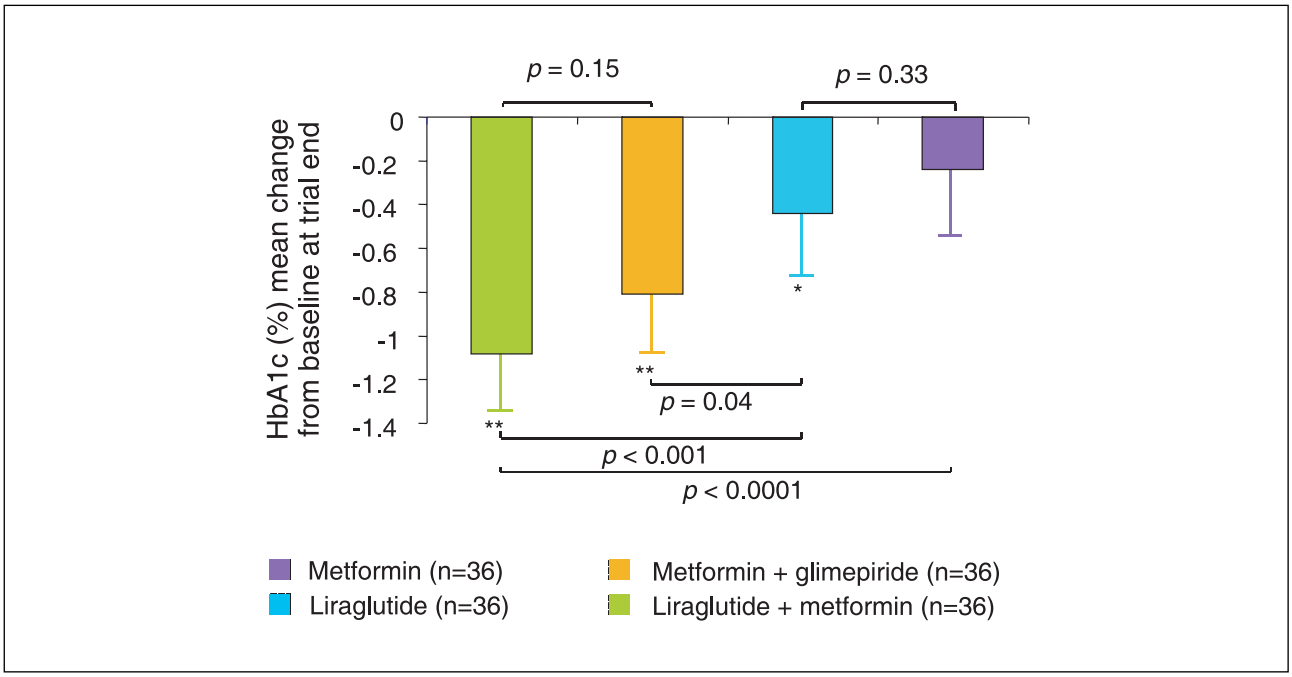

Fig. 7. Addition of liraglutide to metformin further decreases HbA1c. In this study, following 2-6 weeks of metformin dose titration (up to 1 g b.i.d.), 144 patients with type 2 diabetes were randomized to treatment with liraglutide monotherapy, liraglutide + metformin, metformin monotherapy or metformin + glimepiride (n=36 for each group) for 5 weeks. Liraglutide was initiated at 0.5 mg once daily and increased by 0.5 mg every week if FPG was > 6.0 mmol/l, up to a maximum of 2 mg/day (if tolerated). Glimepiride was initiated at 2 mg and increased to 4 mg in 1-mg increments during the first 2 weeks if FPG was > 6.0 mmol/l. Metformin was continued at the run-in dose. Following 5 weeks of treatment, HbA1c was significantly reduced relative to baseline in all groups except the group receiving metformin. Furthermore, combination therapy with liraglutide + metformin resulted in significantly greater reductions in HbA1c than liraglutide or metformin monotherapy alone. Modified according to Ref. 30.

A vast study program of phase III clinical trials was conducted to investigate the efficacy and safety of liraglutide as monotherapy or as part of combination therapies and comparing the effects of liraglutide to established forms of type 2 diabetes therapy (LEAD studies [Liraglutide Effect and Action in Diabetes]) (35-39). Results from the LEAD studies have been presented recently in press releases (40-43). The LEAD-1 and -2 studies evaluated liraglutide as add-on therapy to an existing oral antidiabetic monotherapy, the LEAD-3 study compared liraglutide and glimepiride monotherapy, and the LEAD-4 and -5 studies investigated the efficacy and safety of liraglutide when added to an existing oral combination therapy of two different drugs. The LEAD-1 study compared the efficacy and safety of liraglutide added to ongoing therapy with the sulfonylurea glimepiride. A total of 1,026 patients were included in this 6-month trial with a placebo arm (glimepiride only) and an active comparator arm (rosiglitazone). The LEAD-2 study had the same design, duration and number of patients included. In this study, however, the efficacy and safety of liraglutide were investigated as add-on therapy to metformin. The active comparator drug was glimepiride. LEAD-3 compared the effects of liraglutide *versus* glimepiride on glycemic control (change in HbA1c) after 1 year of monotherapy in 702 patients with type 2 diabetes. The LEAD-4 study investigated the efficacy and safety of liraglutide daily compared to placebo as add-on therapy in 492 patients treated with a stable-dose combination of metformin and rosiglitazone for 6 months. LEAD-5 assessed a combination of metformin and glimepiride as baseline therapy. Liraglutide as add-on therapy was tested against placebo or insulin glargine in this 6-month study in a total of 570 patients.

The average HbA1c at baseline in the LEAD-1 and LEAD-2 trials was approximately 8.5% and the body weight of the patients was 80-90 kg. The primary endpoint of all LEAD studies is HbA1c, and secondary endpoints are FPG and glucose profiles, body weight, safety and tolerability parameters and markers of β-cell function, as well as cardiovascular risk parameters. In the LEAD-1 study, liraglutide improved glucose control significantly better than rosiglitazone. Liraglutide treatment resulted in approximately 40% of patients reaching the ADA goal of HbA1c < 7% at study completion. In the subgroup of patients who had previously been treated with only a single oral antidiabetic drug, liraglutide treatment resulted in over 50% of patients reaching this goal. The average HbA1c reduction was in the range of 1-1.5%. As would be expected from a study in which all patients received glimepiride treatment, hypoglycemia related to the degree of blood glucose control was observed in all study arms.

In the LEAD-2 study, liraglutide improved HbA1c similarly to glimepiride. At the highest dose of liraglutide, more than 40% of patients achieved the HbA1c target of 7%. Among patients previously treated with a single oral antidiabetic drug, close to 65% of the patients on this dose reached this target, corresponding to an HbA1c reduction of 1-1.5%. Patients on liraglutide experienced hypoglycemia rates similar to placebo, in contrast with the glimepiride-treated group where hypoglycemia occurred in a larger number of patients (40).

In LEAD-4, treatment with liraglutide in combination with metformin and rosiglitazone in 533 patients resulted in more than 50% of the patients in the liraglutide-treated group reaching an HbA1c of < 7% and over 35% of patients achieved an HbA1c of < 6.5%. The HbA1c reduction achieved in the liraglutide-treated group was close to 1.5% compared to baseline. At the end of the LEAD studies, a weight reduction of 2-4 kg in favor of liraglutide was observed compared to rosiglitazone and glimepiride (40, 41).

LEAD-5 showed better blood glucose control when liraglutide was added to an existing oral therapy with metformin and glimepiride in comparison to the addition of insulin glargine. The HbA1c reduction was comparable to that observed in the other LEAD studies. Compared to insulin glargine, liraglutide caused a significant weight loss and the rate of hypoglycemic events was lower than in insulin glargine-treated patients (42).

In the LEAD-3 trial, liraglutide was associated with significantly better glucose control than glimepiride, liraglutide-treated patients showing a drop in HbA1c of about 1-1.5%; the ADA goal of HbA1c < 7% was reached by over 50% of the patients on 8 mg liraglutide. Liraglutide was associated with fewer hypoglycemic events compared to glimepiride and it also significantly reduced body weight and systolic blood pressure compared to glimepiride (34).

So far, in all clinical trials with liraglutide hypoglycemic events have been rare and the incidence of hypoglycemic episodes was similar to in patients on metformin or placebo. No major hypoglycemic episodes (defined as hypoglycemic episodes requiring medical assistance) have been reported in any subject treated with liraglutide (Table I) (27-31, 33, 40-43).

The most frequently reported adverse events during liraglutide treatment were gastrointestinal in nature, corresponding to GLP-1 receptor activation. Gradual dose escalation of liraglutide successfully reduced the proportion of subjects experiencing dose-limiting nausea, as has also been observed with other GLP-1 receptor agonists (11). Gastrointestinal complaints often occurred within the first week of treatment, diarrhea and nausea being the most frequent. The majority of subjects reported adverse events of mild to moderate severity (26, 27, 30, 33). With a high dose of 1.9 mg/day liraglutide, the most frequent single event was diarrhea in approximately 20% of the liraglutide-treated patients compared to 12.5% of the placebo-treated patients. Transient, mild nausea was reported in up to 10% of the liraglutide-treated subjects compared to 3% of the placebo-treated subjects (33). In the LEAD studies, liraglutide was well tolerated in combination with glimepiride or metformin. The most frequently reported adverse event during liraglutide treatment was nausea, reported by 5-20% of patients receiving liraglutide in combination with glimepiride and metformin. In the LEAD-4 study, nausea was reported by around 30-40% of the subjects, with frequency decreasing over time. A low rate of hypoglycemic events was reported, comparable to the placebo-treated patients. So far, no anti-liraglutide antibodies have been detected in clinical studies.

Conclusions

The therapeutic principle of GLP-1 adds a completely novel and attractive perspective to diabetes therapy. The multimodal actions, including glucose-dependent stimulation of insulin secretion, the glucagonostatic effect, slowing of gastric emptying, as well as effects on appetite regulation and the potential to improve β-cell function, are very promising. The most exciting aspect is the possibility that such compounds –perhaps especially because of their trophic effects on pancreatic β-cells– may halt the progression of the disease associated with conventional treatment options.

Table I: Hypoglycemia associated with liraglutide treatment as monotherapy and in combination with metformin.

	Liraglutide (0.045-2 mg once daily) n=347	Glimepiride (1-4 mg) n=26	Metformin (1 g b.i.d.) n=70	Liraglutide (0.5-2 mg once daily) + Metformin (up to 1 g b.i.d.) n=36
Minor events (< 2.8 mmol/l [50 mg/dl])				
Madsbad *et al.* (27)	1%	15%	–	–
Feinglos *et al.* (28)	3%	–	6%	–
Nauck *et al.* (30)	0%	–	0%	0%
Symptoms only				
Madsbad *et al.* (27)	5%	19%	–	–
Feinglos *et al.* (28)	7%	–	6%	–
Nauck *et al.* (30)	0%	–	0%	3%

No major hypoglycemic events were reported. Minor hypoglycemic events were defined as plasma glucose of < 50 mg/dl (2.8 mM). Data from Refs. 27, 28, 30.

Clinical studies with liraglutide have demonstrated an improvement in HbA1c and FPG, weight reduction and improved β-cell function parameters in patients with type 2 diabetes. Compared to the currently available incretin mimetic exenatide which must be administered twice daily, liraglutide is a once-daily GLP-1 analogue. In comparison to exenatide, liraglutide was associated with a more effective lowering of FPG and postprandial glucose concentrations under the conditions of the studies published so far. Comparing efficacy data on glycemic parameters between insulin glargine as add-on therapy to an existing oral antidiabetic treatment plus add-on liraglutide, liraglutide proved superior to insulin glargine in terms of not only the glycemic parameters, but also body weight and the incidence of hypoglycemic events. The exact indications for liraglutide in type 2 diabetes need to be defined and the ongoing clinical study program (LEAD studies) is generating clinical data for these decisions. These studies will also provide more data on the effects of liraglutide on disease progression in type 2 diabetes.

Source

Novo Nordisk A/S (DK).

Online links

Subscribers to the on-line version of *Drugs of the Future* and/or Integrity® can access the animation: GLP-1 and DPP IV as Therapeutic Targets for Type 2 Diabetes and Obesity.

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