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Liraglutide: A Molecule for Treatment of Type II Diabetes Mellitus

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ABSTRACT

Type 2 diabetes mellitus is a common chronic disease that causes significant morbidity and mortality worldwide. Currently available antidiabetic agents work by different mechanisms to lower blood glucose levels. Available treatments (such as metformin, sulfonylureas, glitazones, and insulin) have proven unsatisfactory in producing a long-lasting impact on glycemic control. In addition, most of these treatments have undesirable side effects such as weight gain and hypoglycemia. As a result, exploring new treatment targets and new therapies is mandatory in order to treat this condition. The incretin pathway, in particular glucagon-like peptide (GLP-1), plays an important pathological role in the development of T2DM, and treatments targeting the incretin system have recently become available. The actions of GLP-1 include (a) a stimulation of insulin secretion in a glucose-dependent manner, (b) a suppression of glucagon, (c) a reduction in appetite and food intake, (d) a deceleration of gastric emptying, (e) a stimulation of ß-cell neogenesis, growth and differentiation in animal and tissue culture experiments. Intravenous GLP-1 can normalize and subcutaneous GLP-1 can significantly lower plasma glucose in the majority of patients with Type 2 diabetes. Current data suggest that liraglutide significant reductions in fasting and postprandial plasma glucose and hemoglobin A1c (HbA1c). Liraglutide is well tolerated and does not increase hypoglycemia. Liraglutide, a GLP-1 analog, offers a novel treatment option for patients with type 2 diabetes mellitus.

Keywords: liraglutide, GLP – 1, Type II Diabetes Mellitus, Incretin based therapies

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INTRODUCTION

It was recognized by Himsworth in 1930s that two types of diabetes mellitus exist. One due to insufficiency of insulin (type 1); the other due to resistance to the action of insulin (type 2) [1]. Type II diabetes mellitus (T2DM) is the most common endocrine disorder worldwide [2], characterized by fasting and postprandial hyperglycemia and relative insulin insufficiency. Untreated hyperglycemia may cause long-term microvascular and macrovascular complications, such as nephropathy, neuropathy, retinopathy, and atherosclerosis and is associated with co morbidities, such as obesity, hypertension, hyperlipidemia (increased VLDL, triglycerides and decreased HDL cholesterol), and cardiovascular disease, which taken together, comprise the 'Metabolic Syndrome' [3]. In 2007, type 2 diabetes represents a major public health issue all over the world, becoming a "diabetes epidemic" as stated by Zimmet. No country escapes the diabetes invasion [4]. According to International Diabetes Federation (IDF) the enormity of the T2DM epidemic, Disease now affects a staggering 246 million people worldwide, with 46% of all those affected in the 40-59 age group and the total number of people living with diabetes will skyrocket to 380 million within 20 years if nothing is done [3]. Obesity, mainly when fat is distributed largely at the abdominal level is the main risk factor for T2DM [4]. For T2DM patients, excess weight can increase the risk of mortality; up to 8-fold for those with weight >40% above ideal target weight [5]. Much of the current crisis stems from our modern lifestyle with the abundance of high calorie foods along with lowered energy expenditure because of the wide availability of cars, TV watching, fewer outside activities, etc. Also, the worldwide trend of developing societies shifting away from an agrarian existence to city living and less physically demanding office and factory jobs also is taking its toll [6]. The natural history of diabetes usually begins with obesity leading to insulin resistance which in turn promotes a state of compensatory hyperinsulinemia leading to other adverse sequelae [7]. Initially, normoglycemia is maintained because of compensatory increase in insulin secretion by the ß-cell. Ultimately insulin secretion and insulin concentration fall leading to increased hepatic glucose production and overt diabetes. Beta-cell function continues to decline in the presence of continued insulin resistance making treatment complex and achievement of therapeutic targets difficult [8]. Hence, the failure of ß-cells to secrete sufficient insulin to overcome insulin resistant (IR) (i.e., ß-cell dysfunction) is the crucial step in the development and progression of T2DM. In addition to ß-cell dysfunction, patients with T2DM have α-cell dysfunction, which manifests as elevated glucagon secretion in the presence of hyperglycemia. Based on the current understanding of the pathophysiology of T2DM, multiple pharmacological and nonpharmacological interventions have been developed over the past five decades to improve glycemic control and slow disease progression [9]. However, gradual loss in drug efficacy over time due to progressive deterioration in beta-cell function is the main limitation as most of the observed initial improvements in glycemic control are not sustained [2]. Furthermore, most of these treatments have undesired side effects: sulfonylureas (SUs) increase insulin secretion, but are associated with hypoglycemia and weight gain; metformin reduces hepatic glucose output, is weight neutral, and is not associated with hypoglycemia, but has a relatively high frequency of gastrointestinal side effects; thiazolidinediones (TZDs) improve ß-cell function and reduce IR, but are associated with weight gain and can cause peripheral edema; meglitinides improve insulin secretion from ß-cells, but increases the incidence of hypoglycemia and weight gain compared with metformin; finally, insulin therapy produces sustainable glycosylated hemoglobin A1c (HbA1c) reductions and might improve ß-cell function, but causes hypoglycemia and weight gain. Hence, interventions that can slow and/or reverse ß-cell decline, which result in weight loss and do not result in hypoglycemia, might be expected to have a significant sustained impact in patients with T2DM. Incretin-based therapies are new class of antidiabetic medication that may address some of the abovementioned shortfalls of current treatments [9].The major advantages of this class of drugs are that they are generally well tolerated, and that the risk of hypoglycemia is less than that of traditional diabetes medication. A further benefit is a neutral, or even reductive, effect on body weight [2].

Treatment of T2DM with incretin based therapies

The increase in plasma levels of insulin following oral administration of glucose exceeds that seen after intravenous glucose administration when glucose levels during the two conditions are matched. This is defined as the incretin effect, which is attributed to the intestinal hormones which are released after oral glucose and which augment insulin secretion. Two gut derived peptides, glucagon like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) account for over half the incretin effect after a meal [10]. Type 2 diabetes is due to a combination of impaired release of GLP-1 and defective action of GIP. Both GIP and GLP-1 stimulate insulin secretion in a glucose-dependent manner, which is the main basis of the incretin effect.

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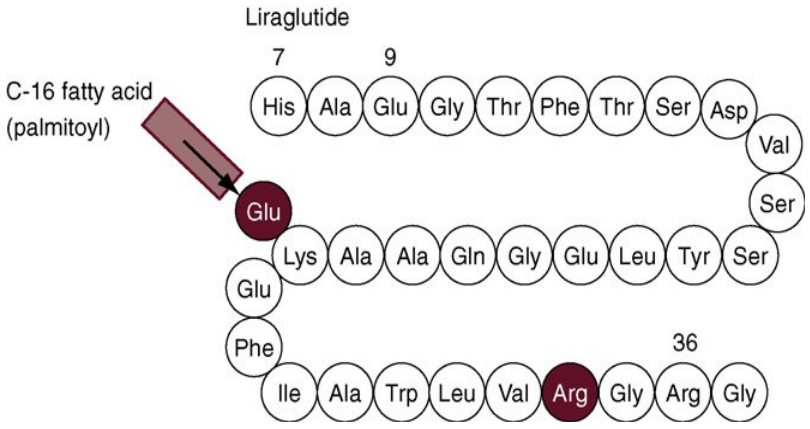
Besides the stimulation of insulin secretion, GLP-1 has also been shown to increase islet neogenesis and differentiation [11] and has shown to have trophic effects on ß-cells: not only does it stimulate ß-cell proliferation but it also enhances the differentiation of new ß-cell from progenitor cells in the pancreatic duct epithelium. Most recently, GLP-1 has been shown to inhibit apoptosis of ß-cell, including human ß-cell. Because the normal number of ß-cells is maintained in a balance between apoptosis and proliferation, this observation is of considerable interest [12]. The incretin hormones also affect glucagon secretion. GIP has thus been demonstrated to stimulate glucagon secretion, whereas GLP-1 inhibits glucagon secretion. The incretin hormones have extrapancreatic effects as well. Both incretins inhibit gastric emptying. GLP-1 thus exerts a multitude of actions, all of which are of potential value in the treatment of diabetes. The hormone has therefore been explored as a novel strategy treatment of diabetes [11]. These actions render GLP-1 highly attractive as a therapeutic agent, but an extremely rapid enzymatic degradation of the molecule makes it unsuitable for injection therapy. This metabolism, which is attributable to the actions of the ubiquitous enzyme dipeptidyl peptidase IV (DPP-4), results in a half-life for GLP-1 of only about two minutes; furthermore, the actions on metabolism of single subcutaneous injection are short-lived. The conclusion drawn was that GLP-1 based therapy has unusually attractive potential in diabetes treatment [12]. Therefore; two strategies were developed, such as incretin mimetics (analogs of GLP-1) and inhibitors of the dipeptidyl peptidase-4 (DPP-IV) that is the enzyme which inactivates native incretins. A recent metanalysis compared efficacy and safety of GLP-1 mimetics and DPP-IV inhibitors, confirming a reduction in HbA1c similar to that of other hypoglycemic agents, in combination with neutral or beneficial effect on body weight. As for the tolerability, GLP-1 analogues were associated with gastrointestinal side effects that tended to attenuate after a few weeks; DPP-IV inhibitors were associated with nasopharygitis, upper respiratory tract infection, and headache [13].

Liraglutide

This article focuses upon liraglutide, being developed by Novo Nordisk, which is based upon mammalian GLP-1. 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 (EMEA) for the approval in Europe [14]. An NDA was also submitted in July of 2008 for the approval of liraglutide in Japan.

Figure 1: Structure of liraglutide



Chemistry, structure and pharmacokinetics

Cleavage of transcription product of preproglucagon gene results in native GLP-1 which is a 30 amino acid peptide [15]. Liraglutide (γ-L-glutamoyl (N-α-hexadecanoyl)-Lys, Arg-GLP-1(7-37) [16] is an acylated GLP-1 analog suitable for once-daily administration [17], obtained by substitution of Lys 34 to Arg, and by addition of a C16 fatty acid at position 26 using a γ-glutamic acid spacer (Figure 1) [15]. It was illustrated by in vitro studies that, in spite of these alterations, liraglutide retains affinity for the GLP-1 receptor. The palmitoyl group facilitates non-covalent binding to albumin [16], both hindering DPP-4 access to the molecule and the peptide escapes glomerular filtration prolonging the half life and duration of action [18].

Liraglutide is administered as an isotonic solution for injection by the subcutaneous route. Liraglutide is slowly absorbed, with maximal concentration after 9-14 hrs and a half life of 12.6 ± 1.1 hrs. Its absolute bioavailability is approximately 55%. Once-daily administration of liraglutide is attributable to its sustained glucose-lowering activity at 24 hrs post administration at steady state concentration. Liraglutide is both intrinsically (because it may form micellar-like aggregates) and as a consequence of binding to albumin, relatively stable towards DPP-4 degradation. It has an elimination half-life of 11-15 hrs. No effect of gender, age, or injection site has been seen on the pharmacokinetics of liraglutide. No clinically significant drug-drug interaction related to inhibition or induction of cytochrome P450 are expected during treatment with liraglutide [18].

Phase II Studies

Positive effects of liraglutide on beta cells, and its association with appetite suppression and weight loss were firstly observed in studies on different animal models. Further encouraging preclinical and phase I clinical pharmacology results with liraglutide led to larger phase II trials in patients with T2DM [13].

The results of clinical studies with liraglutide are given in Table 1. Early clinical studies with liraglutide revealed that a single subcutaneous injection (10µg/kg) reduced both fasting and postprandial blood glucose concentration in subjects with T2DM [16]. Subsequently, treatment with liraglutide (6 µg/kg) for 1 week improved both α and β-cell function, resulting in improved 24-hour glycemic control in patients with T2DM [19].

Eight weeks of 0.6mg liraglutide treatment in obese subjects with T2DM (baseline HbA1c 7.5%) significantly improved glycemic control (−0.33% for liraglutide, +0.47% for placebo) without major effect on body weight (−0.7 kg for liraglutide, −0.9 kg for placebo). In this study, body composition was assessed, showing that liraglutide was associated with small (non-significant) trends towards a reduction in total fat mass and an increase in lean body mass. Overall 24-hour energy expenditure was not affected by liraglutide treatment [20].

In a 12-week randomized, placebo-controlled dose response study (baseline HbA1c 7.6%), monotherapy with liraglutide in doses of 0.045 up to 0.75 mg led to reductions in HbA1c with all but the lowest dose. Compared with placebo, the two highest doses of liraglutide (0.60 and 0.75 mg) resulted in HbA1c changes of −0.70% and −0.75% after 12 weeks, which were similar to the reduction obtained with the active comparator (glimepiride, −0.74%). Fasting plasma glucose (FPG) levels also decreased, with the maximal effect being observed after the first week of treatment and maintained over the 12-week study period. As with the effect on HbA_{1c}, the effect of the two highest doses of liraglutide was comparable to that of glimepiride. In this study, body weight did not increase, but there was no clear dose-response relationship; a significant reduction (−1.2 kg) was obtained with the 0.45 mg dose but not with the two highest liraglutide doses. No safety issues were raised for liraglutide; observed adverse events were mild and transient [21].

In another study on subjects with T2DM who were previously treated with an oral anti-diabetic drug (OAD) monotherapy (69% with metformin) and had $HbA_{1c} \leq 10\%$ were enrolled. After a 4-week metformin run-in period, subjects were randomized to receive liraglutide (0.045-0.75mg) once daily or continued on metformin 1000mg b.d. No significant differences in HbA_{1c} were observed between liraglutide and metformin groups at the three highest liraglutide dose levels (0.45, 0.6, 0.75mg). The two lowest liraglutide doses (0.045mg and 0.225mg) were not sufficient to maintain the fasting plasma glucose values achieved by metformin. This study showed that treatment with liraglutide at dose levels of 0.045-.75mg resulted in changes in weight and body compositions that were comparable with the metformin control group. Liraglutide was safe and well tolerated in the trial. The incidence of hypoglycemia and GI side-effects in liraglutide treatment groups was similar to that of metformin. Antibody levels to liraglutide were monitored during the trial, and there were no patients who tested positive for antibodies during 12 weeks of treatment [17].

Collectively, therefore, these results indicated that higher doses of liraglutide may have greater efficacy, and subsequently, Nauck et al investigated the effect of higher doses of liraglutide (titrated weekly in 0.5 mg increments from 0.5 to 2.0 mg) in a randomized double-blinded placebo-controlled protocol in patients with poorly controlled diabetes (HbA1c −9.4%). Subjects on metformin monotherapy (1000 mg bid) were randomized to receive continuing metformin monotherapy, metformin plus the addition of liraglutide, or

liraglutide monotherapy. In addition, an openlabel group received metformin plus glimepiride. FPG levels remained unchanged on metformin monotherapy, whereas they were reduced by 1.4 mmol/L in the subjects switched from metformin to liraglutide monotherapy. When compared to metformin monotherapy, the addition of liraglutide resulted in a further reduction of 3.9 mmol/L after 5 weeks of treatment, accompanied by a 0.8% reduction in HbA1c (baseline HbA1c −9.4%). Furthermore, the combination of metformin plus liraglutide gave a greater reduction in FPG levels compared with metformin plus glimeperide (between group difference of 1.4 mmol/L in favor of liraglutide). In terms of body weight, both liraglutide as monotherapy and in combination with metformin led to body weight reductions (−2.1 and −2.2 kg from baseline, respectively) compared with metformin (−1.7 kg) and metformin plus glimepiride (+0.8 kg) after 5 weeks of treatment. Treatment effects on body weight and fasting glucose remained largely unchanged when patients experiencing nausea for more than 1 week were excluded from the analysis [16].

In a phase II study, three doses (0.65, 1.25 and 1.9mg) of liraglutide were compared with placebo over 14 weeks [22]. The HbA1c reduction was -1.45% point for the 1.9mg dose compared with an increase of +0.29% point in the placebo-treated group (1.74% placebo-adjusted reduction), and 46% of liraglutide-treated patients reached an HbA1c below 7.0% (baseline:8.5%) [22] (Table 1). Fasting plasma glucose was reduced by 3.4 mmol/L compared with placebo. Body weight decreased by 2.9 kg (1.2 kg compared to placebo) in the 1.9mg group [22].

Recently, a randomized placebo-controlled phase 2 trial in Japanese patients with T2D was published. The insulin-secretory capacity in Japanese patients with T2D is less than that seen in Caucasian patients. Furthermore, Japanese patients typically display less insulin resistance and are less obese compared with Caucasian subjects with T2D. A total of 226 patients treated with diet with or without OADs and with BMI <30 kg/m^2 were randomized to treatment with liraglutide 0.1, 0.3, 0.6 and 0.9mg and placebo for 14 weeks. The mean body weight was about 62-65 kg, mean BMI from 23-25kg/m^2 and mean basal HbA1c was 8.3%. The reduction in HbA1c ranged from 0.8% to 1.9% in the liraglutide treated patients, and for the two highest doses of liraglutide 62-75% of the patient obtained an HbA1c <7.0%, compared with 9% of the placebo treated group (Table 1). In addition, fasting and post-prandial glucose levels showed a dose-related reduction. Surprisingly, no significant changes in body weight were observed in the liraglutide-treated patients, while the placebo-treated group lost about 1 kg. The reduction in HbA1c in the present trial is comparable with the results of the study in Caucasians using double the dose of liraglutide, which may indicate that the 'lean' Japanese phenotype of people with T2D respond better to incretin-based therapy than the obese Caucasian patient characterized by profound insulin resistance. Notable, during treatment with liraglutide, the weight remained stable in the present Japanese cohort with BMI of 23.9 kg/ m^2 [22,23]. Treatment with liraglutide has also been associated with reduced systolic (-7.8 mmHg) and diastolic blood pressure and improvement of several cardiovascular risk factors: CRP and B-type natriuretic peptide (BNP) (data in press).

The Phase III Liraglutide Effect and Action in Diabetes (LEAD) Studies

The LEAD program is composed of 6 randomized, controlled, double blind, Phase 3 clinical studies which includes around 6500 people worldwide, of which approximately 4200 received liraglutide. The program was designed to obtain the indication of use of liraglutide to treat people with T2D in monotherapy and in combination therapy with commonly used antidiabetic medications. The LEAD program has compared the efficacy and safety of liraglutide with Sulphonylurea, glitazone, insulin and exenatide. The lead program includes six studies. In all studies, the initial dose of liraglutide was escalated weekly in a stepwise manner from 0.6 to 1.8 mg/day [18].

Aim of LEAD-1 (combination with sulphonyurea) was to compare the effects of combining liraglutide (0.6, 1.2 or 1.8 mg/day) or rosiglitazone 4mg/day (all n≥ 228) or placebo (n=114) with glimepiride (2-4mg/day) on glycaemic control, body weight and safety in T2D. Baseline HbA1c was 8.4 ± 1.0% 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 treated 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% ($p < 0.0003$). The changes in weight were superior for all doses of liraglutide compared to rosiglitazone (Table I). The main adverse event with liraglutide was

nausea (all <11%), mostly mild and transient. Therefore, liraglutide in combination with glimepiride provided superior control compared with rosiglitazone with a favourable weight regulation [24].

Liraglutide was added to metformin in the LEAD-2 (combination with metformin) trial, a 26-week randomized, double blind study including participants with T2D and baseline HbA1c was 8.4 ± 1.0%. 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 [18].

LEAD-3 (liraglutide as monotherapy) study was a double blind, double dummy, active control; parallel group trial. liraglutide or glimepiride were administered for 1 year as monotherapy to T2DM patients The trial comparing two doses of liraglutide (1.2 and 1.8 mg QD) to glimepiride (8 mg QD). A total of 746 subjects previously treated with diet and exercise (36%) or OADs in monotherapy were randomised (basal HbA1c: 8.3 ± 1.1%, BMI: 33.1 ± 5.8 kgm_2) to the three groups of Treatment. The primary outcome was change in proportion of glycosylated haemoglobin. Analysis was done by intention-to-treat. At 52 weeks, HbA1c decreased by 0.51% with glimepiride, compared with 0.84% with liraglutide 1.2mg and 1.14% with liraglutide 1.8mg. Five patients in the liraglutide 1.2mg and one in 1.8 mg groups discontinued treatment because of vomiting, whereas none in the glimepiride group did so. 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 [25].

LEAD-4 (triple therapy with metformin and rosiglitazone) Was a placebo-controlled trial evaluating patients with T2D and a mean baseline HbA1c of 8.3%. LEAD-4 assessed the effect of adding liraglutide to metformin plus rosiglitazone in patients not adequately controlled on metformin or rosiglitazone alone. Mean A1C values decreased significantly more in the liraglutide groups versus placebo (mean ± SE -1.5 ± 0.1% for both 1.2 and 1.8 mg liraglutide and -0.5 ± 0.1% for placebo). Fasting plasma glucose decreased by 40, 44, and 8 mg/dl for 1.2 and 1.8 mg and placebo, respectively, and 90-min postprandial glucose decreased by 47, 49, and 14 mg/dl, respectively ($P<0.001$ for all liraglutide groups vs. placebo). Dose-dependent weight loss occurred with 1.2 and 1.8 mg liraglutide (1.0 ± 0.3 and 2.0 ± 0.3 kg, respectively) ($P<0.0001$) compared with weight gain with placebo (0.6 ± 0.3 kg). Systolic blood pressure decreased by 6.7, 5.6, and 1.1 mmHg with 1.2 and 1.8 mg liraglutide and placebo, respectively. Significant increases in C-peptide and homeostasis model assessment of β-cell function and significant decreases in the proinsulin-to-insulin ratio occurred with liraglutide versus placebo. Minor hypoglycemia occurred more frequently with liraglutide, but there was no major hypoglycemia. Gastrointestinal adverse events were more common with liraglutide, but most occurred early and were transient [26].

LEAD-5 (liraglutide in triple therapy with metformin and sulphonylurea) evaluated patients with type 2 diabetes and a mean baseline HbA1C of 8.2%. 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 [18].

LEAD-6 (comparison of efficacy of liraglutide with exenatide). LEAD-6 included patients inadequately treated with metformin and/or a sulfonylurea with a mean baseline A1C of 8.2%.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 ($p < 0.0001$). Both groups lost around 3 kg in weight, with a trend towards more weight loss in the liraglutide group. Among the patients previously treated with metformin alone, this difference was 1 kg in

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Table 1: Clinical studies with liraglutide

Study (references)	Compound	Dose per day	Patients included in the study (n)	Duration (weeks)	Other treatments	HbA1c	Effect on	
							FPG	Weight
Degn et al	Liraglutide	6µg/kg	13	1	Diet	--	-1.9mM	--
Madsbad et al	Liraglutide	0.045 mg/day	193	12	Diet	+0.45%	+1.3mM	0.0 kg
	Liraglutide	0.225 mg/day		12	Diet	-0.23%	-1.3mM	-0.7 kg
	Liraglutide	0.450 mg/day		12	Diet	-0.49%	-0.8mM	-1.2 kg
	Liraglutide	0.600 mg/day		12	Diet	-0.48%	-1.9mM	+0.3 kg
	Liraglutide	0.750 mg/day		12	Diet	-0.54%	-1.2mM	-0.4 kg
	Placebo			12	Diet	+0.20%	+0.7mM	0.0 kg
	Glimepiride			12	Diet	-0.60%	-2.1mM	+1.0 kg
Seino Y et al	Liraglutide	0.1 mg/day	226	14	Diet	-0.72%	-1.0mM	-0.0 kg
	Liraglutide	0.3 mg/day		14	Diet	-1.07%	-1.4mM	+0.1 kg
	Liraglutide	0.6 mg/day		14	Diet	-1.50%	-2.4mM	-0.1 kg
	LiraglutidePla	0.9 mg/day		14	Diet	-1.67%	-2.4mM	-0.5 kg
	cebo			14	Diet	+0.09%	-0.2mM	-0.9 kg
Harder et al	Liraglutide	0.6 mg/day	33	8	Diet	-0.33%	-1.9mM	-0.7 kg
	Placebo				Diet	+0.47%	+0.3mM	-0.9 kg
Feinglos et al	Liraglutide	0.045 mg/day	210	12	Diet	+1.28%	+2.0mM	0.0%
	Liraglutide	0.225 mg/day		12	Diet	+0.86%	+2.0mM	-1.9%
	Liraglutide	0.450 mg/day		12	Diet	+0.22%	+0.6mM	-1.2%
	Liraglutide	0.600 mg/day		12	Diet	+0.16%	+0.0mM	-0.6%
	Liraglutide	0.750 mg/day		12	Diet	+0.30%	+0.9mM	-0.9%
	Placebo			12	Metformin	+0.09%	-0.2mM	-0.6%
Nauck et al	Liraglutide	0.5-2.0 mg/day	144	5	Metformin+SU	-0.8%	-2.8mM	-1.5 kg
Vilsbol et al	Liraglutide	0.6 mg/day	165	14	Diet	-0.98%	-2.3mM	+0.2 kg
	Liraglutide	1.2 mg/day		14	Diet	-1.40%	-3.0mM	-0.7 kg
	Liraglutide	1.9 mg/day		14	Diet	-1.45%	-3.0mM	-3.0 kg
	Placebo			14	Diet	+0.20%	+0.3mM	-1.8 kg
LEAD 1	Liraglutide	0.6 mg/day	1041	26	glimepiride	-0.6%	-0.7mM	+0.7 kg
	Liraglutide	1.2 mg/day		26	glimepiride	-1.1%	-1.6mM	+0.3 kg
	Liragluitde	1.8 mg/day		26	glimepiride	-1.1%	-1.6mM	-0.2 kg
	Placebo			26	glimepiride	+0.2%	+1.0mM	-0.1 kg
	rosiglitazone	8 mg/day		26	glimepiride	-0.4%	-0.9mM	+2.1 kg
LEAD 2	Liraglutide	0.6 mg/day	1041	26	Metformin	-0.7%	-0.7mM	-1.8 kg
	Liraglutide	1.2 mg/day		26	Metformin	-1.0%	-1.6mM	-2.6 kg
	Liraglutide	1.8 mg/day		26	Metformin	-1.0%	-1.6mM	-2.8 kg
	Placebo			26	Metformin	+0.1%	+1.0mM	-1.5 kg
	glimepiride	8 mg/day		26	Metformin	-1.0%	-0.9mM	+1.0 kg
LEAD 3	Liragluitde	1.2 mg/day	746	52	Diet	-0.8%	-0.8mM	-2.1 kg--
	Liraglutide	1.8 mg/day		52	Diet	-1.1%	-1.4mM	2.5 kg
	glimepiride	8 mg/day		52	Diet	+0.5%	-0.3mM	+1.1 kg
LEAD 4	Liraglutide	1.2 mg/day	533	26	Metfor+tzd	-1.5%	-2.2mM	-1.0 kg
	Liraglutide	1.8 mg/day		26	Metfor+tzd	-1.5%	-2.4mM	-2.0 kg
	Placebo			26	Metfor+tzd	-0.5%	-0.4mM	+0.6 kg
LEAD 5	Liraglutide	1.8 mg/day	581	26	Metfor+SU	-1.3%	-1.6mM	-1.8 kg
	Placebo			26	Metfor+SU	-0.2%	-0.6mM	-0.4 kg
	Glargine			26	Metfor+SU	-1.1%	-1.8mM	+1.6 kg

SU = Sulphonylurea, which was glimepiride, Metfor = metformin, tzd = rosiglitazone

favour liraglutide (not statistically significant). Most frequently reported adverse events for both liraglutide and exenatide were nausea at a level of about 25% (percentage of all study participants reporting nausea at least once). After week 8– 10 the percentage of patients reporting nausea with liraglutide was below 10%, while in the exenatide group the level remained about 10%. The rate of minor hypoglycaemia was statistically

significantly lower in the liraglutide group, but the overall rate was low for both the groups [27]. Table 2 provides a comparison of liraglutide and exenatide based on data obtained in LEAD [18].

Meta-analysis of LEAD studies

Participants from LEAD 1, 2 and 5 were stratified by baseline HbA1c quartiles. Treatment with liraglutide resulted in a reduction of HbA1c of about 0.6–1.0% point in quartile 1 (mean HbA1c about 7.3%) to a reduction of 1.4–1.8% point in quartile 4 (mean HbA1c of about 9.7%). The greatest decrease in body weight occurred in subjects with BMI >35 kg/m^2. The weight reduction in subjects with BMI <25 kg/$m^2$was from 0 to 2 kg increasing to 1 to 4.5 kg in subjects with a BMI >35 kg/m^2.The greatest weight loss was observed with the combination of liraglutide and metformin. The highest dose of liraglutide (1.8 mg/day) reduces systolic blood pressure with 2.7 to 4.5 mmHg versus comparator treatment. No change in the diastolic blood pressure was observed. Lastly, liraglutide improved beta-cell function evaluated from HOMA beta-cell function and the proinsulin/insulin ratio.

Liraglutide as an obesity drug

The GLP-1 analogues may have a potential as a weight-loss medication. In a 32-week open-label extension of a randomised, 20-week study comparing liraglutide, xenecal and placebo in obese nondiabetic subjects, the weight loss in groups treated with 2.4 mg liraglutide daily was about 7–8 kg compared with approximately 4 kg with xenecal and 2–3 kg with placebo. After 52 weeks, 45% and 15% achieved a weight loss larger than 5% and 10%, respectively (press release, Novo Nordisk, 2007).

Safety and tolerability of liraglutide

Liraglutide has been well tolerated with a low risk of hypoglycaemia, primarily in participants also treated with sulphonylurea. The incidence of nausea has been acceptable and mostly observed during the first weeks of treatment and has thereafter been minimal or completely absent. The low incidence of nausea is probably explained by the rather flat profile of action for liraglutide, and that a 3-week titration scheme was introduced in all the studies. In few patients, antibodies to liraglutide were measured, but were without influence on the glycaemic control. Six cases of pancreatitis have been registered in the liraglutide-treated patients. Whether this is more than expected needs further studies. The thyroid C- cell neoplastic changes, which have been observed in rodents and mice, have not been observed in humans.

Table 2: Comparison of liraglutide and exenatide

Parameter [a]	Liraglutide Daily	Exenatide Twice Daily
Effect 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 = heamoglobin A_{1c}; FPG = Fasting Plasma Glucose

[a]26-week data

[b] p<0.0001 versus exenatide

[c] p=0.0015 versus exenatide

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CONCLUSION

Liraglutide, a human GLP-1 analogue with high homology to native GLP-1, has structural modifications sufficient to amend pharmacokinetics for once-daily administration without compromising biological activity. Data from large, controlled, clinical studies have confirmed the therapeutic profile of liraglutide, with robust reductions in HbA1c, low risk of hypoglycaemia and clinically relevant reductions in body weight and systolic blood pressure.

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