

Liraglutide : Bench to Bedside

V Mohan¹, V Balaji², S Jain³, S Kalra⁴, A Mittal⁵



Abstract

Good glycaemic control in type 2 diabetes can be achieved by current medications, but often at the expense of hypoglycaemia and weight gain. The glucose-dependent stimulation of insulin secretion, the reduction in appetite and the improvement in β -cell function with glucagon-like peptide-1 (GLP-1), suggest that incretin-based therapies could be an attractive pharmacological target for treatment of type 2 diabetes.

Encouraging results with liraglutide from clinical pharmacology trials and phase 2 trials led to a well-designed, comprehensive, phase 3 clinical programme comprising six large randomised controlled trials – The Liraglutide Effect and Action on Diabetes (LEAD) programme. The purpose of the LEAD programme was to investigate the clinical efficacy and safety of liraglutide as monotherapy or in combination with commonly used treatments in patients with type 2 diabetes. The application of liraglutide across the continuum of progression of type 2 diabetes was thoroughly evaluated in the LEAD trials. Overall, the LEAD programme demonstrated that once-daily liraglutide improved glycaemic control, decreased body weight with minimal risk of hypoglycaemia and was well tolerated in patients with type 2 diabetes. It also showed that liraglutide reduced systolic blood pressure (SBP) and promoted β -cell function.

Liraglutide is a novel drug that can address the current unmet medical needs in the early treatment of diabetes, both as a monotherapy and as an add-on therapy to conventional type 2 diabetes therapies.

Introduction

Type 2 diabetes is a chronic metabolic disorder, characterised by continuous deterioration in β -cell function and insulin resistance that eventually results in poor glycaemic control.¹ When optimal overall glycaemic control cannot be obtained over a longer time period, the risk of developing microvascular (neuropathy, retinopathy and nephropathy) and macrovascular (coronary heart disease, stroke and peripheral vascular disease) complications is increased.^{2,3} To achieve and maintain long-term, near-normal glycaemic control, thereby reducing the risk of developing late diabetic complications, is to successfully manage type 2 diabetes.

Usually, treatment for type 2 diabetes starts with diet and exercise. If good glycaemic control is not attained with lifestyle changes, treatment with oral antidiabetic drugs (OADs) is prescribed. In many cases, existing therapies eventually fail to maintain a long-term satisfactory glycaemic control due to the continuous decline in β -cell function. Therefore, as the diabetes progresses and the OAD therapies no longer sustain good glycaemic control, additional treatments (such as insulin) are often required.⁴ In patients treated with insulin secretagogues and/or insulin, good glycaemic control can be achieved, but it is often at the expense of increased risk of hypoglycaemic episodes and weight gain.^{1,5} Hence, there are unmet medical needs for developing new treatments for type 2 diabetes.

Development of the Liraglutide Molecule and its Pharmacokinetics

GLP-1 is an incretin hormone secreted from the L cells of the intestine and has been considered as a new and promising treatment for type 2 diabetes since its discovery in 1984.⁶ Native

GLP-1 stimulates endogenous insulin secretion when plasma glucose levels are elevated and decreases glucagon secretion.⁷ It also decreases gastric motility, which delays gastric emptying and leads to reduced appetite and food intake.⁸ The combination of these mechanisms makes GLP-1 a potent blood glucose-lowering agent and an attractive pharmacological treatment for type 2 diabetes.

However, the endogenous GLP-1 has a short half-life (1.5–2.1 min), and therefore has limited use as a pharmaceutical treatment. The fast elimination of the hormone is mainly due to a fast degradation by dipeptidyl peptidase-4 (DPP-4) and rapid kidney clearance.⁶ Thus, treatment strategies have been developed in order to overcome the limitation with native GLP-1 and to develop it further for its full therapeutic potential.

Liraglutide is a human GLP-1 analogue with 97% amino acid homology to endogenous GLP-1. The structure of the native 30-amino acid peptide GLP-1 hormone has been modified in order to develop a compound with pharmacokinetic properties (t_{max} of 9–13 h and a t_{1/2} of 13 h) appropriate for once-daily injection. These modifications include: 1) a C16 fatty (palmitic) acid chain that has been attached to the position 26 (lysine) via a glutamoyl spacer, and 2) lysine at position 34 that has been replaced by arginine.⁶

Liraglutide is administered as an isotonic solution by subcutaneous injection. The protracted pharmacokinetic profile of liraglutide is due to a combination of delayed absorption from the injection site, albumin binding (98–99%) in the bloodstream and the decreased susceptibility to degradation by DPP-4.⁹

Pre-clinical Studies

GLP-1 affects the β -cell mass through several mechanisms: stimulation of β -cell proliferation, promotion of neogenesis and inhibition of apoptosis.¹⁰

Bregenholt et al. demonstrated that liraglutide protected rat β -cells from both cytokine- and free fatty acid (FFA)-mediated apoptosis *in vitro*, under conditions that mimic the pathological mechanisms associated with the natural history of type 2 diabetes.¹¹

Pre-clinical studies in animal models demonstrated that liraglutide stimulated β -cell proliferation, promoted neogenesis and inhibited apoptosis through several mechanisms.^{10,12,13}

¹Chairman & Chief Diabetologist, Madras Diabetes Research Foundation, Dr Mohan's Diabetes Specialities Centre, WHO Collaborating Centre for Non Communicable Diseases Prevention & Control, International Diabetes Federation (IDF) Centre of Education, Chennai, India; ²Director & Senior Consultant Diabetologist, Dr V. Seshiah Diabetes Research Institute and Dr Balaji Diabetes Care Centre, Chennai, India; ³Director, TOTAL Diabetes Hormone Institute, Indore, India; ⁴Consultant Endocrinologist, Bharti Research Institute of Diabetes & Endocrinology, Karnal, India; ⁵Chairman, Division of Endocrinology and Diabetes, Medanta Medicity, Gurgaon (Delhi NCR), India

Table 1 : LEAD trial designs

Trial	LEAD 3	LEAD 2	LEAD 1	LEAD 4	LEAD 5	LEAD 6
Overall description	Effect of liraglutide in monotherapy	Effect of liraglutide in combination with metformin	Effect of liraglutide in combination with glimepiride	Effect of liraglutide in combination with metformin and rosiglitazone	Effect of liraglutide in combination with metformin and glimepiride	Effect of liraglutide in combination with metformin, glimepiride or both
Comparator arms	Glimepiride + placebo	Metformin + placebo Metformin + glimepiride	Glimepiride + placebo Glimepiride + rosiglitazone	Metformin + rosiglitazone + placebo	Metformin + glimepiride + placebo Metformin + glimepiride + insulin glargine	Metformin and/or + glimepiride + exenatide
Background medication	None	Metformin	Glimepiride	Metformin + rosiglitazone	Metformin + glimepiride	Metformin + glimepiride
Overall inclusion criteria	Patients with T2DM treated with diet/exercise or OAD	Patients with T2DM treated with OADs	Patients with T2DM treated with OADs	Patients with T2DM treated with OADs	Patients with T2DM treated with OADs	Patients with T2DM treated with OADs
Patients (N)	746	1091	1041	533	581	464
Primary endpoint	HbA _{1c} (52 weeks)	HbA _{1c} (26 weeks)	HbA _{1c} (26 weeks)	HbA _{1c} (26 weeks)	HbA _{1c} (26 weeks)	HbA _{1c} (26 weeks) with 14-week extension
Clinicaltrials.gov identifier	NCT00294723	NCT00318461	NCT00318422	NCT00333151	NCT00331851	NCT00518882

HbA_{1c}: glycated haemoglobin A_{1c}; LEAD: Liraglutide Effect and Action in Diabetes; OAD: oral antidiabetic drug; T2DM: type 2 diabetes mellitus.

In a pre-clinical study with rats, six weeks' subcutaneous administration of liraglutide significantly increased β -cell mass with a tendency of increased β -cell proliferation.¹²

Moreover, along with the positive effects on β cells, Bock et al. established that liraglutide had long-term beneficial effects on eating behaviour and reduced weight in diabetic rats.¹³ This observation was in agreement with another pre-clinical study in obese mini-pigs, where liraglutide treatment reduced the weight significantly. A dose-dependent trend was noted with liraglutide treatment.¹⁴

Animal data also suggest that liraglutide has cardioprotective effects. Noyan-Ashraf et al. investigated the pathophysiology and outcome of coronary artery occlusion in normal and diabetic mice pre-treated with liraglutide. The preliminary findings of this study demonstrated that pre-treatment with liraglutide improved cardiomyocyte survival and cardiac function after induction of experimental myocardial infarction. The beneficial effects were independent of effects on body weight or blood glucose.¹⁵

The actions of GLP-1 are mediated by the GLP-1 receptor, which is expressed in many types of cells, including thyroid C-cells. Calcitonin which is produced by the C-cells is a classical marker for C-cells activation and increased C-cell mass. Knudsen et al. investigated the effect of GLP-1 receptor activation in C-cells with different GLP-1 analogues (including liraglutide and exenatide) in rodents and non-human primates *in vitro* and *in vivo*.¹⁰ The study showed that the GLP-1 analogues stimulated calcitonin release, up-regulation of calcitonin gene expression and subsequently C-cell hyperplasia in rats and, to a lesser extent, mice. In contrast, the GLP-1 analogues did not increase calcitonin levels and C-cell hyperplasia were not detected in non-human primates even after 20 months of treatment with liraglutide (at >60 times human exposure). It could be due to low GLP-1 receptor expression in primates' thyroid C-cells compared to rodents, which the study also showed. The results were consistent with results obtained from nine clinical trials in patients with type 2 diabetes who were exposed to liraglutide up to 2 years. Knudsen et al. concluded that there is a difference

between rodents and primates in thyroid C-cell responsiveness to GLP-1 analogues.¹⁰

The US FDA has concluded that the risk of carcinomas in humans is low, since the incidence in rodents was only statistically significant at drug exposure levels many times higher than recommended human dose, and it did not affect overall survival rates.¹⁶ To further explore possible associations between medullary thyroid cancer and liraglutide use, the FDA suggested the establishment of a cancer registry to monitor the annual incidence of medullary thyroid cancer over the next 15 years.¹⁶

Overview of Phase 2 and Phase 3 Trials

A 14-week, double-blind, randomised and placebo-controlled phase 2 trial investigated the effects of once-daily liraglutide at three dosages (0.65 mg, 1.25 mg or 1.90 mg) in patients with type 2 diabetes, who had not maintained good glycaemic control with diet or an OAD. It showed that liraglutide monotherapy resulted in a good glycaemic control without causing any major or minor hypoglycaemic episodes. Liraglutide 1.90 mg reduced glycated haemoglobin A_{1c} (HbA_{1c}) by 1.74% compared to placebo. Approximately 50% of the patients treated with 1.25 mg or 1.90 mg achieved the American Diabetes Association (ADA) target for post-prandial control (≤ 10 mmol/l). The fasting plasma glucose (FPG) levels were significantly decreased versus placebo in patients who received the two highest doses of liraglutide. A significant dose-dependent decrease in body weight (a maximum decrease of 3 kg with 1.90 mg) was found in this trial.¹⁷

The encouraging results from phase 2 trials with liraglutide paved the way for larger-scale phase 3 trials. The Liraglutide Effect and Action on Diabetes (LEAD) programme comprised six large randomised, controlled phase 3 trials. More than 4000 patients were recruited from more than 600 sites in 40 countries, of which approximately 2700 received liraglutide administration. The LEAD programme investigated liraglutide as monotherapy or in combination with one or more OADs in patients with type 2 diabetes who failed to achieve good glycaemic control with their pre-trial therapeutic regimens. The purpose of the LEAD trials design was to evaluate the application of liraglutide across the continuum of progression of type 2 diabetes and compare it with commonly used treatments (sulfonylurea [SU], rosiglitazone, insulin glargine and

exenatide) for type 2 diabetes (Table 1).^{1,4,5,18,19,20}

Data from the different LEAD trials consistently showed that liraglutide improved clinical outcomes in terms of glycaemic control, body weight and SBP when compared with various comparators. In general, the LEAD trials illustrated that liraglutide (1.2 mg or 1.8 mg) reduced HbA_{1c} by 1.1–1.5%, induced weight loss of 1.0–3.2 kg, decreased blood pressure by 2.1–6.7 mmHg, and reduced the cardiovascular risk biomarkers.^{1,4,5,18,19,20} It was also demonstrated that liraglutide had a positive effect on β -cell function. However, additional and long-term future studies are needed to evaluate whether liraglutide delays the progression of type 2 diabetes.^{1,4,5,18,19,20}

Liraglutide was well tolerated in patients participating in all LEAD trials. Gastrointestinal disorders, mainly nausea and diarrhea, were the most common reported adverse events. However, the majority of these events were reported as mild and rarely resulted in discontinuation of therapy. Furthermore, the highest frequency of the gastrointestinal disorders was seen during the initiation of therapy, and therefore transient.^{1,4,5,18,19,20}

In LEAD trials, treatment with liraglutide also presented a lower risk of hypoglycaemia. This finding was expected, since liraglutide stimulates insulin secretion in a glucose-dependent manner and has no effect on glucagon secretion when plasma glucose is low.^{1,4,5,18,19,20}

Calcitonin concentrations were also monitored in order to assess any effect of GLP-1 analogues on C cells. All LEAD trials demonstrated no safety concern in terms of C-cell proliferation in patients treated with once-daily liraglutide. In the controlled clinical trials, increases in calcitonin levels occurred in a slightly higher percentage of the patients treated with liraglutide than in control patients; Increased calcitonin levels with liraglutide were shifts from below to slightly above the assay's detection limit (0.7 ng per liter) and the levels were still within normal ranges.^{10,16} In longer term studies, there were no treatment related differences in calcitonin levels between liraglutide and control groups.¹⁰

Sitagliptin is an oral DPP-4 inhibitor, which is another class of incretin-based therapy that has been developed for the treatment of type 2 diabetes. Compared to GLP-1 analogues that increase GLP-1 action, DPP-4 inhibitors prevent native GLP-1 from rapid degradation by the DPP-4 enzyme. Thereby, DPP-4 inhibitors work indirectly to increase endogenous GLP-1 levels.

A phase 3 trial was designed to directly compare liraglutide and sitagliptin, when added to metformin therapy, and thereby address differences between the two treatments. This randomised, open-label, three-armed, parallel-group trial was conducted using 665 patients with type 2 diabetes who were assigned to once-daily liraglutide 1.2 mg, liraglutide 1.8 mg or 100 mg/day sitagliptin (all added on to 1500 mg/day metformin) for a period of 26 weeks. The findings of this trial illustrated: 1) better glycaemic control was achieved with liraglutide 1.2 mg or 1.8 mg/day than sitagliptin 100 mg/day; 2) more patients treated with liraglutide achieved the ADA target for good glycaemic control than sitagliptin; 3) reduction in body weight from baseline to end of treatment was observed with all treatments; however, more pronounced weight reduction was associated with liraglutide administration; 4) gastrointestinal disorders were more frequently reported as adverse events in patients treated with liraglutide, but were transient and 5) all treatments were associated with low risk of hypoglycaemia.²¹

Liraglutide has been approved as Victoza® in India, to be used in the early treatment of type 2 diabetes either as monotherapy or in combination therapy with other antidiabetic agents (metformin, SUs or thiazolidinediones [TZDs]). Liraglutide can be taken independent of meals,²⁰ and the injection timing can be modified during the day without the need for dose adjustment.¹⁸ This provides the maximum treatment flexibility to those diabetic patients with a very busy lifestyle.

Conclusions

Liraglutide is a novel GLP-1 analogue developed for the treatment of type 2 diabetes as mono- or combination therapy. It possesses additional advantages to its existing blood glucose-lowering effect, such as reducing body weight and SBP with minimal risk of hypoglycaemia in comparison with currently available anti-diabetes treatments. Liraglutide also improves the β -cell function. It has been widely documented in clinical trials that liraglutide is safe and can be well tolerated in patients with type 2 diabetes. It is reasonable to believe that current unmet medical needs in terms of attaining optimal diabetes management can well be addressed with liraglutide.

Acknowledgements

The authors wish to thank Frey C, of Novo Nordisk International Operations for providing medical editorial assistance.

References

1. Nauck M, Frid A, Hermansen K, et al. Efficacy and safety comparison of liraglutide, glimepiride, and placebo, all in combination with metformin, in type 2 diabetes: The LEAD (liraglutide effect and action in diabetes)-2 study. *Diabetes Care* 2009;32:84–90.
2. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998;352:837–53.
3. DeFronzo RA. Pharmacologic therapy for type 2 diabetes mellitus. *Ann Intern Med* 1999; 131: 281–303.
4. Buse JB, Rosenstock J, Sesti G, et al. Liraglutide once a day versus exenatide twice a day for type 2 diabetes: A 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6). *Lancet* 2009;374:39–47.
5. Marre M, Shaw J, Brandle M, et al. Liraglutide, a once-daily human GLP-1 analogue, added to a sulphonylurea over 26 weeks produces greater improvements in glycaemic and weight control compared with adding rosiglitazone or placebo in subjects with Type 2 diabetes (LEAD-1 SU). *Diabet Med* 2009;26:268–78.
6. Knudsen LB, Nielsen PF, Huusfeldt PO, et al. Potent derivatives of glucagon-like peptide-1 with pharmacokinetic properties suitable for once daily administration. *J Med Chem* 2000;43:1664–9.
7. Chang AM, Jakobsen G, Sturis J, et al. The GLP-1 derivative NN2211 restores beta-cell sensitivity to glucose in type 2 diabetic patients after a single dose. *Diabetes* 2003;52:1786–91.
8. Holst JJ. The physiology of glucagon-like peptide 1. *Physiol Rev* 2007;87:1409–39.
9. Russell-Jones D. Molecular, pharmacological and clinical aspects of liraglutide, a once-daily human GLP-1 analogue. *Mol Cell Endocrinol* 2009;297:137–40.
10. Bjerre Knudsen L, Madsen LW, Andersen S, et al. Glucagon-like peptide-1 receptor agonists activate rodent thyroid C-cells causing calcitonin release and C-cell proliferation. *Endocrinology* 2010;151:1473–86.
11. Bregenholt S, Moldrup A, Blume N, et al. The long-acting glucagon-like peptide-1 analogue, liraglutide, inhibits beta-cell apoptosis in vitro. *Biochem Biophys Res Commun* 2005;330:577–84.
12. Sturis J, Gotfredsen CF, Romer J, et al. GLP-1 derivative liraglutide in rats with beta-cell deficiencies: influence of metabolic state on beta-cell mass dynamics. *Br J Pharmacol* 2003;140:123–32.
13. Bock T, Pakkenberg B, Buschard K. The endocrine pancreas in non-diabetic rats after short-term and long-term treatment with the long-acting GLP-1 derivative NN2211. *APMIS* 2003;111:1117–24.
14. Ribeil U, Larsen MO, Rolin B, et al. NN2211: a long-acting glucagon-like peptide-1 derivative with anti-diabetic effects in glucose-intolerant pigs. *Eur J Pharmacol* 2002;451:217–25.
15. Noyan-Ashraf MH, Momen MA, Ban K, et al. GLP-1R agonist liraglutide activates cytoprotective pathways and improves outcomes after experimental myocardial infarction in mice. *Diabetes* 2009;58:975–83.
16. Parks M, Rosebraugh C. Weighing risks and benefits of liraglutide – The FDA's review of a new antidiabetic therapy. *N Engl J Med* 2010;362:774.
17. Vilboll T, Zdravkovic M, Le-Thi T, et al. Liraglutide, a long-acting human glucagon-like peptide-1 analog, given as monotherapy significantly improves glycemic control and lowers body weight without risk of hypoglycemia in patients with type 2 diabetes. *Diabetes Care* 2007;30:1608–10.
18. Garber A, Henry R, Ratner R, et al. Liraglutide versus glimepiride monotherapy for type 2 diabetes (LEAD-3 Mono): A randomised, 52-week, phase III, double-blind, parallel-treatment trial. *Lancet* 2009;373:473–81.
19. Russell-Jones D, Vaag A, Schmitz O, et al. Liraglutide vs insulin glargine and placebo in combination with metformin and sulfonylurea therapy in type 2 diabetes mellitus (LEAD-5 met+SU): a randomised controlled trial. *Diabetologia* 2009;52:2046–55.
20. Zinman B, Gerich J, Buse JB, et al. Efficacy and safety of the human glucagon-like peptide-1 analog liraglutide in combination with metformin and thiazolidinedione in patients with type 2 diabetes (LEAD-4 Met+TZD). *Diabetes Care* 2009;32:1224–30.
21. Pratley RE, Nauck M, Bailey T, et al. Liraglutide versus sitagliptin for patients with type 2 diabetes who did not have adequate glycaemic control with metformin: a 26-week, randomised, parallel-group, open-label trial. *Lancet* 2010;375:1447–56.