■ *Review Article*

LIRAGLUTIDE: THE LATEST ADDITION TO ARMAMENTARIUM OF ANTIDIABETIC DRUGS

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Introduction

Type 2 diabetes mellitus (T2DM) is a chronic progressive disease which leads to various micro- and macro vascular complications with increased morbidity and mortality if the hyperglycemia is not controlled properly. To prevent T2DM, its progress and the late stage complications, recent efforts have been to introduce drugs based upon the functions of the intestinal hormone glucagon-like peptide-1 (GLP-1). Glucagon-like peptide 1 (GLP-1) is an intestinal hormone which increases insulin secretion. The insulin secretion is more after oral as compared to intravenous glucose administration. This increased secretion which is due to the intestinal hormones or incretins, is not found adequately in patients with T2DM. The insulin secretion by GLP-1 is glucose-dependent. GLP-1 also suppresses glucagon, causes a reduction in appetite and delays gastric emptying. It has been shown to stimulate beta-cell neogenesis, growth and differentiation. In vitro it also inhibits beta-cell apoptosis induced by different toxins. But the natural GLP-1 is inactivated rapidly by the enzyme dipeptidyl peptidase-4 (DPP-4) and thus is not useful as a therapeutic agent in the long-term treatment of Type 2 diabetes. So in recent past there have been efforts to develop the "incretin mimetics" acting on GLP-1 receptors (like exendin-4) or long acting GLP-1 analogues. [1, 2]

Liraglutide is the first true human GLP-1 analogue which has been approved by FDA on 25th January 2010.

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Chemistry

Liraglutide has 97% amino acid sequence similar to the natural GLP-1. The molecular formula of liraglutide is $C_{172}H_{265}N_{43}O_{51}$. Modifications have been done with the two lysine residues in the mammalian GLP-1 amino acid sequence. Glutamic acid has been attached to one lysine to facilitate the addition of a palmitoyl group. Another lysine has been replaced by arginine. These modifications help liraglutide in self association, binding to albumin and providing stability against degradation by enzymes. Thus its absorption and duration of action becomes prolonged making it suitable for therapeutic use.[2, 3]

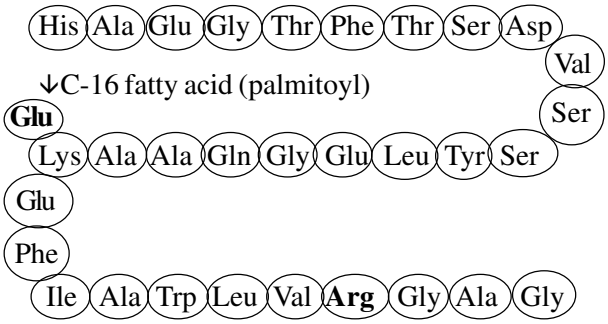

Figure: Chemical Structure of liraglutide (Amino acids residues in bold indicate differences from mammalian GLP-1)[4]

Pharmacokinetics

Liraglutide is given 0.6 mg subcutaneously once daily, independent of meals. After the initial week for gastrointestinal adaptation the dose is increased to 1.2 mg daily for the therapeutic effect. The dose can be escalated up to 1.8 mg in subsequent weeks depending on the response. It has slow absorption (Tmax of ~10–14 hours) and a long half-life of around 12½ hours.[5]

Liraglutide in once daily dosage has been shown to provide better pharmacokinetic coverage in comparison with twice-daily exenatide. Presence of T2DM does not affect the pharmacokinetic properties of the drug as no clinically relevant differences were found in liraglutide pharmacokinetics between healthy volunteers and subjects with T2D.[6] Nearly 90% of liraglutide after injection is found in the plasma as the intact molecule. It is very slowly disintegrated into smaller moieties and eliminated via the liver and kidney. The breakdown products as amino acids and fatty acids are utilized in new endogenous proteins and lipid synthesis.[2]

No safety concerns have been found regarding use of liraglutide in patients with renal impairment. Renal impairment does not increase the exposure of liraglutide, and patients with Type 2 diabetes having compromised renal function can use standard treatment regimens of liraglutide without any dose adjustment.[7] Adjustments for body weight, age or gender has no effect upon the pharmacokinetics of liraglutide in healthy subjects.[8] No dose adjustment is needed for the patients with hepatic impairment.[9] Because of lack of adequate studies in pregnant and lactating women, it should be used with caution in these patient groups.

Pharmacodynamics

Liraglutide acts as GLP-1 receptor agonist.GLP-1 is a membrane-bound cell-surface receptor coupled to adenylyl cyclase by the stimulatory G-protein, Gs, in pancreatic beta cells. Liraglutide increases intracellular cyclic AMP (cAMP) leading to insulin release in the presence of elevated glucose concentrations. Liraglutide also helps in restoring normoglycemia by increasing insulin sensitivity and significantly improving the function of the beta-cells. Liraglutide has been found to be useful as immunotherapy and in combination with oral anti diabetic drugs.[10,11,12,13] Combined with oral antidiabetic drugs it leads to rapid improvement in fasting plasma glucose levels.[14] It reduces food intake, delays gastric emptying and suppresses prandial glucagon release.[15,16,17]

The reduction in HbA1c is seen to be up to approximately 1.3% to 1.7% from baseline (8.2%-8.4%).[18] Since the action of liraglutide is glucose dependent, there is very low incidence of hypoglycemia.[19] It significantly decreases body fat mass and improves obesity related risk factors, thus helping in reduction of prediabetes.[20] Weight loss of up to 3.8 kg has been seen with liraglutide therapy.[21, 22] It reduces the systolic blood pressure and has cardio protective effect.[22,23] It may improve the endothelial cell dysfunction associated with premature atherosclerosis identified in type 2 diabetic patients.[24] The cardio protective effects may be partly direct, because liraglutide increases cyclic AMP formation and reduces the extent of caspase-3 activation in cardiomyocytes in a GLP-1R-dependent manner thus playing an important and favorable role in apoptosis in vitro.[25] It has been shown to cause no clinically relevant increases in the QTc interval and has a neutral effect on myocardial infarct size.[26, 27]

Indications

Liraglutide can be used in adult patients of type 2 diabetes mellitus having poor glycemic control with oral hypoglycemic agents.[28] It is a good option as early add-on therapy for patients on single oral antidiabetic drug needing the second drug for optimal blood glucose control.[29]

Liraglutide has been approved for the combination with metformin and/or a sulfonylurea or with metformin and a thiazolidinedione, if treatment with one or a combination of these drugs is not sufficient.[30] In patients failing to sulphonylureas and/or metformin, GLP-1 receptor agonists are shown to be as effective as insulin.[31]

In the treatment of type 2 diabetes long-term projected survival, diabetes complications, and costs have shown to be favorable with liraglutide in comparison with glimepiride or rosiglitazone.[32,33,34] When compared to exenatide twice a day liraglutide provided significantly greater improvements in glycaemic control and was seen to be generally better tolerated. It may be particularly beneficial in obese patients whose weight is a significant risk factor for cardiovascular diseases. It may also be useful in those patients who are at risk of hypoglycemia. It can be used early in those at risk of developing diabetes and can play a role in preventing the disease incidence. Early use may also be effective in those who already have diabetes, where the disease progression can be slowed or stopped.[35]

Adverse effects

The most common adverse events reported with liraglutide are gastrointestinal. There can be occurrence of nausea, vomiting and diarrhea. Most cases of the treatment discontinuation have been reported to be due to the gastrointestinal adverse events.[29, 36] These are generally seen to be more prominent during the initial period of therapy and decrease during later days of the drug use.[37] Transient nausea is the most common side effect.[38] It has been reported by 11-19% of the liraglutide-treated subjects.[39]

Headache, dizziness, fever have been reported in a few cases. The urine output can decrease but there is no clinically relevant change in packed cell volume. The vital signs, ECG parameters, physical examination or safety laboratory parameters remain within normal limits.[5] Four patients have been found to have developed acute (n = 3) or chronic (1) pancreatitis during the various liraglutide clinical trials. Observational reports and clinical trial data suggest that GLP-1 agonist use can be associated with acute pancreatitis; however, more studies and in-depth case report analysis are needed for further evaluation and verification of this association.[40]

A safety concern related to Liraglutide is that it caused C-cell stimulation in mice leading to hyperplasia and neoplasia including medullary thyroid carcinoma through a GLP-1 receptor stimulation of the C-cells. In clinical trials there have been no reported cases of medullary thyroid carcinoma in patients treated with liraglutide. More studies will be needed to rule out the carcinogenic potential of the drug in human beings and it cannot be concluded that the preclinical findings in the rodents have no relevance. So Liraglutide is contraindicated in patients with a personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2.[41]

Summary

The human GLP-1 analogue liraglutide can play an important role among the main options for treatment of type 2 DM. It can be efficiently used as add-on therapy in case of secondary failure. It can also be part of an early strategy to reduce the burden of the disease and its complications.

References

1. Nauck MA, Meier JJ. Glucagon-like peptide 1 and its derivatives in the treatment of diabetes. Regul Pept 2005 Jun 15;128(2):135-48.
2. Deacon, Carolyn F. Potential of liraglutide in the treatment of patients with type 2 diabetes. Vascular Health and Risk Management 2009, Jan, 01; 5:199-211.
3. Vilsboll T. Liraglutide: a new treatment for type 2 diabetes. Drugs Today (Barc). 2009 Feb; 45(2):101-13.
4. 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; 43:1664–1669.
5. Agersø H, Jensen LB, Elbrønd B, Rolan P, Zdravkovic M. The pharmacokinetics, pharmacodynamics, safety and tolerability of NN2211, a new long-acting GLP-1 derivative, in healthy men. Diabetologia. 2002 Feb;45(2):195-202.
6. Watson E, Jonker DM, Jacobsen LV, Ingwersen SH. Population Pharmacokinetics of Liraglutide, a Once-Daily Human Glucagon-Like Peptide-1 Analog, in Healthy Volunteers and Subjects With Type 2 Diabetes, and Comparison to Twice-Daily Exenatide. J Clin Pharmacol. 2010 Feb 4. [Epub ahead of print]
7. Jacobsen LV, Hindsberger C, Robson R, Zdravkovic M. Effect of renal impairment on the pharmacokinetics of the GLP-1 analogue liraglutide. Br J Clin Pharmacol. 2009 Dec;68(6):898-905.
8. Damholt B, Golor G, Wierich W, Pedersen P, Ekblom M, Zdravkovic M. An open-label, parallel group study investigating the effects of age and gender on the pharmacokinetics of the once-daily glucagon-like peptide-1 analogue liraglutide. J Clin Pharmacol. 2006 Jun;46(6):635-41
9. Mudaliar S, Henry RR. Effects of incretin hormones on beta-cell mass and function, body weight, and hepatic and myocardial function. Am J Med. 2010 Mar;123(3 Suppl):S19-27.
10. Montanya E, Sesti G. A review of efficacy and safety data regarding the use of liraglutide, a once-daily human glucagon-like peptide 1 analogue, in the treatment of type 2 diabetes mellitus.Clin Ther. 2009 Nov;31(11):2472-88.

11. Rolin B, Larsen MO, Gotfredsen CF, Deacon CF, Carr RD, Wilken M, et al. The long-acting GLP-1 derivative NN2211 ameliorates glycemia and increases beta-cell mass in diabetic mice. Am J Physiol Endocrinol Metab. 2002 Oct;283(4):E745-52.
12. Chang AM, Jakobsen G, Sturis J, Smith MJ, Bloem CJ, An B, et al .The GLP-1 derivative NN2211 restores beta-cell sensitivity to glucose in type 2 diabetic patients after a single dose. Diabetes. 2003 Jul;52(7):1786-91.)
13. Degn KB, Juhl CB, Sturis J, Jakobsen G, Brock B, Chandramouli V, Rungby J, et al. One week's treatment with the long-acting glucagon-like peptide 1 derivative liraglutide (NN2211) markedly improves 24-h glycemia and alpha- and beta-cell function and reduces endogenous glucose release in patients with type 2 diabetes. Diabetes. 2004 May;53(5):1187-94.)
14. Russell-Jones D, Vaag A, Schmitz O, Sethi BK, Lalic N, Antic S, 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 Oct;52(10):2046-55.
15. Sturis J, Gotfredsen CF, Rømer J, Rolin B, Ribel U, Brand CL, 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 Sep;140(1):123-32. Epub 2003 Jul 29.
16. Ribel U, Larsen MO, Rolin B, Carr RD, Wilken M, et al. NN2211: a long-acting glucagon-like peptide-1 derivative with anti-diabetic effects in glucose-intolerant pigs. Eur J Pharmacol. 2002 Sep 13;451(2):217-25
17. Juhl CB, Hollingdal M, Sturis J, Jakobsen G, Agersø H, Veldhuis J, et al. Bedtime administration of NN2211, a long-acting GLP-1 derivative, substantially reduces fasting and postprandial glycemia in type 2 diabetes. Diabetes. 2002 Feb;51(2):424-9.
18. Nauck M, Frid A, Hermansen K, Shah NS, Tankova T, Mitha IH, 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 Jan;32(1):84-90.
19. Deacon CF. Potential of liraglutide in the treatment of patients with type 2 diabetes. Vasc Health Risk Manag. 2009;5(1):199-211.
20. Astrup A, Rössner S, Van Gaal L, Rissanen A, Niskanen L, Al Hakim M,et al. Effects of liraglutide in the treatment of obesity: a randomised, double-blind, placebo-controlled study. Lancet. 2009 Nov 7;374(9701):1606-16.
21. Jendle J, Nauck MA, Matthews DR, Frid A, Hermansen K, Düring M et al. Weight loss with liraglutide, a once-daily human glucagon-like peptide-1 analogue for type 2 diabetes treatment as monotherapy or added to metformin, is primarily as a result of a reduction in fat tissue. Diabetes Obes Metab. 2009 Dec;11(12):1163-72.
22. Madsbad S, Schmitz O, Ranstam J, Jakobsen G, Matthews DR.Improved glycemic control with no weight increase in patients with type 2 diabetes after once-daily treatment with the long-acting glucagon-like peptide 1 analog liraglutide (NN2211): a 12-week, double-blind, randomized, controlled trial. Diabetes Care. 2004 Jun;27(6):1335-42.
23. Gallwitz B, Vaag A, Falahati A, Madsbad S. Adding liraglutide to oral antidiabetic drug therapy: onset of treatment effects over time. Int J Clin Pract. 2010 Jan;64(2):267-76.
24. Liu H, Dear AE, Knudsen LB, Simpson RW.A long-acting glucagon-like peptide-1 analogue attenuates induction of plasminogen activator inhibitor type-1 and vascular adhesion molecules. J Endocrinol. 2009 Apr;201(1):59-66.
25. Chatterjee DJ, Khutoryansky N, Zdravkovic M, Sprenger CR, Litwin JS. Absence of QTc prolongation in a thorough QT study with subcutaneous liraglutide, a once-daily human GLP-1 analog for treatment of type 2 diabetes. J Clin Pharmacol. 2009 Nov;49(11):1353-62.
26. Chatterjee DJ, Khutoryansky N, Zdravkovic M, Sprenger CR, Litwin JS. Absence of QTc prolongation in a thorough QT study with subcutaneous liraglutide, a once-daily human GLP-1 analog for treatment of type 2 diabetes. J Clin Pharmacol. 2009 Nov;49(11):1353-62.
27. Kristensen J, Mortensen UM, Schmidt M, Nielsen PH, Nielsen TT, Maeng M. Lack of cardioprotection from subcutaneously and preischemic administered liraglutide in a closed chest porcine ischemia reperfusion model. BMC Cardiovasc Disord. 2009 Jul 23;9:31.

28. Drab SR. Clinical studies of liraglutide, a novel, once-daily human glucagon-like peptide-1 analog for improved management of type 2 diabetes mellitus. Pharmacotherapy. 2009 Dec;29(12 Pt 2):43S-54S.
29. Nauck M, Marre M. Adding liraglutide to oral antidiabetic drug monotherapy: efficacy and weight benefits. Postgrad Med. 2009 May;121(3):5-15
30. Zinman B, Gerich J, Buse JB, Lewin A, Schwartz S, Raskin P, et al. Efficacy and safety of the human glucagon-like peptide-1 analog liraglutide in combination with metformin and thiazolidinedione in diabetes mellitus. Diabetes Care. 2009 Jul;32(7):1224-30.
31. Monami M, Marchionni N, Mannucci E. Glucagon-like peptide-1 receptor agonists in type 2 diabetes: a meta-analysis of randomized clinical trials. Eur J Endocrinol. 2009 Jun;160(6):909-17.
32. Sullivan SD, Alfonso-Cristancho R, Conner C, Hammer M, Blonde L. A simulation of the comparative long-term effectiveness of liraglutide and glimepiride monotherapies in patients with type 2 diabetes mellitus. Pharmacotherapy. 2009 Nov;29(11):1280-8.
33. Marre M, Shaw J, Brändle M, Bebakar WM, Kamaruddin NA, Strand J, 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 Mar;26(3):268-78.
34. Sullivan SD, Alfonso-Cristancho R, Conner C, Hammer M, Blonde L. Long-term outcomes in patients with type 2 diabetes receiving glimepiride combined with liraglutide or rosiglitazone. Cardiovasc Diabetol. 2009 Feb 26;8:12.
35. Buse JB, Rosenstock J, Sesti G, Schmidt WE, Montanya E, Brett JH. 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 Jul 4;374(9683):39-47.
36. Halimi S.DPP-4 inhibitors and GLP-1 analogues: for whom? Which place for incretins in the management of type 2 diabetic patients? Diabetes Metab. 2008 Feb;34 Suppl 2:S91-5.
37. Deacon CF. Potential of liraglutide in the treatment of patients with type 2 diabetes. Vasc Health Risk Manag. 2009;5(1):199-211.
38. Rossi MC, Nicolucci A. Liraglutide in type 2 diabetes: from pharmacological development to clinical practice. Acta Biomed. 2009 Aug;80(2):93-101.
39. Nauck M, Frid A, Hermansen K, Shah NS, Tankova T, Mitha IH 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 Jan;32(1):84-90.
40. Anderson SL, Trujillo JM. Association of Pancreatitis with Glucagon-Like Peptide-1 Agonist Use. Ann Pharmacother. 2010 Apr 6. [Epub ahead of print]
41. Parks M, Rosebraugh C.Weighing risks and benefits of liraglutide—the FDA's review of a new antidiabetic therapy. N Engl J Med. 2010 Mar 4;362(9):774-7.