Review Article

Liraglutide: A review of its therapeutic use as a once daily GLP-1 analog for the management of type 2 diabetes mellitus

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ABSTRACT

Type 2 diabetes mellitus (T2DM) is a progressive disease associated with significant morbidity and mortality. Even though progress have been accomplished in the management of type 2 diabetes, current treatment preferences for patients with this disease still fall short to address disease progression. With the present therapy, glycaemic control remains suboptimal and are often associated with weight gain and hypoglycaemia. Glucagon like peptide-1 (GLP-1) is an incretin hormone secreted from the small intestine that lowers fasting and postprandial glucose through multiple mechanisms including glucose-dependent insulin secretion, reduction of glucagon secretion, delaying gastric emptying and increased satiety. Liraglutide, a human glucagon-like peptide 1 (GLP-1) analogue is a treatment for T2DM that is administered as a once-daily subcutaneous injection. The efficacy and tolerability of liraglutide at doses of 0.6, 1.2, and 1.8 mg for T2DM, in combination with, and compared with, other T2DM treatments were investigated in the Liraglutide Effect and Action in Diabetes (LEAD) Phase III clinical trial program. In the LEAD trial, treatment with liraglutide was associated with substantial improvements in glycaemic control and low risk of hypoglycaemia. In addition liraglutide significantly improved β-cell function, reduced systolic blood pressure (BP) and induced weight loss. Overall, liraglutide was well tolerated. Recent data on safety and efficacy of liraglutide from real-life clinical practice settings also reiterate the better therapeutic profile of this molecule. Based on results from the LEAD programme, and real-life clinical experience, liraglutide has been demonstrated as an effective therapeutic intervention even at the early stage of diabetes regardless of with what, it has been used.

Key words: Diabetes, GLP-1 analog, liraglutide

Introduction

Current treatment strategies in type 2 diabetes mellitus (T2DM) address twin issues of insulin resistance and relative deficiency. Despite the proliferation of newer novel treatment options, majority of people with T2DM do not achieve the glycemic goals and are at risk for serious diabetic complications. Recent advances in diabetes research have revealed the important role of incretin hormones in maintaining glucose control. These findings create a unique platform for newer therapeutic options that improve pancreatic islet function, including insulin secretion by the β-cells and glucagon secretion by the α-cells. Studies have shown that incretin pathways play a role in the progression of T2DM.[1,2] The significant reduction in the incretin effect seen in patients with T2DM has been attributed to several factors, including impaired secretion of glucagon-like peptide-1 (GLP-1), accelerated metabolism of GLP-1 and glucose-dependent insulinotropic polypeptide (GIP), and defective responsiveness to both the hormones.[1] Many patients with T2DM also have accelerated gastric emptying that may contribute to deterioration of their glycemic control.[3]

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The Concept of GLP-1

The term 'incretin' was used to denote these glucose-lowering, intestinal-derived factors as outlined in La Barre[4] in 1932. With the development of radioimmunoassay, this communication between the intestine and the endocrine pancreas was confirmed, when it was demonstrated that glucose ingestion is associated with a much greater increase in plasma insulin levels when compared to the insulin release after intravenous glucose administration.[5,6] This phenomenon has been dubbed the 'incretin effect' and is estimated to account for approximately 50-70% of the total insulin secreted following oral glucose administration. Thus, incretins are hormones secreted from the gastrointestinal tract into circulation in response to nutrient ingestion and enhance glucose-stimulated insulin secretion.

GLP-1 contributes to the maintenance of circulating glucose levels also through its actions in the gastrointestinal tract, by inhibiting gastric emptying[7] and small bowel motility in a fed, but not fasting state.[8] The former effect is especially beneficial after an ingestion of a meal when there is a spike in glucose concentrations in circulation, and provides the pancreatic β-cell with a certain lag period during which it can adapt its secretory response with a proper release of insulin. Biological action fo GLP-1 is provided in Table 1.

GLP-1 is a physiological mediator of satiety and regulates energy absorption and disposal.[9] In the central nervous system GLP-1 has been shown to suppress food intake.[10] GLP-1 is an insulinotropic hormone. It is a potent stimulator of insulin release in pancreas[11-14] and has the ability to render pancreatic β-cells glucose-competent[15] and has been used in the therapy of T2DM.[16] The bioactivities of GLP-1 are limited in duration by proteolytic inactivation involving the cleavage at the *N*-terminal penultimate alanine by dipeptidyl peptidase 4 (DPP-4).[17] Bioactive GLP-1 has a very short half-life in plasma due to the rapid degradation by DPP-4,[18,19] a problem that has been solved by employing protease-resistant analogs.

Table 1: Biological actions of GLP-1 in relation to the pathophysiology of type 2 diabetes mellitus.

Organ/tissue or function	GLP-1 activity
Pancreas	Preserved activity
Insulin Secretion	Increases
Glucagon secretion	Decreases
β-cell apoptosis	Decreases
β-cell mass	Increases due to replication
Food intake	Decreases
Body weight	Decreases
Gastric emptying	Decreases
Triglycerides (Post-prandial)	Decreases
Free fatty acids (Post-prandial)	Decreases
Insulin resistance	Decreases
Insulin sensitivity	Increases
Insulin biosynthesis	Increases
Glucose uptake and storage in peripheral tissue	Increases
Hepatic glucose output	Decreases
Cardioprotection	Increases
Cardiac function	Improves
Neuroprotection	Increases
Appetite	Decreases

In addition to its physiological effects on β-cells, GLP-1 has cytokine activity, although it is not classified as such due its small size. GLP-1 enhances cell differentiation, plays a role in tissue regeneration, and mediates cytoprotection.[9,10] GLP-1 directly regulates signaling pathways coupled to cell proliferation and apoptosis.[20]

GLP-1 stimulates proliferation of pancreatic β-cells and thus contributes to islet regeneration. β-cell mass regeneration is significantly impaired in knock-out mice lacking expression of the GLP-1 receptor.[21] The effects of GLP-1 on β-cells are mediated by transactivation of the epithelial growth factor (EGF) receptor and its ligand, betacellulin.[22] GLP-1 also promotes cell differentiation of immature islet progenitors toward a more differentiated β-cell phenotype.[23]

GLP-1 has been shown to promote islet cell growth and inhibit apoptosis *in vivo* in Zucker Diabetic rats, in which the onset of diabetes occurs when the proliferative potential and the rate of β-cell apoptosis no longer compensate for increased insulin demands.[24]

Regardless of the beneficial actions of GLP-1 on glucose control, their use as anti-diabetic agents was unfeasible due to their short half-life as result of their rapid inactivation by DPP-4. The half-life of GLP-1 is approximately 2 min following intravenous administration. Accordingly, two approaches have been carried out to surmount this drawback. The first consists of the development of GLP-1 analogs, also called incretin mimetics that bind to the GLP-1 receptors with the same affinity as GLP-1 but resist the degradation by DPP-4. The second is to design drugs that inhibit the action of DPP-4, called incretin enhancers. The latter agents prolong the effects of native GLP-1 and increase their serum levels approximately two-fold.[25]

Structure and Pharmacological Actions of Liraglutide

The drug substance, liraglutide, is a long acting analog of the naturally occurring human GLP-1(7-37) with 97% homology and a lipophilic substituent for prolongation

of half life [Figure 1]. Unlike GLP-1, liraglutide has a pharmacokinetic and pharmacodynamic profile in human suitable for once daily administration. Following subcutaneous administration, the protracted action profile is based on three mechanisms: self-association, which results in slow absorption, binding to albumin and stability toward the DPP-4 enzyme both resulting in a prolonged plasma half-life. The analog is produced as the polypeptide precursor by r-DNA technology with *Saccharomyces cerevisiae* strain YES2085 as the production strain. The peptide is acylated with a fatty acid chain during down-stream processing. Liraglutide is a GLP-1 analog in which lysine at position 34 has been replaced with arginine, and palmitic acid has been attached via glutamoyl spacer to lysine at position 26. No animal-derived raw materials or excipients are used in the production of liraglutide. The drug product is a solution for subcutaneous injection containing 6.0 mg/ml of the drug substance presented in a pre-filled, multi-dose pen-injector.

Liraglutide is a long-acting GLP-1 analog, designed to bind to albumin as the main molecular mechanism of protraction. *In vitro*, this was shown in the receptor cAMP as well as binding assay where addition of albumin shifted the dose-response and/or binding curve to the right. The apparent reduced potency of liraglutide underlines that only the free fraction of liraglutide is responsible for its pharmacological effect *in vitro* as well as *in vivo*. Furthermore, liraglutide in a pharmaceutical solution forms a micell-like heptamer which may contribute to the slow absorption from the subcutis. Liraglutide is a potent, selective and efficacious agonist on the human as well as mouse, rat, rabbit, pig and Cynomolgus monkey GLP-1 receptor. Liraglutide has been shown to exert a number of actions *in vitro* that are known to be specific GLP-1 effects. Liraglutide has also been shown stimulate insulin secretion from isolated β-cell islets in a glucose-dependent manner *in vitro*. Liraglutide-attenuated β-cell apoptosis *in vitro* under adverse conditions with high concentrations of free fatty acids and proinflammatory cytokines. Moreover, a proliferative effect on primary rat β-cells was demonstrated for liraglutide *in vitro* whereas no consistent effect was observed under hyperglycemic conditions *in vivo*.[26]

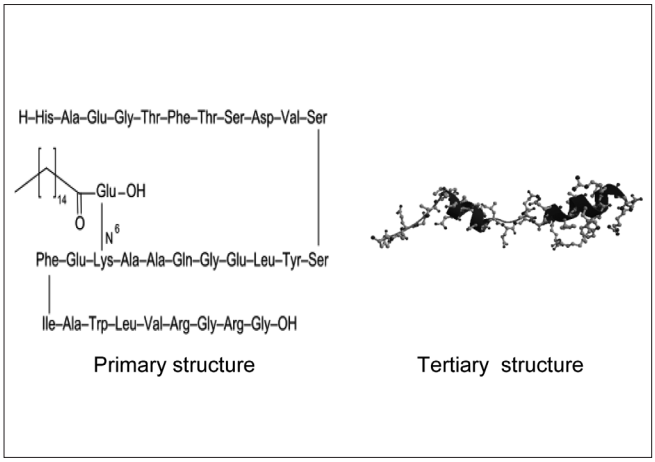


Figure 1: Structure of liraglutide

Liraglutide Effect and Action in Diabetes Studies

The liraglutide effect and action in diabetes (LEAD) program was composed of six randomized, controlled, Phase 3 clinical studies in participants with T2DM inadequately controlled with lifestyle and dietary interventions or oral antidiabetic drugs (OADs) [Table 2]. The implementation of liraglutide therapy throughout the continuum of care is shown in Figure 2. A total of 4,456 subjects were included, recruited at more than 600 sites across 40 countries, of which 2,739 patients were treated with liraglutide. LEAD trial was designed to investigate the efficacy and safety of patients treated with liraglutide across the continuum of care of T2DM versus placebo. In the LEAD trials, liraglutide was also compared to some commonly used antidiabetic therapies. In addition to the registration studies (LEAD-1 to LEAD-5),[27-31] a head-to-head trial against exenatide (LEAD-6)[32] was also completed. The LEAD program established that liraglutide, used as monotherapy or in combination with one or two OADs, provides substantial reductions in HbA1c. Liraglutide reduced HbA1c levels to a significantly greater extent than its active comparators, except in LEAD-2, where HbA1c reductions with liraglutide were comparable to glimepiride plus metformin (−1.0%) in the overall study population.[26]

Glycemic Control

Across the LEAD trials, reductions in HbA1c of up to 1.6% were achieved with the higher doses of liraglutide (1.2 and 1.8 mg) relative to baseline [Figure 3].[27-32] Reductions in HbA1c primarily occurred within 8-12 weeks when liraglutide 1.2 and 1.8 mg were added to metformin (LEAD-2),[28] glimepiride (LEAD-1)[27] and metformin plus rosiglitazone (LEAD-4).[30] These reductions were sustained throughout each study period and were significantly greater compared with placebo [Figure 3]. A higher percentage of subjects in the liraglutide-treated groups reached American Diabetes Association (ADA) target HbA1c < 7.0% in all of the LEAD studies compared with active comparators [Figure 4].[27-32] The greatest reduction in HbA1c (−1.60%) was experienced in the LEAD-3 trial (liraglutide monotherapy) by the subgroup of patients

Table 2: Efficacy data of liraglutide as observed in liraglutide effect and action in diabetes studies

Treatment arm	N (randomized)	Mean HbA1c Change from baseline (%)	Reaching ADA target <7.0% (%)	Reaching IDF target <6.5 (%)	Mean FPG Change from Baseline (mmol/L)	Mean weight change from baseline (Kg)	Mean SBP Change from baseline (mmHg)
LEAD-3: Liraglutide as monotherapy vs. glimepiride							
Liraglutide 1.2 mg	251	-0.8	43	28	-0.84	-2.05	-2.12
Liraglutide 1.8 mg	247	-1.1	51	38	1.42	2.45	3.64
Glimepiride 8 mg	248	-0.5	28	16	0.29	1.12	0.69
Liraglutide 1.8 mg Previously drug-naive	87	-1.6	62	49	-2.33	-1.61	-4.73
LEAD-2: Liraglutide added on to metformin vs. glimepiride							
Liraglutide 1.2 mg	241	-1.0	35	20	-1.64	-2.6	-2.8
Liraglutide 1.8 mg	242	-1.0	42	24	1.69	-2.8	2.3
Glimepiride 4 mg	244	-1.0	36	22	1.31	1.0	0.4
Placebo	122	0.1	11	4	0.40	-1.5	-1.8
Liraglutide 1.8 mg Previously drug-naive	83	-1.30	66	39	-1.36	-2.1	-1.18
LEAD-1: Liraglutide added on to glimepiride vs. rosiglitazone							
Liraglutide 1.2 mg	228	-1.1	34	21	-1.57	0.3	-2.6
Liraglutide 1.8 mg	234	-1.1	42	21	1.59	-0.2	2.8
Rosiglitazone 4 mg	232	-0.4	21	9.5	0.88	2.1	0.9
Placebo	114	0.2	8	4	1.01	-0.1	2.3
Liraglutide 1.8 mg on previous OAD monotherapy	63	-1.38	56	32.2	-0.71	-0.11	-3.49
LEAD-4: Liraglutide added on to metformin + rosiglitazone vs. placebo							
Liraglutide 1.2 mg	178	-1.5	58	37	-2.20	-1.0	-6.7
Liraglutide 1.8 mg	178	-1.5	54	36	-2.40	-2.0	-5.6
Placebo	177	-0.5	28	14	-0.43	0.6	-1.1
LEAD-5: Liraglutide added on to metformin + glimepiride vs. insulin glargine							
Liraglutide 1.8 mg	232	-1.3	53	37	-1.55	-1.81	-4.0
Insulin glargine	234	-1.1	46	24	-1.79	1.62	0.5
Placebo	115	-0.2	16	11	0.53	-0.42	-1.4
LEAD-6: Liraglutide added on to metformin and/or glimepiride vs. exenatide							
Liraglutide 1.8 mg	233	-1.1	54	35	-1.61	-3.24	-2.51
Exenatide 10 μg BID	231	-0.8	43	21	-0.60	-2.87	-2.0

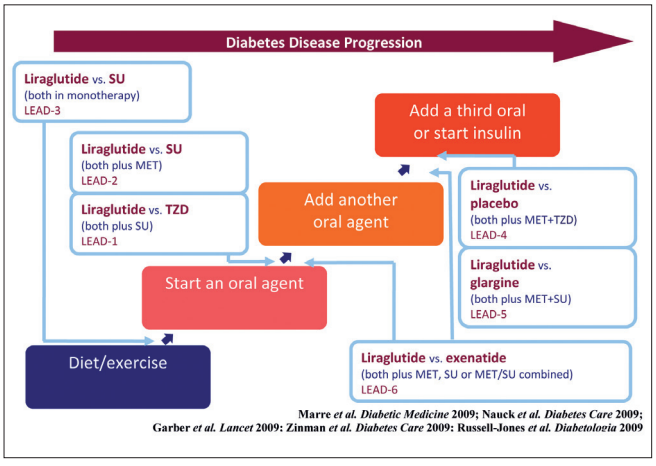
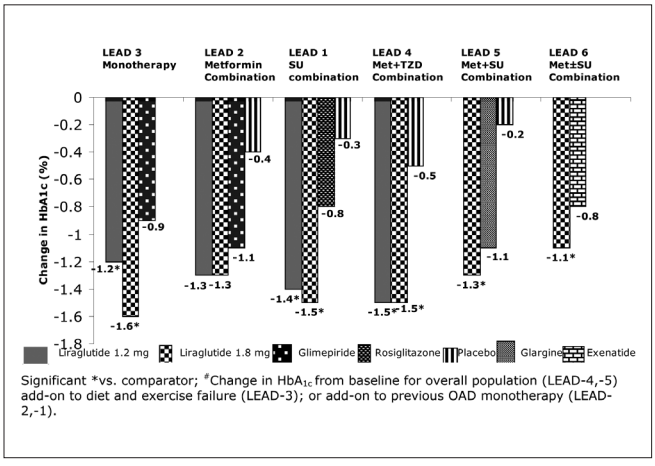


Figure 2: Liraglutide implementation throughout the continuum of care



Significant *vs. comparator; #Change in HbA_{1c} from baseline for overall population (LEAD-4,-5) add-on to diet and exercise failure (LEAD-3); or add-on to previous OAD monotherapy (LEAD-2,-1).

Figure 3: Change in HbA1c from baseline (LEAD-1-6) for overall population (LEAD-4-6), add-on to diet and exercise (LEAD-3) and add-on to previous OAD monotherapy (LEAD-1-2)

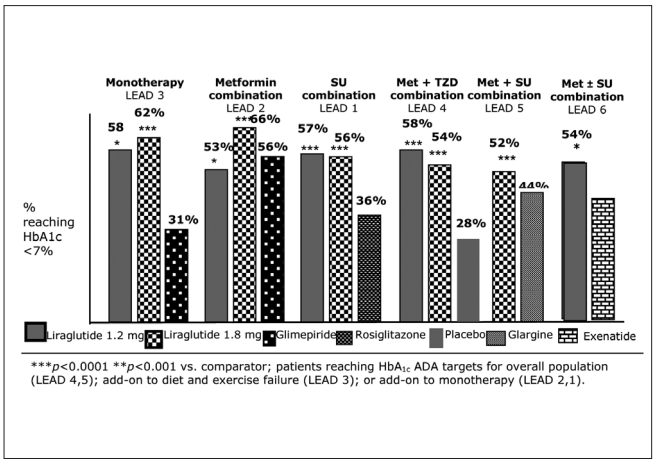


Figure 4: Percentage of subjects reaching ADA target HbA1c <7.0% in the LEAD-1-6 trials

previously on diet and exercise: the true initial monotherapy population.[29] In the head-to-head study of liraglutide 1.8 mg once daily *versus* exenatide 10 µg twice daily (as add-on to metformin and/or SU therapy), mean HbA1c reduction was significantly greater with liraglutide treatment than with exenatide (-1.12% vs. -0.79%, *P*<0.0001), and corresponded to more patients achieving HbA1c <7.0% (54% vs. 43%, respectively; odds ratio 2.02; 95% confidence interval [CI] 1.31 to 3.11; *P*=0.0015).[32] Both the drugs resulted in comparable weight loss, with 3.2 kg with liraglutide and 2.9 kg with exenatide. In general, both drugs were well accepted. In the liraglutide group there was less nausea and hypoglycemia caused by low blood sugar was less frequent, than with exenatide.[32]

Liraglutide also provided substantial reductions in fasting plasma glucose (FPG) across the continuum of care. FPG reductions of up to −43.2 mg/dl were reported with liraglutide across the LEAD-1-6 studies. Liraglutide was also shown to be effective at reducing postprandial glucose (PPG); consistent reductions were observed in peak PPG (across all three meals) in the LEAD-1-5 studies).[27-31] In the LEAD-6 study, there was a numerically greater reduction in mean PPG after lunch with liraglutide compared with exenatide (2.74 vs. 2.35; not significant). However, exenatide is given twice daily, before morning and evening meals, thus PPG was reduced more with exenatide *versus* liraglutide during these peak times.

β-CELL FUNCTION

Improvements in homoeostasis model assessment of β-cell function (HOMA-B) and proinsulin: insulin ratio has been well-established using liraglutide. HOMA-B increased significantly with liraglutide (1.2 and 1.8 mg) in combination with glimepiride when compared to glimepiride plus rosiglitazone. An improvement of 62-71% in HOMA-B were reported from baseline values of 40-47% with all liraglutide treatment groups in combination with metformin. For instance, when liraglutide was added to metformin, HOMA-B increased to the same extent as with glimepiride (68%) and significantly greater than that with placebo which demonstrated no change from baseline.[33] Improvement was also observed in β -cell function when liraglutide was combined with two OADs. HOMA-B increased by 27.2% from a baseline of 34.4% with liraglutide 1.8 mg in combination with rosiglitazone plus metformin. This increment in HOMA-B assessment was significantly greater (*P*<0.0001) than the 5.8% increase from baseline of 39.5% observed with placebo added to rosiglitazone plus metformin. HOMA-B also significantly increased by 32.86 absolute percentage points with liraglutide 1.8 mg in combination with glimepiride plus metformin from baseline values of 54.3% in comparison with a slight reduction (-1.14%) with the addition of placebo to glimepiride plus metformin (*P*< 0.0001).[34] A reduction in pro-insulin:insulin ratio is a marker for improved β-cell function; in the LEAD-1 study, reductions in the pro-insulin:insulin ratio with liraglutide 1.2 mg (−0.11) and 1.8 mg (−0.10) were significantly greater compared with rosiglitazone (−0.05) and placebo (−0.01; *P*< 0.05 for all comparisons).[27]

Body weight

Liraglutide has consistently offered a significant weight advantage compared with trial comparators. In LEAD-1 study, unlike rosiglitazone, weight did not increase substantially with liraglutide and the differences between rosiglitazone and liraglutide were statistically significant (−2.3 to −1.4 kg; *P*<0.0001), although there were no significant differences compared with placebo. A significant and continuous weight reduction with liraglutide monotherapy (at 1.8 and 1.2 mg) was reported in comparison with glimepiride (*P*<0.0001 for both). In liraglutide monotherapy weight loss occurred mostly in the initial 16 weeks; however, it was subsequently continued throughout the 52 weeks of the study. Weight loss with liraglutide has a tendency to be dose dependent both in monotherapy and in combination regimens. For instance, liraglutide 0.6, 1.2 and 1.8 mg administered in combination with metformin for a 26-week duration resulted in weight reductions of -1.8, -2.6 and -2.8 kg respectively. This reduction was significantly different to the weight gain that occurred when metformin was combined with glimepiride (1.0 kg, *P*<0.0001). The 1.2 and 1.8 mg doses of liraglutide when combined with metformin and rosiglitazone, resulted in weight reductions of -1.02 and -2.02 kg, respectively, and it was significantly

different from the 0.6 kg weight gain observed with the addition of placebo to metformin and rosiglitazone ($P<0.0001$ for both comparisons vs. placebo). Besides, in LEAD 5 trial weight loss with liraglutide was greater than that with placebo (difference 1.4 kg, $P<0.0001$) or insulin glargine (difference 3.4 kg, $P<0.0001$).

LEAD 2 trial subgroup of 160 patients with T2DM demonstrated that the greater part of weight loss reported was fat tissue and it was mostly due to visceral adipose tissue loss as demonstrated by dual energy X-ray absorptiometry and computed tomography.[33]

Systolic blood pressure

Liraglutide provides clinically significant reductions in systolic blood pressure (SBP), as demonstrated across all of the LEAD trials, with reductions up to 6.7 mmHg seen for liraglutide with metformin+TZD, whereas metformin+TZD was associated with a reduction in SBP from baseline of 1.1 mm Hg.[30] Significant reductions in SBP were observed as early as 2 weeks after initiation of liraglutide treatment and could be observed before any significant weight loss occurred.

Potential benefits on cardiovascular function

Liraglutide has demonstrated preliminary beneficial effects on the cardiovascular function.[34,35] Beyond the effects on weight loss, blood pressure reduction and lipid profile improvement, liraglutide has a direct natriuretic effect[36] and a causes endothelial vasodilatation.[37] Supplementary data show that liraglutide reduces several markers of cardiovascular risk, such as C-reactive protein, type 2 natriuretic peptide, and PAI-1.[38] These findings underline the potential role of liraglutide in individuals with heart failure or coronary artery disease, also suggested by animal and clinical studies. In particular, continuous infusion of liraglutide is associated with an improvement in left ventricular function in patients with acute myocardial infarction and severe systolic dysfunction[38] and in patients with congestive heart failure.[39] The protective effect of liraglutide on ischemic and reperfusion injury, mediated by inhibition of apoptosis, has been documented in animal models showing that these compounds may reduce infarct size and improve outcomes after experimental myocardial infarction.[33,38]

Safety and tolerability

Since liraglutide acts in a glucose-dependent manner[40,41] the risk of hypoglycemia is low [Table 3]. It ranged from 3 to 12%, in monotherapy or combination therapy trials and was mild to moderate, with no major episodes.[28-30] In studies where liraglutide was combined with a sulfonylurea, which is known to increase the risk of hypoglycemia, the incidence ranged from 5 to 27%. Six liraglutide-treated patients experienced major episodes in these trials.[27,31] As noted above, the only head-to-head comparison of liraglutide and found a significantly lower rate of minor hypoglycemia with liraglutide in comparison to exenatide.[32] Gastrointestinal adverse events were the most common side effects with liraglutide, but were transient in nature. Nausea, which occurred in 5 to 40% of liraglutide-treated patients, subsided within the first 4 weeks of use.[27-31] In LEAD-6 study where the head-to-head comparison of liraglutide and exenatide was done, the incidence rate of nausea was initially similar, but less persistent in the liraglutide group.[32] By week 6, less than 10% of patients in the liraglutide group experienced nausea. The exenatide group reached this level at 22 weeks.

Primary, data from studies in rodents suggested that liraglutide was associated with an increased risk of thyroid C-cell focal hyperplasia and C-cell tumors.[42] These findings were not seen in non-human primates like Cynomolgus monkey. Rat thyroid contains more C-cells and also expresses more GLP receptor, hence they are more prone, primates have less and human have even lesser hence risk is minimal.[42] Other long acting GLP-1 analogs too have shown similar finding in *in vitro* experiments but no incidence in human has been reported after so many patient years of use.[42]

Serum calcitonin levels, below 10 pg/ml are considered to be evidence of the absence of medullary thyroid cancer, whereas levels above 100 pg per milliliter are highly predictive of medullary thyroid cancer.[43] In the controlled clinical trials with liraglutide, increases in calcitonin levels occurred in a slightly higher percentage of the patients treated with liraglutide than in control patients; although the increases represented shifts from below to slightly above the assay's detection limit (0.7 ng/L), calcitonin levels were still within normal ranges. Furthermore, data from a long-term study did not reveal any notable difference in mean calcitonin levels between liraglutide and control groups over 2 years of follow-up.[44]

Few cases (<0.2%) of acute pancreatitis have been reported during long-term clinical trials with liraglutide. A causal relationship between liraglutide and pancreatitis can neither be established nor excluded.[26]

Experience from Real Life Practice

Recent data published on safety and efficacy of liraglutide from real-life clinical practice setting proved the significant reduction in mean HbA1c, FPG and PPG at the end of 12 weeks treatment with liraglutide.[45] There was

Table 3: Safety and tolerability data of liraglutide as demonstrated in liraglutide effect and action in diabetes trials

Treatment arm	N (randomized)	Nausea (% of subjects)	Hypos-Major (Events per subject year)	Hypos-Minor (Events per subject year)	Antibodies (%)	SAE/ Withdrawals/ withdrawals AE (% of subjects)
LEAD-3: Liraglutide as monotherapy vs. glimepiride						
Liraglutide 1.2 mg	251	27.5	0	0.30	7.1	6.4/35.5/10.0
Liraglutide 1.8 mg	247	29.3	0	0.25	5.4	3.3/30.0/7.3
Glimepiride 8 mg	248	8.5	0	1.96	N/A	5.2/38.7/6.0
Liraglutide 1.8 mg Previously drug-naïve	87	29.9	0	0.43	9.1	3/25/4.6
LEAD-2: Liraglutide added on to metformin vs. glimepiride						
Liraglutide 1.2 mg	241	16.2	0	0.03	4.0	5.8/18.3/9.5
Liraglutide 1.8 mg	242	18.6	0	0.09	0	3.7/21.0/12.0
Glimepiride 4 mg	244	3.3	0	1.23	N/A	4.1/14.0/3.3
Placebo	122	4.1	0	0.13	N/A	3.3/39.3/1.6
Liraglutide 1.8 mg Previously drug-naive	83	20.5	0	0.17	0	3/17/ 14.5
LEAD-1: Liraglutide added on to glimepiride vs. rosiglitazone						
Liraglutide 1.2 mg	228	10.5	0	0.51	9-13	3.5/14/4.8
Liraglutide 1.8 mg	234	6.8	0.009	0.47		4.7/9/3.8
Rosiglitazone 4 mg	232	2.6	0	0.12	N/A	2.6/16.4/3
Placebo	114	1.8	0	0.17	N/A	2.6/27.2/5.3
Liraglutide 1.8 mg on previous OAD monotherapy	63	9.5	0	0.27	10.5	3.0/6/6.3
LEAD-4: Liraglutide added on to metformin+rosiglitazone vs. placebo						
Liraglutide 1.2 mg	178	29	0	0.4	4.1	4.5/14/7.9
Liraglutide 1.8 mg	178	40	0	0.6	6.7	3.9/25.3/15.2
Placebo	177	8.6	0	0.2	N/A	6.9/31.6/4
LEAD-5: Liraglutide added on to metformin+glimepiride vs. insulin glargine						
Liraglutide 1.8 mg	232	13.9	0.059	1.2	9.8	4/10.8/4.7
Insulin glargine	234	1.3	1.3	N/A	N/A	7/6.4/2.1
Placebo	115	3.5	1.0	N/A	N/A	7/16.5/0.9
LEAD-6: Liraglutide added on to metformin and/or glimepiride versus exenatide						
Liraglutide 1.8 mg	233	25.5	0	1.93	TBA	5.1/14/9.8
Exenatide 10 μg BID	231	28	0.02	2.60	TBA	2.6/19.4/13.4

significant reductions in body weight and with liraglutide at the end of week 12. Liraglutide also reduced systolic blood pressure and diastolic BP significantly. Significant reductions in serum creatinine and urine albumin levels were observed. Significant improvement was also observed in lipid profile of the patients.[45] According to Ghosal,[46] initiation of liraglutide in patients failing on OADs plus insulin combination effectively improved all glycemic and lipid parameters. In addition there was more than 50% reduction in average daily dose of insulin and close to one third of the patients were completely weaned off insulin. There were reductions in SBP and diastolic BP, total body weight, BMI, waist circumference, serum creatinine and urine albumin while improvement in HDL level

Position of Liraglutide in the Management of T2DM

The LEAD program has demonstrated that liraglutide is effective and well tolerated as a starting therapy (monotherapy) or as an add-on therapy for subjects at a later stage of disease progression. Although the trial data suggest a broad application, experience of liraglutide in clinical practice is limited. The best possible stage of treatment intervention is still speculative. Given a potential effect, if as yet unsubstantiated, on β-cell preservation, it seems possible that earlier use will extend the endogenous insulin function of patients, and perhaps slow progression of the disease. ADA/EASD consensus algorithm also

considers liraglutide and other GLP-1 receptor agonists, for early in the course of T2DM after metformin.[47]

Conclusions

The incretin mimetics and enhancers are novel therapeutic agents for the treatment of T2DM. Liraglutide, the first human once a day GLP-1 analog, improves glycemia with minimal risk of hypoglycemia and enhances β-cell function. In addition, it lowers body weight and has favorable cardiovascular benefits. Liraglutide has the potential to provide long term control of hyperglycemia and improve the cardiometabolic profile of T2DM patients.

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