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Review

Liraglutide in type 2 diabetes: from pharmacological development to clinical practice

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Abstract. The novel drug class of GLP-1 analogues is extremely promising, since existing evidence suggests they can address many of the unmet needs of diabetes treatment, i.e. long-term efficacy, low risk of hypoglycemia, cardiovascular protection, weight loss, long-term safety and tolerability. Besides the already available exenatide, liraglutide is expected to arrive soon on the market. It is a human GLP-1 analogue with high homology (97%) to native hormone. A comprehensive phase III evaluation consisting of six randomized clinical trials - the "Liraglutide Effect and Action Diabetes (LEAD) program" - was recently completed, involving 6500 people seen in 600 sites in 41 countries worldwide. Aim of the LEAD program was to evaluate efficacy and safety of liraglutide as monotherapy and in combination with commonly used antidiabetic drugs. In all studies, once-daily liraglutide was well tolerated, significantly improved metabolic control, and reduced body weight, with low rates of hypoglycemia. Transient nausea was the most common side effects. Additional beneficial effects of liraglutide on beta-cell function, systolic blood pressure, and cardiovascular risk were also documented. If these encouraging results will be confirmed by long-term studies, liraglutide will acquire a prominent role among the main therapeutic options not only as add-on treatments in case of secondary failure, but also as an early strategy to reduce the burden of diabetes and its complications. (www.actabiomedica.it)

Key words: Type 2 diabetes, incretin-mimetics, liraglutide

Introduction

Type 2 diabetes mellitus (T2DM) is a global epidemic and a leading cause of morbidity and mortality that places a substantial economic and health burden on the public (1).

Successful management of T2DM requires strict control of glycemia as well as other risk factors to prevent disease complications (2). Despite the availability of multiple classes of oral antidiabetic drugs (OADs) (i.e. metformin, sulfonylureas, glitazones) and insulin, the majority of patients fail to attain or maintain tight glycemic control over time, raising their risk of serious microvascular and macrovascular complications (3-5).

Current American Diabetes Association (ADA)/ European Association for the Study of Diabetes (EASD) treatment guidelines recommend metformin as the first-line anti-hyperglycemic drug for patients with type 2 diabetes (6-7).

However, when metformin fails, the recommended add-on treatment options (sulfonylureas, glitazones and basal insulin) can lead to significant side effects causing a delay in therapy intensification (8). Weight gain and hypoglycemia are considered among the most common causes of clinical inertia. Weight gain in general affects not only the physiological capability of patients with diabetes to achieve glycemic and cardiovascular risk control, but also their psychological well-being, quality of life and persistence with anti-hyperglycemic treatment (9). In addition, hypoglycemia and fear of hypoglycemia also have a sub-

stantial clinical and economic impact, in terms of mortality, morbidity and quality of life (10).

As a result, exploring new treatment targets and new therapies is mandatory in order to improve diabetes outcomes.

Incretin-based treatments

The incretins-glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are key factors in maintaining the normal balance between insulin and glucagon levels. Intestinal absorption of glucose stimulates secretion of these hormones, which act to increase insulin and decrease glucagon secretion (11).

Studies demonstrating that incretin activity is impaired in type 2 diabetes (12,13) have led to investigations into incretin-based therapies. Two classes of drugs were developed, such as incretin mimetics (analogues of GLP-1) and inhibitors of the dipeptidyl peptidase-4 (DPP-IV), that is the enzyme which inactivates native incretins (14,15).

Incretin-mimetics, like endogenous hormones, act by stimulating the insulin secretion in a glucose-dependent manner and by inhibiting the glucagon release. Besides a reduction in HbA1c and blood glucose levels, further benefits are expected to be obtained during the therapy in terms of:

• *Hypoglycemia:* incretin-mimetics should be associated with a decreased risk of hypoglycaemia in comparison with other classes of diabetes drugs, due to the induction of insulin secretion in a glucose-dependent way;

• *Effect on satiety and body weight:* GLP-1 is associated with enhanced satiety, reduced food intake, and weight loss or neutrality. It remains unclear whether the reason for the increased satiety is the slowed gastric emptying or a central mechanism.

• *Effect on beta-cell health:* GLP-1 preserves beta-cell morphology and function and reduces cellular apoptosis.

• *Effect on post-prandial hyperglycemia:* incretins can impact on this crucial parameter through both the direct inhibition of the glucagon release and the paracrine inhibitory effect exerted by the increased insulin secretion. Moreover, the preservation of beta-cell function represents another factor that may contribute to the long-term control of post-prandial hyperglycemia (16).

A recent meta-analysis (17) 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 nasopharyngitis, upper respiratory infections, and headache.

To date, three drugs, exenatide (GLP-1 mimetic), sitagliptin and vildagliptin (DPP-IV inhibitors) have been approved by regulatory agencies for treating T2DM, whereas a new drug application for liraglutide (GLP-1 mimetic) has been submitted to the US FDA and EMEA (18).

The purpose of this review is to summarize the properties of liraglutide that have been documented in clinical pharmacology studies, as well as the evidence provided by the clinical trials in which its therapeutic efficacy and safety have been assessed in T2DM patients.

Liraglutide

Liraglutide (Novo Nordisk, Bagsvaerd, Denmark) is a modified form of human GLP-1 (19). Native GLP-1 is a 30-amino acid peptide produced by cleavage of the transcription product of the preproglucagon gene (20). Liraglutide is a human GLP-1 analogue with high homology to native hormone. It was obtained by substitution of Lys 34 to Arg, and by addition of a C16 fatty acid at position 26 using a a-glutamic acid spacer. Since there is only one amino acid replacement, the resultant molecule shares 97% (36/37 amino acids) sequence identity with native human GLP-1.

By contrast, exenatide, that was originally identified as a derivate of Gila monster (Heloderma suspectum) venom, shares only 53% sequence identity with native GLP-1 (20,21).

Pharmacology

Liraglutide is administered as an isotonic solution through subcutaneous injection. Pharmacokinetics studies show that liraglutide has a Tmax of 9–13 hrs. and a T1/2 of 13 hrs. The structural modifications of liraglutide are responsible for the prolonged half-life. In fact, following subcutaneous (SC) injection, the fatty acid chain allows liraglutide to self-associate and form heptamers at the injection site depot. It is thought that the size of the heptamer and the strong self-association are the most likely mechanisms by which delayed absorption of liraglutide from the subcutis is facilitated (21).

Once in the bloodstream, the fatty acid chain allows reversible binding to serum albumin providing partial stability and resistance to metabolism by DPP-IV and reduces renal clearance. This stability coupled with albumin-binding gives liraglutide a protracted mechanism of action. The half-life of liraglutide is 13 hrs. following subcutis injection (19) compared with just 1.5–2.1 min for native GLP-1 and 2.4 hrs. for exenatide (22). The prolonged action makes liraglutide suitable for once-daily dosing.

From animals to human trials

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 (23, 24). Further encouraging preclinical and phase I clinical pharmacology results with liraglutide led to larger phase II trials in patients with T2DM, demonstrating that liraglutide is effective and well tolerated, both in monotherapy and in combination therapy with OADs in up to 14 weeks treatment (25-28). Finally, a comprehensive phase III evaluation consisting of six randomized clinical trials was started: overall, the "LEAD (Liraglutide Effect and Action Diabetes) program" (18) involved 6500 people seen in 600 sites in 41 countries worldwide; out of the recruited patients, 4445 received liraglutide. The aim was to evaluate efficacy and safety of liraglutide as monotherapy and in combination with commonly used antidiabetic drugs. In particular, patients were recruited from across the continuum of disease progression to mimic as closely as possible the spectrum of patients seen in the clinical practice.

The LEAD program was completed in 2007. Results of an extension phase for LEAD-3 and LEAD-6 studies have also been recently presented. Table 1 summarizes design and patient characteristics of the LEAD studies, while Table 2 shows the main results obtained.

• *LEAD 3 (liraglutide as monotherapy)* (29): this was a 52 week randomized trial comparing liraglutide (1.2 and 1.8 mg) and glimepiride (8 mg daily). Overall, 36% of participants were on diet and lifestyle and 64% were treated con OADs as monotherapy at baseline. In comparison with glimepiride, HbA1c values decreased significantly more with liraglutide 1.2 mg (difference -0.33%; p=0.0014) and liraglutide 1.8 mg (difference -0.62%; p<0.0001).

A positive effect of liraglutide was also documented on the reduction in fasting and post-prandial blood-glucose levels.

Treatment with liraglutide was associated with weight loss, whereas treatment with glimepiride was associated with weight gain (table 2). Rates of minor hypoglycemia were also lower with liraglutide than with glimepiride.

Five patients in liraglutide 1.2 mg and one in 1.8 mg discontinued treatment for vomiting, in contrast with none in the glimepiride group. In conclusion, liraglutide was documented to be safe and effective as initial pharmacological therapy for T2DM by leading to greater reduction in HbA1c, weight and hypoglycemia than does glimepiride.

The double-blind period has been followed by an open-label, 2 years extension, involving 73% of the patients who had completed the 1-year follow-up. Results of the extension phase show that the greater benefits of liraglutide on metabolic control and body weight as compared to glimepiride are maintained after 2 years, with lower risk of hypoglycemia (30).

• *LEAD 1 (combination with sulfonylurea)* (31): this was a 26-week, five-arm randomized trial testing the effect of three doses of liraglutide (0.8, 1.2 and 1.8 mg) added to glimepiride (4 mg/day) in comparison

Table 1. The LEAD program

Trial	Liraglutide intervention	Control group(s)	N	Duration	Patients characteristics (means±std)
LEAD 1	Liraglutide + glimepiride	Glimepiride + placebo Glimepiride + rosiglitazone	1041	26 weeks	T2DM treated with OADs; age 55±10 years, BMI 30±5 Kg/m^2, HbA1c 8.4±0.9%
LEAD 2	Liraglutide + metformin	Metformin + placebo Metformin + glimepiride	1091	26 weeks	T2DM treated with OADs; age 57±9 years, BMI 30±5 Kg/m^2, HbA1c 8.4±1.0%
LEAD 3	Liraglutide in monotherapy	Glimepiride + placebo	746	52 weeks	T2DM treated with diet/lifestyle or OADs; age 53±11 years, BMI 33±6 Kg/m^2, HbA1c 8.3±1.1%
LEAD 4	Liraglutide + metformin + rosiglitazone	Metformin + rosiglitazone + placebo	533	26 weeks	T2DM treated with OADs; age 55±10 years, BMI 33±5 Kg/m^2, HbA1c 8.3±1.0%
LEAD 5	Liraglutide + metformin + glimepiride	Metformin + glimepiride + placebo Metformin + glimepiride + glargine	581	26 weeks	T2DM treated with OADs; age 57.5±9.9 years, BMI 30.5±5.3 Kg/m^2, HbA1c 8.2±0.9%
LEAD 6	Liraglutide + metformin and/or glimepiride	Exenatide + metformin and/or glimepiride	464	26 weeks with 14 weeks extension	T2DM treated with OADs; age 56.7±10.3 years, BMI 32.9±5.6 Kg/m^2, HbA1c 8.2±1.0%

with the same dose of glimepiride in combination with placebo or rosiglitazone (4 mg/day). At study entry, 30% of patients were on monotherapy with OAD and 70% were treated with multiple OADs. At the end of the study, HbA1c values were significantly reduced more ($p<0.0001$) in all liraglutide groups (-0.6, -1.08, -1.13 for doses of 0.6, 1.2, 1.8 mg, respectively) than in placebo (+0.23%) or rosiglitazone (-0.44%) groups.

Changes in body weight were trivial in the liraglutide and placebo groups, whereas a weight increase by 2.1 Kg was documented with rosiglitazone (Tab. 2). Hypoglycemia episodes occurred in less than 10% of patients in all groups.

Nausea was reported from 5 to 10% of patients treated with the different doses of liraglutide, while it was present in less than 3% of patients in the placebo and rosiglitazone groups.

In conclusion, liraglutide added to a sulfonylurea was well tolerated and provided improved glycemic control with a favorable weight profile as compared with sulfonylurea and glitazone combination therapy.

• *LEAD 2 (combination with metformin)* (32): this was a placebo-controlled, double-blind, 26-week, five-arm, randomized trial testing the effect of three doses of liraglutide (0.8, 1.2 and 1.8 mg) added to metformin (1 g twice daily) as compared with the same dose of metformin in combination with placebo or glimepiride (4 mg/day). At study entry, 35% of patients was on monotherapy with OAD and 65% was treated with multiple OADs.

In comparison with placebo, HbA1c values decreased significantly more with liraglutide 0.6 mg (difference -0.8%), liraglutide 1.2 mg (difference -1.1%) and liraglutide 1.8 mg (difference -1.1%). No differences between liraglutide (1.2 mg and 1.8 mg) and glimepiride were documented.

Body weight decreased in all the liraglutide groups, whereas it increased in the glimepiride group (Tab. 2).

Table 2. Main results obtained in the LEAD studies

	LEAD 1 Glimepiride plus:					LEAD 2 Metformin plus:					LEAD 3 Monotherapies with:			LEAD 4 Metformin rosiglitazone plus:			LEAD 5 Metformin glimepiride plus:			LEAD 6 Metformin and/or sulponylurea plus:	
	Lira 0.6 mg	Lira 1.2 mg	Lira 1.8 mg	Rosi	Plac	Lira 0.6 mg	Lira 1.2 mg	Lira 1.8 mg	Gli	PI	Lira 1.2 mg	Lira 1.8 mg	Gli	Lira 1.2 mg	Lira 1.8 mg	PL	Lira 1.8 mg	Pl	Glar	Lira 1.8 mg	Exe
Completers (%)	91	86	89	84	73	86	82	79	86	61	65	70	61	86	75	68	-	-	-	86	81
Change in HbA1c (%)	-0.6	-1.1	-1.1	-0.4	0.2	-0.7	-1.0	-1.0	-1.0	0.1	-0.8	-1.1	-0.5	-1.5	-1.5	-0.5	-1.3	-0.2	-1.1	-1.1	-0.8
HbA1c <7%	23	34	40	21	7	28	35	42	36	11	43	51	28	58	54	28	52	15	44	54	43
Change in FPG (mg/dl)	-13	-29	-29	-16	18	-20	-29	-31	-23	7	-14	-25	-5	-27	-27	-9	-29	9	-32	-29	-11
Change in PPG (mg/dl)	-	-	-	-	-	-31	-41	-47	-45	-11	-31	-38	-25	-47	-49	-14	-	-	-	-	-
Weight Change (Kg)	0.7	0.3	-0.2	2.1	-0.1	-1.8	-2.6	-2.8	1.0	-1.5	-2.1	-2.5	1.1	-1.0	-2.0	0.6	-1.8	-0.4	1.6	-3.2	-2.9
Minor hypoglycemic events/person/yr	0.17	0.51	0.47	0.12	0.17	-	0.03	0.09	1.23	0.13	0.30	0.25	1.96	0.38	0.64	0.17	1.2	1.0	1.3	1.9	2.6
Nausea (%)	5.2	10.5	6.8	1.7	2.6	11	16	19	3	4	27.5	29.3	8.5	29	40	8.6	13.9	3.5	1.3	25	28

*Lira=liraglutide; Gli=glimepiride; Pl=placebo; Glar=insulin glargine; Exe=exenatide

The incidence of minor hypoglycemia with liraglutide was comparable to that occurred with placebo but markedly less than that with glimepiride.

Nausea was reported by 11-19% of the liraglutide-treated subjects versus 3-4% in the placebo and glimepiride groups. However, the incidence of nausea declined over time.

In conclusion, once-daily liraglutide induced similar glycemic control, reduced body weight, and lowered the occurrence of hypoglycemia compared with glimepiride, when both had background therapy with metformin.

• *LEAD 4 (triple therapy with metformin and rosiglitazone)* (33): this was a placebo-controlled, double-blind, 26-week, parallel-group randomized trial testing the effect of two doses of liraglutide (1.2 and 1.8 mg) added to metformin (1 g twice daily) and rosiglitazione (4 mg/die) as compared with the same dose of metformin and rosiglitazione in combination with placebo. At study entry, 20% of patients were on monotherapy with OAD and 80% were treated with multiple OADs. Mean HbA1c values decreased significantly more in the liraglutide groups than in the placebo group (-0.9 and -1.1% for liraglutide 1.2 and 1.8 mg, respectively).

Fasting and post-prandial plasma glucose levels were decreased significantly more with liraglutide 1.2 and 1.8 mg than with placebo (Tab. 2).

Dose-dependent weight loss occurred with liraglutide 1.2 and 1.8 mg, while weight gain was found in patients on placebo.

Minor hypoglycemia more frequently occurred with liraglutide than with placebo, but there was no major hypoglycemia. Gastrointestinal adverse events were more common with liraglutide, but most occurred within the first month of therapy and were transient.

In conclusion, once-daily liraglutide in combination with metformin and rosiglitazone was generally well tolerated, significantly improved metabolic control, and reduced body weight, with low rates of hypoglycemia.

• *LEAD 5 (liraglutide in triple therapy with metformin and sulfonylurea)* (34): it was a placebo-controlled, double-blind, 26-week, parallel-group randomized trial testing the effect of 1.8 mg of liraglutide added to metformin (1 g twice daily) plus glimepiride (2-4 mg once daily) in comparison with the same dose of metformin and glimepiride in combination with placebo or insulin glargine. At study entry, 6% of patients were on monotherapy with OAD and 94% were treated with multiple OADs.

The combination of liraglutide + metformin + glimepiride reduced HbA1c more than metformin and glimepiride combined with either placebo or glargine (Tab. 2).

Fasting blood glucose levels were reduced with liraglutide and insulin glargine, while they increased in the placebo group. Body weight was reduced by 1.8 Kg with liraglutide, while it increased by 1.6 Kg in the insulin glargine group.

A similar rate of minor hypoglycemia was found in the liraglutide and insulin glargine groups. Transient nausea occurred in 14% of patients in the liraglutide group. Antibodies anti-liraglutide were registered in 9.8% of patients.

In conclusion, once-daily liraglutide in combination with metformin and glimepiride was generally well tolerated, significantly improved metabolic control, and reduced body weight.

• *LEAD 6 (liraglutide vs. exenatide)* (35): this is the first study that directly compares two GLP-1 analogues. It was a 26-week, randomized trial testing the effect of 1.8 mg of liraglutide once daily vs. exenatide 10 micrograms twice daily in combination with metformin (1 g twice daily) and/or glimepiride (2-4 mg once daily). Patients treated with liraglutide achieved a reduction in HbA1c of 1.12% , compared with a reduction of 0.79% in the exenatide group. Liraglutide produced a greater reduction in fasting plasma glucose, while postprandial glucose control was less effective after breakfast and dinner. Weigh loss was similar in the two groups and was approximately of 3.0 Kg. The incidence of nausea was initially similar, but it was less persistent with liraglutide (3% vs. 9% at week 26). Liraglutide caused less minor hypoglycemia, however representing a rare event in both groups (1.9 vs. 2.6 events/patient/year; p=0.01). HOMA-B was significantly greater for liraglutide than for the exenatide group; reductions of triglycerides and free fatty acids values were significantly greater with liraglutide than with exenatide, while increases in very low-density lipoprotein cholesterol were smaller in the liraglutide group than in the exenatide one. In conclusion, liraglutide once daily provided significantly higher improvements in glycemic control than exenatide twice daily and was generally better tolerated. After the conclusion of the LEAD-6 trial, in a 14-week extension study patients initially assigned to exenatide group were switched to liraglutide group. Conversion from exenatide to liraglutide was well tolerated and provided significant additional benefits in glycemic control, beta-cell function, body weight, and blood pressure (36).

• *Meta-analyses of LEAD studies:* recently, the results of several meta-analyses of the LEAD trials have been presented, summarizing the effect of liraglutide on different parameters, such as metabolic control, blood pressure, body weight, and beta-cell function. The first meta-analysis (37) determined the effects on HbA1c, fasting plasma glucose, body weight, and systolic blood pressure of either substituting liraglutide for an existing oral agent or combining liraglutide with existing therapy or as an add-on to diet/exercise. Liraglutide was more effective in reducing HbA1c levels and FPG when used as an add-on therapy rather than substituted for a prior OAD. On the other hand, SBP and body weight were reduced relative to baseline regardless of whether liraglutide was used as add-on or substitution therapy. In a second meta-analysis (38),

treatment with liraglutide 1.8 mg was associated with a higher probability of reaching HbA1c <7% with respect to any comparator, active or placebo (66% with liraglutide vs. 18%-54% with placebo/active drugs). Also, the composite target (HbA1c <7%, SBP <130 mmHg, and no weight gain) was achieved by 26% of patients treated with liraglutide 1.8 mg, as compared with 3-16% with placebo/active drugs. A third (39) meta-analysis specifically explored the effect of liraglutide on SBP. Overall, the average reduction in SBP was of 2.5 mmHg. Reduction in SBP occurs within two weeks of initiating treatment, is sustained over 26 weeks, and is greater in patients with high SBP at baseline. In fact, the average SBP reduction reaches 11.4 mmHg in individuals with SBP values between 140 and 190 mmHg at baseline. The fourth meta-analysis (40) evaluated the comparative effect of liraglutide vs. glimepiride on metabolic control in relation to baseline beta-cell function. This meta-analysis shows that liraglutide is effective across the continuum of beta-cell activity, but was even more effective in subjects with baseline comparatively well-preserved beta-cell function, which may imply greater clinical benefits when liraglutide is initiated early. A final study summarized the impact of liraglutide treatment on beta-cell function in the LEAD 1-5 studies. An increase in HOMA-B between 28% and 34% from baseline vs. comparator was demonstrated with 1.8 mg liraglutide (41).

Potential benefits on cardiovascular function

Both exenatide and liraglutide have demonstrated preliminary beneficial effects on the cardiovascular function. Further to the documented effects on weight loss, blood pressure reduction, and lipid profile improvement, GLP-1 analogues have been documented to have a direct natriuretic effect (42) and a direct action of endothelial vasodilatation (43). Additional data show that liraglutide reduces several markers of cardiovascular risk, such as C-reactive protein, type 2 natriuretic peptide, and PAI-1 (44). These findings underline the potential role of these drugs in individuals with heart failure or coronary artery disease, as also suggested by animal and clinical studies. In particular, continuous infusion of GLP-1 is associated with an improvement in left ventricular function in patients with acute myocardial infarction and severe systolic dysfunction (45) and in patients with congestive heart failure (46).

The protective effect of GLP-1 and GLP-1 analogues on ischemic and reperfusion injury, mediated by inhibition of apoptosis, have been documented in animal models showing that these compounds may reduce infarct size and improve outcomes after experimental myocardial infarction (47-49).

Conclusions

The ideal profile of any glucose-lowering drug should include the following features: long-term efficacy, low risk of hypoglycemia, cardiovascular protection, neutral effect on body weight or weight loss, long-term safety and tolerability. So far, none of the available drug classes fully satisfy all these requirements. The novel drug class of GLP-1 analogues, particularly liraglutide, is extremely promising, and existing evidence suggests that it may address the unmet needs of diabetes treatment. If data on efficacy and safety of these drugs will be confirmed by long-term studies and post-marketing surveillance, they will acquire a prominent role among the main therapeutic options not only as add-on treatments in case of secondary failure, but also as an early strategy to reduce the burden of diabetes and its complications.

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