REVIEW

Management of Type 2 diabetes with liraglutide

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Practice Points

- Liraglutide is administered subcutaneously once daily independently of meals and time of day.
- The main adverse events are gastrointestinal symptoms (nausea, vomiting and diarrhea); they are dose-dependent and transient.
- Liraglutide is contraindicated in persons with a personal or a family history of medullary thyroid cancer, a personal history of multiple endocrine neoplasia syndrome Type 2, or hypersensitivity towards liraglutide. Suspicion of acute pancreatitis should lead to drug discontinuation.

SUMMARY Liraglutide is a once daily subcutaneously administered GLP-1 receptor agonist approved for Type 2 diabetes treatment. The standard treatment dose is 1.2 mg/day, but dose titration up to 1.8 mg/day is approved. Liraglutide lowers HbA1c by 0.8–1.6% and causes sustained glucose lowering for up to 2 years. Its effect on glycemic control is superior to that of placebo and several comparator drugs. Liraglutide causes a weight reduction of up to 3.6 kg. Its main adverse effects are transient gastrointestinal symptoms. The risk of onset of hypoglycemia in response to liraglutide is very low. An association with acute pancreatitis cannot be entirely excluded. We await data on its impact on cardiovascular disease. GLP-1 receptor agonists are accepted as a second-line treatment in Type 2 diabetes.

Background

Type 2 diabetes mellitus (T2D) is a progressive disease characterized by insulin resistance, failure of pancreatic β-cell secretion and α-cell dysfunction. T2D is closely associated with obesity, hypertension and dyslipidemia, and T2D subjects are therefore at an increased risk of developing cardiovascular disease (CVD). First-line treatment of T2D consists of lifestyle intervention and metformin administration. Treatment must, however, usually be intensified over time. For decades, insulin and sulfonylurea (SU) were second-line drugs of choice, but they both unfortunately cause weight gain and hypoglycemia.

Liraglutide (Victoza®, Novo Nordisk A/S, Bagsvaerd, Denmark) is a once daily GLP-1 receptor agonist for treatment of T2D. Native GLP-1 secretion is nutrient-stimulated from intestinal L cells; it stimulates insulin secretion and suppresses glucagon secretion in a glucose-dependent way, delays gastric emptying and reduces appetite [1]. However, the enzyme DPP-4 degrades native GLP-1 rapidly (the GLP-1 half-life is approximately 2 min).

The aim of this review is to provide an overview of the use of liraglutide in the treatment of T2D. Although liraglutide has been studied in subjects with Type 1 diabetes and obesity, its use for treatment of these conditions is not approved.

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Studies eligible for inclusion were identified by searching six electronic databases (bibliotek.dk, SveMed+, Cinahl, PubMed/MEDLINE, EMBASE and the Cochrane Library). Search terms were 'liraglutide', 'GLP-1 agonist', 'incretin', 'inkretin', 'glucagon-like peptide 1 receptor agonist', 'glukagonlignende peptid' and 'GLP' in combination with 'Type 2 diabetes', 'diabetes mellitus Type 2', 'non-insulin dependent diabetes mellitus', 'sukkersyge' and 'diabetes'. Papers including all languages were considered for this review. The initial search resulted in 2485 papers, 1197 papers remained after doubles were removed. Title and abstract was read to identify intervention studies, meta-analyses, *post hoc* analyses and observational studies involving human adults treated with liraglutide, hereby identifying 154 papers. Thirteen long-term, large-scale, interventions studies involving patients with T2D were identified and used to evaluate efficacy and safety of liraglutide along with five papers describing extension-phases of five Phase III studies. Relevant papers were identified and used to further evaluate safety, interactions, and treatment of special populations. Homepages of the US FDA, the EMA, and the manufacturer, Novo Nordisk, were also searched.

Indication & usage

Liraglutide was approved for treatment of adults with T2D by the EMA on 30 June 2009 and by the FDA on 25 January 2010 [101,102]. It is not recommended as the first choice of medication. Newer FDA licensing revisions approve the combination of liraglutide and basal insulin (but not prandial insulin) [103], whereas the EMA only approves adding insulin detemir to liraglutide [104].

A pediatric investigational plan for liraglutide was approved in January 2013 [105], but liraglutide is not yet recommended for use in children.

Liraglutide is contraindicated in patients who are hypersensitive towards liraglutide or any of the product's components. According to the FDA, a personal or a family history of medullary thyroid cancer or a personal history of multiple endocrine neoplasia syndrome Type 2 are also contraindications. The EMA only warns about thyroid adverse effects (AEs), which have been reported in preclinical trials [101,103].

The 2012 consensus algorithms for management of T2D of the American Diabetes Association (ADA) and the European Association for Study of Diabetes (EASD) recommend liraglutide as second-line therapy equal to SU, thiazolidinedione (TZD), DPP-4 inhibitors, and basal insulin [2]. According to the 2013 consensus algorithm of the American Association of Clinical Endocrinologists and the American College of Endocrinology, liraglutide is considered to be superior to SU, TZD and basal insulin as second-line treatment [3].

Dosage & administration

Liraglutide is subcutaneously injected once daily in the upper arm, the abdomen or the thigh. The administration is independent of meals and the time of the day. It is recommended to start with 0.6 mg/day for at least 1 week and to subsequently increase the dose to 1.2 mg/day. Dose escalation up to 1.8 mg/day is approved if acceptable glycemic control has not been reached. However, in Japan the maximal approved dose is 0.9 mg/day. Blood glucose monitoring during dose adjustment and age-based dose adjustment is unnecessary [101,103]. It may be necessary to monitor blood glucose and reduce the dose of concomitant SU or insulin when liraglutide is added to the treatment regimen.

Pharmacology, pharmacokinetics & pharmacodynamics

Liraglutide is a 31-amino acid peptide with structural modifications compared to the native GLP-1. C-16 fatty acid (palmitoyl acid) is attached to Lys26 via a glutamate spacer, and Lys34 is substituted by arginine. Liraglutide has 97% homology to the endogenous GLP-1 [4].

The bioavailability of liraglutide is 55% and its maximum concentration is reached 9–12 h after dosing [5,6]. Interactions between hydrophobic palmitate residues allow self-association into heptamers and hence a slow release from the place of injection into the blood stream [7]. Once liraglutide enters the blood stream, its side chain enables reversible binding to plasma protein, mainly albumin. The plasma protein binding is approximately 99% [4].

Liraglutide may be degraded in the same way as native GLP-1 by DPP-4 and neutral endopetidases. However, molecular modifications reduce the DDP-4-induced degradation [8]. The half-life of liraglutide is approximately 13 h [9]. Intact liraglutide is fully metabolized in the body by enzymatic activity and therefore not excreted in urine or feces [6]. The slower enzymatic degradation along with the high protein binding prevents

elimination from the circulation by renal filtration, and this is suggested to minimize risk of liraglutide accumulation in case of renal disease [10]. It has been determined that liraglutide has no clinically relevant impact on the CYP450 system and that it is not metabolized by the CYP450-metabolizing enzymes [8]. No clinically relevant drug–drug interactions regarding protein binding have been predicted. Pharmacokinetic interaction studies have been performed with atorvastatin, griseofulvin, digoxin, lisinopril, acetaminophen, and oral contraceptive drugs (combination of ethinyl estradiol and levonorgestrel) [11,12]. Liraglutide does not seem to affect the absorption to any clinically relevant degree, but caution is advised when using concomitant orally administered drugs. Coadministration of liraglutide and insulin detemir shows neither pharmacokinetic nor pharmacodynamic interactions when administered in patients with T2D [6].

Native GLP-1 delays gastric emptying. Treatment with liraglutide resulted in delayed gastric emptying during the first postprandial hour in one study [13], whereas other studies found no differences between placebo and liraglutide during the entire postprandial period [11,14]. This disagreement may reflect tachyphylaxia with liraglutide treatment.

Given that therapeutic peptides can cause an immunogenic response, antibody data were collected during the LEAD trials. After 26 weeks of treatment, the mean proportion of patients developing low-level liraglutide antibodies was 8.3–8.7% in liraglutide-treated groups. Liraglutide antibodies affected neither the safety nor the glycemic efficacy [15].

Clinical evidence in T2D patients

Overview of clinical trials

A series of Phase III randomized, parallel-controlled studies, including the LEAD program, have examined the efficacy and safety of liraglutide [16–26].

The LEAD program consisted of six clinical trials (LEAD 1–6), which involved 4456 T2D patients who were unable to maintain glycemic control (glycated hemoglobin [HbA1c] ≤7%) [16,18,20–22,26]. Liraglutide as monotherapy [26] or in combination with one [16,18,22] or two [20–22] oral antidiabetic drugs (OAD) was compared with rosiglitazone [16], glimepiride [18,26], insulin glargine [21] or exenatide twice daily (exenatide b.i.d.) [22]. All studies were double-blinded except from the LEAD-6 study and the insulin glargine arm in the LEAD-5 study. The main outcome was a change in HbA1c. All trials lasted 26 weeks, except the LEAD-3 trial, which lasted 52 weeks. In addition, a 1-year open-label extension of the LEAD-3 trial [27] and an open-label 18-month extension of the LEAD-2 study were conducted [28].

Studies similar to the LEAD-1 [17], LEAD-2 [29] and LEAD-3 study [19] were also conducted in an Asian population setting. The study similar to LEAD-3 was extended to 1 year [30].

Two open-label studies compared liraglutide to sitagliptin for 26 weeks as an add-on to OAD [23,31] and one of the studies was extended to 1 year [32]. The study by Charbonnel *et al.* [31] compared an oral treatment strategy based on sitagliptin with an injection strategy based on liraglutide, both as add-on to metformin [31].

One study examined the effect of adding insulin detemir to liraglutide plus metformin after a 12-week run-in phase with liraglutide. Patients who did not reach HbA1c <7.0% after the run-in phase were randomized to add insulin detemir or not [25]. The initial 26-week study was continued in an open-label setting for 1 year [33]. Adding insulin detemir to liraglutide treatment was approved in 2012 [106,107].

The DURATION-6 open-label study compared liraglutide to exenatide once weekly (exenatide QW), both added to OAD [24].

In addition to the many large clinical trials, the effect and safety of liraglutide was evaluated in The Association of British Clinical Diabetologists (ABCD) real-life liraglutide audit from 2009–2012, which involved 4129 patients with T2D [108].

A new drug (iDegLira, Novo Nordisk A/S) combining liraglutide and insulin degludec (a once daily new-generation basal insulin analogue) was filed for regulatory approval in Europe on 31 May 2013 [109]. The IDegLira combination drug will not be evaluated in this review.

Glycemic control

Table 1 gives an overview of the impact of liraglutide on glycemic control.

Liraglutide monotherapy induced an HbA1c reduction of 0.84–1.14% from baseline [26], and the reduction tended to persist after 2 years [27].

Liraglutide added to metformin or SU reduced HbA1c by 0.60–1.56% after 26 weeks. Liraglutide 1.2 and 1.8 mg/day were superior to

Table 1. Effect of liraglutide treatment on glycemic control in patients with Type 2 diabetes.

Study	Background therapy	Comparator	Patients (n)	Follow-up (weeks)	Mean HbA1c (%) across groups	HbA1c change from baseline (%)				Mean FPG (mmol/l) across groups	FPG change from baseline (mmol/l)				Ref.
						LGT 0.6 mg/day	LGT 1.2 mg/day	LGT 1.8 mg/day	AC		LGT 0.6 mg/day	LGT 1.2 mg/day	LGT 1.8 mg/day	AC	
Marre *et al.* LEAD-1	Glimepiride	Placebo or rosiglitazone 4 mg/day	1041	26	8.4	-0.60†	-1.08†‡	-1.13†‡	-0.44†	9.5–10.0	-0.7†	-1.6†‡	-1.6†‡	-0.9†	[16]
Kaku *et al.*	SU	Placebo	264	24	8.4	-1.46†	-1.56†§	–	–	9.5	-2.3†	-2.3†§	–	–	[17]
Nauck *et al.* LEAD-2¶	Metformin	Placebo or glimepiride 4 mg/day	1091	26	8.3–8.4	-0.69†	-0.97†	-1.00†	-0.98†	9.9–10.2	-1.1†	-1.6†	-1.7†	-1.3†	[18]
Yang *et al.*	Metformin	Glimepiride 4 mg/day	929	16	8.5–8.6	-1.14	-1.36	-1.45	-1.39	9.5–9.9	–	-2.1	-2.1	-2.2	[29]
Garber *et al.* LEAD-3¶	Diet	Glimepiride 8 mg/day	746	52	8.2	–	-0.84‡	-1.14‡	-0.51	9.5	–	-0.8‡	-1.4‡	-0.3	[26]
Seino *et al.*¶	Diet	Glibenclamide max. 2.5 mg/day	411	24	8.9	–	-1.74‡§	–	-1.18	11.2–11.3	–	-3.7‡§	–	-2.9	[19]
Zinman *et al.* LEAD-4	Metformin + rosiglitazone	Placebo	533	26	8.4–8.6	–	-1.5†	-1.5†	–	10.0–10.3	–	-2.2†	-2.4†	–	[20]
Russell-Jones *et al.* LEAD-5	Metformin + glimepiride	Placebo or insulin glargine (titrated)	581	26	8.2–8.3	–	–	-1.33†‡	-1.09†	9.1–9.4	–	–	-1.6†	-1.8†	[21]
Buse *et al.* LEAD-6	Metformin, SU or metformin + SU	Exenatide b.i.d. 10 µg/day	464	26	8.2	–	–	-1.12‡	-0.79	9.5–9.8	–	–	-1.6‡	-0.6	[22]
Buse *et al.* DURATION-6	OAD	Exenatide QW 2 mg/week	912	26	8.4–8.5	–	–	-1.48‡#	-1.28#	9.6–9.8	–	–	-2.1‡#	-1.8#	[24]

†p < 0.05 compared with placebo.
‡p < 0.05 compared with AC.
§LGT dose of 0.9 mg/day.
¶This study had an additional extension phase.
#Least square mean.
††Data given for randomization phase, not run-in phase.
AC: Active comparator; b.i.d.: Twice daily; FPG: Fasting plasma glucose; LGT: Liraglutide; OAD: Oral antidiabetic drug; QW: Once weekly; SU: Sulfonylurea.

Table 1. Effect of liraglutide treatment on glycemic control in patients with Type 2 diabetes (cont.).

Study	Background therapy	Comparator	Patients (n)	Follow-up (weeks)	Mean HbA1c (%) across groups	HbA1c change from baseline (%)				Mean FPG (mmol/l) across groups	FPG change from baseline (mmol/l)				Ref.
						LGT 0.6 mg/day	LGT 1.2 mg/day	LGT 1.8 mg/day	AC		LGT 0.6 mg/day	LGT 1.2 mg/day	LGT 1.8 mg/day	AC	
Pratley *et al.* Lira-DPP4[¶]	Metformin	Sitagliptin 100 mg/day	665	26	8.5	–	-1.24[‡]	-1.50[‡]	-0.90	9.9–10.1	–	-1.9[‡]	-2.1[‡]	-0.8	[23]
Charbonnel *et al.*	Metformin	Oral strategy including sitagliptin 100 mg/day	653	26	8.2	–	–	-1.4[#]	-1.3[#]	9.7	–	–	-2.2[#‡]	-1.9[#]	[31]
DeVries *et al.*[¶††]	Metformin + liraglutide (run-in for 12 weeks)	± insulin detemir	323	26	7.6	–	–	–	-0.51[†]	8.8–9.2	–	–	–	-2.1[†]	[25]

[†]$p < 0.05$ compared with placebo.
[‡]$p < 0.05$ compared with AC.
[§]LGT dose of 0.9 mg/day.
[¶]This study had an additional extension phase.
[#]Least square mean.
[††]Data given for randomization phase, not run-in phase.
AC: Active comparator; b.i.d.: Twice daily; FPG: Fasting plasma glucose; LGT: Liraglutide; OAD: Oral antidiabetic drug; QW: Once weekly; SU: Sulfonylurea.

placebo [16–18], rosiglitazone [16] and sitagliptin [23], but not to glimepiride [18,29]. Glycemic control was maintained during the extension of the LEAD-2 study [28] and the Lira-DPP4 study [32]. Intensification after 12 weeks was needed in 50.2% in the sitagliptin group, whereas only 28.5% needed uptitration in the liraglutide group [31].

In four studies, liraglutide was added to different OADs [20–22,24]. Despite previous dual therapy, liraglutide treatment caused an additional decrease in HbA1c of 1.1–1.5% compared to placebo [20,21]. The reduction of HbA1c with liraglutide of 1.8 mg/day was superior to the reduction obtained with both insulin glargine [21], exenatide b.i.d [22] and exenatide QW [24].

Adding insulin detemir reduced HbA1c by another 0.51%, whereas HbA1c remained virtually stable (+0.02%) in the group that received liraglutide plus metformin [25]. The improvement of glycemic control persisted for 1 year [33].

Fasting plasma glucose (FPG) was significantly reduced with liraglutide compared to placebo, regardless of background therapy [16–18,20,21]. The reduction in FPG in response to liraglutide was superior to that of several comparators **(Table 1)**. Like the reduction in HbA1c, the reduction in FPG persisted when the trials were prolonged to 1 or 2 years [27,28,30,32,33].

Postprandial glucose (PPG) responses have also been evaluated [16–22,26,29]. Like FPG, they were significantly reduced in liraglutide-treated groups compared to placebo regardless of the background therapy, except in the LEAD-4 study where PPG was reduced significantly over breakfast, but not over lunch and dinner [20]. However, liraglutide was less effective in reducing PPG than exenatide b.i.d [22]. No PPG response studies have compared liraglutide to sitagliptin or exenatide QW.

In conclusion, liraglutide caused a clear and sustained improvement of glycemic control and was superior to several other antidiabetic treatment regimens. While ethnicity did not alter the overall results, the effect of liraglutide was obtained at a lower dose in the Japanese population than in other populations **(Table 1)**. The effect of liraglutide was dose dependent. Despite this dose dependency, the proportion of patients across the studies reaching the ADA/EASD target of HbA1c <7.0% was similar, that is, 30–58% at 1.2 mg/day and 31–63% at 1.8 mg/day in liraglutide-treated groups, respectively. Only minor advantages were observed with the higher dose of liraglutide [16–20,22–24,26–32].

■ Islet-cell function

β-cell function was assessed by measuring the proinsulin:insulin ratio or using fasting insulin and glucose to calculate the homeostasis model assessment index of the β-cell function (HOMA-B). Increased proinsulin:insulin ratio and decreased HOMA-B are both independently associated with an increased risk of developing T2D [34,35]. Across studies, liraglutide (1.2 mg/day and 1.8 mg/day) increased HOMA-B from baseline by 23–35% [16,18,20,22,23]. HOMA-B was significantly increased compared to placebo (in the LEAD-1 study only for liraglutide 1.2 mg/day) when liraglutide was combined with glimepiride [16] or metformin plus rosiglitazone [20]. Liraglutide 1.2 and 1.8 mg/day significantly changed the proinsulin:insulin ratio (-0.12 to 0.00) compared to placebo [16,18,20,21]. Liraglutide decreased fasting glucagon in the extended LEAD-2 [28] and the LEAD-6 group [22] and was hence superior to placebo, but not to exenatide b.i.d. The suppressive action on the glucagon level may be ascribed to a direct effect on the α-cell or an indirect paracrine effect via the δ-cell and/or the β-cell. However, the LEAD-4 group experienced no change in fasting glucagon compared to placebo [20].

■ Bodyweight

Table 2 gives an overview of weight loss across the clinical trials.

The mean bodyweight was reduced by liraglutide monotherapy (by 2.0 and 2.4 kg for liraglutide 1.2 and 1.8 mg/day, respectively), and this reduction was maintained after 2 years [26,27]. Adding liraglutide to metformin reduced the mean bodyweight significantly compared with adding glimepiride [18,29] or sitagliptin [23,31]. Interestingly, liraglutide primarily reduced fat mass and fat percentage [36]. Liraglutide added to SU induced insignificant changes in bodyweight, whereas rosiglitazone added to SU caused weight gain [16,17]. A comparable reduction in bodyweight was seen when liraglutide and exenatide b.i.d were given, while patients lost more weight when receiving liraglutide than if they received exenatide QW [24].

Insulin increases weight, but the run-in weight loss of -3.5 kg was maintained over 52 weeks when insulin detemir was added to liraglutide plus metformin treatment [33]. A difference of

Table 2. Effect of liraglutide treatment on weight in patients with Type 2 diabetes.

Study	Mean weight (kg)	Weight change from baseline (kg)				Ref.
		Liraglutide 0.6 mg/day	Liraglutide 1.2 mg/day	Liraglutide 1.8 mg/day	Active comparator	
Marre *et al.* LEAD-1	82	+0.7†	+0.3†	-0.2†	+2.1	[16]
Kaku *et al.*	66	+0.1	-0.4‡	–	–	[17]
Nauck *et al.* LEAD-2§	–	-1.8†	-2.6†¶	-2.8†¶	+1.0	[18]
Yang *et al.*	68	-1.8†	-2.4†	-2.4†	+0.1	[29]
Garber *et al.* LEAD-3§	93	–	-2.0†	-2.4†	+1.2	[26]
Seino *et al.*§	65	–	-0.9†‡	–	+1.0	[19]
Zinman *et al.* LEAD-4	–	–	-1.0¶	-2.0¶	–	[20]
Russell-Jones *et al.* LEAD-5	85–86	–	–	-1.8†¶	+1.6	[21]
Buse *et al.* LEAD-6	93	–	–	-3.2	-2.9	[22]
Buse *et al.* DURATION-6	91	–	–	-3.6†#	-2.7#	[24]
Pratley *et al.* Lira-DPP4§	93–95	–	-2.9†	-3.4†	-1.0	[23]
Charbonnel *et al.*	91–92	–	–	-2.8†#	-0.4#	[31]
DeVries *et al.*§††	95–96	–	–	–	-0.16	[25]

†$p < 0.05$ compared with active comparator.
‡Liraglutide dose of 0.9 mg/day.
§This study had an additional extension phase.
¶Decreased significant ($p < 0.05$) compared with placebo.
#Least square mean.
††Data given for the randomization phase, not the run-in phase.

3.4 kg was observed in weight change between treatment groups on triple-therapy involving liraglutide and triple-therapy involving insulin glargine [21].

A meta-analysis shows that liraglutide has a dose-dependent weight loss effect [37]. A higher proportion of subjects lost ≥5% of their initial bodyweight at a dose of 1.8 mg/day (24.4%) than at 1.2 mg/day (17.7%) or placebo (9.9%). In comparison, the proportion reaching a ≥5% weight loss in active comparator-treated groups ranged from 2.6% (TZD and insulin glargine) to 17.7% (exenatide b.i.d.) [37].

Weight loss with liraglutide occurred regardless of nausea, vomiting and/or diarrhea, but the weight loss was found to be larger in those patients who experienced gastrointestinal side effects than in those without such side effects [26,38]. The higher the initial BMI, the greater the weight loss [37].

Cardiovascular safety

According to FDA guideline demands, all new antidiabetic drugs must be investigated for possible cardiovascular AEs. Consequently, the long-term, placebo-controlled Phase IIIb study LEADER is currently being carried out [39].

Postprandial hypertriglyceridemia is a well-established independent risk factor for CVD in both individuals with and without T2D [40,41]. Native GLP-1 abolished the postprandial hypertriglyceridemia in nondiabetic males in a study from 2006 [42] where the effect was linked to delayed gastric emptying and insulin-mediated inhibition of lipolysis. Interestingly, our group recently demonstrated that a 3-week long treatment with liraglutide significantly lowered postprandial triglyceride and low-density lipoprotein cholesterol levels in patients with T2D independently of gastric emptying [14]. In the LEAD-4 study, a significant lipid-lowering effect was shown on triglyceride (0.38 mmol/l), low-density lipoprotein (0.28 mmol/l) and free fatty acids, while the difference did not reach significance for the dose of 1.8 mg/day [20]. One of the mechanisms behind the lipid-lowering effect of GLP-1 analogues seems to be a decrease in intestinal secretion of triglyceride-rich lipoproteins

(apoB48-containing chylomicrons) [14]. It has also been speculated that changes in the hepatic lipid biosynthesis and oxidation might play a role [43].

Arterial hypertension is a well-established risk factor for CVD and CVD-related mortality [44]. It is therefore of importance that GLP-1 analogues induce a lowering of both systolic and diastolic blood pressure (BP), that is, liraglutide lowered the systolic BP in the range of 2.1–6.7 mmHg [18,20,21,26]. In individuals aged 40–69 years, each reduction of the systolic BP by 20 mmHg is associated with a twofold reduction in cardiovascular death rates [44]. The modest blood pressure reduction to liraglutide may, however, also be of clinical relevance. The BP-lowering effect of GLP-1 analogues may be mediated through a natriuretic effect and through endothelial vasodilatation [45]. The LEAD studies demonstrate a higher mean heart rate with liraglutide than with placebo or active comparator (SU, TZD and insulin glargine; 2.7 and 2.5 beats per min, respectively) [46]. An increase in heart rate is associated with an increase in CVD [47].

Low-grade inflammation comprises a complicated interplay of numerous immune system cells and cytokines. It is suggested to play a role as an independent risk factor for CVD. Although GLP-1 has been found to improve endothelial function and reduce markers of local vascular inflammation by modulating the cellular immune system [45], little evidence has so far been furnished to demonstrate a convincing, beneficial effect of liraglutide on low-grade inflammation.

AEs

The most common adverse events (AEs) for liraglutide are gastrointestinal side effects such as nausea, diarrhea and vomiting. Most AEs are mild/moderate and the incidence does not differ considerably between uses of liraglutide as monotherapy or combination therapy. Incidents of nausea, diarrhea and vomiting are in the range 16–40, 7–19 and 4–17% of subjects, respectively (liraglutide 1.2 and 1.8 mg/day) [16,18,20–24,26,31]. However, most gastrointestinal symptoms decreased after the first month and hereafter remained low and similar to the symptoms in active comparators throughout these studies. In general, higher withdrawal rates (2–11%) due to gastrointestinal side effects were seen with liraglutide than with comparator drugs [18,20,26,31]. The initial incidence of nausea was similar for liraglutide and exenatide b.i.d., although it was less persistent for liraglutide [22]. However, nausea, diarrhea and vomiting were more frequent in the liraglutide than in the exenatide QW group [24]. Thus, longer-acting drugs seem to reduce gastrointestinal side effects compared with shorter-acting drugs.

The rate of serious AEs related to liraglutide was low (≤5%) [16,19,21–23,29,31]. Serious AEs were infrequent and showed no dose-dependency. Postmarketing reports of serious hypersensitive reactions resulted in a warning in the latest licensing revision of liraglutide [101,103].

■ Hypoglycemia

Hypoglycemia is a major concern for diabetic patients. Severe hypoglycemia is associated with an increase in both deaths, and major and minor macrovascular events [48]. Fear of hypoglycaemia reduces quality of life for patients and often leads to poor compliance.

The safety reports from the 13 studies (including the five extension periods) only report ten major hypoglycemic episodes (defined as episodes requiring third-party assistance) in the liraglutide treatment groups, which included >5000 exposed patients [16–33]. Only one episode was reported when liraglutide was used as monotherapy (and this episode happened after insulin infusion was performed as a part of a subgroup procedure) [27].

The rate of minor hypoglycemic episodes (defined as a plasma glucose level <3.1 mmol/l in the LEAD studies) to liraglutide monotherapy ranged from 0.21 to 0.30 events/patient/year, which was significantly lower than with SU monotherapy (1.58–1.96 events/patient/year) [19,26,27]. Subgroup studies in the LEAD-6 study [22] and the DURATION-6 study [24] showed that the minor hypoglycemic rate were higher when adding liraglutide to background monotherapy of SU than to metformin. In the LEAD-1 study [16], liraglutide plus SU resulted in higher event rates for minor hypoglycemia than SU monotherapy. Addition of insulin detemir to patients on liraglutide plus metformin increased the number of minor hypoglycemic events, but no increase in major hypoglycemia [25].

In conclusion, liraglutide carries a very low risk of inducing hypoglycemia, which may reflect the glucose-dependent insulinotropic action of GLP-1. The risk of hypoglycemia increases when liraglutide is combined with SU or insulin.

■ Glandula thyroidea

Preclinical studies of rodents showed an association between long-term liraglutide exposure and calcitonin release, upregulation of calcitonin gene expression and subsequent C-cell hyperplasia in rats and mice [49]. In the LEAD program (including the Japanese studies), the calcitonin level was assessed over time. The calcitonin level was statistically significantly higher in weeks 26 and 52 in the liraglutide-treated groups than in the comparator groups, but these levels were still within the normal range and there was no indication of clinical relevance [50]. In addition, *in vitro* and *in vivo* studies find that human thyroid tissue has far fewer GLP-1 receptors than rodent C cells [50].

■ Pancreatitis & pancreatic cancer

The prescribing information for liraglutide has included a section on pancreatitis (signs, symptoms and precautions) since April 2013 [103]. This warning was issued because it was detected that some of the patients in the LEAD program developed pancreatitis [51,52] and because of postmarketing reports associating incretin-based drugs with pancreatitis. A recent meta-analysis showed that the reporting rate of acute pancreatitis (1.6 cases/1000 patient-years of exposure) for liraglutide versus comparators was 2.3 (95% CI: 0.3–100.6), p = 0.694 [53], while another study found an estimated odds ratio of liraglutide and acute pancreatitis of 0.97 (95% CI: 0.21–4.39) [54]. However, these meta-analyses can neither establish nor exclude a causal association with pancreatitis given that the numbers of events studied are very small and that minor, random fluctuations are likely to have had a major impact on the reported rates. In addition, the interpretation is complicated by the fact that T2D subjects have an increased (up to 2.8-fold) risk of pancreatitis [55]. To further clarify an association between liraglutide and pancreatitis, it is of interest to closely monitor postmarketing registrations and to perform long-term studies such as the ongoing LEADER trial; however, the question arises whether such studies will be powered for this rare outcome.

A highly debated case–control study of tissue from pancreatic autopsies reports that incretin-based treatment (seven of eight cases were treated with DPP-4 inhibitors, one with exenatide b.i.d., and none with liraglutide) carried an increased risk of dysplasia owing to findings of exocrine and endocrine pancreatic compartment expansion [56]. However, this study has been strongly criticized mainly owing to an inappropriate match with controls regarding age, duration of diabetes, and because of this subjects treated with incretins did not match subjects treated with other agents [57]. Neither the EMA nor the FDA has found evidence indicating that pancreatic cancer is associated with incretin-based treatment [110]. In addition, a recent meta-analysis found no association between pancreatic cancer and liraglutide treatment [58].

Special populations

■ Renal impairment

As mentioned above, liraglutide is not eliminated by the kidney, and no dose reduction is therefore required in the presence of mild renal impairment [59]. A meta-analysis found liraglutide to be safe and well tolerated in patients with mild renal impairment (estimated creatinine clearance [eCrCl] at 60–89 ml/min) [60]. This is supported by the retrospective ABCD audit [61], where the effect of liraglutide (1.2 mg/day) was analyzed in patients with renal impairment. The same number of AEs was found in different groups regardless of concomitant renal impairment (none [eCrCl: ≥90 ml/min], mild [eCrCl: 60–89 ml/min], or moderate [eCrCl: 30–59 ml/min]) [61]. Studies of liraglutide in patients with moderate or severe renal impairment (eCrCl: <30 ml/min) are lacking. Liraglutide is therefore not recommended for use by the EMA, and caution is advised by the FDA when liraglutide is used for these patients. However, subgroup analysis on subjects with severe and moderate chronic renal failure will be carried out in the ongoing LEADER study [62], and a placebo-controlled clinical study [63] is currently investigating the safety and efficacy of liraglutide in patients with T2D and end-stage renal disease.

Postmarketing reports have been issued stating that caution should be exercised when initiating treatment with liraglutide in patients with renal impairment (primarily because of vomiting, diarrhea and dehydration) [101,103]. It should also be underlined that liraglutide should be paused in subjects with T2D who are dehydrated or suffer from moderate to severe vomiting or diarrhea.

■ Liver impairment

A meta-analysis of the LEAD program assessed the safety of liraglutide on liver parameters [64]. Liraglutide causes a dose-dependent reduction in

baseline liver enzymes, an effect primarily related to weight loss. In addition, a LEAD-2 substudy showed a trend towards improving steatosis, which was again related to weight loss [64]. The improvement in liver parameters is supported by the ABCD audit, where liraglutide treatment reduced elevated baseline alanine aminotransferase in T2D patients [65]. A Japanese study found a significant improvement of the liver inflammation and the liver fibrosis score in T2D patients with nonalcoholic fatty liver disease after they had been treated with liraglutide [66].

According to the EMA, the therapeutic experience in patients with all degrees of hepatic impairment is currently too limited to recommend the use of liraglutide in those who have mild, moderate or severe hepatic impairment [101], while the FDA states that liraglutide should be used with caution in such patients [103].

Conclusion

Treatment with liraglutide improves glycemic control in patients with T2D and possesses a very low risk of inducing hypoglycemia. The effect on glycemic control is superior to that of placebo and several comparator drugs. Importantly liraglutide causes weight reduction. Its main adverse effects are transient gastrointestinal symptoms. An association with acute pancreatitis cannot be excluded. There seems not to be an association with thyroid or pancreatic cancer. Caution is needed if liraglutide is used to treat diabetic patients with renal or liver impairment. We await long-term data regarding the impact of liraglutide on CVD.

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