

Lixisenatide: clinical profile and available evidence



Ilaria Dicembrini¹, Michela Bigiarini² & Edoardo Mannucci*¹

Practice Points

- Lixisenatide (formerly known as AVE0010) is a synthetic agonist of the gastrointestinal hormone GLP-1 receptor with extended biological activity.
- The selective interaction of lixisenatide leads to an increase in intracellular cAMP and stimulates glucose-dependent insulin secretion from pancreatic β -cells, simultaneously decreasing glucagon secretion from α -cells. Lixisenatide slows gastric emptying, thus improving postprandial glucose control.
- Following subcutaneous administration, maximal circulating levels of lixisenatide are achieved within 1.25–2.25 h. Lixisenatide is eliminated via glomerular filtration, followed by tubular reabsorption and subsequent degradation in renal tubules. Lixisenatide is not metabolized by cytochrome P450. Available data in animal models show that lixisenatide crosses the blood–brain barrier.
- Lixisenatide is effective in reducing HbA1c and blood glucose in Type 2 diabetes, either as a monotherapy or an add-on therapy. The efficacy of lixisenatide on blood glucose after a meal is greater than that of longer-acting GLP-1 receptor agonists, whereas the effects on fasting glucose and HbA1c are smaller.
- Lixisenatide is generally well tolerated. The most common adverse events involve the gastrointestinal system, with nausea being the most frequent. Lixisenatide has been reported to be associated with a lower incidence of diarrhea than liraglutide and a lower rate of nausea than exenatide. In comparison with liraglutide, lixisenatide seems to have a more favorable action on heart rate. There is no evidence of increased risk of thyroid medullary cancer or pancreatic cancer with lixisenatide, although this deserves careful surveillance, and its effect on the risk of pancreatitis needs further study.
- Administration of lixisenatide 1–4 h before paracetamol reduces paracetamol's maximum concentration and causes a 2-h delay in the time to maximum concentration, but no dose adjustment is necessary during concomitant treatment with atorvastatin, oral contraceptives, ramipril, digoxin and warfarin.
- Careful monitoring of the international normalized ratio is recommended at the time of starting treatment with lixisenatide.
- Lixisenatide should be given at once-daily 20- μ g fixed doses by subcutaneous administration.

¹Diabetes Agency, Careggi Teaching Hospital, Via delle Oblate 4, Florence, Italy

²Obesity Agency, Careggi Teaching Hospital, Florence, Italy

*Author for correspondence: edoardo.mannucci@unifi.it

SUMMARY Incretin-based therapies, which exploit the physiological actions of GLP-1, have attracted interest as a novel therapeutic option for Type 2 diabetes. In particular, GLP-1 receptor agonists provide significant improvements in HbA1c, with a low risk of hypoglycemia, as well as improvements in a wide spectrum of extraglycemic factors. These drugs can be categorized as either short- or long-acting compounds. Their efficacy on glucose homeostasis and safety profiles seems to be significantly affected by pharmacokinetics, thus enabling incretin-based therapy to be tailored for each patient affected by Type 2 diabetes. This review gives an overview of pharmacological, preclinical and clinical evidence of the most recently developed short-acting GLP-1 receptor agonist lixisenatide. Medline was searched for English-language articles that evaluated pharmacodynamics, pharmacokinetics, metabolism and mechanism of action of lixisenatide. An extensive Medline and Embase search for 'lixisenatide' and 'glucagon-like peptide-1 receptor agonist' was performed, collecting all randomized clinical trial data for humans. Completed but still unpublished trials were identified through a search of the www.clinicaltrials.gov website. US FDA and EMA reviews were also searched for data from unpublished trials. The most relevant papers and meeting abstracts published up to June 2013 were identified for inclusion in this review.

Recently, incretin-based therapy has attracted interest as a novel therapeutic option for Type 2 diabetes mellitus (T2DM). Incretin-based therapies exploit the physiological actions of GLP-1, a gastrointestinal hormone predominantly secreted in the postprandial phase from the distal small intestine and colon. The activation of GLP-1 receptors potentiates insulin secretion in a glucose-dependent manner, inhibits glucagon release, delays gastric emptying and reduces appetite. In particular, synthetic GLP-1 receptor agonists currently approved for the treatment of T2DM provide significant improvements in HbA1c, despite different pharmacokinetic and pharmacodynamic profiles. Moreover, available evidence strongly supports the hypothesis that GLP-1 receptor agonists are effective as glucose-lowering agents with a low hypoglycemic risk [1], have favorable actions on several extraglycemic risk factors (bodyweight, lipid levels and blood pressure profile), together with direct actions on myocardium and endothelial cells, which could contribute to cardiovascular protection in the T2DM population [2,3]. According to their structure, GLP-1 receptor agonists currently available on the market or in very late clinical development can be identified as either analogs of the native GLP-1 molecule (e.g., liraglutide and albiglutide) or derivatives of the natural GLP-1 receptor agonist isolated from the salivary gland of the Gila monster, exendin-4 (e.g., exenatide, exenatide long-acting release [LAR] and lixisenatide). The proteins can also be bound or coupled to albumin, which further prolongs the biological action of the peptides. They are administered subcutaneously twice daily (exenatide), once daily (liraglutide and lixisenatide) or once

weekly (exenatide LAR, dulaglutide, semaglutide and albiglutide) [4]. These drugs can be alternatively categorized as short-acting GLP-1 receptor agonists (e.g., exenatide and lixisenatide), which provide short-term receptor activation, or as long-acting compounds (e.g., liraglutide, exenatide LAR, dulaglutide, semaglutide and albiglutide), which provide a more stable plasma concentration and receptor stimulation. The differences in pharmacokinetics lead to different profiles of action on glucose homeostasis; short-acting GLP-1 receptor agonists primarily improve postprandial glycemic (PPG) control through inhibition of gastric emptying, whereas long-acting drugs mainly affect fasting glucose levels through their insulinotropic and glucagonostatic actions.

Overview of the market

T2DM is a chronic and progressive disease characterized by a deterioration of blood glucose control over time. As a result, during the natural course of the disease, there is growing need to up-titrate and add multiple glucose-lowering agents to achieve and maintain therapeutic targets. As a consequence, the search for new drugs with innovative mechanisms of action that could be combined with presently available agents is actively pursued by many companies.

After the encouraging results of the UKPDS, which documented the efficacy of intensification of diabetes therapy for preventing long-term complications [5,6], subsequent large-scale trials, such as the ADVANCE study [7], VADT [8] and ACCORD study [9], generated some concerns about the safety and efficacy of more aggressive oral glucose-lowering treatments and traditional insulin administration. These trials dealt with

patients with a long duration of diabetes and with a prior history of poor glycemic control. Meta-analyses of those trials showed that improvements in metabolic control are, indeed, associated with a small, but significant, reduction in the incidence of major cardiovascular events, without any overall effect on cardiovascular morbidity or mortality [10–12]. Further analyses suggested that hypoglycemia, a common side effect of many glucose-lowering treatments, could have a negative impact on cardiovascular mortality. In order to limit hypoglycemic risk in patients who are potentially more susceptible to the detrimental effects of low glucose, many experts suggest differing glycemic targets depending on patients' characteristics. In fact, the recent position statement from the American Diabetes Association (ADA) and European Association for the study of Diabetes (EASD) promotes less stringent glycemic goals in those with a history of severe hypoglycemia, lower life expectancy, presence of complications and/or comorbidities [13].

In addition, it has been suggested that some of the drugs used in T2DM could have beneficial or detrimental effects on cardiovascular risk irrespective of their glucose-lowering action [14–17]. Cardiovascular safety is an increasing concern for antidiabetic drugs. To date, the US FDA requires an assessment of the effect of new hypoglycemic drugs on major cardiovascular events through randomized trials, unless the upper limit of the confidence interval for major cardiovascular events in pooled Phase III trials is below 1.30 [101]. Several of these studies are currently ongoing for exenatide LAR, liraglutide and dulaglutide. Theoretically, the results will be available from 2016 onwards, unless they are prematurely terminated due to superiority or inferiority of the active treatments being studied.

Introduction to the compound

Lixisenatide (formerly known as AVE0010) is a synthetic GLP-1 receptor agonist with extended biological activity compared with native GLP-1,

recommended for once-daily subcutaneous administration either before breakfast or a main meal [102].

Chemistry

The 44-amino acid sequence of lixisenatide is based on that of exendin-4 (exenatide), a natural GLP-1 receptor agonist. The modifications consist of the deletion of a proline residue and addition of six C-terminal lysine residues (Table 1), thus offering significant resistance to cleavage by DPP-4. In preclinical binding studies in Chinese hamster ovary cells overexpressing the human GLP-1 receptor, lixisenatide demonstrated an affinity ($K_i = 1.33 \pm 0.22$ nM) four-times higher than that of native human GLP-1 ($K_i = 5.09 \pm 1.19$ nM) [18]. No head-to-head *in vitro* comparison of receptor binding between lixisenatide and other synthetic GLP-1 receptor agonists has been made.

Pharmacodynamics

The mechanism by which lixisenatide exerts its effects on glucose homeostasis have been investigated in several studies. The mechanism of action is mediated via a selective interaction with the GLP-1 receptor, leading to an increase in the intracellular cAMP concentration. The receptor for GLP-1 is widely distributed, and is detected in pancreatic islets, the brain, heart, kidneys and gastrointestinal tract. In the pancreas, lixisenatide acts in a glucose-dependent manner by stimulating insulin secretion from β -cells, while simultaneously decreasing glucagon secretion from α -cells [102]. Following an intravenous glucose challenge, lixisenatide enhances the first-phase insulin response (insulin mean area under the curve [AUC] in the first 10 min) by 6.6-fold (90% CI: 5.0–8.7) and second-phase insulin secretion (insulin AUC within 10–120 min) by 3.0-fold (90% CI: 2.7–3.3) compared with placebo [102].

Gastric emptying is slowed by lixisenatide and this probably contributes to PPG control. The

Table 1. Differences between GLP-1 receptor agonists.

Compound	Amino acids
GLP-1 (7–37)	H ₂ N-HAEGTFTSDVSSYLEGQAAKEFIAWLKGRG-COOH
GLP-1 (7–36 amide)	H ₂ N-HAEGTFTSDVSSYLEGQAAKEFIAWLKGR-CONH ₂
Exendin-4	H ₂ N-HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPS-CONH ₂
Lixisenatide	H ₂ N-HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPKKKKK-CONH ₂

Bold amino acids show elements of lixisenatide that differ from the pharmacologically active forms of human GLP-1 and natural GLP-1 (exendin-4) receptor agonists.

magnitude of this effect is influenced by many factors, including the baseline rate of emptying (i.e., slowing is more marked in those with more rapid gastric emptying) [19]. In a randomized, double-blind, 4-week trial in 43 patients with T2DM, lixisenatide 20 µg significantly reduced PPG-AUC after breakfast ($p < 0.0001$), lunch ($p < 0.0001$) and dinner ($p < 0.05$) in comparison with placebo, with proportionally greater reductions after breakfast when administered in the morning. These reductions were accompanied by a slowing in gastric emptying at breakfast, as assessed by the ^{13}C -octanoic acid breath test (mean change from baseline \pm standard deviation for 50% gastric emptying: -24.1 ± 32.3 min vs 211.5 ± 67.6 min for placebo vs lixisenatide, respectively; $p < 0.01$). Moreover, similar to findings with exogenous GLP-1 [20] and exenatide [21], an inverse relationship between PPG-AUC and the rate of gastric emptying with lixisenatide 20 µg ($r^2 = 0.51$; $p < 0.05$) has been described, and is not associated with any rise in insulin levels [22]. Conversely, only an apparently modest delay in gastric emptying, limited to 1 h after a meal, has been detected in T2DM patients treated with liraglutide, suggesting that the sustained exposure to long-acting GLP-1 receptor agonist could induce receptor desensitization and tachyphylaxis [23]. A minor effect, considered not clinically relevant, has also been reported for exenatide LAR [103].

Pharmacokinetics & metabolism

Following subcutaneous administration, lixisenatide is rapidly absorbed and exhibits dose-dependent pharmacokinetics. In a randomized, placebo-controlled study in 64 T2DM patients, steady-state plasma concentrations, mean AUC and peak plasma concentrations increased according to the dose (5, 10 and 20 µg) and frequency of administration. Maximal circulating levels were achieved within 1.25–2.25 h [102]. The kinetic profile suggests that twice-daily dosing is most appropriate. However, interesting results can also be obtained using a once-daily administration. In a placebo-controlled, dose-ranging study comparing once- (before breakfast) and twice-daily (before breakfast and dinner) administration, the twice-daily dosing produced a greater improvement in HbA1c; although differences did not reach statistical significance due to the small sample size. However, after 12 weeks, the reduction in HbA1c versus placebo, and the proportion of patients achieving HbA1c $< 6.5\%$

with lixisenatide 5 µg twice daily were very similar to those observed with 20 µg once a day [24]. Therefore, considering that the efficacy was not that different, the subsequent development of lixisenatide used once-daily dosing for better convenience. Lixisenatide has a wide distribution volume. Available data in rodents show that lixisenatide crosses the blood–brain barrier [25]. Based on the chemical structure and pharmacokinetic data, lixisenatide is eliminated via glomerular filtration, followed by tubular reabsorption and subsequent metabolic degradation in the renal tubules. After repeated administration, lixisenatide 20 µg showed a mean elimination half-life of 2.8 h [26]. Although pharmacokinetics were not significantly altered in patients with mild renal impairment (creatinine clearance, calculated by the Cockcroft–Gault formula, was 50–80 ml/min), the AUC increased by 24 and 46% in subjects with moderately (creatinine clearance: 30–50 ml/min) and severely (creatinine clearance: < 30 ml/min; not requiring renal dialysis) impaired renal function, respectively. The kinetic profile of lixisenatide is not affected by gender, race or bodyweight. There is no available information on the pharmacokinetics of lixisenatide in patients with hepatic dysfunction; although no alteration is expected, considering that the liver does not play a relevant role in drug elimination. In elderly nondiabetic subjects (11 subjects aged 65–74 years and seven subjects aged ≥ 75 years), the administration of lixisenatide 20 µg resulted in a mean AUC increase of 29% in the elderly population compared with 18 subjects aged 18–45 years, probably as a result of reduced renal function in the older age group [102]. A Phase I clinical trial to evaluate the pharmacodynamics, pharmacokinetics and safety profile of lixisenatide in the pediatric (10–17 years) T2DM population is currently ongoing [104].

Lixisenatide is not metabolized by cytochrome P450 and did not affect the activity of cytochrome P450 isoenzymes. However, the delay in gastric emptying may affect the rate of absorption of drugs orally administered during the following 4 h, as shown with the model medicinal product, paracetamol. When administered 1–4 h after lixisenatide, the paracetamol maximum concentration was reduced by 30% together with a 2 h delayed time to maximum concentration.

Similarly, reduced absorption and delayed drug action have been detected when oral contraceptives were administered immediately after

lixisenatide. The ethinylestradiol and levonorgestrel maximum concentration values decreased by 40–50% and 20–50%, respectively, together with a median delay in the time to maximum concentration of 1–3 h [27]. These effects have not been considered to be of clinical relevance. Moreover, pharmacokinetics evaluation of potential interaction with atorvastatin, ramipril, digoxin [102], and warfarin or coumarin derivatives [28], failed to detect any adjustment of drug dosage requirements. However, careful monitoring of the international normalized ratio is recommended at the time of starting or ending treatment with lixisenatide [102].

Clinical efficacy

■ Phase II clinical trials

A placebo-controlled 12-week trial in patients on metformin monotherapy was performed to identify the most suitable doses of lixisenatide, exploring both once- and twice-daily administrations [24]. Based on the results obtained, which showed a dose-dependent effect of the drug both on clinical efficacy and side effects, a 20 µg once-daily dose was chosen as the focus for further development. The 5- and 10-µg twice-daily doses could have also been valid alternatives. In this trial, a significant dose-dependent reduction of bodyweight was also observed compared with placebo (-3.01 ± 0.41 kg for 20 µg once daily in compared with -1.94 ± 0.32 kg in the placebo group; $p < 0.01$). In addition, a trend of blood pressure decrease from baseline occurred with each lixisenatide dose (ranging from -2 to -9 mmHg for systolic and -2 to -4 mmHg for diastolic blood pressure). This effect, observed as early as a week after the initiation of treatment, appears to be independent of weight loss [24].

Lixisenatide has been compared with liraglutide in a 28-day, randomized, open-label trial. In 120 diabetic patients receiving a stable dose of metformin, lixisenatide (two-step dose regimen: 10–20 µg/day) provided a significantly greater reduction in post-breakfast values compared with liraglutide (three-step dose regimen: 0.6–1.2–1.8 mg/day), whereas fasting and post-dinner glucose levels, as well as mean 24-h glycemia, were significantly lower with liraglutide. This different profile of action on glucose patterns is compatible with differences in pharmacokinetics, with liraglutide exhibiting a longer duration of action than lixisenatide. On the other hand, a lower incidence of diarrhea was reported for lixisenatide (3 vs 15%

for liraglutide), whereas the incidence of nausea was similar with the two drugs. The difference in the incidence of gastrointestinal side effects could be partly responsible for the slightly greater weight loss observed with liraglutide in comparison with lixisenatide (-2.4 vs -1.6 kg, respectively; $p < 0.01$). Interestingly, an opposite impact on heart rate was observed, with a decrease from baseline in the lixisenatide group versus an increase with liraglutide, and a statistically significant treatment difference of 8.9 bpm [29]. This latter observation could be relevant for the overall cardiovascular risk profile.

■ Phase III clinical trials

The safety and efficacy profiles of lixisenatide 20 µg once daily have been investigated in adult patients affected by T2DM in the GetGoal Phase III clinical trial program. In this series of randomized, placebo-controlled studies, lixisenatide was evaluated as a monotherapy, an add-on therapy to metformin, sulfonylureas or thiazolidinediones, and in combination with basal insulin. The GetGoal trial program is summarized in [Table 2](#).

■ Placebo-controlled studies on lixisenatide as a monotherapy

In the randomized, double-blind, multicenter, 12-week GetGoal-Mono study, lixisenatide monotherapy has been tested in comparison with placebo in 361 T2DM subjects. Patients were randomized to one-step (10 µg/day for 2 weeks then 20 µg/day) or two-step (10 µg/day for 1 week, then 15 µg/day for 1 week and then 20 µg/day) lixisenatide or placebo. With one- and two-step titrations, lixisenatide provided a significant improvement in HbA1c in comparison with placebo (-0.85 and -0.73 vs -0.19%; $p < 0.0001$). In a subgroup ($n = 169$) undergoing a standardized breakfast meal test, both regimens showed a statistically significant reduction ($p < 0.0001$ for all) from baseline in 2-h PPG (-3.9 mmol/l; 95% CI: -5.38 to -2.35 for the lixisenatide two-step and -4.8 mmol/l; 95% CI: -6.29 to -3.36 for the lixisenatide one-step dose increase arm), PPG excursion (-3.1 mmol/l; 95% CI: -4.30 to -1.90 and -3.7 mmol/l; 95% CI: -4.85 to -2.53, respectively) and fasting plasma glucose (-0.80 mmol/l; 95% CI: -0.95 to -0.60 and -0.95 mmol/l; 95% CI: -1.1 to -0.8, respectively). Changes from baseline in bodyweight did not show any significant difference between lixisenatide and placebo [30].

Table 2. Completed Phase III clinical trials with lixisenatide.

Study (year)	Trial	Duration (weeks)	Patients (n)	Mean age (years)	Male (%)	Combination	Treatment arm	End points		Ref.
								HbA1c (%)†	Weight change	
Fonseca <i>et al.</i> (2012)	GetGoal-Mono	12	361	53.5	52	Monotherapy	Lixisenatide 20 µg one step Lixisenatide 20 µg two steps Placebo	-0.54 (p < 0.0001)	=	[30]
Seino <i>et al.</i> (2012)	GetGoal-Mono-Japan	76	69	58.7	84	Monotherapy	Lixisenatide 20 µg one or two steps	-0.72	=	[31]
Ahrén <i>et al.</i> (2013)	GetGoal-M	24	680	55	43	Metformin	Lixisenatide 20 µg two steps (morning) Lixisenatide 20 µg two steps (evening) Placebo	-0.5 (p < 0.0001)	↑	[32]
								-0.4 (p < 0.0001)	↑	
Bolli (2011)	GetGoal-F1	24	482	56.1	45	Metformin	Lixisenatide 20 µg one step Lixisenatide 20 µg two steps Placebo	-0.49 (p < 0.0001)	↓ (p < 0.05)	[33]
								-0.41 (p < 0.0001)	↓ (p < 0.05)	
Pan <i>et al.</i> (2012)	GetGoal-M Asia	24	391	54.8	-	Metformin ± sulfonylurea	Lixisenatide 20 µg Placebo	-0.36 (p = 0.0004)	↑	[34]
Pinget <i>et al.</i> (2013)	GetGoal-P	24	484	55.6	52	Pioglitazone ± metformin	Lixisenatide 20 µg Placebo	-0.56 (p < 0.0001)	=	[35]
Ratner <i>et al.</i> (2011)	GetGoal-S	24	859	57	50	Sulfonylurea ± metformin	Lixisenatide 20 µg two steps Placebo	-0.74 (p < 0.0001)	↓ (p < 0.0001)	[36]
Riddle <i>et al.</i> (2013)	GetGoal-L	24	493	57.5	46	Basal insulin ± metformin	Lixisenatide 20 µg (morning) Placebo	-0.4 (p = 0.0002)	↓ (p < 0.0001)	[37]
Riddle <i>et al.</i> (2013)	GetGoal-Duo1	24	446	56	50	Basal insulin, metformin ± thiazolidinedione	Lixisenatide 20 µg (morning) Placebo	-0.3 (p < 0.0001)	↓ (p = 0.0012)	[38]
Seino <i>et al.</i> (2012)	GetGoal-L-Asia	24	311	58	48	Basal insulin ± sulfonylurea	Lixisenatide 20 µg two steps (morning)	-0.88 (p < 0.0001)	↑	[39]
Rosenstock <i>et al.</i> (2013)	GetGoal-X	24	634	57	53	Metformin	Lixisenatide 20 µg two steps (morning) Exenatide 10 µg three-times a day	=	↓ (p < 0.05)	[40]

†Comparator-corrected HbA1c reduction.
↑: Increase; ↓: Decrease; =: No difference.

The randomized, open-label, multicenter GetGoal Mono-Japan study analyzed the glycaemic efficacy of the same two titration regimens on 69 T2DM patients. At week 24, mean HbA1c decreased by 0.74 and 0.99% for the one- and two-step regimens, respectively. Lixisenatide 20 µg once daily was associated with sustained efficacy over 76 weeks. No data on bodyweight are available for this study, which, to date, has only been disclosed in abstract form [31].

■ Placebo-controlled studies on lixisenatide as an add-on treatment to oral drugs

The efficacy of 20 µg lixisenatide as an add-on to metformin has been studied in two placebo-controlled 24-week trials (GetGoal-M and GetGoal-F1). In the GetGoal-M trial, a significant reduction in HbA1c was observed for both morning and evening lixisenatide (mean difference from placebo: -0.5 and -0.4%, respectively) without any differences in bodyweight (placebo corrected: -0.4 kg; $p > 0.05$). Prebreakfast administration of lixisenatide also reduced 2-h glucose levels after a standard breakfast (mean difference from placebo: -4.5 mmol/l) [32]. Interestingly, in the GetGoal-M study, some cases of symptomatic hypoglycemia were reported in the active treatment arms, although none of them was classified as severe. Similar results for efficacy were provided by the GetGoal-F1 (mean HbA1c reduction vs placebo: -0.4%), which is still only available in abstract form [33]. Lixisenatide therapy was also related to similar improvements in glycaemic control in 391 T2DM Asian patients in an uncontrolled trial combining lixisenatide and metformin with/without sulfonylureas (mean HbA1c difference from placebo at week 24: -0.36%) [34].

Lixisenatide has also been shown to reduce HbA1c when added to pioglitazone. The 24-week, randomized, placebo-controlled GetGoal-P study enrolled 484 patients (mean disease duration: 8.1 ± 5.5 years). Adding lixisenatide to pioglitazone with/without metformin in this population significantly reduced HbA1c (mean difference from placebo: -0.6%). During a double-blind extension period, the efficacy was maintained for up to 76 weeks. No significant weight loss was observed with lixisenatide treatment (placebo corrected: -0.41 kg; $p > 0.05$). The overall incidence of hypoglycemia was similar to placebo (4.7 and 3.1 events per 100 patient-years), with no cases of severe

hypoglycemia. The most commonly reported adverse events were gastrointestinal, mostly mild or moderate nausea (26 vs 13.7% with placebo), and this rarely led to discontinuation of the study drug [35].

The GetGoal-S trial was designed to explore the effects of lixisenatide, at the usual 20-µg once-daily dose, as an add-on to sulfonylurea, with or without metformin. The results have not yet been published extensively; the findings disclosed in abstract form showed a placebo-subtracted reduction of HbA1c of approximately 0.9%, together with a significant reduction in bodyweight compared with placebo (placebo corrected: -0.9 kg; $p < 0.001$) [36].

■ Placebo-controlled studies on lixisenatide as an add-on treatment to insulin

The 24-week, randomized, double-blind, placebo-controlled GetGoal-L study analyzed 495 individuals affected by T2DM inadequately controlled by basal insulin with/without metformin (mean disease duration: 12.5 ± 6.8 years). With lixisenatide, the placebo-corrected change of HbA1c from baseline was -0.4%, due to a pronounced improvement on PPG (mean difference versus placebo: -3.8 mmol/l; from -4.7 to -2.9; $p < 0.001$). The study protocol limited the possibility of dose titration for basal insulin; however, an initial 20% reduction in basal insulin dose, with the possibility of subsequent up-titration, was recommended in patients with baseline HbA1c $< 7.5\%$, in order to reduce hypoglycemic risk, and further dose reductions were to be made if hypoglycemia occurred. It is possible that the variations in the insulin doses reduced the effect of lixisenatide on HbA1c, which was smaller than in other studies. Significant reductions in insulin dose (-3.7 U/day; $p = 0.012$) and bodyweight (placebo corrected: -1.3 kg; $p < 0.001$) were also observed. Notably, the incidence of hypoglycemia did not increase, despite the lower HbA1c levels [37].

In the GetGoal-Duo 1 study, lixisenatide was compared with placebo in patients treated with basal insulin (glargine) and metformin, with/without thiazolidinediones. In this study, titration of glargine was allowed throughout, with a fasting plasma glucose target of 4.4–5.6 mmol/l. As a consequence, the mean placebo-subtracted reduction of HbA1c (-0.3%) was smaller than in other trials, but it was accompanied by a smaller increase in insulin doses. In addition, significant improvements

were observed for PPG, glucose daily excursions and bodyweight (placebo corrected: -0.89 kg; $p < 0.001$). Regarding adverse effects, lixisenatide was associated with a significant increase in gastrointestinal side effects, together with a higher rate of symptomatic nonsevere hypoglycemia (0.80 vs 0.44 events/patient-year) [38].

The combination of lixisenatide with basal insulin with or without sulfonylureas has been studied in a trial performed in Asian countries (GetGoal-L-Asia). The reduction of HbA1c in comparison with placebo was greater than in other trials combining lixisenatide with basal insulin (-0.8%). The incidence of symptomatic hypoglycemia was also high (43 vs 24% with placebo over 24 weeks), whereas in the subgroup of patients not receiving sulfonylureas, the incidence of hypoglycemia in lixisenatide-treated patients was close to that of placebo (32.6 vs 28.3% , respectively). It can be speculated that the association between insulin and sulfonylureas produces a greater hypoglycemic risk than other combinations of drugs. Lixisenatide significantly reduced 2-h plasma glucose after a test meal compared with placebo. The decrease in bodyweight was not significant (placebo corrected: -0.44 kg; $p = 0.08$), but this result could be the consequence of the relatively low baseline BMI [39].

Previously reported placebo-controlled studies explored the effects of lixisenatide as an add-on to basal insulin. In this context, the drug could be considered an alternative prandial rapid-acting insulin. A trial comparing the efficacy and safety of lixisenatide with insulin glulisine in patients with T2DM already receiving insulin glargine (GetGoal-Duo 2) is currently ongoing [105].

■ Trials with active comparators

Liraglutide was used as an active comparator in an open-label Phase II trial. This study, compared 20 μ g of lixisenatide and 1.8 mg of liraglutide, both administered once daily in the morning for 28 days, as an add-on to metformin, and showed a greater efficacy of lixisenatide on post-breakfast glucose, and a greater efficacy of liraglutide on fasting, post-dinner and mean daily glucose [29].

The primary end point of the randomized, open-label, 24-week GetGoal-X trial was to demonstrate the noninferiority on HbA1c of lixisenatide 20 μ g once daily ($n = 311$) versus exenatide 10 μ g twice daily ($n = 305$), both

combined with metformin. A similar reduction of HbA1c from baseline was observed with lixisenatide and exenatide (mean difference: $-0.79 \pm 0.05\%$ vs $-0.96 \pm 0.05\%$; $p = 0.17$). A significantly lower incidence of symptomatic hypoglycemia (2.5 vs 7.9% ; $p < 0.05$) and nausea (24.5 vs 35.1% ; $p < 0.05$) was observed with lixisenatide compared with exenatide. Weight loss was slightly greater with exenatide, but the difference did not reach statistical significance (-2.96 ± 0.23 kg for lixisenatide vs -3.98 ± 0.23 for exenatide; $p > 0.05$) [40]. A 24-week study comparing lixisenatide with sitagliptin as an add-on to metformin in obese T2DM patients younger than 50 years of age has recently been completed, but no results are currently available [106].

Safety & tolerability

Lixisenatide was generally well tolerated in Phase II and III studies. The overall incidence of serious adverse events was similar between lixisenatide and placebo, both in monotherapy and as an add-on to other glucose-lowering drugs. The most common adverse events reported involved the gastrointestinal system, which is similar to what is observed with other GLP-1 receptor agonists, with nausea being the most frequent. The majority of these events were of mild-to-moderate intensity and resolved without requiring treatment interruption. Most cases of nausea occurred in the first 5 weeks of treatment, in a dose-dependent manner [24].

Available head-to-head comparisons suggest that the incidence of gastrointestinal side effects could be smaller with lixisenatide than with other GLP-1 receptor agonists. In fact, lixisenatide has been reported to be associated with a lower rate of diarrhea than liraglutide [29] and a lower rate of nausea than exenatide [40]. This phenomenon is not easy to explain. In fact, longer-acting GLP-1 receptor agonists (e.g., liraglutide or exenatide LAR) are commonly associated with a lower incidence of gastrointestinal side effects, attributed to tachyphylaxis [41,42]. The lower incidence of nausea, together with smaller effect on bodyweight – both of which are at least partly centrally mediated – would be compatible with a drug that does not cross the blood–brain barrier; however, experimental studies suggest that lixisenatide crosses this barrier even more efficiently than liraglutide [25].

Other adverse events reported in clinical trials, which include headache, dizziness,

somnolence, dyspepsia, back pain, injection-site pruritus, influenza, upper respiratory tract infections, cystitis and viral infections, are usually mild and do not occur any more frequently than with placebo [102].

In the GetGoal studies, symptomatic hypoglycemia was defined as symptoms consistent with hypoglycemia, together with detection of blood glucose levels <3.3 mmol/l and/or prompt recovery with carbohydrate ingestion. In monotherapy studies, or when lixisenatide was used as an add-on to metformin or pioglitazone, the incidence of hypoglycemia was low and not significantly different from that observed with placebo. This is consistent with the known mechanism of the glucose-lowering action of GLP-1 receptor agonists, which stimulate insulin secretion and suppress glucagon release in a glucose-dependent manner [43]. In fact, the other GLP-1 receptor agonists do not induce any increase in the incidence of hypoglycemia unless combined with sulfonylureas or insulin [44]. It is, therefore, surprising that a lower incidence of hypoglycemia was reported with lixisenatide than with exenatide in a head-to-head comparison [40]. This finding is very difficult to explain, unless the open-label nature of the study has led to some selective reporting of this adverse event. On the other hand, when lixisenatide was added to basal insulin, the risk of hypoglycemia increased, as expected.

As expected, the development of anti-lixisenatide antibodies can occur during treatment, but without any apparent consequence in terms of safety and tolerability. When antibodies are present, the kinetics of lixisenatide appear to be affected, with a delay in the time to maximum concentration and an increased half-life. The presence of anti-lixisenatide antibodies has not been associated with the occurrence of any relevant adverse event; however, high-titer antibodies could be associated with a modest reduction in efficacy [102]. The proportion of patients positive for the presence of anti-lixisenatide antibodies ranges from 43 to 71% depending on the drug doses.

Current studies are insufficient to make any assumption about the cardiovascular safety of lixisenatide, which is being explored by a specifically designed ongoing study [107]. In a meta-analysis of clinical trials submitted to the European Medicine Agency (EMA), the risk of major cardiovascular events with lixisenatide compared with placebo was 1.25 (95%

CI: 0.67–2.35) [102]. To date, lixisenatide has not been reported to cause any detrimental effects on cardiovascular risk factors. In fact, small but significant improvements have been described for blood pressure [24], which is similar to what has been observed for other GLP-1 receptor agonists [44]. This effect, which is independent of weight loss, could contribute to cardiovascular protection [2,3]. In addition, unlike liraglutide, lixisenatide does not determine any increase in heart rate. In the only available head-to-head comparison, the difference in heart rate between lixisenatide and liraglutide was statistically significant and clinically relevant [29]. It is possible that divergent effects on heart rate, possibly in part due to the differing drug half-lives, produce a different effect on long-term cardiovascular risk, although this hypothesis needs to be verified through long-term, large-scale randomized trials.

Recently, there has been increasing concern about the possibility that long-term overstimulation of pancreatic GLP-1 receptors induces an increased risk of pancreatitis [45], and endocrine and exocrine tumors [46]. In trials submitted to EMA, the incidence of pancreatitis was slightly higher with lixisenatide than with comparators (nine vs two cases; 0.3 vs 0.1%); however, most cases were not confirmed at *post hoc* adjudication [102]. On the other hand, the same trials showed no evidence of an increase in the risk of pancreatic cancer.

In mice and rats, similar to what is observed with other GLP-1 receptor agonists, lixisenatide stimulates thyroid C-cell proliferation [102]. This effect, which is thought to be GLP-1 receptor-dependent, seems to be largely specific to rodents and much reduced in primates [47]. In clinical studies, no cases of medullary carcinoma and no increase in calcitonin levels were observed in lixisenatide-treated patients [102].

There are no data on the safety of lixisenatide during pregnancy or lactation. In rats and rabbits, treatment with lixisenatide has been reported to increase the risk of malformations, independent of the dose used. For this reason, EMA recommends that the drug is not used in women of childbearing potential who are not using contraceptives [102].

Regulatory affairs

On 1 February 2013, the EMA granted lixisenatide marketing authorization in Europe for the treatment of adults with T2DM. Subsequently,

on 29 February 2013 the FDA accepted the new drug application for lixisenatide, which is currently under review.

Conclusion

GLP-1 receptor agonists, alone or combined with other drugs, are capable of improving glycemic control in T2DM patients with a low risk of hypoglycemia, unless associated with sulfonylureas or insulin. Available data suggest that GLP-1 receptor agonists could have a greater efficacy than most other drugs used for lowering blood glucose in T2DM [1,48]. In addition, GLP-1 receptor agonists could have favorable effects on cardiovascular risk, and this could be independent of their action on hyperglycemia. Potential improvements in the cardiovascular risk profile of the T2DM population are currently under investigation in a large number of clinical trials [107–110]. In the meantime, a meta-analysis on available (mainly Phase III) clinical trials with metabolic outcomes has shown that GLP-1 receptor agonists are associated with a significant reduction in major cardiovascular events in short- and medium-term placebo-controlled studies [49]; although, unfortunately, no trials with lixisenatide were available at the time of analysis.

Benefits of GLP-1 receptor agonists include weight loss, which can be useful in the management of obese patients with T2DM. Based on the results of placebo-controlled studies, it is possible that lixisenatide induces a smaller weight loss than other agents of the same class; however, the few available direct comparisons failed to show significant differences from exenatide or liraglutide. In addition, several *in vitro* studies performed in human pancreatic islets, as well as *in vivo* studies on animal models of diabetes, suggested that GLP-1 receptor agonists could inhibit β -cell apoptosis and stimulate β -cell regeneration, thus potentially delaying the natural progression of T2DM [44]. However, this supposed benefit has not been demonstrated in clinical studies so far.

The main difference between available GLP-1 receptor agonists is in their pharmacokinetics, with longer-acting drugs (administered once daily or once weekly) having a greater effect on fasting glucose and shorter-acting molecules (administered before meals) having a greater effect on PPG. Lixisenatide has a shorter duration of action than liraglutide and a longer duration of action than exenatide, and has been developed as a once-daily agent. Administered

before a meal, it provides glucose control in the following hours similar to that of exenatide. The efficacy on PPG after meals that are eaten several hours after drug administration is not documented and the effect on fasting glycemia appears to be smaller than that of longer-acting agents.

Although GLP-1 receptor agonists have been shown to be effective in combination with many drugs, studies of GLP-1 receptor agonists as an add-on to basal insulin therapy are uncommon. However, a large-scale clinical development program has been performed for lixisenatide in combination with basal insulin, with or without oral drugs. To date, lixisenatide is the GLP-1 receptor agonist with the widest and most detailed clinical information on combination therapy with insulin.

Although all GLP-1 receptor agonists are reported to be rather specific for their molecular target (i.e., the GLP-1 receptor), there are some differences that cannot be completely explained by their duration of action. Some agents (e.g., albiglutide and possibly lixisenatide) seem unable to provide a relevant weight loss [50], whereas others (e.g., exenatide [51] and liraglutide [52]) consistently reduce bodyweight in obese/overweight individuals. Treatment with lixisenatide is associated with a significant reduction of bodyweight; although its effects could be slightly smaller than those of exenatide [40]. On the other hand, despite its relatively short duration of action, lixisenatide seems to be associated with an incidence of nausea and vomiting similar to that of long-acting GLP-1 receptor agonists.

Another relevant point is the effect of lixisenatide on heart rate, which is increased by GLP-1 receptor agonists [53]. Lixisenatide seems to have a more favorable profile in this respect than longer-acting drugs of the same class. However, the overall cardiovascular effect of lixisenatide deserves to be further investigated in larger-scale trials.

Lixisenatide adds to the range of available GLP-1 receptor agonists. Compared with exenatide three-times daily, lixisenatide has the advantage of a lower number of injections. Compared with liraglutide and longer-acting agents, lixisenatide has the advantage of a greater effect on PPG when taken before a main meal. The availability of many studies that combined lixisenatide with insulin makes this agent preferable in insulin-treated patients. In addition, it could be useful for tailored treatment of patients with a

marked increase in blood glucose after one meal, without severe postprandial hyperglycemia at other times of the day.

Future perspective

The number of available GLP-1 receptor agonists will probably increase in the next few years, as some other molecules complete their clinical development programs. Interestingly, the majority of drugs in this class will be represented by long-acting (once-daily or once-weekly) analogs of human GLP-1 (liraglutide, exenatide LAR, albiglutide, dulaglutide and semaglutide). Lixisenatide, together with exenatide three-times a day, will remain the only short-acting agents with a relevant structural difference from human GLP-1.

The difference in pharmacokinetics is relevant for lixisenatide's efficacy profile, with a predominant prandial action and a smaller effect on fasting glucose. This means that exenatide and lixisenatide will be targeted to different patients than those receiving other molecules of the class, allowing for greater personalization of treatment.

It is more difficult to predict whether the structural differences between exendin-4-derived agents (exenatide and lixisenatide) and human GLP-1 analogs (all other molecules of the class) will have a greater clinical relevance in the future. Some experimental studies suggest that a few actions of GLP-1 could be mediated by pathways that are independent of the known GLP-1 receptor [54]; agents with different structures, although they are all active as GLP-1 receptor agonists, could have differential effects on GLP-1 receptor-independent pathways, with unpredictable

effects on cardiovascular risk and other safety issues. With respect to cardiovascular risk, the effect of lixisenatide on heart rate seems to be more reassuring than that of other molecules of the class, but a much wider body of evidence is needed to establish the action of individual agents on major cardiovascular events.

Presently, GLP-1 receptor agonists are mainly used as add-on therapies to metformin with/without sulfonylurea as an alternative to insulin. Trials performed with other drugs suggest the possibility of an earlier use, as a monotherapy, in newly diagnosed patients with T2DM [55] or even in obese patients without diabetes [52]. The clinical development of lixisenatide will expand the use of this class of drugs to later stages of diabetes, in patients who are already treated with basal insulin, as an alternative to the addition of prandial (bolus) rapid-acting insulin. In some countries, the development of such an approach could be limited by the relatively high cost of the combination. A further possible development is the use of lixisenatide in a fixed combination with basal insulin for treatment of T2DM, and this is currently under investigation [111].

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