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Emerging GLP-1 receptor agonists

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Introduction: Recently, glucagon-like peptide-1 receptor (GLP-1R) agonists have become available for the treatment of type 2 diabetes. These agents exploit the physiological effects of GLP-1, which is able to address several of the pathophysiological features of type 2 diabetes. GLP-1R agonists presently available are administered once or twice daily, but several once-weekly GLP-1R agonists are in late clinical development.

Areas covered: The present review aims to give an overview of the clinical data on the currently available GLP-1R agonists used for treatment of type 2 diabetes, exenatide and liraglutide, as well as the emerging GLP-1R agonists including the long-acting compounds.

Expert opinion: An emerging therapeutic trend toward initial or early combination therapy with metformin- and incretin-based therapy is anticipated for patients with type 2 diabetes. GLP-1-based therapy has so far proven safe and tolerable. The determination of which incretin-based therapy to choose necessitates comparisons between the various GLP-1R agonists. The available GLP-1R agonists cause sustained weight loss and clinical relevant improvement of glycemic control. The long-acting GLP-1R agonists in late development may improve the effects of GLP-1 even further with optimized pharmacokinetic profiles resulting in fewer side effects. Meta-analyses have shown promising effects on cardiovascular disease and data from ongoing multicenter trials with cardiovascular endpoints are expected in 2015.

Keywords: albiglutide, CJC-1134-PC, dulaglutide, exenatide, exenatide once-weekly, glucagon-like peptide-1 receptor agonists, liraglutide, lixisenatide, semaglutide, type 2 diabetes

Expert Opin. Emerging Drugs (2011) 16(4):607-618

1. Background

Oral glucose administration elicits a greater insulin response than intravenous (i.v.) glucose at identical plasma glucose profiles. This is called the incretin effect, and is conveyed by the two incretin hormones: glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) [1]. GIP is a 42 amino acid peptide, synthesized and released from enteroendocrine K cells mainly located in the duodenum and upper jejunum [1]. GLP-1 is a 30 amino acid peptide, a product of proglucagon gene expression in the intestinal enteroendocrine L cells and is, like GIP, secreted after meal ingestion [1,2]. Together the insulinotropic effect of GIP and GLP-1 accounts for up to 70% of the insulin secreted after a meal in healthy subjects, and, thus, plays a very important role in postprandial glucose homeostasis [1]. In patients with type 2 diabetes, the ability of exogenous GIP and GLP-1 to stimulate insulin secretion is severely diminished when compared with healthy subjects. However, the glucose-lowering effect of supraphysiological infusion of GLP-1 is preserved [3] while that of GIP is absent [4,5].

GLP-1 asserts its effects on the beta cells through binding to the GLP-1 receptor (GLP-1R), a cell surface receptor highly expressed on the cell membrane of pancreatic beta cells [2,6]. Receptor binding of GLP-1 results in stimulation of insulin secretion in a strict glucose-dependent manner [7,8]. GLP-1 also has potential effects on beta cell mass as pre-clinical studies have shown: stimulation of beta

cell proliferation [9,10], differentiation of new beta cells from progenitor cells [11] and by inhibition of beta cell apoptosis [12]. Furthermore, GLP-1 robustly inhibits glucagon secretion, and the combined effects on insulin and glucagon secretion results in inhibition of hepatic glucose production, which contributes significantly to the overall glucose-lowering effect of GLP-1 [13]. Additionally, GLP-1 decreases gastrointestinal motility [14] and promotes satiety [15], probably through activation of GLP-1Rs in the brain in combination with GLP-1-induced decrease in gastric emptying. Chronic administration of GLP-1 therefore leads to weight loss [16]. All of these effects are potentially beneficial in the treatment of patients with type 2 diabetes, and much attention have, therefore, been given to the development of pharmacological strategies based on the effects of GLP-1.

One of the major challenges in developing GLP-1-based therapy is that native GLP-1 is very rapidly degraded in the circulation by the enzyme dipeptidyl peptidase 4 (DPP-4), which cleaves off the two N-terminal amino acids and leaves the molecule inactive with regard to insulin secretion [17], resulting in a half-life of less than 2 min [18]. Because of the rapid elimination, native GLP-1 is unsuitable for clinical use. Two different strategies of circumventing this problem have been successful so far. One approach is to inhibit DPP-4, thereby enhancing the survival and therefore the effect of endogenously released GLP-1. The other strategy is to use GLP-1R agonists that are resistant to inactivation by DPP-4 and modified in a way that prolongs the effect of the hormone. In the following sections, the emerging GLP-1R agonists are reviewed.

2. Medical need

Type 2 diabetes is a progressive and multifactorial disease. There were an estimated 285 million adults with type 2 diabetes in 2010 worldwide, and, as the western lifestyle is making its entry into the developing countries, this number will continue to increase [19]. Projections for 2030 show that the prevalence of type 2 diabetes is likely to reach almost 450 million [20]. Type 2 diabetes leads to serious complications that broadly can be classified as microvascular (neuropathy, nephropathy and retinopathy) or macrovascular (atherosclerosis resulting in myocardial infarction and stroke). The ultimate goal of diabetes therapy is to prevent these complications in order to improve life expectancy and quality of life. The United Kingdom Prospective Diabetes Study (UKPDS) showed that improved glycemic control (HbA1c) resulted in less microvascular complications in patients with type 2 diabetes [21]. Furthermore, recent follow-up studies from the UKPDS have shown that tight glucose control in the early years of disease impacts dramatically on the development of complications related to the disease [22].

Despite recognition that type 2 diabetes is a huge public health concern, and major efforts to attract attention to the importance of tight glycemic control, data from World Health Organization (WHO) show that the percentage of individuals reaching International Diabetes Federation (IDF) treatment goals is still very low [23]. Common barriers to patient adherence include concern about unwanted weight gain [24], fear of hypoglycemia and perceived inconvenience [25], and these may all indirectly undermine glycemic control if the prescribed therapy is not followed.

3. Existing treatment

International guidelines for the treatment of patients with type 2 diabetes have been suggested by the European Association for the Study of Diabetes (EASD) and the American Diabetes Association (ADA) [26]. Based on data from the UKPDS it is recommended that metformin should be started in all patients with newly diagnosed type 2 diabetes who do not have contraindications to metformin treatment (e.g., renal disease) [26-29]. However, often metformin is not enough to treat the patients with the target HbA1c levels below 7%. Therefore, the guidelines suggest additional treatment options on which agents to add to metformin treatment [29]. Classical therapeutic additives are: i) the insulin secretagogues sulfonylureas (SU), ii) the insulin-sensitizing thiazolidiones (TZD) and iii) exogenous insulin. However, all of these agents are associated with different adverse effects including risk of hypoglycemia (SU and insulin), weight gain (SU, insulin and TZD) and increased risk of bone fractures and even heart disease (TZD) [30]. Additionally, none of these medications are able to correct either the impairment or the progressive decline of beta cell function. Recently, the incretin-based therapies including GLP-1R agonists and DPP-4 inhibitors were introduced into clinical practice, and these agents are now widely used for the treatment of type 2 diabetes [31], with the GLP-1R agonists being part of the latest ADA/EASD treatment guidelines [26].

The development of the GLP-1R agonists is based on two different approaches. One strategy exploits the structure of native human GLP-1, modified in a way so that it is resistant to degradation by DPP-4, as the backbone for the compounds (Figure 1). The other approach uses a naturally occurring protein – exendin-4, originally isolated from the saliva of the lizard Heloderma suspectum – as the backbone of the compounds (Figure 1). Exendin-4 has a 53% sequence homology with human GLP-1 in its first 30 amino acids [32], and binds to and activates the GLP-1R with equal potency as native GLP-1. Two GLP-1R agonists have so far been approved for the treatment of type 2 diabetes: exenatide, based on exendin-4, for twice-daily subcutaneous (s.c.) injection and liraglutide, based on the structure of native GLP-1, for once-daily s.c. injection.

3.1 Exenatide

Exenatide (Byetta®, Amylin Pharmaceuticals, Inc., San Diego, CA, US/Eli Lilly, Indianapolis, Indiana, US), the first GLP-1R agonist to reach the market, was approved by the US Food

GLP-1 receptor agonists for sc injection			
GLP-1-based		Exendin-4-based	
Daily	Weekly	Daily	Weekly
Liraglutide	Albiglutide	Exenatide	Exenatide-LAR
	Dulaglutide	Lixisenatide	CJC-1134-PC
	Semaglutide		

Figure 1. Overview of the existing and emerging GLP-1R agonists; two approaches based on human GLP-1 and exendin-4.
GLP-1R: Glucagon-like peptide-1 receptor.

and Drug Administration (FDA) in April 2005 and by European Medicines Agency (EMA) in 2007 (Table 1). Exenatide is a synthetic version of exendin-4, a 39 amino acid peptide (Table 2) [1,32], and is resistant to inactivation by DPP-4. Exenatide is primarily cleared in the kidneys by glomerular filtration [33], and the half-life after s.c. injection is approximately 2 – 3 h [34]. Exenatide, therefore, has to be administered twice daily to achieve 24-h pharmacological plasma concentrations. In the early clinical AC2993: Diabetes Management for Improving Glucose Outcome (AMIGO) trials, the effects of exenatide was investigated in a total of 1446 randomized patients [35-37]. Exenatide was given as add-on therapy to metformin, SU or both and these studies reported statistically significant improvement of glycemic control in the exenatide treatment groups (change of HbA1c of -1.0% (baseline of 8.2%) vs. an increase of approximately 0.2% in the placebo groups) and change in fasting plasma glucose (FPG) (-0.5 mM vs. an increase of nearly 1 mM in the placebo groups). On average, the weight loss in the three studies comparing exenatide with oral anti-diabetics amounted to 1.6 kg (baseline of 95 kg) in the exenatide-treated patients [38]. Additionally, significant reduction in systolic blood pressure compared with placebo (difference of 2.8 mmHg) or insulin (difference of 3.7 mmHg) have been reported after 6 months of treatment with exenatide [39]. In 2011, a large retrospective database analysis looking at the relative incidence of cardiovascular disease (CVD) events in patients with type 2 diabetes either treated with exenatide twice-daily (n = 39,275) or with other glucose-lowering agents (n = 381,218) was published [40]. The study reported that treatment with exenatide twice-daily was associated with a significantly lower risk of CVD events than treatment with other glucose-lowering agents.

3.2 Liraglutide

Liraglutide (Victoza®, Novo Nordisk, Bagsværd, Copenhagen, Denmark) is an acylated analog of human GLP-1 (with 97% homology with native GLP-1), which was approved for clinical use in Europe in 2009 and in the USA in 2010 (Table 1). In liraglutide, a C-16 acyl chain is linked to amino acid 20 via a γ-glutamic acid spacer and the lysine in position 28 of native GLP-1 is exchanged with arginine (Table 2) [41]. These changes results in a half-life in the range of approximately 11 – 15 h after s.c. administration [42], making it suitable for once-daily dosing [43]. The clinical effects of liraglutide treatment have been investigated in the Liraglutide Effect and Action in Diabetes (LEAD) series of Phase III studies. These trials lasting up to 52 weeks, showed that treatment with liraglutide both as monotherapy and in combination with metformin, SU or TZD plus metformin lowered HbA1c and body weight. Liraglutide-induced change in HbA1c varied from -0.8 to -1.5% (baseline HbA1c of 8.2 – 8.5%) [44-49], reductions that in most cases were similar or greater than compared with the oral comparator drug [42]. Overall, a reduction in body weight was seen in all trials in the range of 2 – 3 kg, much like other Phase III studies with liraglutide compared with placebo, and not different from exenatide. In the LEAD-6 study, liraglutide and exenatide were compared head-to-head [47]. A significantly greater reduction in HbA1c with liraglutide than with exenatide treatment was observed (1.1 vs. 0.8%), as well as greater reduction in FPG (1.6 vs. 0.6 mM). Greater reductions in triglycerides (0.4 vs. 0.2 mM) and free fatty acids (0.17 vs. 0.10 mM) in the liraglutide group were observed. Both liraglutide and exenatide caused significant decreases in blood pressure. Newly published data from a 14-week extension of the LEAD-6 Phase IIIb study, where subjects either continued with liraglutide or switched from exenatide to liraglutide, showed that switching from exenatide to liraglutide further and significantly reduced HbA1c (0.3%), FPG (0.9 mM), body weight (0.9 kg) and systolic blood pressure (3.8 mmHg) [50].

3.3 Side effects of exenatide and liraglutide

The side effects during treatment with exenatide and liraglutide are mild to moderate nausea and vomiting. These side effects are dose-dependent and often decline over time [51]. The incidence of treatment-associated hypoglycemia is reported to be low. In fact, occurrence of hypoglycemia during exenatide treatment combined with metformin is similar to when metformin is used as monotherapy [52]. However, combined with SU the risk of minor hypoglycemic episodes is reported to be in the range of 15 – 36% for exenatide [51] and 8 – 25% for liraglutide [53]. Approximately 50% of exenatide-treated patients in long-term, placebo-controlled studies developed low titres of anti-exenatide antibodies, and an additional 6% developed higher levels of antibodies, during the initial 30 weeks of treatment [51]. Among liraglutide-treated patients, 4 – 13% developed antibodies (low titres) [44-46,48,49]. The exact impact of autoantibodies on efficacy and safety in the longer term remains to be established, but patients with high titres seem to have an impaired effect on glycemic control [54]. After the approval of exenatide and liraglutide post-marketing reports of several incidents of

Table 1. Overview of the existing and emerging GLP-1R agonists, their state of development and ongoing trials.

Compound	Company	Formulation	Status of development	Ongoing trials
Exenatide	Eli Lilly/Amylin Pharmaceuticals, Inc.	Twice-daily	Launched	Combination with insulin/ obesity + CVD
Liraglutide	Novo Nordisk	Once-daily	Launched	Combination with insulin/ obesity + CVD
Exenatide once-weekly	Eli Lilly/Amylin Pharmaceutical, Inc./ Alkermes, Inc.	Once-weekly	Expected 2011	Combination with insulin/ obesity
Lixisenatide	Zealand Pharma A/S/Sanofi-Aventis	Once-daily	Expected 2011	Phase III, GetGoal
CJC-1134-PC	ConjuChem	Once-weekly	Phase I/II	Phase I/II
Albiglutide	GlaxoSmithKline	Once-weekly	Expected 2012	Phase III, Harmony
Dulaglutide (LY2189265)	Eli Lilly	Once-weekly	Expected 2013	Phase III, Award
Semaglutide (NN9535)	Novo Nordisk	Once-weekly	Phase II	On hold

CVD: Cardiovascular disease; GLP-1R: Glucagon-like peptide-1 receptor.

Table 2. Amino acid structures of GLP-1 and the GLP-1R agonists on the market or in late clinical development (published data).

Name	Structure
Native GLP-1	His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg
Liraglutide	His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Arg-Gly-Arg-Gly | Glu-C16 fatty acid
Albiglutide	(His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg)$_2$ – linked to human albumin
Exenatide	His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser
Lixisenatide	His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser-Lys-Lys-Lys-Lys-Lys-Lys
CJC-1134-PC	His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys-C13H19O6N3 (linker molecule)

GLP-1: Glucagon-like peptide-1; GLP-1R: Glucagon-like peptide-1 receptor.

acute pancreatitis in patients treated with exenatide and liraglutide have been disclosed [55]. However, it is not evident that the incidence of acute pancreatitis is higher in those receiving exenatide or liraglutide than in the background diabetic population [56]. Still it is recommended that these GLP-1R agonists should not be used in subjects with a history of or increased risk of pancreatitis. Lately, the risk of pancreatic cancer has been discussed in patients treated with exenatide compared with other anti-diabetic medications [57,58]. However, the EMA recently concluded that a relationship between GLP-1R agonists and pancreatic malignancies could not yet be confirmed nor excluded [59]. In carcinogenicity studies with liraglutide, C cell tumors were observed in thyroid tissue of mice and rats [60]. However, recent data identify key differences between rodent models, non-human primates and humans with regard to this, and the long-term consequences of sustained GLP-1R activation in the human thyroid require further investigation [61], but so far no changes in thyroid function have been reported in clinical trials with GLP-1R agonists. Furthermore, large studies are underway aiming to assess and confirm the cardiovascular safety of both exenatide and liraglutide.

4. Current research goals

The GLP-1R agonists have already proved to be a valuable asset to the treatment of patients with type 2 diabetes. However, despite the many beneficial effects of the GLP-1R agonists on weight loss and improved glycemic control, the gastrointestinal intolerability and daily s.c. administration may lead to discontinuation [62]. Currently, GLP-1R agonists with optimized pharmacokinetic profiles and a lower number

of adverse events are under development. Most of the emerging GLP-1R agonists are for once-weekly s.c. administration. The once-weekly regime is thought to improve compliance, and to offer an improved throughout-the-day glycemic control compared with the currently available GLP-1R agonists (exenatide and liraglutide).

5. Competitive environment

5.1 Exenatide once-weekly

Exenatide has been developed in a sustained-release formulation planned for once-weekly s.c. administration by Amylin Pharmaceuticals, Inc., Eli Lilly and Alkermes Inc. (Table 1). The exenatide molecules are encapsulated in injectable microspheres, which consist of a biodegradable medical polymer also used in other extended-release pharmaceuticals [63]. These microspheres allow gradual drug delivery at a controlled rate by diffusion and erosion of the microspheres. The drug is now in late clinical development, and the clinical effects of exenatide once-weekly have been examined in the 'Diabetes therapy Utilization: Researching changes in HbA1c weight and other factors Through Intervention with exenatide Once-weekly' (DURATION) 1 – 6 trials [64-69]. In DURATION-1, exenatide once-weekly was studied in a head-to-head comparison with exenatide twice-daily in 295 patients with type 2 diabetes (HbA1c 8.3 ± 1%, weight 103 ± 20 kg, BMI 35 ± 5 kg/m^2, diabetes duration 7 ± 5 years) over 30 weeks [69]. Exenatide once-weekly was superior to exenatide twice-daily in terms of glycemic parameters (HbA1c change: -1.9 vs. -1.5%, proportion of patients reaching HbA1c of 7.0% or less: 77 vs. 61%; FPG: -2.3 vs. -1.4 mM). Interestingly, glucagon levels decreased significantly more with exenatide once-weekly vs. exenatide twice-daily, likely contributing to the improvement in FPG levels. Additionally, significantly greater reductions in total cholesterol and low-density lipoprotein cholesterol were observed with the once-weekly exenatide compared with the twice-daily exenatide. Equal significant improvements in fasting triglyceride and systolic and diastolic blood pressures were observed with both treatments. No difference in body weight reduction was observed (3.7 vs. 3.6 kg), and about 75% of the patients lose weight [69]. A 22-week *open-label* extension of the DURATION-1 study, where patients either continued with exenatide once-weekly or switched from exenatide once-daily to exenatide once-weekly, showed that the improved glycemic control and weight loss were sustained over the 52 weeks of therapy and patients who switched from exenatide twice-daily to once-weekly achieved a further reduction in HbA1c, ending up with the same improvements in glycemic control as the group treated with exenatide once-weekly for the entire 52 weeks [70].

In the DURATION-2 to 5 studies, exenatide once-weekly was compared against: a TZD, a DPP-4 inhibitor, insulin glargine, metformin and the commercial formulation of exenatide once-weekly was compared against exenatide twice-daily [64-67]. In all studies, exenatide once-weekly lowered HbA1c and body weight significantly. The HbA1c reduction by exenatide once-weekly was up to 1.6%, and in most cases this reduction was greater or similar to that of the comparator. Overall, a reduction in body weight by exenatide once-weekly was seen in the range of 2.1 – 2.6 kg. Very recently, the preliminary results from the DURATION-6 study comparing exenatide once-weekly with liraglutide once-daily were reported in a press release [68]. This 26-week head-to-head, *open-label*, study enrolled approximately 900 patients with type 2 diabetes who were not achieving adequate HbA1c with diet and exercise in conjunction with metformin, SU, metformin plus a SU or metformin plus a TZD. The study revealed that patients receiving exenatide once-weekly experienced a reduction in HbA1c of 1.3% compared with 1.5% for liraglutide. Exenatide once-weekly did, therefore, not meet the pre-specified primary end point of non-inferiority to liraglutide with regard to HbA1c reduction since liraglutide was significantly more efficacious than exenatide once-weekly. However, exenatide once-weekly did appear to be slightly better tolerated than liraglutide with less gastrointestinal side effects (such as nausea and vomiting), although more patients experienced local site reactions with exenatide compared with liraglutide [68]. Data on changes in body weight have not yet been reported.

The most frequently reported adverse events among exenatide once-weekly-treated patients in the DURATION studies were nausea (predominately mild in intensity) (9 – 26%) and vomiting (4 – 11%) [64-70]. Other side effects included diarrhea (6 – 18%), and injection site adverse effects (pruritus, erythema, induration or pain) (10 – 18%) [64-70]. Pooled data of the safety and tolerability of exenatide once-weekly from 1095 patients (from the DURATION 1, 2 and 3 studies) showed that exenatide once-weekly were generally well tolerated, and that the overall incidence rates of adverse events, serious adverse events and discontinuations due to serious adverse events were similar for exenatide once-weekly versus the pooled comparators. No major episodes of hypoglycemia have been observed and the incidence of mild to moderate hypoglycemic events observed with exenatide once-weekly treatment was lower compared with the pooled comparator cohort (16 vs. 22%) [71].

Recently, a probable correlation between plasma exenatide concentrations and changes from baseline in the QT interval in healthy subjects was discussed [72]. Thus, the FDA recently requested a thorough QT interval study with exenatide levels higher than typical therapeutic levels of exenatide once-weekly [73]. Additionally, the FDA requested the results of the DURATION-5 study to evaluate the efficacy, safety and effectiveness, of the commercial formulation of exenatide once-weekly. Amylin Pharmaceuticals, Inc., Eli Lilly and Alkermes, Inc. are planning to submit their reply to the FDA by the end of 2011. In April 2011, the EMA has issued a positive opinion and exenatide once-weekly will reach the European market (tradename: Bydureon) by the end of 2011.

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