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Once-Weekly GLP-1 Agonists: How Do They Differ from Exenatide and Liraglutide?

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Abstract Incretin mimetics offer a new modality in diabetes treatment. This modality is based on the effects of the naturally occurring glucoregulatory gut hormone glucagon-like peptide-1 (GLP-1), which counteracts several pathophysiologic traits in type 2 diabetes. GLP-1 receptor agonists with extended half-lives entailing fewer injections and presumably an improved throughout-the-day glycemic control are in clinical development. This article summarizes the physiologic effects of GLP-1; the effects of the already marketed GLP-1 analogues for daily dosing, exenatide and liraglutide; and reviews the presently published data (with emphasis on clinical pharmacokinetics, efficacy, and safety) on GLP-1 agonists, which currently are in development and intended for once-weekly dosing: albiglutide/albugon, CJC-1131, CJC-1134-PC, exenatide once weekly, and taspoglutide.

Keywords Albiglutide · Albugon · CJC-1131 · CJC-1134-PC · Exenatide · Exenatide once weekly · Glucagon-like peptide-1 · GLP-1 agonist · Incretin mimetics · Long-acting release · Taspoglutide · Type 2 diabetes

Introduction

The increasing global prevalence of obesity goes hand in hand with the pandemic of type 2 diabetes. In 2025, it is estimated that almost 400 million people worldwide will suffer from diabetes, with type 2 diabetes comprising more than 90% of the cases. In most cases, type 2 diabetes develops on the background of a genetic disposition combined with a lifestyle of overeating and too little physical activity. Patients with type 2 diabetes are pathophysiologically characterized by insulin resistance, β-cell dysfunction, reduced β-cell mass, increased β-cell apoptosis, glucagon hypersecretion, and fasting and postprandial hyperglycemia, which increase the risk of microvascular (nephropathy, neuropathy, and retinopathy) and macrovascular complications dramatically.

The traditional treatment modalities, whether used in monotherapy or combination, do not seem to alter the progressive nature of type 2 diabetes. Additionally, these therapies associate with adverse events such as increased risk of hypoglycemia (sulfonylurea [SU] compounds and insulin), weight gain (SU, insulin, and thiazolidinediones), and/or gastrointestinal side effects (metformin). Since 2005, the glucagon-like peptide-1 (GLP-1) receptor analogue exenatide (Byetta; Amylin Pharmaceuticals, San Diego, CA) has been available as a treatment modality for type 2 diabetes; in 2009, another analogue, liraglutide (Victoza; Novo Nordisk, Bagsværd, Denmark), was introduced to the European markets (launched in the US and Japan in February 2010). These treatments are based on the effects of the naturally occurring glucoregulatory gut hormone GLP-1, which seem to counteract several pathophysiologic traits in type 2 diabetes. Exenatide and liraglutide are resistant to the ubiquitous enzyme dipeptidyl peptidase-4 (DPP-4), which under normal circumstances degrades and inactivates GLP-1. Consequently, the compounds have severalfold longer half-lives, which suit them for twice-daily (exenatide) or once-daily (liraglutide) subcutaneous (SC) injections. With the aim of achieving better glycemic control and less side

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effects combined with less frequent dosing, long-acting release (LAR) formulations of several GLP-1 analogues are being developed. This review aims to compile the present published data on GLP-1 agonists, which are in current development and intended for once-weekly (or less) dosing juxtaposed to the effects of the already marketed shorter-acting GLP-1 analogues exenatide and liraglutide.

GLP-1 Physiology

GLP-1 is a 30-amino acid polypeptide produced in the endocrine L cells of the intestinal epithelium as a product of proglucagon gene expression [1•]. L cells are found throughout the intestinal tract, with the highest density in the ileum and in parts of the colon [1•]. GLP-1 is secreted rapidly in response to ingestion of nutrients with peak concentrations 30 to 45 min after ingestion of, for example, glucose [1•]. As mentioned, DPP-4 is responsible for the degradation and inactivation of GLP-1 [2]. This enzyme is found in numerous tissues as well as in a soluble form in plasma and is responsible for the low apparent half-life of circulating GLP-1 of 1 to 1.5 min [3, 4].

GLP-1 exerts its physiologic effects through a G-protein–coupled receptor, which is widely distributed across different tissues. In the pancreatic β cells, GLP-1 augments insulin secretion in a glucose-dependent manner, and GLP-1 has also been shown to enhance all steps of insulin biosynthesis and insulin gene transcription [5]. In rodents, GLP-1 has trophic effects on β cells, stimulates β-cell proliferation [6], and enhances the differentiation of new β cells from progenitor cells in the pancreatic duct epithelium [7]. In isolated human islets, GLP-1 has been shown to inhibit apoptosis of β cells [8]. Additionally, GLP-1 inhibits glucagon secretion, which in turn reduces hepatic glucose production [9]. Furthermore, GLP-1 decreases gastrointestinal motility, which in combination with afferent signaling through the vagus nerve and activation of GLP-1 receptors (GLP-1Rs) in the central nervous system, promotes satiety and reduces food intake, thereby controlling body weight [10]. GLP-1Rs are also found in the heart; and GLP-1 has been shown to improve left ventricular function in the failing and ischemic heart [11, 12]. Furthermore, GLP-1 has been found to reduce the postprandial rise in triglycerides and lower the concentration of free fatty acids in healthy subjects [13], and improve endothelial dysfunction in patients with type 2 diabetes and coronary heart disease [14]. Renal Na^+/H^+ exchange is also affected by GLP-1 and the resulting natriuretic and diuretic properties could contribute to a blood pressure (BP)–lowering effect [15]. Finally, GLP-1 has been associated with improved learning and displayed neuroprotective effects in rodents [16, 17].

GLP-1 Analogues on the Market

The beneficial actions of GLP-1 in type 2 diabetes have been exploited in the development of DPP-4–resistant GLP-1R agonists (incretin mimetics). In the following sections, the current clinical data regarding GLP-1R agonists already on the market (exenatide and liraglutide) are compared with formulations of GLP-1 analogues with extended actions suited for once-weekly dosing in clinical development (CJC-1134-PC, albiglutide, taspoglutide, and exenatide once weekly).

Exenatide

Exenatide was isolated from the saliva of the lizard Heloderma Suspectum in a search for biologically active peptides [18]. Exenatide shares 53% sequence homology with native GLP-1, but is equipotent with regard to binding and activation of GLP-1Rs on pancreatic β cells [19].

After SC administration, exenatide is rapidly absorbed, reaching peak concentrations in approximately 2 h [20]. Exenatide is cleared primarily in the kidneys by glomerular filtration [21], and, as a result, the half-life of SC-administered exenatide is approximately 2 h. Consequently, significant plasma levels of exenatide in plasma are only evident for 5 to 6 h after SC administration of the maximally tolerated dose.

The clinical effects of exenatide treatment were originally investigated in a total of 2731 patients [22]. Exenatide as add-on therapy to metformin, SU, or both conferred statistically significant improvement in glycemic control (hemoglobin A_{1c} [HbA_{1c}] reduction of -1.0% from a baseline of 8.2% vs an increase of ~ 1.5% in the placebo groups) and reduction in fasting plasma glucose (-0.5 mM in the exenatide groups vs an increase of ~ 1 mM in the placebo groups). Exenatide induces similar reductions in HbA_{1c} (about -1%) as insulin glargine [23] and insulin aspart [24]. On average, the weight loss in the three studies comparing exenatide to oral antidiabetic agents amounted to 1.6 kg in the exenatide-treated patients [25]. In an open-label extension of the three studies (with the limitations of a substantial dropout rate), 3-year sustained effects were demonstrated with respect to glycemic control and body weight (change in HbA_{1c} of -1%, body weight of -5.3 kg) [26]. Minor, but significant improvements in triglycerides, total cholesterol, low-density lipoprotein levels, and high-density lipoprotein levels in favor of a reduced cardiovascular risk with exenatide have been reported [26]. Additionally, 6 months of exenatide treatment is associated with reduction in systolic BP compared with placebo (-2.8 mm Hg) or insulin (-3.7 mm Hg) [27].

Liraglutide

Liraglutide is an acylated analogue of human GLP-1. It has a 97% sequence homology to native GLP-1 and, therefore,

has similar interactions with the GLP-1R as GLP-1. A high degree of plasma protein binding causes decreased susceptibility to metabolism by DPP-4, and the half-life after SC administration of liraglutide is approximately 13 h [28], which makes it suitable for once-daily dosing.

The clinical effects of liraglutide treatment have been investigated in the LEAD (Liraglutide Effect and Action in Diabetes) series of phase 3 studies. Liraglutide in monotherapy (52 weeks of treatment) lowered HbA_{1c} by -0.8% and -1.1% in doses of 1.2 and 1.8 mg, respectively, which was significantly more than the -0.5% reached with the SU glimepiride [29]. In LEAD 2 [30], liraglutide (1.8 mg) added to existing metformin treatment reduced HbA_{1c} by -1.0%, significantly more than placebo, which increased HbA_{1c} by 0.09%, and was comparable to the reduction observed with glimepiride (-0.7%). In LEAD 1 [31], liraglutide (1.8 mg) reduced HbA_{1c} by 1.1% when added to glimepiride treatment; this was significantly more than the 0.4% reduction with the addition of rosiglitazone and the 0.2% increase with placebo. In LEAD 4 [32], liraglutide (1.8 mg) added to metformin in combination with rosiglitazone achieved a reduction in HbA_{1c} of 1.5% (significantly better than the 0.5% reduction with placebo). A reduction of -1.3% was reached when liraglutide was added to metformin in combination with glimepiride in the LEAD 5 study (significantly better than placebo [-0.2%] and the active comparator insulin glargine [-1.1%]). In LEAD 6 [33], HbA_{1c} reduction was significantly greater with liraglutide treatment than with exenatide (1.1% vs 0.8%). As for exenatide, liraglutide has significant effect on body weight. In LEAD 3, body weight reduction of 2.5 kg (baseline, 93 kg) was significantly different compared with a 1.1-kg increase with glimepiride [29]. In LEAD 2, there was a 2.8-kg weight reduction (significantly different from a 1.0-kg increase with glimepiride) [30]. In LEAD 1, a decrease of 0.2 kg was significantly different compared with a 2.1-kg increase with rosiglitazone [31]. In LEAD 6 [33], greater reductions in triglycerides (-0.4 vs -0.2 mM) and free fatty acids (-0.17 vs -0.10) in the liraglutide group were observed. Both compounds caused a significant decrease in BP (systolic BP, -2.2 mm Hg; diastolic BP, -1.5 mm Hg).

Safety of Exenatide and Liraglutide

The major side effects of the two drugs are mild to moderate nausea and vomiting. These side effects are dose dependent and decline over time [34]. Other frequently reported side effects include headache and upper respiratory infection [20, 35]. The incidence of treatment-associated hypoglycemia is reported to be low [20, 35]. However, combined with SU the risk of minor hypoglycemic episodes is reported to be in the range 15% to 36% for exenatide [34] and 8% to 25% for liraglutide [36]. Approximately 40% of exenatide-treated patients in long-term, placebo-controlled studies developed antibodies against exenatide during the initial 30 weeks of treatment [34]. There is some evidence of lacking glycemic response in subsets of patients with high exenatide antibody titers [20]. Among liraglutide-treated patients, only 8% exhibited antibodies [29-32, 37]. The exact impact of antibodies on efficacy and safety in the longer term remains to be established. Since 2005, the US Food and Drug Administration has received at least 200 reports on pancreatitis in exenatide-treated patients. At this point, it is not clear whether a causal relationship between pancreatitis and GLP-1–based therapy exists or the cases are incidental. In carcinogenicity studies with liraglutide, C-cell tumors were observed in the thyroid tissue of mice and rats. Potential mechanisms behind C-cell tumor development and possible clinical implications remain to be established [35].

Once-Weekly Formulations of GLP-1 Analogues in Development

This review of long-acting formulations is built on a systematic search on PubMed and the European Association for the Study of Diabetes and American Diabetes Association homepages for publications and abstracts with the key words GLP-1, CJC-1131, CJC-1134-PC, albugon, albiglutide, taspoglutide, exenatide LAR, and exenatide once weekly, up to January 2010.

CJC-1134-PC

CJC-1134-PC is a modified exendin-4 analogue conjugated to human recombinant albumin (HRA) in vitro to form a long-acting DPP-4–resistant GLP-1R agonist [38-40]. The development of CJC-1134-PC is based on the distinctive ConjuChem's drug affinity complex PC-DAC (ConjuChem; Montreal, Quebec, Canada) technology and is analogous to the one previously described in the development of CJC-1131 [41, 42]. However, CJC-1131 is based on in vivo (ie, after parenteral administration) binding of GLP-1 (7–36) to HRA [41, 42], and has been abandoned in clinical development. Thus, CJC-1134-PC is a preformed bioconjugate of exendin-4 covalently bound through a low-molecular chemical linker (cys-$C_{13}H_{19}O_6N_3$-lys) to the cysteine residue in position 34 of HRA.

Currently available preclinical data show that CJC-1134-PC, despite being a much larger molecule than exendin-4, retains the ability to bind to and activate the GLP-1R [43]. Thus, acute CJC-1134-PC administration dose dependently increased cyclic AMP (cAMP) production in vitro, although slightly less potently than exendin-4 (ED_{50} of 3.47 vs 2.62 mM for exendin-4). Furthermore, acute administra-

tion of CJC-1134-PC in wild-type mice led to reduced glucose excursions, food intake, and gastric emptying compared with exendin-4 [43]. With chronic administration (4 weeks), CJC-1134-PC once daily also improved glucose tolerance and reduced body weight in high-fat diet mice similar to the effects of twice-daily exendin-4 [43]. In addition, chronic administration of CJC-1134-PC increased mRNA of genes that contribute to pancreatic β-cell function and proliferation (ie, glucokinase, GLP-1R, pancreatic and duodenal homeobox factor 1 genes), but with no measurable effect on β-cell mass. Notably, insulin receptor substrate 2 and insulin mRNA levels were increased by exendin-4, but not by CJC-1134-PC [43].

At present, the clinical pharmacology data for CJC-1134-PC are very limited, and results of phase 1 and 2 studies have been published solely as abstracts [39, 40]. Therefore, complete pharmacokinetic data are not available; however, available pharmacokinetic profiles showing peak plasma concentrations from day 2 to 7 after single-dose administration support once-weekly dosing [39].

A phase 1/2 clinical dose-finding study (N=58) with daily administration of SC CJC-1134-PC at doses between 310 to 5000 μg evaluated efficacy and safety in diabetic subjects [39]. Doses above 1250 μg produced reductions in mean daily and fasting glucose levels, persisting for 1 to 3 weeks after a single SC dose. A body weight reduction of 2.5 kg (placebo, 1.2 kg) was observed at the 3,000-μg dose at 3 weeks [39]. The efficacy of HbA_{1c} of CJC-1134-PC compared with placebo was evaluated in a 3-month phase 2 clinical trial comprising two individual studies with a total of 224 patients with type 2 diabetes inadequately controlled on metformin. CJC-1134-PC reduced HbA_{1c} by 0.8% (1.5–2 mg once weekly) and 1.4% (1.5 mg twice weekly), compared to a 0.4% reduction with placebo. Body weight decreased during the 3-month treatment period with reductions of 1.2 kg (with 1.5 mg twice weekly); however, this was nonsignificant compared with placebo (-0.4 kg) [40].

In the phase 1/2 clinical dose-finding study, no safety or tolerability issues were identified at dose levels up to 3,000 μg; at higher doses, vomiting observed in two patients (ie, 3%), was the only encountered tolerability issue [39]. In the phase 2 clinical trial, across all treatment arms, drug-related nausea (23%), vomiting (11%), and diarrhea (10%) were observed with corresponding values of 10%, 6%, and 8%, respectively, with placebo treatment [40]. These gastrointestinal side effects were reported to diminish over time [40].

Albiglutide

Albiglutide is a long-acting GLP-1 agonist generated by fusion of a DPP-4–resistant GLP-1 analogous dimer to human albumin. Albiglutide, formerly named albugon, is currently under development by GlaxoSmithKline (Research Triangle Park, NC). The compound has a long half-life as a result of its fusion with albumin and its resistance to degradation by DPP-4, caused by connecting two copies of GLP-1, each with an amino acid substitution (Ala to Glu) at the DPP-4–sensitive hydrolysis site.

Preclinical trial data showed that the tandem GLP-1 region of albiglutide was able to activate the GLP-1R. Thus, albiglutide administration dose dependently increased cAMP production in vitro, although much less potently than exendin-4 (20 vs 0.2 nM for exendin-4) [44]. Furthermore, acute administration of albiglutide in wild-type mice led to similar biological actions as exendin-4 (ie, reductions in glucose excursions, food intake, and gastric emptying rates) [44].

Evaluation of the clinical pharmacology of albiglutide is based on four clinical trials that have been published as full scientific articles [45-48]. Pharmacokinetic data from trials evaluating albiglutide in healthy volunteers [45], non-Japanese type 2 diabetic patients [46, 47], and Japanese type 2 diabetic patients [48], respectively, demonstrated that peak plasma levels were achieved in 2.3 to 5 days (time of maximum concentration [T_{max}]) after SC administration, and albiglutide was eliminated with a terminal half-life ($T_{½}$) ranging from 5 to 8 days. The data are slightly variable with regard to dose dependency of kinetics, but showed linear kinetics in the Japanese subjects [48]. The Japanese subjects in general also had a higher exposure (ie, maximum concentration and area under the curve [AUC] values) than non-Japanese subjects [48].

In Matthews et al.'s study [47], 54 patients with type 2 diabetes (baseline HbA_{1c}, 8.0%), drug naïve or withdrawn from oral antidiabetic medication, were administered single albiglutide injections (9–32 mg repeated once at day 8). The treatment resulted in significant improvements in fasting blood glucose, 24-hour blood glucose profiles, and postprandial plasma glucose at day 9. The efficacy of 4 weeks of high-dose albiglutide treatment on glycemic parameters was reported by Seino et al. [48], in which Japanese type 2 diabetic patients (N=40) on monotherapy or drug naïve were randomized to placebo or albiglutide, 15 mg once weekly, 30 mg once weekly, 50 mg once every 2 weeks, or 100 mg monthly. Fasting plasma glucose at 4 weeks was correspondingly reduced by 1.2, 1.8, 1.1, and 0.7 mM in the albiglutide-treated groups versus 0.2 mM with placebo. HbA_{1c} was lowered by 0.7% at 4 weeks in all albiglutide-treated groups (vs 0.1% in the placebo group) [48]. The efficacy of albiglutide on HbA_{1c} was evaluated by Rosenstock et al. [46] in a phase 2 clinical trial in which 356 patients with type 2 diabetes on metformin or drug naïve (baseline HbA_{1c}, 8.0%) were randomized to receive 16 weeks of double-blind SC treatment with placebo, open-

label exenatide (5 μg twice daily for 4 weeks followed by 10 μg twice daily), or albiglutide in three dosing schedules: weekly (4, 15, or 30 mg), biweekly (15, 30, or 50 mg), or monthly (50 or 100 mg). Placebo reduced HbA_{1c} by 0.2%, exenatide by 0.5%, and albiglutide reduced HbA_{1c} dose dependently in each dosing schedule by maximally 0.9% (30 mg once weekly), 0.8% (50 mg biweekly), and 0.9% (100 mg monthly). Reductions in fasting plasma glucose amounted to 0.1 mM (placebo), 0.8 mM (exenatide), 1.4 mM (30 mg once weekly), 1.2 mM (50 mg biweekly), and 1.2 mM (100 mg monthly). There was a trend toward decreased body weight with average weight losses between 1.1 and 1.7 kg with the highest albiglutide doses in each schedule, compared with 0.7 kg in the placebo and 2.4 kg in the exenatide-treated group. Glucagon and insulin levels were not affected significantly. A trend toward BP reduction, and no significant impact on lipid profiles, was also reported [46].

In the two single-dose studies, headache and nausea were the most frequently reported adverse events [45, 47]. However, probably owing to a small sample size, no differences in adverse events between albiglutide-treated and placebo-treated groups were demonstrated. In the 4-week study by Seino et al. [48], the most common adverse events were related to the gastrointestinal tract, with nausea, vomiting, and flatulence being the most frequent and only in the highest dose group (100 mg monthly) reported more frequently than placebo. In Rosenstock et al.'s [46] phase 2 clinical trial, nausea and vomiting were the most common adverse events, and occurred dose dependently in 29% (30 mg once weekly), 54% (50 mg biweekly), and 56% (100 mg monthly). The frequency of nausea and vomiting diminished over the course of the study. Documented hypoglycemia was not increased with albiglutide. Anti-albiglutide antibodies were found in 2.5% of subjects, and were not associated with efficacy of safety problems [46]. A universal rash occurred in one patient and was considered a serious adverse event [45]. Clinically relevant abnormalities in electrocardiograms (ECGs) or in clinical laboratory tests attributed to albiglutide treatment did not occur in any of the four clinical studies.

Taspoglutide

Taspoglutide (R1583/BIM51077) is a human GLP-1 analogue developed by Ipsen SA (Boulogne-Billancourt, France) and is now licensed and moved into phase 3 clinical trials by Hoffmann-La Roche (Basel, Switzerland). Taspoglutide is similar in structure to native GLP-1 except for two amino acid substitutions (93% sequence homology with native GLP-1) in positions 8 and 35 with amino-isobutyric acid, which render the molecule resistant to degradation by DPP-4.

Modest amounts of preclinical data on taspoglutide have been published. In vitro findings suggest strong resistance to DPP-4 [49] and glucose-dependent insulinotropic properties in cultured rat islets and the perfused rat pancreas [50]. Also, findings in rodents have confirmed the glucose-dependent insulinotropic properties and shown them to be associated with lowered blood glucose (eg, in a diabetic mouse model of type 2 diabetes) [51].

At present, only two clinical trials have been published as full scientific articles [52, 53], and these are the basis for the evaluation of the clinical pharmacology. Plasma concentrations peaked rapidly (T_{max}: 4 [1 mg], 6 [8 mg], and 8 h [30 mg], respectively), indicating a nonsignificant trend toward an increased T_{max} with higher doses. Taspoglutide showed dose-proportional exposure, however, with slightly variable absorption as one or more secondary plasma concentration peaks occurred. The apparent terminal half-life of taspoglutide was 165 h (high variability: SD=146 h), which should allow once-weekly dosing [52].

Short-term efficacy of taspoglutide was evaluated by Kapitza et al. [52] in patients with type 2 diabetes. Three cohorts with 12 type 2 diabetic patients in each were given single SC injections of taspoglutide (1, 8, or 30 mg) and four patients with type 2 diabetes were randomized to placebo treatment. The highest doses (8 and 30 mg) resulted in significant improvements in glycemic parameters such as fasting blood glucose (placebo-adjusted median change: -0.8 and -0.9 mM), 24-hour blood glucose AUC, and 5-hour postprandial blood glucose AUC [52]. With the 30-mg dose, the maximum effect on glycemic parameters was observed 14 days after injection, but was still evident for up to 28 days after injection; with the 8-mg dose, effects were observed for up to 7 days.

The efficacy of taspoglutide on HbA_{1c} was evaluated by Nauck et al. [53] in a phase 2 clinical trial in which 306 patients with type 2 diabetes inadequately controlled on metformin (baseline HbA_{1c}, 7.9%) were randomized to receive 8 weeks of double-blind SC treatment with placebo or taspoglutide (5, 10, or 20 mg once weekly or 10 or 20 mg once every 2 weeks) as add-on therapy. Placebo reduced HbA_{1c} by 0.2% and taspoglutide reduced HbA_{1c} by 1.0% (5 mg once weekly, 10 and 20 mg once every 2 weeks) and 1.2% (10 and 20 mg once weekly). Reductions in fasting plasma glucose in the once-weekly groups amounted to 0.8 mM (placebo), 1.8 mM (5 mg), and 2.5 mM (10 and 20 mg), whereas the once-every-2-weeks groups rebounded during the second week (with the 20-mg once-every-2-weeks group still exhibiting a significant reduction of 1.4 mM). Taspoglutide also reduced median postprandial plasma glucose by 18% to 22%, accompanied by an increase of median plasma insulin of 22% to 45% 2 h after meal ingestion in the once-weekly–treated groups. Mean fasting plasma C-peptide increased and fasting

proinsulin-to-insulin ratio decreased. Body weight decreased in a dose-dependent manner throughout the 8-week treatment period with significant reductions of 2.1 (10 mg once weekly), 2.8 (20 mg once weekly), and 1.9 kg (20 mg once every 2 weeks) compared to 0.8 kg with placebo. No significant impact on lipid profile or glucagon levels was reported [53].

The efficacy of 8 weeks of high-dose taspoglutide treatment on glycemic parameters was reported by Ratner et al. [54]. Type 2 diabetic patients (N=133) inadequately controlled on metformin were randomized to placebo or 20 mg of taspoglutide once weekly for 4 weeks, after which taspoglutide-treated patients were maintained at 20 mg once weekly or uptitrated to 30 or 40 mg once weekly for an additional 4-week period. Fasting plasma glucose was reduced by 2.3, 1.6, and 2.2 mM in the 20+20, 20+30, and 20+40 arms versus 0.6 mM in the placebo arm.

In Kapitza et al.'s [52] single-dose study, headache was the most frequent complaint (42% in the 30-mg group vs 8% in the placebo group) followed by gastrointestinal adverse events (nausea, abdominal distension, vomiting, and dyspepsia), which occurred in 39% of taspoglutide-treated patients (most frequent and with the greatest severity in the 30-mg cohort) versus 25% of those receiving placebo. Of taspoglutide-treated patients, 19% experienced nausea, and vomiting was reported by 11%. No patient withdrawals and only mild and self-limiting injection site reactions were reported. In Nauck et al.'s [53] phase 2 clinical trial, nausea and vomiting were the most common adverse events (52% and 22%, respectively, in the 20-mg once-weekly group). These side effects tended to occur during the first day after drug administration, were associated with peak plasma drug concentration, and resolved within 1 day. Six out of the 297 patients experienced mild to moderate hypoglycemia (two of these were asymptomatic). In the escalating dose study by Ratner et al. [54], the most common adverse event was transient mild to moderate nausea resolving spontaneously in most cases and causing no withdrawals. Three taspoglutide-treated patients withdrew due to other gastrointestinal adverse events. In none of the three clinical studies did clinically relevant abnormalities in ECGs or in clinical laboratory tests occur after taspoglutide administration [52-54].

Exenatide Once Weekly

Exenatide has been developed (by Amylin Pharmaceuticals, San Diego, CA) in a sustained-release (LAR) formulation planned for once-weekly SC administration. The sustained-release formulation is based on a common biodegradable medical polymer used in absorbable sutures and other extended-release pharmaceuticals with 3% exenatide peptide [55, 56].

Available preclinical data on exenatide LAR are limited. In a 4-week study in Zucker diabetic fatty (ZDF) rats, single SC injections of exenatide LAR (in doses ranging from 0–9 mg) resulted in sustained plasma exenatide concentrations (related to dose) for 28 days [60]. HbA_{1c} reductions (as opposed to a progressive increase in ZDF controls) were associated with dose and plasma exenatide concentration. β-Cell function improved with lower doses of exenatide LAR and insulin sensitization was evident with higher doses [60].

Pharmacokinetic parameters of the LAR formulation were evaluated in three clinical trials with inadequately controlled type 2 diabetic patients on diet or various drug therapy [57-59]. Effective plasma concentrations above 50 pg/mL were generally reached within 2 weeks. Steady-state plasma concentrations of exenatide LAR given once weekly were reached between week 6 and 10 and amounted to 232 to 301 pg/mL with 2.0-mg doses [57, 58••]. In Japanese patients (N=30), steady-state plasma concentrations of exenatide LAR were observed at week 8 and amounted to 345 pg/mL with 2-mg doses [59].

In patients with type 2 diabetes inadequately controlled on metformin (60%) and/or diet (40%; baseline HbA_{1c}, 8.5%), 0.8 and 2.0 mg of exenatide once weekly for 15 weeks resulted in HbA_{1c} reductions of 1.4% and 1.7% compared with an increase of 0.4% in the placebo group [57]. Changes in fasting plasma glucose amounted to -2.4 (0.8 mg), -2.2 (2.0 mg), and +1.0 mM (placebo). The 2.0-mg group experienced a weight loss of 3.6 kg versus no weight change in the other groups [57]. In Drucker et al.'s [58••] study comparing the effect of 10 μg of exenatide twice daily and 2.0 mg of exenatide LAR once weekly in 295 patients with type 2 diabetes (inadequately controlled on lifestyle intervention and/or monotherapy or double therapy with metformin, SU, or thiazolidinedione [baseline HbA_{1c}, 8.3%]), exenatide LAR once weekly was superior to exenatide twice daily in terms of glycemic parameters (HbA_{1c} reductions: 1.9% vs 1.5%; proportion of patients reaching HbA_{1c} of 7% or less: 77% vs 61%; fasting plasma glucose: -2.3 vs -1.4 mM). Interestingly, glucagon levels decreased significantly more with exenatide once weekly versus exenatide twice daily. Additionally, significantly greater reductions in total and low-density lipoprotein cholesterol were observed with the once-weekly exenatide compared with twice-daily exenatide. Equal significant improvements in fasting triglyceride and systolic and diastolic BPs were observed with both treatments. No difference in body weight reduction was observed (-3.7 vs -3.6 kg) [58••]. In a subgroup analysis of seven patients monitored using continuous glucose monitoring [58••], no association of changes in HbA_{1c} and diurnal glucose patterns was observed [61]. In Japanese patients with type 2 diabetes (suboptimally controlled by lifestyle intervention

alone or combined with monotherapy or combination therapy with metformin, SU or thiazolidinedione [baseline HbA_{1c}, 7.4%]), 0.8 and 2.0 mg of exenatide LAR once weekly for 10 weeks resulted in HbA_{1c} reductions of 1.05% and 1.5%, respectively (vs 0.4% reduction for placebo) [59]. When switched from exenatide twice weekly to exenatide LAR once weekly, patient-reported treatment satisfaction and quality of life seemed to improve [62].

Nausea (predominantly mild in intensity) is the most frequently reported adverse event among exenatide LAR–treated patients (19% [0.8 mg] and 27% [2.0 mg] vs 15% [placebo] [57]; 39% [2.0 mg] vs 50% [10 μg of exenatide twice daily] [58••]; and 33% [2.0 mg] [59]). Other side effects include gastroenteritis (19% [0.8 mg] and 13% [2.0 mg] vs 0% [placebo]) in one study [57], and injection site adverse events (13% [0.8 mg] and 7% [2.0 mg] vs 0% [placebo]) in one study [57], and 7% (2 mg) vs 15% (10 μg of exenatide twice daily) in another study [58••]. No vomiting was recorded in one study [57], whereas the incidence of vomiting in exenatide LAR–treated patients was 16% (vs 27%; 10 μg of exenatide twice daily) in Drucker et al.'s [58••] study and 5% in Iwamoto et al.'s [59] study. No major episodes of hypoglycemia have been reported; the 17 minor episodes reported in the largest study [58••] were equally distributed between the two groups, and 16 occurred in patients on an SU background treatment. No clinically significant abnormalities in vital signs, ECGs, hematologic, chemistry or urine analyses have been reported in exenatide LAR–treated patients [57, 58••] except for two Japanese patients with increased plasma amylase (not associated with clinical signs or symptoms) [59]. Anti-exenatide antibodies were formed in a mean of 68% of exenatide LAR–treated patients [57, 59], and comparatively antibody levels were higher among exenatide LAR–treated patients as opposed to exenatide twice-daily–treated patients [58••]. It cannot be excluded that high titers of antibodies were associated with lack of efficacy [58••].

Conclusions

Incretin mimetics offer a new modality in diabetes treatment, and several new GLP-1R agonists are in clinical development. Most of these are characterized by extended half-lives entailing fewer injections. The longer-acting agonists presumably also offer an improved-throughout-the-day glycemic control compared with the already marketed drugs (ie, exenatide and liraglutide). However, only one head-to-head trial has been reported [58••]. It demonstrated that the longer-acting agonists were superior with regard to glycemic control and noninferior in terms of body weight change. Notably, patient-reported treatment satisfaction and quality of life were also improved with the longer-acting agonist.

Considering the multifaceted physiologic roles of GLP-1, additional beneficial effects could be expected. Clinical studies of the already marketed drugs have also shown lowering effects on lipid profile and BP, which could imply substantial benefit on macrovascular outcomes, a critical therapeutic goal in the treatment of type 2 diabetes. Not to mention the possible β-cell–preserving effects demonstrated in animal studies and in isolated human β cells. New compounds need to provide at least comparable benefits, but will be a step behind the already marketed drugs in the demonstration of such. The pharmacology (eg, concerning potency and perhaps penetration to the central nervous system) differs between some of the long-acting incretin mimetics and the polypeptide molecules of the already marketed drugs. This could prove important with regard to weight loss, as suggested in one study [46], but could also affect the gastrointestinal tolerability (which could to some extent be elicited through receptors in the central nervous system). Safety and tolerability are increasingly important issues. Thus, the obvious benefits of infrequent administrations could be offset by changes in safety. Nonetheless, the reviewed trials with the novel long-acting incretin mimetics did not bring forth new safety issues. The major side effects remain gastrointestinally related and, comparable to the situation with established incretin mimetics, decline over time. The concerns about generation of antibodies, pancreatitis, and carcinogenicity can only be dealt with in large clinical trials.

Thus, the novel long-acting incretin mimetics appear as promising antidiabetic drug candidates. However, these compounds are not one uniform group, and pharmacologic differences could influence the therapeutic achievements of these agents. The role of the incretin mimetics in the treatment algorithm for the management of type 2 diabetes is still somewhat uncertain (primarily due to limited clinical experience), and firm conclusions on the comparable efficacy and safety of the various GLP-1R agonists are even more distant and will have to rely on the results of large clinical trials comparing glycemic effect and microvascular and macrovascular risk reduction of the individual compounds.

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- •• Of major importance

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