review article

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An overview of once-weekly glucagon-like peptide-1 receptor agonists—available efficacy and safety data and perspectives for the future

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Incretin-based therapies, such as the injectable glucagon-like peptide-1 (GLP-1) receptor agonists and orally administered dipeptidyl peptidase-4 (DPP-4) inhibitors, have recently been introduced into clinical practice. At present, the GLP-1 receptor agonists need to be administered once or twice daily. Several once-weekly GLP-1 receptor agonists are in phase 3 development. This review examines the efficacy, safety and perspective for the future of the once-weekly GLP-1 receptor agonists: exenatide once weekly, taspoglutide, albiglutide, LY2189265 and CJC-1134-PC, and compared them to the currently available agonists, exenatide BID and liraglutide QD. A greater reduction in haemoglobin A1c (HbA1c) and fasting plasma glucose was found with the once-weekly GLP-1 receptor agonists compared with exenatide BID, while the effect on postprandial hyperglycaemia was modest with the once-weekly GLP-1 receptor agonist. The reduction in HbA1c was in most studies greater compared to oral antidiabetic drugs and insulin glargine. The reduction in weight did not differ between the short- and long-acting agonists. The gastrointestinal side effects were less with the once-weekly agonists compared with exenatide BID, except for taspoglutide. Antibodies seem to be most frequent with exenatide once weekly, while hypersensitivity has been described in few patients treated with taspoglutide. Injection site reactions differ among the long-acting GLP-1 receptor agonists and are observed more frequently than with exenatide BID and liraglutide. In humans, no signal has been found indicating an association between the once-weekly agonists and C-cell cancer. The cardiovascular safety, durability of glucose control and effect on weight will emerge from several ongoing major long-term trials. The once-weekly GLP-1 receptor analogues are promising candidates for the treatment of type 2 diabetes, although their efficacy may not be superior to once-daily analogue liraglutide.

Keywords: albiglutide, antidiabetic drug, CJC-1134-PC, exenatide once weekly, GLP-1 analogue, GLP-1 receptor agonists, incretin therapy, LY2189265, taspoglutide, type 2 diabetes mellitus

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Introduction

The incidence and prevalence of type 2 diabetes are rising steadily worldwide, primarily as a consequence of the increasing prevalence of obesity [1]. Type 2 diabetes mellitus is a complex disease that involves genetic susceptibility for abnormal β-cell function resulting in relative insulin deficiency and insulin resistance in liver, muscle and fat cells as well as excessive glucagon secretion [2]. The defective β-cell function also involves an impaired responsiveness to the two incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) [2–4]. The increased morbidity and mortality in type 2 diabetes are both consequences of microvascular (renal disease, neuropathy, retinopathy) and macrovascular complications [5].

A variety of therapeutic options for the treatment of hyperglycaemia in people with type 2 diabetes are available. It is generally accepted that the initial therapy should consist of lifestyle changes plus metformin [6–9]. Some years after diagnosis most patients require combination therapy to achieve effective glycaemic control, but the lack of consensus regarding which agent to add to metformin has provoked debate among physicians [6–10]. Sulphonylurea (SU) and metformin represent together with insulin the 'old agents', while thiazolidinediones (TZD) have been used for the last decade. The incretin-based therapies, such as GLP-1 receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors, were recently introduced into clinical practice [11–13]. In addition, all of the agents, used alone or in combination, are associated with different adverse events including hypoglycaemia (SU and insulin), weight gain (SU, insulin and TZD), gastrointestinal side effects (metformin and GLP-1 receptor agonist) and increased risk of fractures (TZD) [2,6–10,12]. The DPP-4 inhibitors are weight neutral [11,12,14,15].

The incretin-based therapies have been the focus of much attention during the last years because of their unique mechanisms of action [3,16–18]. The GLP-1 receptor agonists potentiate insulin secretion, inhibit glucagon release, delay gastric emptying and reduce appetite and thereby

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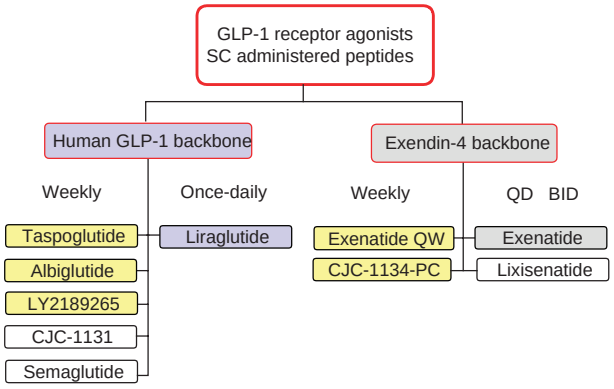

Figure 1. Shows the glucagon-like peptide-1 (GLP-1) receptor agonists, which have already been approved (exenatide BID and liraglutide). The agonists are subdivided in relation to whether the backbone of the compound is human GLP-1 or exenatide, and in relation to the frequency of administration (once weekly or once daily or twice daily). The once-weekly GLP-1 receptor agonists illustrated with yellow are discussed in details in the present review.

induce weight loss [3,16]. The DPP-4 inhibitors primarily improve insulin secretion and inhibit glucagon release, but have no clinically relevant effects on gastric emptying and appetite [3,11,16,17,19]. The potentiation of insulin and glucagon release is glucose dependent and therefore associated with a low risk of hypoglycaemia [3,11,16,17,19–21]. The combined improvement of glycaemic control and weight loss has promoted a particular interest in GLP-1 receptor agonists [11–13].

The short half-life of native GLP-1 (1–2 min) has necessitated the development of long-acting GLP-1 receptor agonists for the management of type 2 diabetes [3,12,13,16, 22]. The short half-life is due to inactivation by cleavage by the enzyme DPP-4 at the alanine residue at position 2 of the molecule [3,16,17,23, 24].

The present review provides an update on currently available clinical trials that have assessed the efficacy and safety of exenatide twice daily (BID) and liraglutide as well as the long-acting once-weekly GLP-1 receptor agonists: exenatide once weekly, taspoglutide and albiglutide (figure 1). The once-weekly LY219265 and CJC-1134-PC will also be presented briefly (figure 1). Two other long-acting GLP-1 receptor agonists in development, CJC-1131 and semaglutide, will not be discussed, as information about the compounds is very sparse.

Exenatide BID (Byetta) and Liraglutide (Victoza)

Currently, two GLP-1 receptor agonists with extended half-lives are available for the treatment of type 2 diabetes [13,25–29]. The first GLP-1 receptor agonist to reach the market (2005), exenatide (synthetic exendin-4; Byetta®, Amylin Pharmaceuticals, Inc., San Diego, CA; Eli Lilly Company, Indianapolis, IN, USA), shares 53% amino acid homology with human GLP-1 [26,28,29]. Liraglutide (Victoza®, Novo Nordisk, Bagsværd, Denmark) is 97% identical to the native hormone and has a fatty acid side chain promoting binding to human albumin after administration [25,27]. The half-life of exenatide after sc administration is about 2.4 h, and exenatide is therefore given twice daily, whereas the half-life of liraglutide is about 13 h and is administered as once-daily sc injection [13,25–29]. Exenatide is given in micrograms (mcg), starting with 5 mcg BID and 10 mcg BID after 4 weeks if tolerated [13,26]. Liraglutide treatment is initiated with 0.6 mg once daily, increasing to 1.2 mg after 1 week and in some patients up to 1.8 mg [13]. The concentration of liraglutide is much higher than that of exenatide, but the fraction of the hormones that is not bound to albumin is very low, so that the concentration of free hormone is probably similar to that of the peak concentration of exenatide [13,25,27]. Because of the large depot of bound liraglutide, its concentration varies little throughout the day (which also means that the timing of injection is uncritical), whereas the concentration of exenatide given twice daily (BID) varies from very low to therapeutic values [26,29]. The uptitration is employed to reduce gastrointestinal side effects [13,25–27,29]. As nausea probably occurs at high peak plasma concentrations of GLP-1 [30], the lower incidence of nausea with liraglutide compared with exenatide BID may be explained by its sustained release formulation and tachyphylaxia resulting from the sustained plasma level [25,27,31,32]. Exenatide BID is currently approved (2005) for use as an adjunct twice-daily (BID) formulation injected before breakfast and dinner [13,26,29]. Once-daily liraglutide was approved in 2009 in Europe and in 2010 in USA and Japan.

The reduction in haemoglobin A1c (HbA1c) with exenatide BID is about 0.5–1.0% in patients with a baseline HbA1c of 7.9–8.4%, whereas open-label comparator studies showed HbA1c reduction of 1.1–1.5% from baseline HbA1c values of 8.2–9.0% [13,26]. The reduction in HbA1c with liraglutide in clinical controlled trials of the LEAD (*L*iraglutide *E*ffect and *A*ction in *D*iabetes) programme was 0.8–1.5% in patients with an average baseline HbA1c of 8.2–8.5%. The reduction was in most cases greater or at least similar to oral comparator antidiabetic drugs [13]. In patients with a mean baseline HbA1c of about 8.5 and 9.8%, the reduction was 1.4 and 2.3%, respectively [13,33]. In a head-to-head comparison (LEAD 6), the reduction in HbA1c was 0.33% greater (−1.12 vs. −0.79%) with liraglutide compared with exenatide [31,32]. Also reduction in fasting plasma glucose was greater (−1.6 vs. −0.6 mmol/l), while weight loss did not differ significantly (−3.24 vs. −2.87 kg) [31,32]. In most phase 3 studies with exenatide and liraglutide, the weight loss was in the range of 2–3 kg after 26 weeks of treatment compared with placebo and greatest when added to metformin [13]. In LEAD 6 pancreatic β-cell function was improved, and triglycerides and free fatty acids were reduced to a greater extent with liraglutide than exenatide. However, the ability to reduce blood pressure (−2.5/1.1 vs. −2.0/1.9 mm Hg) was similar [31,32]. The gastrointestinal side effects were most pronounced with exenatide BID, 28% having nausea and 9.9% vomiting compared with 25.5 and 6.0%, respectively, during treatment with liraglutide [31,32]. After 8–10 weeks the percentage of patients reporting nausea with liraglutide was below 10%, while in the exenatide group the level remained at about 10% [31]. At week 26, only 2.5% of the liraglutide group

had nausea compared with 8.6% in the exenatide group [31]. Antibodies have been reported in approximately 50% during treatment with exenatide versus 4–13% in patients receiving liraglutide [13,34]. In most patients, the antibodies were of low titres and without apparent effect on efficacy [34,35]. In LEAD 6 liraglutide was less immunogenic than exenatide, and fewer than 10% of liraglutide-treated patients developed antibodies to liraglutide [34]. Overall, antiliraglutide antibodies were low, and did not impact the efficacy or safety of liraglutide treatment [34]. Overall, treatment satisfaction was rated slightly higher with liraglutide than exenatide BID [31,32].

Exenatide Once Weekly (Bydureon®)

An exenatide once-weekly (QW) formulation has been developed using biodegradable polymeric microspheres that entrap exenatide (Amylin Pharmaceutical, Ely Lilly and Alkermes Incorporated, Cambridge, MA, USA) [36,37]. Exenatide is incorporated into a matrix of poly(D,L-lactide-co-glycolide) (PLG), which previously has been used as a biomaterial in sutures and in extended release preparations that allow gradual drug delivery at controlled rates [38]. Once released, exenatide is eliminated via the kidneys. After sc injection of 2 mg of exenatide once weekly, a stable plasma exenatide level is obtained after 5–10 weeks, a level which is comparable to the peak concentrations observed with exenatide BID [36,37]. A plasma level of exenatide >50 pg/ml, which is known to reduce fasting plasma glucose concentration, is observed after about 2 weeks of treatment [36].

Clinical Controlled Studies With Exenatide Once Weekly

In a small clinical trial, patients with type 2 diabetes treated with diet and exercise or metformin monotherapy were randomized to placebo (n = 14), 0.8 mg exenatide once weekly (QW) (n = 16) or 2.0 mg exenatide QW (n = 15) [36]. The trial composed of 15 weeks of active treatment followed by a 12-week follow-up. Average baseline HbA1c was 8.5%, and the reduction in HbA1c was −1.4 and −1.7% in the 0.8 and 2 mg groups, compared with an increase of +0.4% in the placebo group. The final HbA1c was 7.2 and 6.6% for the 0.8 and 2.0 mg groups, respectively. More than 80% of patients treated with 2.0 mg reached HbA1c <7.0%. The study showed that the dose–response relationship for HbA1c reduction and weight control differs [36]. Thus, the 2.0 mg dose reduced weight significantly (−3.4 kg) compared with placebo treatment, while the 0.8 mg dose was without any effect on weight [36].

DURATION-1

In the DURATION-1 (*D*iabetes therapy *U*tilisation: *R*esearching changes in Hb*A*1c, weight and other factors *T*hough *I*ntervention with exenatide *ON*ce weekly) trial, 10 mcg exenatide BID and 2 mg exenatide QW were compared in a 30-week trial including 295 type 2 patients [35]. Average baseline HbA1c was 8.2%, weight 102 kg, body mass index (BMI) 35 kg/m^2 and duration of diabetes 6–7 years. The reduction in HbA1c was greater in the exenatide QW group (−1.9%) compared with—1.5% in the exenatide BID-treated patients (figure 2). Mean difference was 0.33% in HbA1c. Most of the patients reached HbA1c ≤7.0 (77% for QW vs. 61% for BID), and 49% in QW reached an HbA1c ≤6.5 and 25% reached HbA1c ≤6.0%. The reduction in fasting plasma glucose was −2.3 and −1.4 mmol/l in QW and BID groups, respectively. Also fasting plasma glucagon was reduced more with QW, while reduction in postprandial glucose excursions and slowing in gastric emptying were less pronounced in QW compared with BID. The weight loss did not differ between the two groups by 30 weeks (−3.7 kg for QW vs. −3.6 kg for BID), and about 75% of the patients lost weight (figure 3). Both treatments were associated with reduction in triglycerides and blood pressure [35].

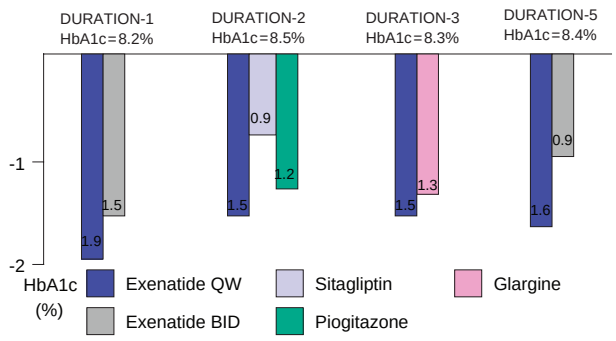

Figure 2. The effect of exenatide once weekly compared with oral antidiabetic agents and insulin glargine on changes in haemoglobin A1c (HbA1c) from baseline. Baseline HbA1c in the individual studies is also given.

After 30 weeks, patients treated with exenatide QW continued treatment, while patients who were treated with exenatide BID shifted to QW for 22 weeks [39]. Two hundred and twenty-eight of the initial 295 patients entered the open-label extension. Patients continuing exenatide QW maintained HbA1c improvement through 52 weeks (−2.0%). Patients switching from exenatide BID to QW achieved further improvements in HbA1c, and both groups displayed the same reduction and mean HbA1c (6.6%) at week 52, and 71 versus 54% achieved HbA1c ≤7.0 and ≤6.5%, respectively. In patients with a basal HbA1c >9.0%, the reduction in HbA1c was 2.6–2.8%. The mean reduction in weight was about −3.6 to −3.7 kg (figure 3) [39]. After 1 year about 78% achieved reduction in both HbA1c and weight. The reduction in fasting plasma glucose was −2.5 mmol/l, but during the shift at week 30 the BID patients experienced a transient increase in fasting plasma glucose for few weeks, which was followed by a further improvement the following weeks. After 52 weeks, the reductions in systolic and diastolic blood pressures were −6.2 and −2.8 mm Hg, respectively. Significant reductions in lipids, especially triglycerides, were shown [39].

Safety and Tolerability. In DURATION-1, the incidence of nausea (26 vs. 35%) and vomiting (11 vs. 19%) was lower in QW compared with BID [35]. Injection site pruritus, or erythema, or induration or pain was observed in 18% of exenatide QW [35]. Most patients developed antibodies to exenatide QW (110 of 148) compared with 71 of 147 patients in the BID group. Antibodies to exenatide peaked in week

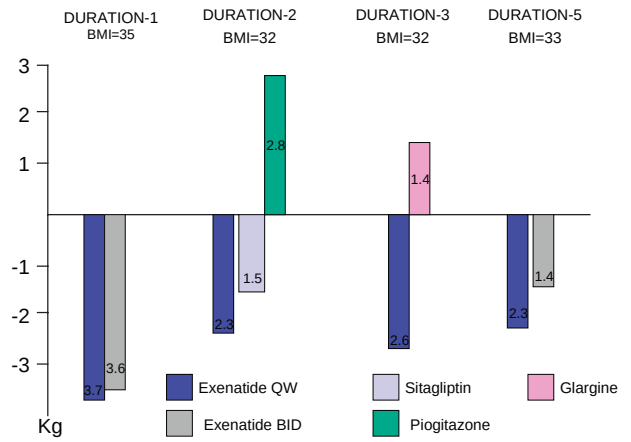

Figure 3. The effect of exenatide once weekly compared with oral antidiabetic agents and insulin glargine on changes in weight (kg) from baseline. Baseline body mass index (BMI) in the individual studies is also given.

6 for both treatments, but the titres were about three times higher during exenatide QW compared with BID [35]. Overall, the titre of antibodies was not predictive of individual HbA1c change or adverse events [35].

The DURATION-1 study illustrates that exenatide QW is more effective in reducing HbA1c and fasting plasma glucose than BID, while the reduction in weight did not differ. Treatment with exenatide QW was generally well tolerated, and the only incidences of hypoglycaemia occurred in patients concomitantly receiving SU. It is also noteworthy that patients switching from the short-acting exenatide BID to QW experience a transient deterioration in glycaemic control, which generally improved 2 weeks after initiating exenatide QW [39]. Furthermore, the reduction in HbA1c was maintained during the 52 weeks and resulted in a mean HbA1c of 6.6%. The greater reduction in HbA1c with exenatide QW compared with BID illustrates the effect of a continuous exposure for exenatide during all 24 h compared with the intermediate exposure obtained with exenatide BID with deterioration of control during night and lunch time. During night time, lower glucagon levels during QW treatment are likely to contribute to the improvement in fasting glucose level. Conversely, although both therapies reduced postprandial glucose excursions, the absolute reduction in postprandial glucose excursion and inhibition of gastric emptying were greater with exenatide BID than QW [35]. Thus, acute exposure to exenatide produces greater inhibition of gastric emptying than that seen with continuous GLP-1 receptor activation, probably illustrating the development of tachyphylaxis during continuous exposure [40]. Both groups experienced significant improvements in treatment satisfaction and quality of life, but patients who switched from BID to QW administration reported further significant improvement after 30 weeks [41]. The mean difference between exenatide QW and BID in reduction in HbA1c (0.33%) did not differ from the 0.33% difference in reduction in HbA1c between exenatide BID and liraglutide 1.8 mg once daily [31].

DURATION-2

Most patients with type 2 diabetes often begin pharmacotherapy with metformin, but eventually need additional treatment. In DURATION-2, exenatide QW was compared with pioglitazone and sitagliptin to assess the potential differences between these antidiabetic drugs as add-on therapy to metformin [42]. The average baseline HbA1c was 8.5%, fasting plasma glucose 9.1 mmol/l and BMI 32 kg/m^2. Patients were randomly assigned to receive 2 mg exenatide QW (n = 170), 100 mg sitagliptin (n = 172) or 45 mg pioglitazone (n = 172) for 26 weeks. Treatment with exenatide QW reduced HbA1c (−1.5%) significantly more than sitagliptin (−0.9%) or pioglitazone (−1.2%) (figure 2). The final HbA1c levels were 7.2, 7.7 and 7.4%, respectively. Significantly more patients reached HbA1c <7.0% with exenatide compared with sitagliptin or pioglitazone. The reduction in fasting plasma glucose was significantly greater with exenatide (−1.8 mmol/l) than with sitagliptin (−0.9 mmol/l) but not with pioglitazone (−1.5 mmol/l). Weight loss with exenatide (−2.3 kg) was significantly greater than with sitagliptin (−1.5 kg) or pioglitazone (+2.8 kg) (figure 3). The reduction in systolic blood pressure was significantly greater with exenatide (−4 mm Hg) compared with sitagliptin, but not pioglitazone. Diastolic blood pressure did not differ between the groups. The improvement in high-density lipoprotein (HDL) and reduction in triglycerides were greatest with pioglitazone. As in other studies with GLP-1 receptor agonists, a reduction in B-type natriuretic peptide as well as microalbuminuria was observed in the exenatide-treated group [13]. No major hypoglycaemia occurred in any group. About 24 and 10% registered nausea with exenatide and sitagliptin, while diarrhoea was observed in 18 and 10%, respectively. Fewer patients withdrew from treatment with sitagliptin (13%) than with exenatide (21%) or pioglitazone (21%). The improvement in treatment satisfaction was greatest with exenatide QW. Thus, the addition of exenatide QW to metformin achieved better glycaemic control and weight loss than sitagliptin and pioglitazone (figures 2 and 3) [42].

It is relevant to compare these data with the results obtained during a 26-week head-to-head comparison between liraglutide and sitagliptin added to metformin in type 2 patients with a baseline HbA1c of 8.5%, fasting plasma glucose 10.0 mmol/l, BMI 33 kg/m^2 and mean duration of diabetes 6–7 years [43]. The lowering of HbA1c with liraglutide 1.2 and 1.8 mg was −1.24 and −1.50%, respectively, and −0.90% with sitagliptin 100 mg. Nausea was more common with liraglutide 1.2 mg (21%) and 1.8 mg (27%) than with sitagliptin (5%). These findings may suggest that the efficacies of exenatide QW and liraglutide 1.8 mg once daily are similar. Currently, a study comparing exenatide QW and liraglutide once daily is ongoing (further information about the design of the study can be obtained at NCT01029886).

DURATION-3

Both exenatide BID and liraglutide once daily have been compared with insulin glargine [13]. In the open-label DURATION-3 trial, once-weekly exenatide QW (2 mg) was compared with once-daily insulin glargine [44]. Seventy

percent of the patients were treated with metformin and 30% metformin plus SU. Starting dose for insulin glargine increased from baseline 10 to 31 IU/day, targeting a fasting glucose range of 4.0–5.5 mmol/l following a prespecified titration algorithm. Average baseline HbA1c was 8.3%, fasting plasma glucose 9.8 mmol/l, BMI 32 kg/m^2 and duration of diabetes about 8.0 years. The reduction in HbA1c was greater in the exenatide group (−1.5%) than in those taken insulin glargine (−1.3%) (figure 2). Endpoint HbA1c was 6.8 versus 7.0%, and 60 versus 48% reached an HbA1c <7.0%. Mean weight changes were −2.6 kg in the exenatide group and +1.4 kg in the insulin glargine-treated patients (figure 3). Seventy-nine percent of the patients allocated to exenatide had both a reduction in HbA1c and weight, whereas 63% of the patients receiving insulin glargine had a reduction in HbA1c paired with a weight gain [44]. Fasting plasma glucose was reduced in both groups (exenatide −2.1 mmol/l, insulin glargine −2.8 mmol/l, $p < 0.001$). Mean heart rate at week 26 was raised compared with baseline in the exenatide but not in the insulin glargine group. No other cardiovascular risk factors including lipid concentrations differed between the groups. One hundred and twenty-seven of 233 patients assigned to exenatide developed antiexenatide antibodies, and a lower mean reduction in HbA1c was observed in the antibody-positive group compared with patients not developing antibodies (−1.3 vs. −1.6%) [44]. Minor hypoglycaemia was reported in 19 of 233 exenatide patients (46 events) compared with 58 of 233 insulin glargine patients (135 events), which was significantly different. One patient taking exenatide developed pancreatitis. Calcitonin concentrations were measured in few patients and were within normal limits in all patients. The number of patients, who discontinued treatment because of adverse effects, was 5 versus 1%, respectively. More patients discontinued exenatide QW than insulin glargine due to nausea and injection site reactions [44].

Thus, the exenatide once-weekly treatment resulted in greater HbA1c reduction after 26 weeks than insulin glargine. Insulin glargine produces greater reduction in fasting glucose than did exenatide, while significantly greater reductions in postprandial glucose excursions were obtained with exenatide. Risk of hypoglycaemia was reduced with exenatide, irrespective of background treatment. A notable strength of the study is that it included a standard next step (insulin treatment) in the treatment of patients not responding to two oral antidiabetic agents as an active comparator. An extension period planned for 2.5 years is in progress.

Exenatide BID has previously been compared with insulin glargine in a 6-month trial, where the reduction in HbA1c did not differ between the groups (i.e. reduction was 1.1% in both groups) [45]. Liraglutide has also been compared with insulin glargine in a 6-month study, with a difference in HbA1c treatment effect (0.2%) and body weight in favour of liraglutide (LEAD 5) [46].

DURATION-4

In the fourth of the series of DURATION studies (DURATION-4), exenatide once weekly is compared with sitagliptin 100 mg, pioglitazone 45 mg or metformin up to 2500 mg, all in monotherapy (the design of the study is given at NCT00876338). No data have been published.

DURATION-5

DURATION-5, like DURATION-1, compared exenatide QW and BID during a 26-week study in 252 type 2 patients with an average baseline HbA1c of 8.4%, fasting plasma glucose 9.1 mmol/l and weight 96 kg [47]. Patients were drug naïve (19%) or treated with one (47%) or a combination of (34%) oral antidiabetic drugs. After 26 weeks, the reduction in HbA1c was greater in QW (−1.6%) than in BID (−0.9%) (figure 2). Fifty-nine percent versus 30% reached the goal of <7.0%. Weight loss was −2.3 versus −1.4 kg after 24 weeks (p = NS) (figure 3). Nausea occurred less frequently with QW (14%) than with BID (35%), and was transient and mild or moderate in intensity in most patients. Injection site reactions were more common with QW. No change in mean calcitonin concentrations was observed, but one patient withdrew due to pancreatitis. Thus, also in DURATION-5 exenatide QW provides superior control compared to exenatide BID [47].

DURATION-6

Is a head-to-head comparison between exenatide QW and once-daily liraglutide 1.8 mg, including approximately 900 patients, estimated completion in 2011 (NCT01029886).

Figures 2 and 3 summarize the changes in HbA1c and weight in the DURATION-1, -2, -3 and -5 studies.

Regulatory Affairs

In a response letter in October 2010, US Food and Drug Administration (FDA) requested a thorough QT interval study with exposures of exenatide higher than typical therapeutic levels of exenatide QW. The background for the request could be that after a single dose of 10 mcg of exenatide in healthy subjects, a slight positive correlation between plasma exenatide concentrations and changes from baseline in QT interval has been observed [48]. Additionally, the FDA has requested the results of DURATION-5 study to evaluate the efficacy and the labelling of the safety and effectiveness of the commercial formulation of exenatide QW. The Amylin, Lilly and Alkermes' goal is to submit their reply to the response letter by the end of 2011. Based on the requirements for additional data, the resubmission will likely require a 6-month review by FDA. The decision from the European Medical Agency (EMA) about exenatide QW can be expected in 2011.

Taspoglutide

The human GLP-1 receptor agonist taspoglutide (Roche, Basel, Switzerland; Ipsen, Paris, France) has 93% homology with the native hormone [49]. Taspoglutide contains two α-aminoisobutyric acid substitutions replacing Ala8 and Gly35 of hGLP-1(7-36)NH2 [49]. Taspoglutide is fully resistant to DPP-4 degradation [49]. The biological actions have been shown to be similar to those of native GLP-1, and after a single dose of 30 mg, a glucose-lowering effect was found for up to 2

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