

# Is Exenatide Improving the Treatment of Type 2 Diabetes? Analysis of the Individual Clinical Trials with Exenatide

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**Abstract:** The obesity epidemic in the developed and developing world is being followed by an epidemic of type 2 diabetes. In type 2 diabetes, subjects cannot manage glucose properly because they do not produce enough insulin, and the peripheral tissues have become resistant to insulin. Glucagon-like peptide 1 (GLP-1) is an intestinal peptide hormone that is secreted in response to food to regulate the postprandial blood glucose concentration. One of the actions of GLP-1 is to stimulate insulin secretion. In subjects with type 2 diabetes, intravenous or subcutaneous GLP-1 stimulated insulin production and decreased blood glucose levels. However, as GLP-1 is rapidly metabolised, it is not suitable for use in most subjects with type 2 diabetes.

Exendin-4 is a 39-amino acid peptide that acts as an agonist at the GLP-1 receptor. After subcutaneous administration, synthetic exendin-4 (exenatide) decreased postprandial concentrations of glucose and insulin, and fasting glucose levels in subjects with type 2 diabetes, and the effects lasted several hours. Subsequently, exenatide was been trialled in subjects taking metformin only, a sulfonylurea only, or metformin and a sulfonylurea, and shown to improve glycaemic control with few adverse events, initially over 30 weeks, and then extended to 82 weeks. Exenatide may also be as effective as insulin glargine in subjects with type 2 diabetes not adequately controlled with the oral agents. In conclusion, exenatide represents a new and beneficial addition to the medicines used to treat type 2 diabetes.

**Keywords:** Clinical trials, Exenatide, Glucagon-like peptide 1, Insulin glargine, Metformin, Sulfonylureas, Type 2 diabetes.

## INTRODUCTION

About 17 million people in the US have diabetes, and 90% of them have type 2 diabetes. In type 2 diabetes, subjects cannot manage glucose properly because they do not produce enough insulin, and the peripheral tissues have become resistant to insulin. Diabetes can cause damage to the retina, kidney, and nerves, and increases the risk of cardiovascular disease and stroke. When subjects develop type 2 diabetes, the first treatment is likely to be lifestyle changes (changes in diet, weight loss, increased physical activity) and, only if or when these are unsuccessful alone, are medicines introduced.

The drugs used in the treatment of type 2 diabetes include metformin, oral insulin secretagogues (sulfonylureas, meglitinides),  $\alpha$ -glucosidase inhibitors (acarbose) and thiazolidinediones. Individually these drugs only cause a decrease of 0.5-2% in HbA<sub>1c</sub> [1]. Metformin does not alter insulin secretion but does decrease plasma glucose levels by decreasing hepatic glucose production. Metformin also increases the action of insulin on muscle and fat. The sulfonylurea and meglitinide secretagogues close the K<sub>ATP</sub> channels on the pancreatic  $\beta$ -cells to stimulate the secretion of insulin. By inhibiting  $\alpha$ -glucosidase in the intestinal brush border, acarbose reduces the absorption of starch, dextrin and disaccharides. The thiazolidinediones activate the nuclear

peroxisome proliferator-activated receptor- $\gamma$  (PPAR- $\gamma$ ) and this leads to an increased sensitivity to insulin. As these drugs have different mechanisms of action, when one agent alone does not control glycaemia, an additive effect can be achieved by combining these agents in the treatment of type 2 diabetes. However, despite this array of treatments, glycaemic control rates (HbA<sub>1c</sub> < 7%) are only about 40% in type 2 diabetes [2], and many subjects progress to insulin treatment to aid in glycaemic control. This suggests that new approaches to the treatment of type 2 diabetes are required.

In normal subjects, oral glucose enhances insulin secretion more than intravenous glucose infusion does – the insulinotropic (incretin) effect. The augmentation of insulin secretion is due to gut hormones such as Glucagon-Like Peptide 1 (GLP-1). Basal levels of GLP-1 are low. GLP-1 is secreted in response to food or glucose from the enteroglucagon-producing L cells in the ileum and colon/rectum. Extensive studies with GLP-1 in subjects with diabetes type 2 have shown that stimulating the receptor for GLP-1 has major short-term beneficial effects. These studies are briefly considered in the first part of this review, as they form the basis for understanding why GLP-1 receptor agonists are likely to be useful in type 2 diabetes. GLP-1 has a short-life half-life and has to be infused continuously, and this limits its clinical application. A compound found in the salivary glands of the Gila monster (*Heloderma suspectum*) stimulates the GLP-1 receptors, and is known as exendin-4. Exendin-4 has subsequently been synthesized and the synthetic compound is known as exenatide (AC2993). The main part of this review is of the clinical trials with exenatide in subjects with type 2 diabetes. Initially, the

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development of exenatide for clinical use is considered, then the clinical trials of exenatide in patients treated with metformin alone or with a sulfonylurea alone. A clinical trial of exenatide in subjects with poorly controlled glycaemia with the combination of metformin and a sulfonylurea is considered. Finally, a clinical trial comparing exenatide and insulin glargine in subjects not obtaining glycaemic control with metformin and a sulfonylurea is described. These clinical trials establish exenatide as a new option in the treatment of type 2 diabetes.

### Studies with GLP-1 in Humans

In addition to stimulating insulin production, GLP-1 inhibits glucagon production, postprandial gastric acid secretion [3], and gastric emptying [4]. As glucagon stimulates glycogenolysis to increase glucose levels, inhibiting its production with GLP-1 will decrease glycogenolysis. In obese men, GLP-1 suppressed feelings of hunger and reduced energy intake [5]. GLP-1 is metabolised by dipeptidyl peptidase IV with an apparent half-life of 60-80 seconds, with the metabolite acting as an antagonist at the GLP-1 receptor [6,7].

The incretin response to GLP-1 is lost in type 2 diabetes [8]. However, exogenously (intravenously) applied GLP-1 still has the ability to promote insulin secretion, inhibit glucagon production and normalize fasting hyperglycemia in subjects with type 2 diabetes [9,10]. In subjects with type 1 diabetes, intravenous GLP-1 was able to inhibit glucagon production and partially reduce fasting glycemia [11]. When GLP-1 was infused overnight (22.00-07.30), in subjects with type 2 diabetes, it reduced the fasting levels of glucose and insulin and increased glucagon during infusion, but did not improve the glucose responses to meals the next day, after the infusion has stopped [12, 13].

Subcutaneous GLP-1, injected into the abdominal wall or the gluteal region, 5 minutes before a standard meal, almost abolished the post-prandial blood glucose rise in obese subjects with type 2 diabetes, but the response to GLP-1 only lasted for 45 minutes [14]. When a high dose of GLP-1 (1.5 nmol/kg) was given subcutaneous to subjects with type 2 diabetes, either during fasting or before a meal, it stimulated insulin secretion while inhibiting glucagon production [15]. GLP-1 also normalized fasting glucose and, given before a meal, prevented gastric emptying for 30-45 minutes [15]. When GLP-1 was infused subcutaneously for 48 hours in 6 subjects with type 2 diabetes, it decreased hunger and increased satiety [16].

In the first chronic study with subcutaneous GLP-1, 50 nmol t.i.d. before meals for 3 weeks in subjects with type 2 diabetes, it was shown that the effect was maintained over the 3 weeks. Thus, the effect of GLP-1 on the area under the curve for glucose was the same reduction at the beginning and end of the 3 week period [17]. GLP-1 also increased plasma insulin and decreased glucagon [18]. In a 6-week trial, in addition to stimulating insulin secretion, inhibiting glucagon secretion and lowering glucose in subjects with type 2 diabetes, continuous subcutaneous GLP-1 also inhibited gastric emptying and reduced the body weight [19]. Importantly, this was the first trial to show that GLP-1

lowered glycosylated haemoglobin (HbA<sub>1c</sub>) levels. Thus, the HbA<sub>1c</sub> levels were lowered by 1.3%, over the 6 weeks [19].

After the administration of a buccal preparation of GLP-1, the half-life was about 20 minutes, and there was an increase in fasting insulin and decrease in glucagon [20, 21]. Insulin secretion was also increased when the buccal tablets of GLP-1 were administered before a standard meal [21]. However, the duration of action was too short to make this preparation a viable clinical option.

GLP-1 has a different mechanism than metformin, acarbose, the sulfonylureas and the thiazolidinediones. Consequently, their effects may be additive. In subjects with type 2 diabetes, both GLP-1 and metformin alone decreased fasting glucose, and together had an additive effect [22]. Similarly, in subjects with type 2 diabetes, GLP-1 and the thiazolidinediones pioglitazone alone reduced fasting glucose levels, and there was an additive effect when the drugs were combined [23]. The ability of GLP-1 to increase insulin levels while reducing glucagon levels was retained when GLP-1 was combined with pioglitazone [23].

After a meal in subjects with type 2 diabetes, GLP-1 alone reduced plasma glucose, whereas the sulfonylurea glibenclamide alone did not [24]. Interestingly, the reduction in plasma glucose was increased when GLP-1 and glibenclamide were combined [24]. Both GLP-1 and glibenclamide increased insulin secretion, with the effect in combination being greater than additive [24]. In subjects with type 2 diabetes who had been successfully treated with sulfonylurea drugs in the past, but who had been treated with insulin for a minimum of 2 years, intravenous GLP-1 transiently increased insulin and lowered glucagon, and this reduced fasting glucose [25]. This suggests that GLP-1 is effective after sulfonylurea failure [25]. When GLP-1 was infused for 16 or 24 hours/day to subjects with type 2 diabetes who were poorly controlled on sulfonylurea treatment, it was shown that it was necessary to infuse continuously for optimal glycaemic control [26]. In elderly patients, continuous subcutaneous infusions of GLP-1 can be substituted for the usual care of metformin and/or sulfonylureas without any loss of glycaemic control [27]. Interestingly, the incidence of hypoglycaemia was much lower in the GLP-1 group than the usual care group [27]. The lack of hypoglycaemia with GLP-1 has also been demonstrated in studies where both GLP-1 and glucose (to stimulate the endogenous glucose lowering system) have been infused in subjects with type 2 diabetes [28, 29].

These studies with GLP-1 clearly established the potential of stimulating the receptor for GLP-1 in subjects with type 2 diabetes. However, the rapid metabolism of GLP-1 means that it has to be continually infused to have an effect, and this is not feasible for most of the subjects with type 2 diabetes. Fortunately, long acting agonists of the GLP-1 receptor have been synthesized (liraglutide, pramlintide and exenatide). The clinical trials with one of these agents, exenatide, are discussed in the following sections.

### Development of Exenatide for Clinical Use

Exendin-4 is a 39-amino acid peptide, originally isolated from the venom of a lizard, which acts as an agonist at the GLP-1 receptors of insulinoma-derived cells [30]. Exendin-

4, like GLP-1, stimulated the glucose-induced insulin secretion from isolated rat islets [30].

Intravenous exenatide is more potent than GLP-1 at stimulating insulin secretion in rats [31]. Of particular interest were the animal studies showing that exenatide had a much longer duration of action than GLP-1. In diabetic mice, once daily intraperitoneal injection of exenatide decreased fasting glucose levels, increased insulin levels, and, after 13 weeks of treatment, decreased HbA<sub>1c</sub> [31]. In obese diabetic mice, the glucose lowering ability of GLP-1 lasted for less than an hour, whereas in the animals treated with exenatide, glucose-lowering persisted for > 4 hours [32]. In obese diabetic Zucker rats, twice daily exenatide caused an increasing drop in HbA<sub>1c</sub> levels over 35 days [32].

In 8 healthy volunteers, intravenous exenatide reduced fasting plasma glucose levels and reduced the peak change of postprandial glucose from baseline [33]. Exenatide also reduced gastric emptying and calorie intake in the volunteers [33]. Intravenous exenatide was subsequently shown to similarly increase insulin levels in response to glucose infusion in both non-diabetic subjects and subjects with type 2 diabetes [34].

Importantly, exenatide was subsequently shown to be effective for several hours when administered subcutaneously. In the first study of this, 24 subjects with type 2 diabetes, discontinued oral anti-diabetic agents for 2 weeks before having exenatide (0.1 µg/kg) administered subcutaneously immediately before breakfast and dinner for 5 days [35]. Postprandial plasma glucose and insulin levels were reduced for 5 hours following exenatide administration compared to the placebo group [35]. Glucagon levels were increased for 3 hours postprandial in the placebo group, but not in subjects treated with exenatide [35]. Exenatide also slowed stomach emptying similarly on days 1 and 5 [35]. In a second study, 13 subjects continued their regular regimen of oral anti-diabetic agents (metformin, a thiazolidinedione alone or in combination), and fasted overnight [35]. Fasting levels of glucose, insulin and glucagon were measured before subjects received exenatide at 0.05, 0.1 or 0.2 µg/kg subcutaneously, and continued fasting [35]. Exenatide reduced the fasting glucose levels, with no additional effect on glucose being observed with exenatide at 0.2 than 0.1 µg/kg [35]. Exenatide increased fasting insulin levels and decreased fasting glucagon levels for 3 hours [35]. In these two studies, mild transient headache, nausea, and vomiting were the main adverse effects reported [35].

In 9 subjects with type-2 diabetes, who were instructed on how to administer exenatide subcutaneous to themselves, fasting glucose levels were reduced by exenatide b.i.d. (not exceeding 0.4 µg/kg/day) for a month at bedtime and before breakfast [36]. Exenatide also reduced fasting insulin levels (before breakfast) and HbA<sub>1c</sub> levels from 9.08 to 8.29% over the month [36]. This protocol lowered post-breakfast glucose, but not post-lunch and post-dinner levels of plasma glucose [36].

Subcutaneous exenatide was then tested in 109 patients with type 2 diabetes being treated with a sulfonylurea and/or metformin, with 3 different regimens for the injections of exenatide for a month; breakfast and dinner, breakfast and

bedtime, and breakfast, dinner and bedtime [37]. With all regimens, exenatide was shown to reduce plasma fructosamine and HbA<sub>1c</sub> levels (indicative of average glycaemic control over the prior 2 weeks and 3 months, respectively) [37]. Homeostasis model assessment (HOMA) was conducted to assess β-cell function, and this was improved by the treatments with exenatide [37]. Exenatide treatment was associated with reductions in postprandial glucose concentrations [37]. There were no significant changes in body weight or lipid levels in this short study [37]. This study also measured the plasma levels of exenatide, and showed that they peaked 2 to 3 hours after administration of 0.08 µg/kg, and were detectable 6 hours after dosing [37]. The t<sub>1/2</sub> for exenatide was 202 minutes on day 1 and 226 minutes on day 28 [37]. Fifteen percent of the exenatide treated patients developed low-titer anti-exenatide antibodies, but there was no evidence that this was associated with a diminished glycaemic response [37]. The most common adverse event with exenatide was transient mild-to-moderate nausea, which occurred in 31% of subjects [37]. Mild hypoglycaemia occurred in 15% of subject, but only occurred in those also taking a sulfonylurea, which are known to induce some hypoglycaemia [37].

A major problem with treating type 2 diabetes with either insulin or the sulfonylureas, is that they cause a gain in body weight. A dose-ranging study with exenatide showed that in 28 days there was a reduction in body weight. In this Phase 2 clinical trial, 156 subjects with type 2 diabetes were randomized to exenatide at 2.5, 5.0, 7.5, and 10 µg, or placebo, b.i.d. for 28 days [38]. At the end of the 28 days, exenatide had reduced HbA<sub>1c</sub>, fasting blood glucose, and body weight [38]. Body weight did not change in the placebo group while there were weight reductions of 0.7 kg with the 2.5 and 5 µg b.i.d. doses of exenatide, 1.4 kg with the 7.5 µg b.i.d. dose, and 1.8 kg with the 10 µg b.i.d. dose [38]. The most common adverse effect was mild-to-moderate nausea with 7 of 123 exenatide-treated subjects withdrawing from the study for this reason [38].

The incidence of nausea and vomiting with exenatide can be reduced by gradually increasing the dose. Thus, if subjects with type 2 diabetes started subcutaneous exenatide at 0.02 µg/kg t.i.d. and increased the dose by 0.02 µg/kg every 3<sup>rd</sup> day until they reached 0.24 µg/kg t.i.d., they had a lower incidence of nausea and vomiting than subjects started with 0.24 µg/kg t.i.d. [39]. Thus, the incidence of severe nausea and vomiting was 29.0% and 9.7% in the primed group, but 47.5% and 31.1% in the exenatide-naïve group, respectively [39].

The bioavailability of exenatide is similar whether it is injected subcutaneously into the arm, thigh, or abdomen [40]. When exenatide is administered subcutaneously before (-60, -15 minutes) or with the meal to subjects with type 2 diabetes, peak postprandial glucose levels are decreased to a greater extent than when the exenatide is administered 30 or 60 minutes after the meal [41]. As exenatide slows gastric emptying, it was anticipated that it may alter the pharmacokinetics of other drugs. However, exenatide does not alter steady-state pharmacokinetics of digoxin [42], or the pharmacokinetics and pharmacodynamics of warfarin [43].

After these developmental studies showing that exenatide was generally beneficial in the treatment of type 2 diabetes with limited adverse effects, it was possible to move on to larger clinical trials with exenatide. Three 30-week controlled trials involving 1446 subjects with type 2 diabetes were undertaken as Diabetes Management for Improving Glucose Outcomes or AMIGO. The first of these was in subjects not achieving therapeutic goals with metformin alone, and is described in the next section with its follow ups. The second of these was in subjects not achieving target blood glucose levels with sulfonylurea therapy alone, and the third was in subjects not achieving targets with metformin and a sulfonylurea and these are discussed in the following sections. All three trials had similar protocols.

### **Clinical Trials with Exenatide in Subjects Treated with Metformin**

The major trial of exenatide in subjects treated with metformin (AMIGO I) started off as a 30-week triple-blind, parallel-group trial, performed at 82 sites in the US [44]. To be enrolled, subjects had to have type 2 diabetes treated with metformin monotherapy [44]. Subjects were included if they had a fasting plasma glucose concentration of  $< 13.3$  mmol/l, BMI of 27-45 kg/m<sup>2</sup>, HbA<sub>1c</sub> of 7.1-11.0%, and metformin  $\geq 1500$  mg/day for 3 months before screening [44]. Subjects were excluded if they were taking other drugs for the treatment of diabetes (e.g. sulfonylureas, thiazolidinediones, insulin) or weight loss drugs [44].

The 336 subjects were predominantly Caucasian with slightly more men than women [44]. They had a mean age of 53 years old, BMI of 34 kg/m<sup>2</sup> and had had diabetes for 5-6 years [44]. Patients continued to take metformin and were assigned to placebo, or exenatide 5 or 10  $\mu$ g bid [44]. The placebo and exenatide were self-injected subcutaneously into the abdomen within the 15 minutes before the morning or evening meals [44].

The primary efficacy end point was glycaemic control as measured by HbA<sub>1c</sub> [44]. The baseline HbA<sub>1c</sub> was  $\sim 8.2\%$  and the maximum effect was observed after 12 weeks, when HbA<sub>1c</sub> had been lowered to 7.5% by exenatide at 5  $\mu$ g, and further (7.1%) by exenatide at 10  $\mu$ g [44]. Of the secondary end points, at 30 weeks, the fasting plasma glucose levels had increased in the placebo group by 0.8 mmol/l while decreasing by 0.4 and 0.6 mmol/l with treatment of exenatide at 5 and 10  $\mu$ g, respectively [44].

Exenatide use was associated with weight loss [44]. Whereas body weight stayed relatively stable in the placebo group over the 30 weeks, it was reduced by 1.6 and 2.8 kg with exenatide at 5 and 10  $\mu$ g, respectively [44].

This study, in metformin-treated subjects with type 2 diabetes, was then extended to 82 weeks, and showed that exenatide remained beneficial at 82 weeks [45]. In the extension, all subjects received exenatide 5  $\mu$ g bid for 4 weeks and then 10  $\mu$ g bid [45]. After 82 weeks there was an analysis of the subjects who had received exenatide throughout (this did not include the original placebo group) [45]. This 82 week cohort was of 150 subjects who continued to take metformin [45]. Only 92 (61%) of the subjects completed the study, and the main reasons for

withdrawal were withdrawal of consent (11%), adverse events (7%), and lost to follow-up (7%) [45].

For those subjects that completed the study, in addition to the 1% fall in HbA<sub>1c</sub> at 30 weeks, there was another 0.2% fall in HbA<sub>1c</sub> by 82 weeks [45]. There was an increased percentage of subjects that achieved HbA<sub>1c</sub> of  $\leq 7\%$  after 82 weeks (59%) than after 30 weeks (46%) [45].

Weight loss was a mean of 3 kg after 30 weeks and this increased to 5.3 kg after 82 weeks in the completer cohort [45]. Greater reductions were observed in those with a higher baseline BMI  $\geq 30$  kg/m<sup>2</sup> (6.9 kg) than those with a BMI  $\leq 30$  kg/m<sup>2</sup> (2.3 kg) [45].

Type 2 diabetes is major risk factor for cardiovascular disease. Exenatide reduced several surrogate markers of cardiovascular disease. Thus, after 82 weeks, there was a 26% reduction in plasma triglycerides, a 4% reduction in LDL-cholesterol, a 5% reduction in apolipoprotein B, and a 11% increase in HDL-cholesterol. Blood pressure was reduced by a mean of 6.3/4.1 mmHg [45]. The biggest benefits in lipids and blood pressure reduction were observed in those that lost most weight [45].

There were no cases of severe hypoglycaemia [45]. Adverse effects led to 7% of withdrawals [45]. The most common causes of adverse effects were nausea and upper respiratory tract infections. Nausea was high (33%) at the start of the extension (when some subjects were being titrated from 5 to 10  $\mu$ g exenatide) and then receded to 14% at 82 weeks [45]. The incidence of upper respiratory tract infection was also higher at the start of the extension period (10%) than at the end (4%) [45].

### **Clinical Trial in Subjects Poorly Controlled with a Sulfonylurea**

A major study has been undertaken of exenatide in subjects with type 2 diabetes failing to obtain glycaemic control (HbA<sub>1c</sub>  $< 7\%$ ) despite maximally effective doses of a sulfonylurea (AMIGO II), and this has also shown favourable results with exenatide [46]. To be included subjects had to have a HbA<sub>1c</sub> or 7.1-11% despite have taken a sulfonylurea for the previous 3 months [46]. Subjects also had to have a body weight that was stable over the previous 3 months [46]. The 377 patients recruited in sites across the U.S. were predominant being treated with glipizide (45%), glyburide (20%) and glimepiride (20%) [46]. In an attempt to decrease the incidence of nausea with exenatide, all the subjects randomised to exenatide were treated with 5  $\mu$ g bid for 4 weeks before the start of the trial [46]. When the trial started, half of these exenatide-treated subjects, had the dose increased to 10  $\mu$ g bid [46].

The primary objective was to evaluate glycaemic control assessed by HbA<sub>1c</sub> [46]. The subjects had a baseline HbA<sub>1c</sub> of about 8.6%, and this was increased in the placebo group by 0.12% over 30 weeks while decreasing by 0.46% and 0.86% in the patients treated with exenatide at 5 and 10  $\mu$ g sc, respectively [46]. Over the 30 weeks, the subjects in the placebo group had an increase of 0.4 mmol/L in their fasting blood glucose levels, whereas the values fell by 0.3 and 0.6 mmol/L in the exenatide 5 and 10  $\mu$ g groups, respectively [46]. Subjects in the placebo group lost 0.6 kg over the 30

weeks, while subjects in the exenatide 5 and 10 µg groups lost 0.9 and 1.6 kg, respectively [46]. Exenatide treatment was associated with a small decrease in LDL-cholesterol levels [46].

Nausea was much more common with exenatide than placebo (placebo, 7%; exenatide 5 µg, 39%; exenatide 10 µg, 51%) but the incidence of severe nausea was low,  $\geq 6\%$  [46]. Hypoglycaemia was also more common with exenatide than placebo (placebo, 3%; exenatide 5 µg, 14%; exenatide 10 µg, 36%), but there were no cases of severe hypoglycaemia [46].

### Clinical Trials in Subjects Treated with Metformin and/or a Sulfonylurea

Favourable results with exenatide have also been obtained subjects with type 2 diabetes, who were taking both metformin and a sulfonylurea. In a major trial of subjects taking metformin and a sulfonylurea (AMIGO III), 734 patients were randomized, and they were mainly Caucasian (~67%) with a reasonably representation of Hispanics (~16%) and Blacks (~11%), and slightly more men than women [47]. The baseline value HbA<sub>1c</sub> was ~8.7% and this remained relatively constant in the placebo group over the 30 weeks, while dropping to ~7.8 and 7.7% in the patients treated with exenatide at 5 and 10 µg, respectively [47]. With HbA<sub>1c</sub>  $\leq 7.0$  representing glycemic control, only 7% of patients in the placebo group had glycemic control and this was increased to 24% and 30% by treatment with exenatide at 5 and 10 µg, respectively [47]. Subjects in the placebo group lost a mean of 0.9 kg during the 30 weeks and this loss was augmented to 1.9 kg by treatment with exenatide at both 5 and 10 µg [47].

Exenatide was mainly safe with nausea being the most common adverse event, occurring in a higher percentage of patients treated with exenatide at 10 µM (49%) than with exenatide at 5 µM (39%) and placebo (21%) [47]. The incidence of nausea decreased with time in all groups [47]. The incidence of hypoglycemia was also more common with exenatide at 10 µg (28%) than with exenatide at 5 µg (19%) and placebo (13%), although almost all of this was mild-to-moderate [47]. At the end of the study, about half of the exenatide-treated subjects had anti-exenatide antibody titers [47].

An extension study took participants from the three short term trials comprising AMIGO (I, II and III). One of these was in metformin-treatment patients [AMIGO I; 44]. The other two were in subjects treated in sulfonylureas either alone [AMIGO II; 46] or with metformin [AMIGO III; 47]. In the extension trial, all subjects received exenatide 5 µg bid for 4 weeks and then 10 µg bid [48]. After 82 weeks there was an analysis of the subjects who had received exenatide throughout [48]. The 551 subjects enrolled in the extension had a mean age of 55 years and were predominantly male (62%) and Caucasian [48]. Only 57% of the subjects completed the 82 week trial, with 11% withdrawing consent and 7% withdrawing because of adverse effects [48].

For those subjects that completed the study, in addition to the 0.9% fall in HbA<sub>1c</sub> at 30 weeks, there was another 0.2% fall in HbA<sub>1c</sub> by 82 weeks [48]. Fasting plasma glucose levels declined by 0.7 mmol/l over the 30 weeks, and this

benefit was maintained at 82 weeks (decline of 0.9 mmol/l) [48].

Weight loss was a mean of 1.6 kg after 30 weeks and this increased to 2.1 kg after 82 weeks in the completer cohort [48]. Greater reductions were observed in those with higher baseline BMIs [48]. The subjects taking exenatide with metformin had the bigger weight loss (5.3 kg), compared to those with a sulphonylurea (3.9 kg), and those taking metformin and a sulphonylurea (4.1 kg) [48].

After 82 weeks, there was a 39% reduction in plasma triglycerides, a 5% reduction in LDL-cholesterol, and a 5% increase in HDL-cholesterol [48]. Blood pressure was reduced by a mean of 1.3/2.7 mmHg [48]. The biggest benefits in lipids and blood pressure reduction were observed in those that lost most weight [48].

The most common causes of adverse effects were nausea and hypoglycemia. Nausea was high (29%) at the start of the extension (when some subjects were being titrated from 5 to 10 µg exenatide) and then receded to 15% at 82 weeks [48]. The incidence of hypoglycaemia, which was mild-to-moderate, was similar throughout, ~10% [48].

The authors have raised the possibility of self-selection having an influence on the outcome, as of the 1446 subjects enrolled in the original 3 studies, 974 chose to enter the open-label extension but only 314 completed the extension [48]. The most common reasons for withdrawal during the 52 weeks of the open-label extension were withdrawal of consent (11%), administrative (mainly closure of site, 10%) and adverse events (7%) [48]. Intention to treat analysis of the population of 551 enrolled in the extension, using last observation carried forward data, gave qualitatively similar results to the completer analysis, but with smaller benefits [48].

Another extension study combined the extensions of two of the three trials included in the extension study described above, and the protocols used, subject demographics, and results were very similar to those described above [48]. The trials included were those in subjects treated with sulphonylureas either alone [46] or with metformin [47, reviewed previously]. The number of subjects that completed the extension was only 222 out of a possible 401, but only 7% of non-completion was due to adverse effects [49]. The reduction in HbA<sub>1c</sub> of 1.0% at 30 weeks was maintained at week 82, 1.2% [49]. Nausea and hypoglycemia accounted for 4% and 0.5% of the withdrawals, respectively [49]. The fasting plasma glucose decline at 30 weeks of 0.52 mmol/L was also maintained at week 81, 0.62 mmol/L [49]. At week 30, the weight reduction was 1.4 kg and 2.1 kg for exenatide 5 µg and 10 µg b.i.d., respectively, and this had increased to a loss of 4 kg at 82 weeks µg [49]. Correlation analysis showed that the weight loss was unlikely to be related to nausea [49].

### Exenatide Compared with Insulin Glargine

The β-cell dysfunction and insulin resistance in type 2 diabetes is progressive. When the oral blood glucose lowering drugs no longer adequately control escalating hyperglycaemia, basal insulin is introduced. One preparation that may be used for basal insulin is insulin glargine, which

is an analog of human insulin with an extended duration of action. Exenatide and insulin glargine have been compared in subjects with type 2 diabetes inadequately controlled with oral agents, and shown to have similar effects on glycaemic control.

The study showing this enrolled 556 patients with inadequately controlled type 2 diabetes despite using metformin and sulfonylurea therapy at maximally effective doses [50]. To be included subjects had to have a HbA<sub>1c</sub> in the range 7 to 10% [50]. Those enrolled had a mean age of about 59 years, were overweight (Body Mass Index of 31 kg/m<sup>2</sup>) and had type 2 diabetes for 9-10 years [50]. The trial was open-label and compared exenatide at a fixed dose of 5 µg twice daily for 4 weeks and then increased to 10 µg twice daily for 22 weeks, with insulin glargine [50]. The initial dose of insulin glargine was 10 U/day, then self-titrated in 2-U increments every 3<sup>rd</sup> day to achieve a fasting blood glucose target of < 5.6 mmol/L [50]. Over 26 weeks both treatment had the same effect on HbA<sub>1c</sub>; a reduction of 1.11% from a baseline of about 8.2% [50]. Insulin glargine caused a greater reduction in fasting glucose levels (2.9 mmol/L) than with exenatide (1.4 mmol/L) [50]. From a baseline body weight of about 88 kg, subjects in the insulin glargine group gained weight throughout (1.8 kg by week 26) whereas those in the exenatide group lost weight (2.3 kg) [50]. Exenatide reduced postprandial glucose levels relative to insulin glargine [50]. Nausea was more common in subjects treated with exenatide (57.1%) than with insulin glargine (8.6%), as were vomiting (17.4 versus 3.7%, respectively) and diarrhea (8.5% versus 3.0%) [50]. Eighteen subjects from the exenatide group withdrew from the study because of gastrointestinal adverse effects whereas only one withdrew from the insulin glargine group for this reason [50]. Subjects who experience hypoglycaemia were told to reduce the sulfonylurea dose by 50% [50]. With this precaution, the overall rate of hypoglycaemia was similar in both groups (7.3 events/patient-year in the exenatide group vs 6.3 in the insulin glargine group) [50].

When surveys were undertaken to identify which medication the patients preferred, there was no difference between the exenatide and insulin glargine [51]. This may seem surprising as there was a higher rate of gastrointestinal adverse effects in the exenatide than insulin glargine group, but it was suggested, the weight loss observed with exenatide may have countered the negative impact of the gastrointestinal effects [51].

### Exenatide Long-Acting Release (LAR)

A long lasting preparation of exenatide is being evaluated in animal studies. Single subcutaneous injection of a polylactide-glycolide microsphere suspension containing exenatide prevented glycaemic deterioration (measured as HbA<sub>1c</sub> values) in diabetic fatty Zucker rats over 28 days [52]. A preliminary report of the effect of exenatide LAR in subjects with type 2 diabetes has shown that in 45 subjects not controlled with metformin, once weekly subcutaneous doses of either 0.8 or 2.0 mg of exenatide LAR once-weekly over 15 weeks reduced HbA<sub>1c</sub> by 1.4% and 1.7%, respectively [53]. Exenatide LAR also reduced fasting glucose levels [53]. Body weight was not reduced by 0.8 mg exenatide LAR, but was reduced by 3.82 kg in the 2.0 mg exenatide

LAR group (placebo weight loss was 0.04 kg) [53]. Mild nausea occurred in 19% and 27% of subjects with 0.8 and 2.0 mg exenatide LAR, respectively, compared to 15% of subjects treated with placebo [53].

### COMMENTS AND CONCLUSIONS

Animal studies have suggested that exenatide may help overcome any loss of β-cells in diabetes. In a partial pancreatectomy rat model of type 2 diabetes, exenatide administration for 10 days stimulated the regeneration of the pancreas and expansion of β-cell mass by both neogenesis (differentiation of beta-cells from ductal progenitor cells) and proliferation of the β-cells [54]. In a genetic rat model of type 2 diabetes (the Goto-Kakizaki rat), GLP-1 or exenatide administered postnatally in the prediabetic period, enhanced pancreatic insulin content and total β-cell mass by stimulation β-cell neogenesis and regeneration [55]. Subsequently, treated animals had lower basal plasma glucose [55]. Presently, it is not known whether GLP-1 or exenatide have similar effects in humans. It would be intriguing to study exenatide in people with impaired fasting glucose (prediabetic) to determine whether it could delay the onset of diabetes, and whether any delay was associated with an increase in β-cell mass.

To date, exenatide has only been studied in large clinical trials in combination with metformin and sulfonylureas. As exenatide has a distinct mechanism of action to the meglitinides, α-glucosidase inhibitors, and thiazolidinediones, it may have additive effects with each of these agents. This should be studied, initially in animal models of diabetes and then (if additive effects are observed) in clinical trials.

To date, the effects of exenatide have only been studied clinically on markers of clinical disease. Long-term studies of the effects of exenatide on clinical outcomes need to be undertaken.

Exenatide is used b.i.d. subcutaneous whereas exenatide LAR is being developed as a once-weekly subcutaneous treatment. All of the clinical trials that have been undertaken exenatide will have to be repeated with exenatide LAR. As subjects will probably prefer once-weekly to b.i.d. administration, it is possible that exenatide LAR may eventually become the formulation of exenatide that is widely used by subjects with type 2 diabetes.

In conclusion, exenatide represents a new and useful addition to the medicines used to treat type 2 diabetes.

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