REVIEW ARTICLE

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Benefit-Risk Assessment of Exenatide in the Therapy of Type 2 Diabetes Mellitus

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Contents

Abstract

Exenatide is the first incretin mimetic, introduced into type 2 diabetes mellitus therapy in 2005, with first approval in the US. It is a glucagon-like peptide-1 (GLP-1) receptor agonist that can be used for treatment by twice-daily injection. A long-acting release formulation for once-weekly injection is in clinical development. Clinical studies and postmarketing experience with exenatide have shown a significant and sustained reduction in glycosylated haemoglobin (HbA_{1c}) by approximately 1% together with other gylcaemic parameters without an intrinsic risk for hypoglycaemias, and a reduction in bodyweight by 5.3 kg in 82 weeks. Blood pressure and lipids are also favourably affected, but hard cardiovascular endpoints are not yet available. Animal studies show an improvement of β-cell function and an increase in β-cell mass after exenatide treatment. The most frequent adverse events associated with exenatide therapy are nausea and antibody formation (both approximately 40%). Nausea, mostly mild and transient, was responsible for a 6% dropout rate in clinical studies. A recent review on the association of acute pancreatitis with exenatide treatment showed no increased risk (relative risk 1.0; 95% CI 0.6, 1.7). This review gives a benefit-risk assessment of exenatide.

Incretin-based therapies represent a new option for the treatment of type 2 diabetes mellitus. Exenatide, the first incretin mimetic, was introduced in 2005 and is approved for the treatment of type 2 diabetes in patients not reaching their therapeutic goal with an oral therapy of metformin and/or a sulfonylurea. This review gives an overview of the mechanism of action, clinical efficacy and adverse effects of exenatide. It outlines the benefits of exenatide in the management of type 2 diabetes versus the potential risks, and evaluates the available evidence to put the agent into perspective.

First, the mechanism of action is summarized. Then, data from clinical phase III studies and postmarketing experience are used to give an overview on the efficacy and safety of exenatide. A subsequent evaluation places exenatide into the treatment algorithm and compares it with other incretin-based therapies.

1. The Need for Novel Therapeutic Strategies for Type 2 Diabetes Mellitus

The incidence and prevalence of type 2 diabetes are rising dramatically globally. Increasingly sedentary life-styles with less physical activity and overnutrition are the underlying causes, leading to a widespread increase of obesity, which is one of the major risk factors for developing type 2 diabetes. Along with these developments, a rising incidence of micro- and macrovascular complications of type 2 diabetes is being observed. Estimates place the number of people with all types of diabetes at 370 million worldwide by the year 2030.[1] A large proportion of patients do not reach their glycaemic goals with the classical antidiabetic agents. Furthermore, many of the established drugs promote further weight gain (sulfonylureas, glitazones and insulin) or bear the risk of hypoglycaemia as a treatment complication (sulfonylureas, glinides and insulin). Therefore, new and safe treatment strategies for the therapy of type 2 diabetes are needed.

The pathophysiology of type 2 diabetes is characterized by an insulin secretion defect and by insulin resistance. Insulin resistance is constant in the course of type 2 diabetes. The insulin secretion defect also contributes to disease progression, leading to the secondary failure of the classical oral antidiabetic drugs. Besides β-cell dysfunction, the glucagon-producing α cells in the islets additionally develop a disturbance in hormone secretion. In healthy individuals, glucagon secretion is suppressed under hyperglycaemic conditions, whereas in patients with type 2 diabetes or prediabetes, glucagon secretion is elevated, leading to excessive glucose production by the liver.[2,3]

The classical drugs (metformin, sulfonylureas, glinides, glitazones, α glucosidase inhibitors and insulin) do not address the problem of α- and β-cell dysfunction. Two important studies on type 2 diabetes therapy – the UKPDS (UK Prospective Diabetes Study)[4] and ADOPT (A Diabetes Outcome Progression Trial)[5] – have demonstrated that glycaemic control deteriorates in type 2 diabetes over time with constant drug treatment due to increasing β-cell dysfunction. Classical insulin secretagogues (sulfonylureas and glinides) exclusively stimulate insulin secretion, with the risk of hypoglycaemia and weight gain. Metformin and glitazones act on insulin resistance by increasing the body's sensitivity to insulin, and α glucosidase inhibitors delay the breakdown of complex carbohydrates in the small intestine. Exogenous insulin replaces the endogenous secretory insulin deficit, although it potentially causes weight gain and hypoglycaemia. The progressive loss of islet function observed in type 2 diabetes is not ameliorated by any of the current therapeutic options.[6]

2. Incretin-Based Therapies

Glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide-1 (GLP-1) are secreted from endocrine cells of the intestinal mucosa. They stimulate insulin secretion postprandially and are responsible for the 'incretin effect', which describes the phenomenon in which orally administered glucose evokes a greater insulin response than intravenously administered glucose.[7] The incretin effect accounts for approximately 70% of the postprandial insulin secretion in healthy individuals and is reduced or even absent in patients with type 2 diabetes.[8]

The potential of GLP-1 physiology as a therapeutic option for type 2 diabetes treatment was discovered in the 1990s. In contrast to classical insulinotropic agents, the insulinotropic effect of GLP-1 is strictly glucose dependent and only present under hyperglycaemic conditions. Therefore, GLP-1 can normalize glucose without the risk of hypoglycaemia. In patients with type 2 diabetes, GLP-1 stimulates insulin secretion and normalizes both fasting and postprandial blood glucose, and further restores the defective first phase of insulin secretion in type 2 diabetes.[9] GLP-1 has additional physiological actions that may be advantageous in type 2 diabetes therapy: it suppresses glucagon secretion from the α cells, slows gastric emptying and acts as a mediator of satiety in the hypothalamus, where it is also found as a neurotransmitter.[6,9] In patients with type 2 diabetes, exogenous GLP-1 causes weight loss.[10] In animal studies and in isolated human islets, GLP-1 stimulates β-cell formation from precursor cells and also inhibits their apoptosis, leading to an increase in β-cell mass and an improvement in β-cell function.[11]

The action of the enzyme dipeptidyl peptidase IV (DPP-IV) limits the biological half-life of exogenous GLP-1 to only 1–2 minutes. Treatment with native GLP-1 is not feasible for this reason. In order to utilize the effects of GLP-1, long-acting GLP-1 receptor agonists can be used.[9] These comprise GLP-1 analogues with a long biological half-life or natural peptides similar to GLP-1 that are DPP-IV resistant and bind to the GLP-1 receptor, termed 'incretin mimetics'. Exenatide is the first incretin mimetic and was introduced into type 2 diabetes therapy in 2005 in the US and in 2007 in many European countries.[12] Exendin-4 is naturally found in the lizard *Heloderma suspectum* (Gila monster).[13] It was found to be a strong GLP-1 receptor agonist. The synthetic form of exendin-4 is termed exenatide. Exenatide belongs to the novel class of incretin mimetics due to its incretin-like action. It has a much longer biological half-life than GLP-1 and is a GLP-1 receptor agonist that can be used for therapeutic purposes by twice-daily injection. A long-acting release formulation for once-weekly injection is in clinical development.[14,15] Long-acting, injectable GLP-1 analogues are already introduced into the market (e.g. liraglutide) or are being developed (e.g. taspoglutide, currently in phase III development, albiglutide and others).[16-18] An alternative approach to utilizing GLP-1 action is the inhibition of the degrading enzyme DPP-IV by orally active DPP-IV inhibitors.[19]

3. Exenatide

3.1 Pharmacological Profile of Exenatide

John Eng and his group isolated and characterized exendin-4, a peptide with 52% amino acid sequence similarity to GLP-1, from the salivary gland of the Gila monster in 1992.[13] Exendin-4 acts as a high potency agonist at the GLP-1 receptor on β cells; amino acid fragment 9–39 is an important high potency GLP-1 or exendin-4 antagonist.[20] Exendin-4 is not the GLP-1 of the Gila monster as such, as it also possesses its own GLP-1. In mammals, no counterpart of exendin-4 appears to exist.[21]

Exenatide is the synthetic recombinant version of exendin-4,[22] and shares the physiological properties of native GLP-1 described in section 2. The biological effect of a single subcutaneous injection of 10 μg exendin-4 or exenatide lasts for approximately 5–7 hours in humans. Exenatide is not cleaved and degraded by DPP-IV. Because of the prolonged *in vivo* half-life compared with GLP-1, sufficient plasma concentrations can be reached with twice-daily subcutaneous administration to achieve the desired GLP-1-like therapeutic effects in patients with type 2 diabetes.[23] After injection, plasma exenatide concentrations increase continuously until reaching peak concentrations 2–3 hours after administration of 0.08 μg/kg bodyweight subcutaneously and are still detectable 6 hours postdose. The half-life in pharmacokinetic studies in type 2 diabetic patients was 202 ± 182 minutes, with a corresponding maximum concentration of 163 ± 86 pg/mL.[23] The mean apparent volume of distribution after administration of a single subcutaneous dose is 28.3 L. Based on animal study data, the bioavailability of exenatide after subcutaneous injection amounts to approximately 65–75%. Exenatide is predominantly

eliminated by glomerular filtration followed by proteolytic degradation. Drug-drug interactions with digoxin, lovastatin, lisinopril and paracetamol (acetaminophen) have been documented. Interactions between exenatide and agents such as digoxin and lisinopril were not considered significant.[24] The recommended starting dosage is 5 μg subcutaneously twice daily within 1 hour before the morning and evening meals for 4 weeks. The dose can then be titrated to 10 μg twice daily.[25]

After administration of exenatide 0.1 μg/kg bodyweight, statistically significant reductions in mean postprandial circulating concentrations of glucose, insulin and glucagon were observed. During fasting, glucose-dependent enhancement of insulin secretion and suppression of glucagon secretion are the predominant mechanisms. The postprandial glucagon area under the plasma concentration-time curve from time 0 to 180 minutes was significantly decreased.[26]

Furthermore, experiments in dogs showed that exenatide directly stimulates glucose turnover by enhancing insulin-mediated whole-body glucose disposal and increasing hepatic uptake of exogenous glucose, contributing to its overall action to lower postprandial glucose excursions.[27] Likewise, in type 2 diabetic patients, an elevation in GLP-1 plasma concentrations suppresses endogenous glucose production.[28]

Animal studies indicate that exenatide has trophic and protective effects on β cells and may halt the progression of disease. To date, this has not been established in any clinical trials, but the replication rate of rodent β cells differs from that in humans.[29] If the β-cell-preserving potential of exenatide and GLP-1 receptor agonists can also be demonstrated in humans in long-term studies, the GLP-1 analogues may be able to address one of the underlying causes of progression of type 2 diabetes.

In humans, it is presently not clear if exenatide has a positive effect on β-cell mass and therefore on disease progression in type 2 diabetes. However, the short-term exposure to exenatide can restore the insulin secretory pattern in response to acute rises in glucose concentrations in type 2 diabetic patients who, in the absence of exenatide, do not display a first phase of insulin secretion. The loss of first-phase insulin secretion in these patients may be restored by treatment with exenatide (figure 1).[30] This finding is in line with the observed improvement of insulin secretion during meal tests in type 2 diabetic patients receiving long-term exenatide treatment.[26] In a study following patients during a 1-year exenatide therapy and a consecutive 12-week washout period, the beneficial effects of exenatide on β-cell function observed during the treatment were not

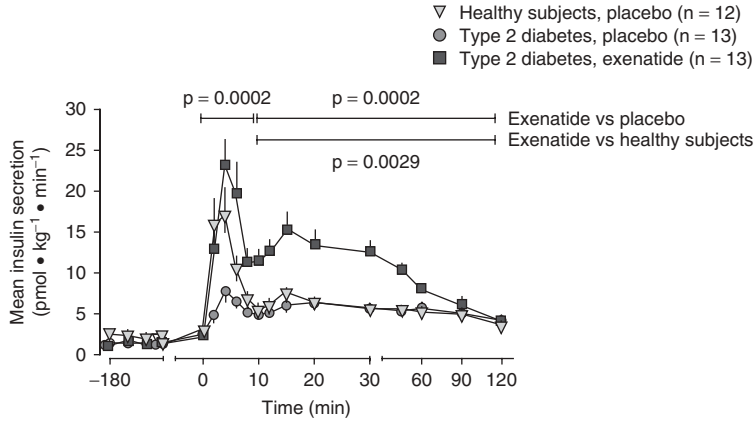

Fig. 1. Effect of exenatide on the first and second phase of insulin secretion after intravenous glucose. Fasted subjects received an intravenous insulin infusion to reach euglycaemia; control subjects received saline. Four hours later, patients with type 2 diabetes mellitus received exenatide or placebo and healthy control subjects received placebo. After 3 hours of study medication infusion, an intravenous glucose tolerance test was performed (reproduced from Fehse et al.,[30] with permission from the Endocrine Society. Copyright 2005).

sustained after the washout, indicating that a longer duration of therapy may be required for disease modifying effects of exenatide to become apparent.[31]

Exenatide was the first incretin mimetic and the first drug using the principle of GLP-1 action to be approved by the US FDA (April 2005) and in Europe (May 2007) for the treatment of type 2 diabetes in patients not sufficiently controlled with an oral therapy of sulfonylureas, metformin or a combination of both. Exenatide (Byetta®, Amylin Pharmaceuticals, San Diego, CA, USA, and Eli Lilly Pharmaceuticals, Indianapolis, IN, USA) is marketed in a pre-filled recyclable pen that allows the release of fixed doses of either 5 μg or 10 μg.

In the development of a long-acting release (LAR) formulation, the biological effects of exenatide LAR (a poly-lactide-glycolide microsphere suspension with 3% peptide content) on glycosylated haemoglobin (HbA_{1c}), insulin sensitivity and β-cell secretion were first studied and characterized in a diabetic rat model. Exenatide LAR dose-proportionally prevented glycaemic deterioration and revealed increases in β-cell response to a glucose challenge, and up to a 2.1-fold increase in insulin sensitivity.[15] In a 15-week, clinical, phase II study investigating the safety, pharmacokinetics and pharmacodynamics of exenatide LAR in 45 patients with type 2 diabetes treated with metformin or diet and exercise, once-weekly subcutaneous exenatide LAR doses of either 0.8 or 2.0 mg were administered after randomization in a double-blind, placebo-controlled fashion. Dose-related increases in plasma exenatide concentrations were observed, reaching steady-state levels between week 6 and 7.[14]

4. Data on Efficacy

4.1 Glycaemic Control

Exenatide has been studied extensively in healthy volunteers and patients with type 2 diabetes and is currently approved as adjunctive therapy to improve glycaemic control in patients with type 2 diabetes who are taking metformin, a sulfonylurea, a thiazolidinedione, or a combination of metformin and either a sulfonylurea or a thiazolidinedione, and who have not achieved adequate glycaemic control.[32]

Most important and relevant for the FDA approval were three pivotal, controlled, phase III studies involving 1446 patients, in whom exenatide was administered for 30 weeks as an add-on therapy to type 2 diabetic patients inadequately treated with sulfonylureas,[33] metformin,[34] or a combination of metformin and sulfonylureas[35] (the AMIGO [Diabetes Management for Improving Glucose Outcomes] studies). All trials had a comparable design: after a 4-week placebo lead-in period, patients were randomized to treatment with exenatide 5 μg twice daily, exenatide 10 μg twice daily (titrated from 5 μg twice daily) or placebo before the morning and evening meals, in addition to their existing oral antidiabetic treatment. The primary outcome measure in these trials was glycaemic control as assessed by change in HbA_{1c} (figure 2).

Thirty weeks of therapy led to a decrease in fasting blood glucose concentrations, and HbA_{1c} levels were reduced by approximately 0.8% overall (figure 3). Less than 50% of treated patients reached the target HbA_{1c} level of ≤7%. The proportion of patients reaching the HbA_{1c} goal ≤7% was 41%, 46% and 34% of the patients in the sulfonylurea, metformin or sulfonylurea plus metformin groups of the three AMIGO trials, respectively.[33-35] When stratified by baseline HbA_{1c} ≥9%, significantly greater reductions in HbA_{1c} from baseline in each exenatide arm compared with placebo were observed.[33,35] The magnitude of decrease in HbA_{1c} is related to the decrease in bodyweight, such that the HbA_{1c} decreases by 0.6% in subjects who do not have a significant weight loss, and it is much larger in those who have significant weight loss. The addition of exenatide to a baseline therapy with a sulfonylurea resulted in similar beneficial effects in patients whose sulfonylurea dose was initially reduced to minimally effective doses, when compared with patients using fixed maximally effective doses of sulfonylurea throughout the study.[35] In the open 82-week extension of the study, the completer cohort on exenatide 2×10 μg twice daily (n = 314) showed an HbA_{1c} reduction of

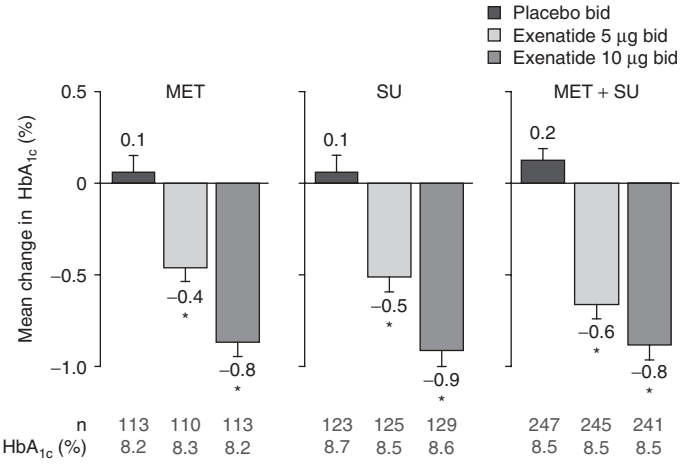

Fig. 2. Clinical efficacy of exenatide in reducing glycosylated haemoglobin (HbA_{1c}). Study data from 30-week studies with exenatide as add-on in patients on a primary therapy of metformin (MET), sulfonylurea (SU) or a combination of both agents are shown (reproduced from Buse et al.,[33] DeFronzo et al.[34] and Kendall et al.,[35] with permission from the American Diabetes Association). Intention to treat population MET = 336; SU = 377; MET + SU = 733. The T-bars represent standard error of the mean. **bid** = twice daily; * $p < 0.05$.

–1.1% ± 0.1% (95% CI –1.0, –1.3) at week 82.[36] In the group with a baseline treatment of metformin only, the reductions in HbA_{1c} were sustained to week 82 with changes from baseline of –1.3 ± 0.1% (95% CI –1.5, –1.0; $p < 0.05$).[37]

Comparable results regarding efficacy of exenatide were observed in a 16-week study that investigated the combination therapy of a thiazolidinedione with exenatide. As in the studies described above, the primary outcome parameter was glycaemic control assessed by HbA_{1c}.[38] Exenatide treatment reduced the HbA_{1c} from 7.9% by 0.98% (95% CI –1.21, –0.74) and lowered fasting plasma glucose significantly.[38]

The effects of exenatide were also compared with those achieved with an insulin therapy. In one large study with a similar cohort of over 500 patients insufficiently controlled with a sulfonylurea and metformin, patients were randomized to receive additionally either the long-acting insulin analogue insulin glargine once daily or exenatide twice daily to compare the effects of insulin glargine and exenatide on glycaemic parameters and bodyweight. The insulin glargine dose was titrated to target a fasting plasma glucose of 100 mg/dL. Exenatide was administered in a fixed dose of 10 μg twice daily. After 26 weeks, both exenatide and insulin glargine comparably reduced HbA_{1c} levels by 1.11%. The difference between treatments was 0.017% (95% CI –0.123, 0.157). For the per-protocol sample, the change in HbA_{1c} amounted to –1.16% and –1.14% for exenatide and insulin glargine, respectively (difference, –0.016%; 95% CI –0.161, 0.129). For each patient sample, the upper limit of the confidence interval was below the prespecified non-inferiority margin of 0.4%.[39] Exenatide reduced postprandial glucose excursions more than insulin glargine, while insulin glargine reduced fasting glucose concentrations more than exenatide.

Another study with a similar design and a comparable patient cohort compared biphasic insulin with exenatide. In this study too, exenatide was non-inferior to biphasic insulin apart from achieving a HbA_{1c} reduction (difference exenatide vs biphasic insulin –0.15%; 95% CI –0.32, 0.01), and appeared to provide better postprandial glucose control, as well as weight reductions.[40]

Exenatide LAR 0.8 and 2.0 mg treatment resulted in reductions from baseline HbA_{1c} by 1.4 and 1.7%, respectively. With exenatide LAR, the proportion of patients achieving an HbA_{1c} below 7% was 33% with 0.8 mg and 86% with 2.0 mg.[14]

In a 30-week, randomized, open-label trial with a 52-week extension in 295 patients with type 2

diabetes, treatment with exenatide LAR led to a more pronounced improvement in HbA_{1c} than exenatide administered twice daily (−1.9 ± 0.1% vs −1.5 ± 0.1%; 95% CI −0.54, −0.12; p = 0.0023) and in fasting plasma glucose (−2.3 vs −1.4 mmol/L). Similar glycaemic control was achieved by both patient groups at week 52 (HbA_{1c} −2.0 ± 0.1%; fasting plasma glucose −2.4 ± 0.2 mmol/L).[41]

4.2 Bodyweight

A dose-dependent, significant and progressive weight loss of 1.6 kg (sulfonylurea and sulfonylurea plus metformin arms) and 2.8 kg (patients only on metformin) from baseline was observed in the AMIGO studies. In open-label extensions of these studies, exenatide was administered for a total of more than 3 years with continued effects on HbA_{1c} and bodyweight.[42] In the published 82-week extension, a progressive reduction in weight of −5.3 kg after 82 weeks was observed,[37] while after 30 weeks, exenatide had led to a decrease in bodyweight from baseline of −3.0 kg in all three study arms of the AMIGO studies. In addition, exenatide treatment produced clinically significant improvements in cardiovascular risk factors after 82 weeks.[36]

In the study investigating the combination therapy of a thiazolidinedione with exenatide, the bodyweight loss observed was −1.51 kg.[38]

The bodyweight loss amounted to 2.3 kg in exenatide-treated patients in the comparator study with insulin glargine, whereas insulin-treated patients experienced a weight gain of 1.8 kg with insulin glargine.[39]

A dose-dependent and significant reduction in bodyweight was also seen with treatment with exenatide LAR.[14] Both groups in the study comparing exenatide twice daily with exenatide LAR lost approximately 4 kg bodyweight by week 30.[41]

4.3 Blood Pressure and Lipids

In the 82-week, open extension of the AMIGO studies, a significant reduction in blood pressure was observed. Mean systolic blood pressure was reduced by −3.5 ± 1.2 mmHg in exenatide-treated patients (baseline mean systolic blood pressure 129.3 ± 1.0 mmHg, mean change −2%; 95% CI −5.9, −1.0; p = 0.0063), while mean diastolic blood pressure was lowered by −3.3 ± 0.8 mmHg (mean baseline diastolic blood pressure 79.2 ± 0.6 mmHg, mean change −4%; 95% CI −4.9, −1.7; p < 0.0001).[42] In the group of patients with metformin as background therapy, mean systolic and diastolic blood pressure was significantly reduced by −6.3 mmHg and −4.1 mmHg, respectively.[37]

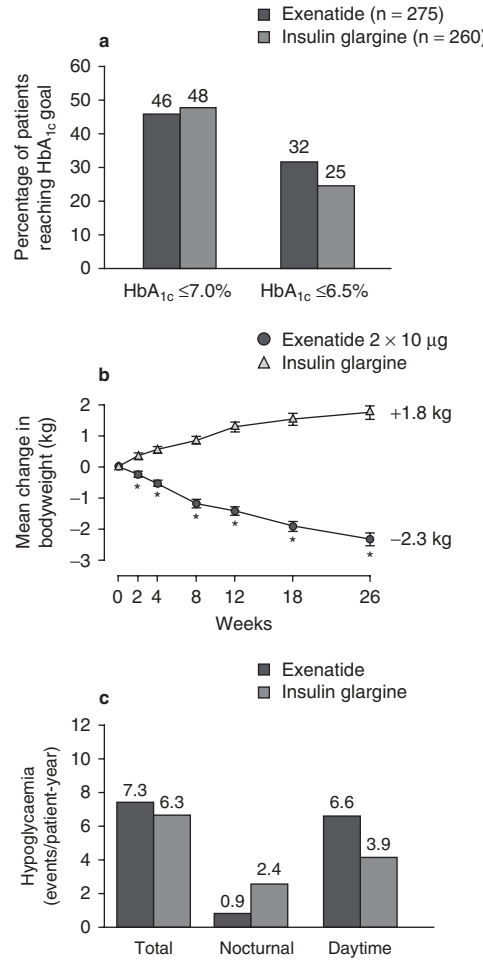

Fig. 3. Effect of exenatide or insulin glargine in patients with suboptimally controlled type 2 diabetes mellitus on an oral medication with metformin and/or a sulfonylurea. (**a**) Percentage of patients reaching glycosylated haemoglobin (HbA1c) goals (≤7.0% or ≤6.5%). (**b**) Effect on bodyweight of insulin glargine or exenatide during the 26-week study. T-bars represent standard error of the mean. (**c**) Incidence of hypoglycaemia in both treatment arms. All data are shown for intention-to-treat population (reproduced from Heine et al.,[39] with permission).

In a study comparing exenatide twice daily with exenatide LAR, a reduction of mean systolic as well as diastolic blood pressure was observed (mean systolic blood pressure −5.7 ± 1.2 and −4.0 ± 1.4 mmHg; mean diastolic blood pressure −2.2 ± 0.8 and −2.1 ± 0.8 mmHg, in patients on exenatide LAR or on exenatide week 1–30, respectively).[41]

In the open-label extension of the AMIGO studies, a total of 151 patients had a period of 3.5 years of exenatide exposure and had serum lipids available for analysis from that time span. Triglycerides decreased by 12% ($p = 0.0003$), and the changes were −5% in total cholesterol ($p = 0.0007$), −6% in low-density lipoprotein cholesterol ($p < 0.0001$) and +24% in high-density lipoprotein cholesterol ($p < 0.0001$).[42]

5. Data on Safety

5.1 Hypoglycaemia

In the AMIGO studies, hypoglycaemic events (primarily mild to moderate) were more frequent in patients with an exenatide dosage of 10 μg twice daily in combination with a sulfonylurea (36% vs 3%) or the combination of metformin and a sulfonylurea (27.8% vs 12.6%). However, the incidence of hypoglycaemic episodes was similar in patients who received exenatide plus metformin or metformin alone.[33-35]

Hypoglycaemic events were reported by 11% and 7% of subjects in the exenatide and placebo groups, respectively, in the study that investigated the efficacy and safety of exenatide in combination with a thiazolidinedione.[38]

The rates of symptomatic hypoglycaemia were similar in the study comparing the efficacy and safety of exenatide with that of insulin glargine as add-on therapy to metformin and/or sulfonylureas, but nocturnal hypoglycaemia occurred less frequently with exenatide.[39]

In studies with exenatide LAR, no hypoglycaemic episode was recorded in patients not using a concomitant sulfonylurea, and no major hypoglycaemia was observed, regardless of background therapy.[14,41]

5.2 Adverse Events in Clinical Studies

Adverse effects were mild, mostly in the beginning of the study, and were generally gastrointestinal (nausea and fullness). Nausea generally decreased with increasing length of treatment. In all studies, gastrointestinal adverse effects were relatively frequent, especially during the early weeks with the 10 μg dose of exenatide. In the sulfonylurea add-on trial, nausea was reported in 51% of patients who received exenatide 10 μg twice daily, compared with only 7% of those who received the sulfonylurea alone[33] (table I).

In patients treated with metformin and exenatide, nausea was observed more frequently compared with metformin monotherapy (45% vs 23%) and when used in combination with metformin plus a sulfonylurea the incidence of nausea in the exenatide groups was 48.5% compared with 20.6% in the placebo groups.[34,35] The dropout rate in the three AMIGO studies due to adverse events ranged from 19%[34,35] to 31%.[33] Nausea (mostly mild to moderate) was reported by 40% of patients in the exenatide-treated group (15% in the placebo group) in a study investigating the combination of a thiazolidinedione with exenatide. In this study, 13% of patients experienced vomiting (1% in the placebo group) and 16% in the exenatide group discontinued the study prematurely due to adverse events compared with 2% in the placebo group.[38] The profile of adverse events was similar in the studies comparing insulin treatment regimens versus exenatide as add-on to a therapy with metformin and/or sulfonylureas, as in the above mentioned studies.[39,40] The most frequent adverse event during exenatide LAR treatment was mild nausea (27% of patients).

Exenatide treatment is associated with the formation of exenatide antibodies, which are detectable in 40–49% of patients. These antibodies do not cross-react with human GLP-1 and do not lead to a significant loss of treatment efficacy of exenatide.[33-35,38-40] In the 16-week study investigating the combination of exenatide with a thiazolidinedione, 40% of patients investigated had positive anti-exenatide antibody titres at the end of the study. Antibody titres were low

Table I. Adverse events of exenatide in large clinical studies[a]

Study (y)	OAD	Nausea (%)	Treatment discontinued		Antibodies[b] (%)
			UAE (%)	GI[c] (%)	
Placebo-controlled					
DeFronzo et al.[34] (2005)	Met	3.5	7.1	1.8	43
Buse et al.[33] (2004)	SU	5.0	10.1	4.0	41
Kendall et al.[35] (2005)	Met + SU	3.0	9.1	4.0	49
Zinman et al.[38] (2007)	TZD ± Met	6.6	15.7	14.0[d]	40
Insulin comparator					
Heine et al.[39] (2005)	Met + SU	4.6	9.6	6.4[d]	43
Nauck et al.[40] (2007)	Met + SU		7.9	5.1[d]	45
Pooled data					
Σ exenatide recipients		4.3	9.6	5.7	44
Σ placebo recipients		<1.0	3.0	<1.0	
Σ insulin recipients		<1.0	<1.0	<1.0	

a The dose in all the studies was 10 μg twice daily (first month: 5 μg)

b Including 5 μg dose.

c Due to nausea.

d Other GI effects.

GI = gastrointestinal; **Met** = metformin; **OAD** = oral antidiabetic drug; **SU** = sulfonylurea; **TZD** = thiazolidinedione; **UAE** = unwanted adverse event.

(1 : 5 to 1 : 125) in 78% of the antibody-positive patients. HbA_{1c} responses between antibody-negative (mean response –0.84%; ±SD 1.03%) and antibody-positive (mean response –0.72%; ±SD 0.68%) patients were similar, and no clinically meaningful differences in adverse events between antibody-positive and antibody-negative patients were observed.[38] At the end of the study investigating the efficacy and safety of exenatide LAR, 67% of patients had detectable exenatide-antibodies.[14] In the comparator study of exenatide twice daily versus once weekly, anti-exenatide antibody levels were higher with exenatide once a week ($p = 0.0002$ vs exenatide twice a day); however, most antibodies were either not detectable or of low (<1/625) titre.[41]

5.3 Adverse Events Reported from Postmarketing Data

In October 2007, the FDA released an 'information for healthcare professionals' report after having received postmarketing reports of acute pancreatitis in patients taking exenatide. Since issuing this report, six cases of haemorrhagic or necrotizing pancreatitis in patients taking exenatide have been reviewed by the FDA.[43,44] All patients required hospitalization and, of these cases, two patients died and four were recovering at the time of reporting. Exenatide was discontinued in all six cases. A further set of 30 cases of pancreatitis possibly associated with the use of exenatide were reviewed. In this report, the median exenatide dose was 10 μg/day and the patients had a median age of 60 years. The median time from the initiation of exenatide treatment to the onset of symptoms was 34 days. Amylase and lipase plasma concentrations showed a wide range (amylase: 40–1845 U/L, median 384 U/L, normal range 30–170 U/L; lipase: 62–16 970 U/L, median 545 U/L, normal range 7–60 U/L). A total of 23 patients reported abdominal pain; in 22 patients, symptoms of pancreatitis ceased when exenatide was discontinued. Three patients had a recurrence of symptoms on re-exposure to exenatide (nausea and vomiting in two and abdominal pain in one). The diagnosis of acute pancreatitis was supported by imaging on either computed tomography or ultrasonography in 11 patients. Hospitalization was required in 70%

of patients. No fatal complications were observed, and serious complications included acute renal failure, suspected ileus, ascites and phlegmon. At least one other risk factor possibly confounding the association between exenatide and acute pancreatitis – including obesity, hyperlipidaemia, hypertriglyceridaemia and alcohol use – was detected in 90% of the patients.[45] Recently, the application of a claims-based active drug safety surveillance system using data from approximately 28 000 exenatide-treated patients and estimating the risk of acute pancreatitis with exenatide compared with classical oral antidiabetic drugs could not provide evidence for an association of acute pancreatitis among patients treated with exenatide compared with those treated with metformin or a sulfonylurea.[46]

In November 2009, the FDA posted another report and label change for healthcare professionals reporting 78 cases of altered renal function that had occurred in patients using exenatide in the time from April 2005 up to October 2008. Of these cases, 62 were associated with acute renal failure and 16 with renal insufficiency. Some patients had one or more risk factors for developing kidney disease and some had already pre-existing kidney problems. The label changes include that exenatide should not be used in patients with pre-existing severe renal insufficiency or end-stage renal disease (creatinine clearance <30 mL/min) and that in patients with moderate renal insufficiency (creatinine clearance 30–50 mL/min) caution should be taken when the dose of exenatide is uptitrated from 5 μg to 10 μg twice daily. Furthermore, the kidney function of patients should be monitored carefully regarding renal dysfunction, and the ongoing need for exenatide therapy should be evaluated if kidney dysfunction is suspected under treatment.[47]

6. Evaluation

Exenatide belongs to the novel class of GLP-1 receptor agonists that are a promising drug class for the treatment of type 2 diabetes. This class comprises the incretin mimetics, peptides with a structure similar, but not identical, to GLP-1 that are also found in nature (e.g. exenatide) and GLP-1 analogues that have a higher amino acid sequence homology to GLP-1 but have a longer biological half-life than native GLP-1 because they are resistant to DPP-IV (e.g. liraglutide[48] and taspoglutide[49]). Treatment with GLP-1 receptor agonists is efficacious and they appear to have a favourable safety profile. The treatment rectifies impaired insulin as well as glucagon secretion and improves the imbalance in the insulin/glucagon ratio. The latter effect is a multimodal and novel principle of action that is characteristic for the incretin-based therapies and not addressed by classical antidiabetic drugs.[17]

Concerning beneficial effects, exenatide has the capacity to sustainably reduce the HbA_{1c} by approximately 1% in monotherapy[50] and various combination therapies.[33-35,38-40] In parallel, postprandial glucose and, to a lesser extent, fasting plasma glucose are also reduced. Apart from the glycaemic effects, a significant reduction in bodyweight is observed, which is desirable. The magnitude of weight loss observed in clinical studies and in post-approval therapeutic use varies considerably between individuals. The magnitude of reduction in HbA_{1c} is correlated to the decrease in bodyweight, such that the HbA_{1c} decreases by 0.6% in subjects who do not have a significant weight loss, and is much larger in those who have significant weight loss. The weight loss is not related to the presence or degree of nausea as an adverse event. Subgroup analyses of the clinical studies with exenatide showed that the weight loss was similar in the groups of patients experiencing nausea and those not experiencing it.[51] The weight loss may therefore be explained by a central action of the drug stimulating satiety.[52]

Additionally, exenatide treatment improves metabolic and cardiovascular parameters like blood pressure and plasma lipids.[36] To date, however, no data are available concerning possible effects of exenatide on both micro- and macrovascular event rates and complications. Data from animal and human studies with either native GLP-1 or liraglutide suggest an improvement in cardiovascular function under normal and ischaemic conditions.[53-56] In view of these beneficial data, as well as the data from recent animal studies with exenatide[57] on cardiovascular effects, long-term clinical studies with exenatide are warranted to

explore the outcomes on micro- and macrovascular endpoints.

Exenatide does not provoke hypoglycaemia on its own, only when sulfonylureas are used in combination; hypoglycaemic events have been observed that are then attributable to the sulfonylurea therapy.

Concerning adverse events and safety, the most frequent adverse effects of exenatide are mild to moderate nausea or fullness and associated gastrointestinal symptoms. These effects are mostly transient and occur during the first few weeks of treatment. For this reason, dose titration is recommended when starting therapy. The dropout rate due to nausea amounted to approximately 6% in the clinical studies evaluating the efficacy and safety of exenatide in various treatment combinations.[33-35,38-40]

Exenatide treatment, like treatment with many non-human peptide therapeutics, leads to antibody formation. These develop in approximately 40–50% of patients.[19] However, this is rarely associated with any reduction in efficacy, and the antibodies do not cross-react with native human GLP-1. However, it is noted in the exenatide prescribing information that high-titre exenatide antibodies develop in between 6% and 9% of patients; in 3–9% of these patients, the glycaemic response to exenatide is attenuated.[32]

Postmarketing reports of a possible association of exenatide treatment with the occurrence of acute pancreatitis have lead to an increasing awareness and reporting of such cases.[43-45] Exenatide treatment therefore should be promptly discontinued if pancreatitis is suspected. There are no known patient characteristics that determine when pancreatitis associated with exenatide will be complicated by the haemorrhagic or necrotizing forms of this condition. As of now, there is no known pathophysiological mechanism explaining or confirming an association of exenatide treatment with pancreatitis. During follow-up of up to 1 year, acute pancreatitis occurred among 0.13% of patients treated with exenatide, using a claims-based drug surveillance system. The risk of acute pancreatitis was comparable for patients with exenatide (relative risk 1.0; 95% CI 0.6, 1.7) relative to the comparison cohorts.[46] Patients with type 2 diabetes and abdominal obesity may have an increased incidence and risk for developing pancreatitis due to hypertriglyceridaemia and biliary obstruction due to gallstones. However, the incidence of acute pancreatitis in this population compared with healthy individuals is not known, and further studies are warranted to clarify the association of pancreatitis in treatment with exenatide and GLP-1 receptor agonists.

Exenatide has been studied extensively in humans and is currently approved as adjunctive therapy to improve glycaemic control in patients with type 2 diabetes who are taking metformin, a sulfonylurea, a thiazolidinedione, or a combination of metformin and either a sulfonylurea or a thiazolidinedione, and who have not achieved adequate glycaemic control.[32] A preferred indication for using exenatide is in treating patients whose type 2 diabetes is not controlled by the classical oral antidiabetics and where the alternative therapeutic escalation with insulin is not desirable either due to the risk of hypoglycaemia (patients operating or supervising heavy machines, actively participating in public traffic, or geriatric patients) or where further weight gain has to be avoided (in pronounced obesity). In the novel guidelines of the German Diabetes Association on pharmacological type 2 diabetes therapy, treatment with exenatide can be considered for the above reasons if patients on oral therapy with metformin or sulfonylureas are not at goal with an HbA_{1c} approximately 1% above the desired therapeutic goal.[58,59] A recent consensus statement by the American Diabetes Association (ADA) and the European Association of the Study for Diabetes (EASD) has placed the therapeutic indication for exenatide in a similar place among the novel, less validated treatment forms after metformin as first-line therapy in patients failing on this regimen (figure 4). [60] Exenatide is not recommended in patients with severe renal insufficiency (creatinine clearance <30 mL/min). In patients with end-stage renal disease on dialysis, exenatide 5 μg has been poorly tolerated because of gastrointestinal adverse effects.[32]

Concerning incretin-based therapies, GLP-1 receptor agonists have the advantage over DPP-IV

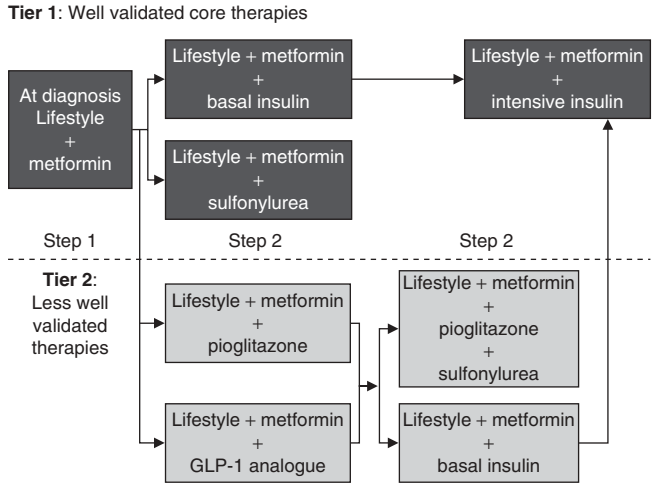

Fig. 4. Algorithm for the treatment of type 2 diabetes mellitus according to a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes (reproduced from Nathan et al.,[60] with permission from the American Diabetes Association). **GLP-1** = glucagon-like peptide-1.

inhibitors in that they do not have to rely on endogenous incretin secretion, and pharmacological levels of exclusive GLP-1 activity are achieved after injection. The efficacy of exenatide is limited by its relatively short half-life and consequent minor effects on fasting glucose levels. Longer-acting GLP-1 agonists, such as liraglutide, exenatide-LAR and other molecules in development, have robust effects on fasting glucose levels and may potentially provide superior efficacy to exenatide.[48,49,61,62] Liraglutide has shown less nausea than exenatide in clinical studies (probably due to smaller fluctuations in peptide concentrations) and only very low antibody titres have been observed with liraglutide due to the sequence similarity with human GLP-1.[17,61] In addition, an important advantage of exenatide and GLP-1 receptor agonists is their ability to facilitate weight reduction. On the other hand, exenatide is an injectable drug, and the incidence of adverse events, particularly nausea, is higher.

7. Conclusion

Exenatide may be particularly beneficial in obese patients with type 2 diabetes, and provides other favourable benefits such as reducing blood pressure and improving lipid profiles. If further clinical studies of long-acting GLP-1 agonists confirm this initial impression of superior efficacy, these drugs could achieve widespread use as second-line, or even first-line, treatments to bring more patients with type 2 diabetes to goal.

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