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REVIEW ARTICLE

Liraglutide: once-daily GLP-1 agonist for the treatment of type 2 diabetes

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SUMMARY

What is known and Objective: **The prevalence of diabetes is increasing worldwide. Over the recent years, new discoveries have led to the development of new pharmacological agents targeting the incretin hormones gastric inhibitory peptide (GIP) and glucagon-like peptide-1 (GLP-1). These agents, called incretin-mimetics, are the newest agents added to the diabetes treatment options. The purpose of this article is to review the relevant literature on the chemistry, pharmacology, pharmacokinetics, metabolism, clinical trials, safety, drug interactions and place in therapy of liraglutide in the treatment of type 2 diabetes.**

Methods: **An extensive search of the literature was performed with liraglutide and NN2211 as key terms. This article presents a review of the literature related to the chemistry, pharmacology, pharmacokinetics, drug interactions and safety and efficacy of liraglutide.**

Results and Discussion: **Liraglutide, a subcutaneously administered GLP-1 agonist, displays phamacodynamic and pharmacokinetic properties that allow for once-daily administration. The agent has been shown to be efficacious as monotherapy, as well as in combination with glimepiride, metformin and/or rosiglitazone, reducing glycoslyated haemoglobin (A1C) between 0·84% and 1·5%. The primary adverse event reported with liraglutide is transient nausea.**

What is new and conclusion: **Liraglutide has been well studied in dual and triple combination therapies with sulfonylureas, metformin and rosiglitazone and appears safe and effective. For patients who cannot tolerate first-line agents, metformin, insulin and sulfonylureas, liraglutide is a reasonable treatment option.**

Keywords: **exenatide, GLP-1 agonist, glucagon-like peptide-1, incretin hormones, liraglutide, NN2211, type 2 diabetes**

INTRODUCTION

Diabetes is disease that is increasing in prevalence all over the world. As of 2010, there are 285 million adults in the world with diabetes. The prevalence rose from 194 million in 2003. By 2030, the number of adults in the world with diabetes is expected to increase to approximately 438 million (1). Type 2 diabetes accounts for approximately 90% of these cases (2).

Glycaemic control, although difficult to maintain, has been shown to prevent microvascular complications (3–5). The effective treatment of type 2 diabetes requires a substantial amount of diabetes self-management and pharmacologic therapy. Drug therapy for type 2 diabetes is complicated because the many components of the disease's pathophysiology, such as – β-cell dysfunction, insulin resistance, incretin hormone malfunction, disruption in renal reabsorption, malfunction in adipose tissues and hypothalamic insensitivity to glucose (6). Although there is quite a substantial

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armamentarium of agents for treating type 2 diabetes, many of which target insulin secretion, insulin sensitivity and hepatic glucose production, few people attain the recommended glycaemic targets (7).

To date, there are eight classes of agents, including insulin, used in the management of type 2 diabetes (Table 1 and Fig. 1). Through various mechanisms of actions, all of the agents reduce blood glucose levels. Sulphonylureas and glinides act on the pancreatic β-cells to cause an increase in insulin release, thereby reducing blood glucose levels (8, 9). Although the mechanism of action of the meglitinide drug class is similar to the sulphonylureas, the glinides have a shorter onset of action and half-life, and, therefore, are used to target post-prandial glucose levels. Both agents can cause about a 2 kg weight gain. Hypoglycaemia is also a risk with these therapies, but less so with glinides. The thiazolidinediones and metformin reduce insulin resistance and hepatic glucose production (10, 11). Metformin is typically weight neutral or causes a small weight loss, and its most common adverse event is flatulence or diarrhoea (12, 13). Thiazolidinediones are peroxiome proliferator-activated receptor-γ agonists and the most frequently reported adverse effects are weight gain and fluid retention. The results of two meta-anal-

Table 1. Antidiabetic agents (excluding insulin) (14)

Drug class	Mechanism of action	Route of administration	Average reduction in A1C[a] (%)
Sulphonylurea	Potentiates insulin secretion	Oral	1–2
Glinide	Potentiates insulin secretion	Oral	0·5–1·5
Thiazolidinediones	Potentiates glucose uptake in skeletal muscle cells; Lessens hepatic glucose production	Oral	0·5–1·45
Metformin	Lessens hepatic glucose production	Oral	1–2
Alpha glucosidase inhibitor	Delays breakdown of oligosaccharides to glucose Delays absorption of carbohydrates	Oral	0·5–0·8
Amylin analogue	Inhibits glucagon secretion; Slows gastric emptying; induces early satiety	Subcutaneous injection	0·5–1·0
Incretin-based therapies DPP-4 inhibitor	Prevents breakdown of GLP-1 and GIP, thereby allowing physiologic effects of GLP-1 and GIP to occur	Oral	0·5–0·8
GLP-1 agonist	Mimics physiologic effects of endogenous GLP-1	Subcutaneous injection	0·8–1·13

[a]As monotherapy.

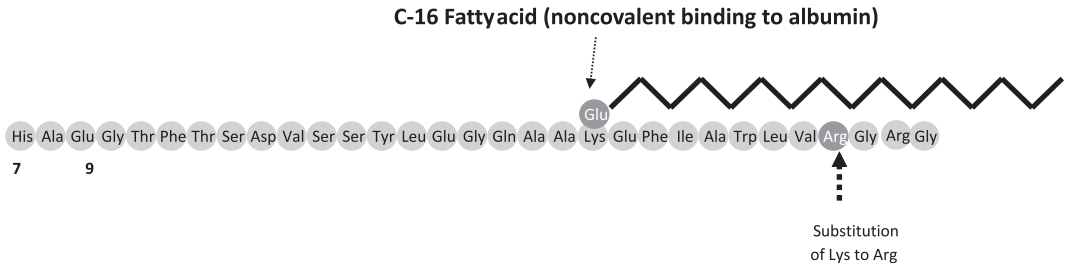

Fig. 1. Liraglutide structure (37).

yses suggest that rosiglitazone increases the risk of myocardial infarction. Therefore, rosiglitazone is not recommended according to the most recent European Association for the Study of Diabetes (EASD); however, pioglitazone is recommended (14). Other drug classes target the components of type 2 diabetes in an indirect manner by slowing the introduction of glucose from the gastrointestinal tract and into the circulation. Alpha-glucosidase inhibitors delay glucose absorption into the circulation by slowing the conversion of oligosaccharides to glucose (15). As a result, post-prandial hyperglycaemia is attenuated. Pramlintide, an amylin analogue, slows gastric emptying and produces early satiety, which results in lower post-prandial glucose levels (16).

A relatively new drug class and treatment strategy for patients with type 2 diabetes is the use of incretin-based therapies. Incretin hormones were discovered after researchers observed that oral ingestion of glucose stimulated a larger secretion of insulin than an intravenous infusion of the same quantity of glucose (17, 18). The two incretin hormones, gastric inhibitory polypeptide (GIP) and glucagon-like peptide-1(GLP-1), are responsible for up to 60% of the post-prandial insulin released in normal glucose tolerant subjects (19). GIP is released from the enteroendocrine K-cells in the duodenum and jejunum and has a half-life of 5–7 min (20, 21). It stimulates glucose-dependent insulin release and regulates fat metabolism (22, 23). Most of GIP receptors are located on the β-cells, and the others are in adipose tissue and central nervous system. The other incretin, GLP-1 is a 31-amino-acid peptide that is released from the L-cells in the ileum and colon. GLP-1 half-life is about 2 min (24). GLP-1 has numerous physiological effects, including stimulating glucose-dependent insulin release, restoring first-phase insulin response, improving β-cell function and increasing β-cell mass, improving insulin sensitivity, delaying gastric emptying and decreasing food intake (25–27). GLP-1 receptors are located in the hypothalamic nuclei, heart, β-cells, heart, lung and kidney (25, 26, 28, 29). GIP and GLP-1 levels begin to rise after ingestion of a meal but before the food reaches the gastrointestinal tract, which suggest that these incretins are regulated by neuronal stimuli (30).

In patients with type 2 diabetes, the incretin effect is significantly diminished or obliterated (18). GIP levels are normal in type 2 diabetes, but the response is defective (18, 31, 32). Although GIP receptors are present on β-cells of patients with type 2 diabetes, the insulinotropic effect of GIP is lost (32, 33). Only small amounts of insulin secretion is observed when high doses of GIP are infused in patients with type 2 diabetes (34). Conversely, GLP-1 levels are lower in patients with type 2 diabetes, and the insulinotropic activity is only slightly reduced rather than lost (33, 35).

Although the physiological effects of GLP-1 make it ideal agent to use for the treatment of type 2 diabetes, its physical properties limit its utility. GLP-1 is rapidly degraded by dipeptidyl peptidase-4 (DPP-4), which accounts for the 2-min half-life, thus making it unsuitable for pharmacologic use (36). To take advantage of GLP-1 effects, DPP-4 must be inhibited or a GLP-1 agonist must be resistant to DPP-4 degradation. In the recent years, DPP-4 inhibitors and DPP-4 resistant GLP-1 agonists have come to market. Sitagliptin (Januvia™, Xelevia™; Merck & Co, Inc, Whitehouse Station, NJ, USA) and vildagliptin (Galvus™; Novartis, Basel, Switzerland) are DPP-4 inhibitors available in EU. Prior to July 2009, the only DPP-4 resistant GLP-1 agonist available in the EU was exenatide (Byetta™; Eli Lilly &Co., Indianapolis, IN, USA; Amlyin Pharmaceuticals, Inc, San Diego, CA, USA). However, in early July 2009, the European Commission granted marketing authorization for liraglutide (Victoza™, Novo Nordisk A/S, Denmark), the second DPP-4 resistant, GLP-1 agonist approved for use in the EU and in the United States. This article reviews the published data on the chemistry, pharmacology, pharmacokinetics, metabolism, clinical trials, drug interactions and place in therapy of liraglutide in the treatment of type 2 diabetes.

METHODS

English-language literature searches of Medline between 1969 and March 2009, International Pharmaceutical Abstracts between 1970 and March 2009, American Diabetes Association Meetings Abstracts, European Association for the Study of Diabetes Abstracts and Canadian Diabetes Association Abstracts were performed using liraglutide and NN2211 as key terms. The reference lists of key publications were also reviewed to identify additional relevant primary literature.

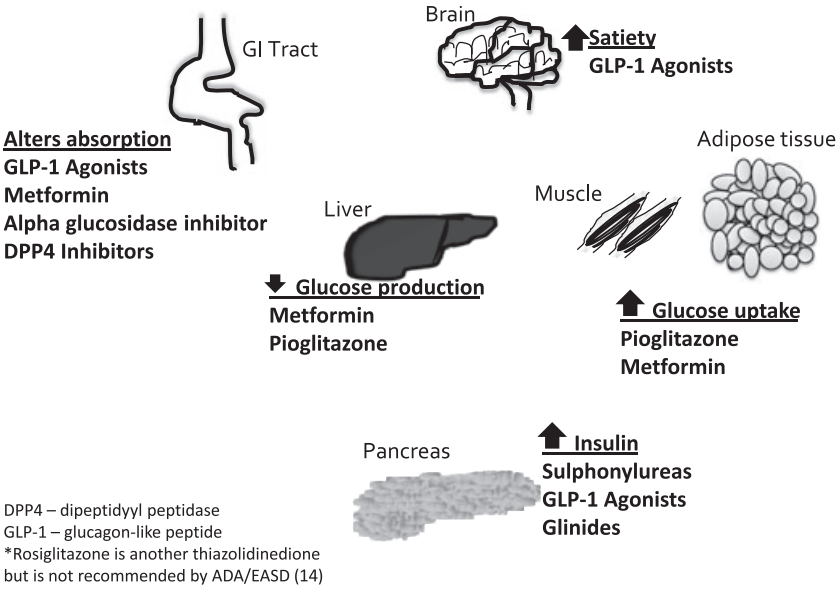

Fig. 2. Mechanism of action of antidiabetic agents.

PHARMACOLOGY AND THERAPEUTICS

Liraglutide, γ-L-glutamoyl (*N*-α-hexadeconyl)-Lys[26], Arg[34]-GLP-1 (7–37), formerly known as NN2211, is formed by substitution of lysine 34 to arginine and the addition of a 16 carbon fatty acid at position 26 using a γ-glutamic acid spacer on GLP-1(Fig. 2) (37). These changes promote aggregation that slows subcutaneous absorption and increases albumin binding, which decreases DPP-4 degradation.

The glycaemic effects of liraglutide mimic those of endogenous GLP-1. In subjects with type 2 diabetes, liraglutide has been shown to increase glucose-dependent first-phase insulin release by 34–118% ($P < 0{\cdot}05$), increase β-cell function by 30–69% ($P < 0{\cdot}01$), and post-prandial glucagon levels by 20% ($P < 0{\cdot}01$) (38–40). In long-term trials in patients, with type 2 diabetes, liraglutide reduced fasting glucose (FG) between 15 and 44 mg/dL ($P < 0{\cdot}05$) and post-prandial glucose (PPG) by 31–49 mg/dL (41–44). Liraglutide reduces PPG levels because of its ability to delay gastric emptying and increase satiety, which has been shown to decrease a single-meal intake by 28% [97% CI (0·6–0·37)] (45). These changes in food intake are likely responsible for the 0·2–2·8 kg weight loss that is reported after liraglutide therapy (41–43, 46–48). One study has shown that the weight loss seen from liraglutide treatment is predominantly adipose tissue rather than lean muscle mass (49).

The effect of liraglutide on insulin sensitivity requires further study. Two studies report an increase in insulin sensitivity with liraglutide. In one 52-week trial, insulin sensitivity was slightly improved by liraglutide therapy by 0·65 ($P = 0{\cdot}0249$) to 1·35% ($P = 0{\cdot}0111$) (41). The clinical significance of this change is doubtful. Insulin sensitivity was also reported in a single dose trial, although the percent of absolute amount change was not reported (27). However, five other studies have reported that insulin sensitivity was either unaltered or not significantly changed by liraglutide (28, 29, 33, 34, 38). Regardless of liraglutide's inability to alter insulin sensitivity, the changes in insulin release and glucagon levels from liraglutide therapy result in lower serum glucose levels. In addition, higher doses of liraglutide reduced hepatic steotosis, which may improve hepatic insulin sensitivity and, therefore, reduce inappropriate hepatic glucose production (49).

In addition to its glycaemic effects, liraglutide has been shown to change cardiovascular biomarkers. *In vitro* trials show that liraglutide attenuates plasminogen activator inhbititor (PAI-1) and vascular cell adhesion molecule induction caused by tumour necrosis factor alpha (TNF-α) stimulation and hyperglycaemia in vascular endothelial cells (50). In one clinical trial, liraglutide lowered

PAI-1 and brain natriuretic peptide. In the same trial, liraglutide had no effect on high-sensitivity C-reactive peptide, adiponectin, leptin, interleukin 6 and TNF-α. Preliminary data show that this new GLP-1 analogue significantly reduces systolic blood pressure (7·9 mmHg vs. 5·2 mmHg placebo, $P < 0{\cdot}0023$), but the change in diastolic blood pressure (2–3 mmHg) was not statistically significant. Very low-density lipoprotein cholesterol levels were the only lipoprotein to change significantly (−22% liraglutide vs. −15% placebo, $P < 0{\cdot}0110$); however, the clinical significance of this data is unclear. Additional data on liraglutide's effects on glycaemic control and cardiovascular outcomes are summarized in the phase III clinical trial section of this article.

As liraglutide is a protein, it is not suitable for oral administration; however, it has been shown to achieve therapeutic levels after subcutaneous administration in the upper arm, abdomen or thigh (51). It is metabolized via enzymatic degradation, similar to other peptides, and no one organ is responsible for the major route of elimination. No intact liraglutide was recovered in urine or faeces (52).

Liraglutide's half-life after subcutaneous administration has been reported to be between 11 and 15 h, and a linear relationship best described the pharmacokinetic and pharmaodymanic effects (53, 54). One study demonstrated that liraglutide's pharmacokinetics are not altered by age or gender (55). Preliminary pharmacokinetic studies in patients with creatinine clearance ranging from >80 (normal) to <30 mL/min showed that standard doses of liraglutide may be used in patients with these levels of renal impairment (56). Liraglutide was also tested in patients with mild, moderate and severe liver disease, assessed by Child–Pugh score (57). Although the results showed that the area-under-the-curve for liraglutide levels, paradoxically, decreased with increasing hepatic impairment, the authors recommended using standard doses of liraglutide for all levels of hepatic impairment. As both of these trials were only published in abstract form, full evaluation of liraglutide's pharmacokinetic parameters and dosing recommendations in liver and renal disease await the publication of peer-reviewed results.

Preliminary research, presented in abstract form only, reports the effects of liraglutide on maximum concentration (C_{max}), time to C_{max} (T_{max}) and area underneath the concentration curve (AUC) of griseofulvin, atorvastatin, lisinopril, digoxin and a combination oral contraceptive containing ethinylestradiol and levonorgestrel (58, 59). C_{max} was 37% higher for griseofulvin, 12–13% lower for both oral contraceptive agents, and between 27% and 38% lower for atrovastatin, lisinopril and digoxin. T_{max} increased between 1 and 2 h for all agents except griseofulvin. Since the 90% CI of the AUC of the liraglutide/placebo ratio of all the agents tested was between 0·80 and 1·25, the authors concluded that there is not a significant drug interaction between liraglutide and any of these agents.

Liraglutide monotherapy

The earliest published clinical trial was a double-blind, randomized, placebo-controlled trial comparing six different once-daily doses of liraglutide (0·045, 0·225, 0·45, 0·6 and 0·75 mg) to glimepiride 1–4 mg and placebo in 193 patients with type 2 diabetes (60). The subjects mean age was 56·6 years and had a baseline A1C of 7·6%. No statistical differences in baseline characteristics were observed. After 12 weeks of therapy, statistically significant reductions in A1C were observed in the 0·6 and 0·75 mg liraglutide groups compared with placebo. Methods and results of compliance assessment were not described. The reductions in A1C in these two liraglutide groups were similar to that seen in the glimepiride group. Fifty-nine per cent of subjects reached an A1C <7% at week 12. Table 2 contains A1C, FG and weight changes observed in this trial.

Another study compared the effects of liraglutide to metformin on glycaemic control, body weight and safety after switching subjects from metformin to one of five doses of liraglutide therapy. In this double-blind, multicentre, double-dummy trial, 210 subjects with type 2 diabetes were randomized to treatment with either 0·045, 0·225, 0·45, 0·6, 0·75 mg of liraglutide per day or metformin 1000 mg twice a day after a 4-week metformin run-in period (61). The design of this trial is not similar enough to the other trials to include the results in Table 2. The average age of the groups ranged between 52·4 and 55·6 years, with the average duration of diabetes ranging from 4·4 to 4·9 years. At baseline, the reported A1C was

Table 2. Summary of clinical trials of liraglutide

Study	Weeks	*N*	Baseline A1C (%)		Observed change relative to baseline			
					A1C (%)	FG (mg/dL)	PPG (mg/dL)	Wt (kg)
Monotherapy								
Madsbad *et al.* (60)	12	193	7·6	Liraglutide 0·045 mg	0·25	13		−0·03
				Liraglutide 0·225 mg	−0·34	−25[a]		−0·74
				Liraglutide 0·45 mg	−0·30	−6		−1·20[a]
				Liraglutide 0·6 mg	−0·70[a]	−39[a]		0·27
				Liraglutide 0·75 mg	−0·75[a]	−33[a]		−0·39
				Glimepiride	−0·74[a]	−47[a]		0·9
				Placebo	not reported			
Garber *et al.* (41) (LEAD-3)	52	746	8·3	Glimepiride	−0·51	−5	−25	1·12
				Liraglutide 1·2 mg once daily	−0·84[b]	−15[b]	−31	−2·05[b]
				Liraglutide 1·8 mg once daily	−1·41[b]	−26[b]	−37[b]	−2·45[b]
Dual-Drug Therapy								
Nauck *et al.* (43) (LEAD-2)	26	1091	8·4	Metformin + liraglutide 0·6 mg once daily	−0·7[a]	−20[a]	−30·6[a]	−1·8[c]
				Metformin + liraglutide 1·2 mg once daily	−1·0[a]	−29[a]	−41·1[a]	−2·6[a,b]
				Metformin + liraglutide 1·8 mg once daily	−1·0[a]	−30[a]	−46·8[a]	−2·8[a,b]
				Metformin + glimepiride	−1·0[a]	−23	−45[a]	1·0
				Metformin + placebo	0·1	7	−10·8	−1·5
Marre (42) (LEAD-1)	26	1041	8·4	Glimepiride + liraglutide 0·6 mg once daily	−0·6[a]	−13[a]	−7·2[a]	0·7[e]
				Glimepiride + liraglutide 1·2 mg once daily	−1·08[a,c]	−28[a]	−45[a, c]	0·3[c]
				Glimepiride + liraglutide 1·8 mg once daily	−1·13[a,c]	−29[a,c]	−49[a, c]	−0·2[c]
				Glimepiride + rosiglitazone 4 mg once daily	−0·44	−16	−32[a]	2·1
				Glimepiride + placebo	0·23	−18	−7·2	−0·1
Triple-drug therapy								
Zinman *et al.* (48) (LEAD-4)	26	533	8·3	Metformin + rosiglitazone + liraglutide 1·2 mg once daily	−1·5[a]	−40[a]	−47[a]	−1·0[a]
				metformin + rosiglitazone + liraglutide 1·8 mg once daily	−1·5[a]	−44[a]	−49[a]	−2·0[a]
				metformin + rosiglitazone + placebo	−0·5	−8	−14	0·60

Table 2. (Continued)

Study	Weeks	*N*	Baseline A1C (%)		Observed change relative to baseline A1C (%)	FG (mg/dL)	PPG (mg/dL)	Wt (kg)
Russell-Jones *et al.* (47) (LEAD-5)	26	581	8·2	Metformin + glimepiride +	−1·3[a,d]	−28[a]		−1·8[a,d]
				liraglutide 1·8 mg once daily	−1·1	−29[a]		1·62
				metformin + glimepiride + glargine	−0·24	10		−0·43
				metformin + glimepiride + placebo				
Buse (46) (LEAD-6)	26	464	8·1–8·2	Liraglutide 1·8 mg + metformin ± sulfonylurea	−1·12[e]	−29[e]		−3·24
					−0·79	−11		−2·87
				exenatide 10 mcg bid metformin ± sulfonylurea				

N, number of patients; A1C, glycosylated haemoglobin; FG, fasting glucose; PPG, post-prandial glucose; wt, weight; rosi, rosiglitazone.
[a]$P < 0{\cdot}05$ vs. placebo.
[b]$P < 0{\cdot}05$ vs. glimepiride.
[c]$P < 0{\cdot}05$ vs. rosiglitazone and glimepiride.
[d]$P < 0{\cdot}05$ vs. glargine.
[e]$P < 0{\cdot}05$ vs. exenatide.

between 6·8% and 7·5%, and average body mass index (BMI) was 33·9–35·0 kg/m^2. Although five patients were removed from the trial because of non-compliance with therapy, no description of the compliance assessment method was given. Treatment with 0·045 mg and 0·22 mg of liraglutide resulted in significant increases in A1C values (1·28% and 0·86% respectively) compared with continuing metformin therapy (no *P* values were reported). The changes in A1C in the 0·45 mg (0·22%), 0·6 mg (0·16%) and 0·75 mg (0·30%) groups were not statistically different than the change observed in the patients continuing metformin (0·09%), (no *P* values were reported). FG values were affected similarly. The two lowest doses of liraglutide resulted in significant increases in FG levels (36 and 35 mg/dL, respectively, $P < 0{\cdot}0001$ for both). However, the increases in fasting plasma glucose levels observed in the other liraglutide groups did not statistically differ from the changes seen with continued metformin therapy ($P \geq 0{\cdot}05$). The observed increases in blood glucoses seen when metformin was switched to liraglutide 0·045 or 0·22 mg are likely because these doses are too low. Weight loss observed in the liraglutide-treated patients ranged from −0·05% to 1·87% was not significantly different from the weight loss seen in the metformin patients (−0·61%).

The aforementioned trials indicate that liraglutide has some promising effects on glycaemic control, is safe, and does not increase weight. These trials, however, were relatively small and short-term. Therefore, it is not possible to establish long-term effectiveness and tolerability of liraglutide using these studies alone. However, as the results of these trials were indeed promising, a series of large longer-term trials, called Liraglutide Effects and Action in Diabetes (LEAD), was undertaken to determine the effects and safety of this GLP-1 agonist.

A double-blind, randomized, double-dummy trial with 746 subjects with type 2 diabetes examined the effects of liraglutide monotherapy on A1C compared with glimepiride over 52 weeks (41). Subjects were either treated with subcutaneous liraglutide 1·2, 1·8 or oral glimepiride 8 mg daily. The mean subject age, BMI and A1C were 53 years, 33·1 kg/m^2, and, 8·3% respectively (62). Subjects were previously treated with all types of oral agents, but the percentages of patients treated with specific agent were not reported. There were no

statistically significant differences in baseline characteristics. A description of compliance assessment and results were not reported. Both doses of liraglutide significantly reduced A1C and fasting plasma glucose more than glimepiride (Table 2). By the end of the trial, 42·8% of patients in the liraglutide 1·2 mg group 50·9% of patients on the liraglutide 1·8 mg, and 27·8% of glimepiride-treated subjects achieved an A1C<7%. Investigators reported that 1·8 mg of liraglutide reduced PPG significantly more ($P = 0·0038$) compared with glimepiride. However, the 1·2 mg dose of liraglutide effects on self-monitored PPG did not differ from glimepiride's effects ($P = 0·1616$). After 52 weeks of treatment, liraglutide reduced weight compared with glimepiride therapy, which resulted in weight gain (Table 2). The 1·2 mg dose of liraglutide reduced systolic blood pressure by 2·1 mmHg ($P = 0·2912$ vs. glimepiride), by 3·6 mmHg with 1·8 mg of liraglutide therapy ($P < 0·0118$ vs. glimepiride), and by 0·7 mmHg with glimepiride treatment. This trial was well designed and large; the limitations were the lack of compliance assessment and no placebo control. However, it may be unethical not to treat patients with type 2 diabetes with at least one glucose lowering agent for 52 weeks. Preliminary results from a second-year analysis showed sustained glycaemic control and weight loss with liraglutide (63).

Dual-drug therapy comparisons

The effects of adding liraglutide to metformin were compared with adding glimepiride or placebo to metformin in a 26-week, double-blind, placebo controlled, multi-national, randomized trial (43). Subjects with type 2 diabetes ($n = 1091$) were randomized to either daily liraglutide 0·6, 1·2 or 1·8 mg subcutaneously, glimepiride 4 mg orally daily or placebo with metformin. The metformin dose was titrated over 3 weeks to a 1000 mg twice a day. Baseline characteristics were not statistically different among the treatment groups. The average subject was 56·8 year old, with an average A1C of 8·4%, and average BMI of 31 kg/m^2 (64). Prior to enrolling in the study 65% of the subjects were treated with any two of the following: metformin (86–93%), sulfonylurea (7–13%) and/or repaglinide (34–38%). No wash-out period and no method or results of compliance assessment were reported. Liraglutide and glimepiride significantly reduced A1C when compared with placebo (Table 2). The two higher doses of liraglutide were shown to be non-inferior to glimepiride [0%, 95% CI (–0·2; 0·2] for both liraglutide doses vs. glimepiride]. The percent of patients achieving an A1C <7% was 28, 35·3, 42·4, 36·3 and 10·8 in the liraglutide 0·6, 1·2, 1·8 mg, glimepiride and placebo groups respectively. Also, self-monitored, 90-min, PPG levels and FG levels were significantly lower in the liraglutide and glimepiride groups compared with placebo (Table 2). Dose-dependent weight loss was observed in the liraglutide groups (Table 2). Compared with baseline, systolic blood pressure was between 2 and 3 mmHg ($P < 0·05$) lower in the liraglutide-treated patients and 0·4 mmHg higher in the glimepiride group. There were no changes in diastolic blood pressure in any treatment group. This large, well-design trial demonstrated that liraglutide was safe and effective in combination with metformin. As metformin is recommended as first-line therapy for type 2 diabetes (14), this study design has particularly useful clinical application. The limitations of this trial are its lack of washout period and the failure of the investigators to assess compliance.

Another trial compared a different two-drug combination. The effects of adding liraglutide, rosiglitazone or placebo to glimepiride in 1041 patients with type 2 diabetes were assessed in this double-blind, double-dummy, randomized, active-control and 26-week study (42). Subjects were treated with liraglutide 0·6, 1·2 or 1·8 mg or rosiglitazone 4 mg/day, and glimepiride 2–4 mg/day. The average subject was 56 years of age, had a BMI between 29·4 and 30·3 kg/m^2, and had diabetes between 6·5 and 6·7 years. The average A1C was 8·4%. A1C, FG, 90-min PPG levels were reduced significantly in all patients (Table 2). The methods of and results regarding compliance assessment were not included. The percent of patients achieving an A1C <7% in the liraglutide 0·6, 1·2 and 1·8 mg treatment groups were 24% ($P < 0·05$ vs. placebo), 35% ($P < 0·05$ vs. placebo and rosiglitazone) and 42% ($P < 0·05$ placebo and rosiglitazone). Rosiglitazone reduced A1C to <7% in 22% ($P < 0·05$ vs. placebo) of subject compared with the placebo group in which only 8% of subjects had final A1C <7%. Weight decreased in patients

receiving 1·8 mg of liraglutide and placebo but increased in the 0·6 and 1·2 mg liraglutide and rosiglitazone group. Although sulfonylureas are not first-line therapy, they are included in the first tier of the European Association for the Study of Diabetes (EASD) algorithm and are commonly used. The fact that the investigation was double-blind, placebo-controlled, randomize and large strengthen the validity of the results. However, the primary limitation was lack of assessment of compliance.

Triple-drug therapy

The most recent EASD consensus statement considered triple-therapy 'less well validated' second step in tier 2 of the two-tier algorithm – the preferred treatment was metformin and intensive insulin. However, liraglutide's effect in a three-drug combination was assessed in three different trials (44, 46, 47). Zinman *et al.* (44) assessed the effects of adding either liraglutide 1·2, 1·8 or placebo to metformin 1000 mg twice a day and rosiglitzone 4 mg twice a day. This 26-week trial was double-blind, randomized, placebo controlled and included 533 patients with type 2 diabetes. The baseline characteristics were not statistically significant different across treatment group. The average subject was 55 years of age, with a BMI between 33·2 and 33·9 kg/m^2, and had diabetes for 9 years. The A1C ranged between 8·4% and 8·6%. Liraglutide was shown to be more effective at reducing A1C, FG, self-monitored 90-min PPG levels, and weight than placebo when added to rosiglitazone and metformin (Table 2). Fewer (28·1%) subjects in the placebo group achieved an A1C <7% than patients on liraglutide 1·2 mg (57·5%, $P < 0·0001$) or 1·8 mg (53·7%, $P < 0·0001$). Small changes, (<5 mmHg), in systolic blood pressure were observed in the liraglutide groups ($P < 0·0001$ vs. placebo), but there were no changes in diastolic blood pressure readings. Similar to the other trials compliance was not assessed, which is a limitation. Although this trial is not as large as some of the others, its study design and length of time for the study contribute to the validity and credibility of the results.

Preliminary findings from adding 1·8 mg of liraglutide, open-label glargine insulin or placebo to metformin and glimepiride were published in an abstract by Russell-Jones *et al.* (47). The 581 subjects participating in this placebo-controlled, randomized 26-week trial had an average age, BMI and baseline A1C was 58 years, 31 kg/m^2, 8·2–8·3% respectively. The dose of liraglutide was increased by 0·6 mg every week until the dose of 1·8 mg was achieved. Insulin glargine was increased twice a week during the first 8 weeks to reach a FG <100 mg/dL per a published protocol (65). After week eight, the dose was increased as necessary. Adding liraglutide to metformin and glimepiride significantly reduced A1C and weight more than placebo or an average dose of 24 units/day of insulin glargine (Table 2). Weight loss was observed in the liraglutide subjects; weight increased in the insulin-treated patients and placebo therapy had a weight neutral effect. This trial was large, and the study design was optimal. The 24 units/day of insulin glargine was similar to the dose (20–23 units) used in a previously published trial that studied the addition of insulin glargine to two oral agents (65). The results of this study, however, may be because insulin glargine was dosed to target FG levels. As post-prandial glucose levels affects A1C more than FG at A1C levels <8·5% (66, 67), liraglutide's ability to lower post-prandial glucose more than insulin glargine may be the reason liraglutide significantly reduced A1C more than insulin glargine in these patients. It will be possible to interpret these results once these preliminary findings are peer-reviewed and published in full.

Additional data are available from a trial that compared liraglutide with exenatide, another GLP-1 agonist, in patients receiving metformin and/or a sulfonylurea (46). Four-hundred and sixty-four subjects with type 2 diabetes, participated in the 26-week, randomized, open-labelled trial. The included subjects had an average baseline A1C of 8·2%, average BMI of 32·9 kg/m^2, and had diabetes for 7·9–8·4 years. Liraglutide 1·8 mg/day decreased A1C and fasting blood glucose significantly more than exenatide 10 μg twice a day (Table 2). Fifty-four percent of the liraglutide-treated patients reached an A1C <7% compared with 43% of those subjects in the exenatide group. Observed weight changes were similar in both groups. This trial was not blinded; therefore, there is greater potential for bias compared with the other studies.

Safety and tolerability

The published trials summarized in this review tested liraglutide in 4649 patients in up to 52 weeks (41–44, 46, 47, 60). All of the trials reported that laboratory values, electrocardiogram and vital signs remained within normal limits (41–44, 46, 47, 60). Gastrointestinal complaints were the most commonly reported adverse effects. There was a wide variation in the rates of nausea, 7–40%. The use of other agents did not seem to affect the rates of reported nausea. Garber *et al.* (41) compared liraglutide monotherapy with glimepiride and the rate of nausea in the liraglutide group was 27–29·5% compared with when liraglutide was combined with metformin (11–19%) and glimepiride (10·5%) (42, 43). However, when liraglutide was combined with metformin and rosiglitazone, nausea was reported by 29–40% of subjects (44). In contrast, when liraglutide, metformin and glimepiride were used together, only 14% of liraglutide-treated subjects reported nausea (47). The rate of nausea did not seem to be affected by the number of agents or the use of metformin, which is known to cause gastrointestinal distress (14). Regardless of the prevalence of nausea, several studies reported that nausea was transient and decreased by the fourth week of the study (41–44, 47). Vomiting occurred in 2–17% of subjects and seemed to correlate with the increased incidence in nausea as studies with a higher rate of nausea reported a higher rate of vomiting. The prevalence of diarrhoea occurred in a similar pattern and was reported by 4–18·7% of liraglutide-treated subjects.

As the presence of glucose is required to for GLP-1 to stimulate insulin release, a low incidence of hypoglycaemia would be expected with liraglutide therapy. Minor hypoglycaemia, defined as blood glucoses lower than 50–55 mg/dL or not requiring third party assistance, was reported by 2·8–12% of liraglutide-treated subjects when a sulfonylurea was not concomitant therapy (41, 43, 44, 46, 60). However, in studies where a sulfonylurea was combined with liraglutide, the incidence of minor hypoglycaemia was 9·2% and 27% (42, 47). Only one study reported major hypoglycaemia, defined as a blood glucose <55 mg/dL, which required third-party assistance, in 2·2% of patients on liraglutide and glimepiride concomitant therapy (47).

As liraglutide is an altered form of GLP-1, there is a potential that it may be antigenic. Only two studies reported performing liraglutide antibody assays and antibodies were detected in 9–13% of subjects treated with the drug (42, 47). One author reported that antibodies did not diminish efficacy (47).

The United States Food and Drug Administration has issued bulletins regarding 30 post-marketing reports of acute pancreatitis and six reports of acute necrotizing or haemorrhagic pancreatitis in patients treated with exenatide, another GLP-1 agonist (68). However, pancreatitis was not reported in any patient in a 3-year, open-label exenatide trial (69). It is likely that the investigators in some of the liraglutide trials examined the prevalence of pancreatitis to determine if it is a class effect of GLP-1 agonists. Three liraglutide studies, containing 1917 liraglutide-treated subjects, reported on the occurrence of pancreatitis (41–43). Pancreatitis was reported in 0·14–0·40% of the liraglutide-treated patients. Pancreatitis occurred in the glimepiride group (0·41%) in one trial compared with 0·14% in the subjects receiving liraglutide (41). Two studies reported that pancreatitis resolved in one patient, in each study, while continuing liraglutide (41, 42). However, a recent retrospective research cohort trial showed that patients with type 2 diabetes are 2·83-fold (95% CI 2·61, 3·06) greater risk of developing pancreatitis (70). Obviously, continued monitoring pancreatitis may be warranted for both GLP-1 agonists until causation is ruled out.

Recently, the US Food and Drug Administration recommended that manufacturers developing new drugs and biologics for type 2 diabetes provide evidence that the therapy will not increase the risk of cardiovascular events, such as a heart attack. This recommendation was part of a new guidance for industry that applies to all diabetes drugs currently under development (71). Sullivan *et al.* (72), using computer modelling, concluded that liraglutide in combination with glimepiride improved survival, cardiovascular mortality, rates of complications and cost compared with glimepiride and rosiglitazone 4 mg. However, the model did not include cost of drug therapy, data from the Veterans Affairs Diabetes Trial (73) and ADVANCE trial (5) and rosiglitazone is not recommended by the EASD for the treatment of type 2 diabetes (14). Therefore, the study is inadequate and the results are not generalizable.

Although blood pressure is a surrogate marker, in a *post-hoc* analysis Nauck *et al.* (43). reported that combination therapy of liraglutide and metformin reduced systolic blood pressure by 2·7 mmHg (95% CI, −5·4 to 0) more than did glimepiride–metformin therapy (74). Patients treated with liraglutide, glimepiride and metformin had a 4·5 mmHg (95% CI, −6·8 to −2·2) lower systolic blood pressure than patients treated with glargine, glimepiride and metformin (74). These changes in blood pressure were seen after 2 weeks of therapy and were independent of weight loss. Further studies are warranted because this data does not provide information cardiovascular outcomes.

PLACE IN THERAPY

In late 2008, the EASD updated their consensus statement on the management of hypoglycaemia (14). The treatment algorithm was divided into two tiers. The first tier had three steps and contains what were considered well-validated core agents. Metformin was recommended as the initial therapy along with lifestyle modification. If A1C was not reduced below 7%, then either a sulfonylurea or basal insulin should be initiated as the second step. The third step was to discontinue the sulfonylurea or basal insulin and switch to basal bolus insulin. Another option after patients have failed metformin monotherapy was the second tier, which contained 'less well-validated therapies'. Adding pioglitazone or a GLP-1 agonist was recommended as part of the second tier. According to the guidelines the main disadvantage of the GLP-1 agonist is nausea, whereas weight loss and a low rate of hypoglycaemia are the main advantages.

Although not mentioned in the EASD s consensus statement, a potential advantage of GLP-1 analogues is their ability to preserve β-cells. It may be possible to preserve remaining β-cell function in patients recently diagnosed with type 2 diabetes, thereby preventing or slowing disease progression. Liraglutide may also be useful in patients with elevated post-prandial glucose levels. Post-prandial glucose levels should be the primary target when the A1C is <8·5% because that is when post-prandial glucose affects the A1C more than FG levels (66, 67). As pancreatitis may be linked to exenatide, another GLP-1 agonist, it may be advisable to avoid liraglutide in patients with a history of pancreatitis until additional data are available.

When initial A1C is between 8·1% and 8·4%, liraglutide 1·2–1·8 mg daily reduces A1C between 0·84% and 1·5%, fasting blood glucose between 15 and 44 m/dL and post-prandial glucose between 31 and 49 mg/dL (41–44, 46, 47, 60). Liraglutide appears to be safe and effective with glimepiride, metformin and rosiglitazone, in dual drug and triple-drug combinations. Direct comparison trials showed that it was superior to monotherapy with metformin, non-inferior to glimepiride 4 mg, when added to metformin therapy, and non-inferior to 24 units of insulin glargine (37, 41, 43). In addition, it significantly reduced A1C more than exenatide (46). However, direct comparative studies with insulin and exenatide have not been published in peer-reviewed journals. Clinical trials indicated that liraglutide improves β-cell function but did not increase insulin sensitivity (41–44, 46). Liraglutide modestly reduced systolic blood pressure (2–3·5 mmHg) but did not alter diastolic readings (41–43). Its advantages were that it rarely caused hypoglycaemia, although combination with a sulfonylurea increased the risk. The effect on weight loss (1·5–3 kg) was an additional benefit observed in clinical trials. The most common adverse event was nausea (7–40%) that lessens after 4 weeks of therapy. Preliminary data shows that it does not affect griseofulvin, atorvastatin, lisinopril, digoxin and a combination oral contraceptive containing ethinylestradiol and levonorgestrel in a clinically significant manner. As liraglutide increased the T_{max} of all of the agents studied, it may be a good idea to separate the administration of liraglutide from these agents when rapid effects are desired, such as with analgesics, as the drug reduces gastric motility and may delay onset of activity of those agents. Patients with renal or hepatic dysfunction will likely not require a dose-adjustment of liraglutide as preliminary data show that the pharmacokinetics of liraglutide are not clinically significantly changed by either disease. Moreover, longer-term trials have shown that liraglutide does not adversely affect liver or kidney function.

WHAT IS NEW AND CONCLUSION

Liraglutide has been well studied in dual and triple combination therapies with sulfonylureas, metfor-

min and rosiglitazone and appears safe and effective. For patients who cannot tolerate first-line agents, metformin, insulin and sulfonylureas, liraglutide is a reasonable treatment option.

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