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REVIEW

Emerging role of GLP-1 receptor agonists in the treatment of obesity

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Abstract: The prevalence of obesity has increased dramatically in recent decades, both in the US and worldwide. Pharmacotherapy can augment the weight-reducing effects of lifestyle modification and can facilitate long-term weight maintenance. However, there is a paucity of pharmacologic agents approved for the treatment of obesity, and the use of existing weight loss medications is frequently limited by contraindications, drug interactions, adverse effects, limited coverage by third-party payers, and cost. In recent years, there has been an increased understanding and appreciation of the role of gastrointestinal hormones in the control of body weight. One such hormone, GLP-1, also plays an important role in glucose homeostasis. GLP-1 receptor agonists, such as exenatide and liraglutide, have been developed and are already approved for the treatment of type 2 diabetes. There has also been interest in the use of GLP-1 receptor agonists for the treatment of obesity in nondiabetic patients. This review explores the potential utility and limitations of exenatide and liraglutide as therapeutic agents for obesity.

Keywords: obesity, GLP-1, exenatide, liraglutide

Introduction

In the US, the prevalence of obesity has increased dramatically in recent decades. Data from the National Health and Nutrition Examination Survey suggest that, in 2007–2008, 34% of American adults had a body mass index (BMI) in the obese range ($\geq 30 \text{ kg/m}^2$), up from just 14% in 1971–1974.^{1,2} Obesity is a chronic metabolic disorder that affects all organ systems. Excess adiposity increases the risk of a variety of comorbid conditions, including type 2 diabetes, hypertension, dyslipidemia, cardiovascular disease, obstructive sleep apnea, nonalcoholic fatty liver disease, osteoarthritis, and some types of cancer. Fortunately, even modest weight loss (eg, 5%–10% of initial body weight) can reduce the severity of existing comorbidities and prevent the development of new ones.^{3–5} However, weight loss also activates a complex system of neuroendocrine signals that increase appetite and reduce energy expenditure, making additional weight loss and maintenance of a lower body weight very challenging.

Pharmacotherapy for obesity

Pharmacotherapy can enhance the weight-reducing effects of lifestyle changes and can facilitate long-term weight maintenance.^{6,7} As a result, weight loss medication can serve as a useful adjunct to lifestyle modification in the treatment of obesity. However, it is important to note that obesity is a chronic condition, and weight regain often occurs if treatment is stopped. Therefore, in patients who choose pharmacotherapy as a tool to aid in weight management, long-term employment of medication

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is usually required. Unfortunately, only two medications, sibutramine and orlistat, are approved by the US Food and Drug Administration (FDA) for long-term use. Several older weight loss medications, including the appetite suppressant phentermine, are approved for short-term use (typically < 12 weeks), but they are frequently used off-label for longer periods. Unfortunately, little is known about the long-term safety of these older medications.

Sibutramine (Meridia[®]) is a centrally-acting norepinephrine, serotonin, and dopamine reuptake inhibitor that works primarily as an appetite suppressant. Orlistat (Xenical[®]), on the other hand, is a lipase inhibitor that acts in the gastrointestinal tract to prevent the absorption of about 30% of ingested fat. Dozens of randomized controlled trials confirm that sibutramine and orlistat are safe and modestly effective for long-term obesity management.^{8,9} Meta-analyses suggest that the average placebo-subtracted weight loss is 4.6% with sibutramine and 2.9% with orlistat.¹⁰ Clinical trials have also demonstrated improvements in triglycerides, high-density lipoprotein (HDL)-cholesterol, fasting plasma glucose, and hemoglobin A_{1c} (HbA_{1c}) with sibutramine and improvements in low-density lipoprotein (LDL)-cholesterol, blood pressure, fasting plasma glucose, and HbA_{1c} with orlistat.^{8–11}

Each of the currently available weight loss agents can be very useful in certain groups of patients, but their clinical utility is often limited by side effects, contraindications, or drug interactions. Sibutramine, for example, can produce small increases in blood pressure and pulse,¹² and its use is contraindicated in patients with uncontrolled hypertension, coronary heart disease, arrhythmias, or a history of stroke. In addition, concomitant use of sibutramine and other serotonergic agents (including many antidepressants) may raise the risk of the rare but potentially fatal serotonin syndrome. Orlistat is minimally absorbed, and systemic side effects are so rare that a lower-dose formulation is now available over-the-counter. However, gastrointestinal symptoms, such as oily stools and fecal urgency, are quite common and can adversely affect patient adherence.¹⁰ Furthermore, orlistat can interfere with the absorption of cyclosporine and amiodarone, and can enhance the effects of warfarin by reducing the absorption of vitamin K. Phentermine, which has sympathomimetic actions, has a side effect profile that is very similar to that of sibutramine, and it too is contraindicated for use in patients with uncontrolled hypertension or cardiovascular disease.

Another barrier to the use of currently available weight loss medications is that their costs are often not covered by health insurance plans. Sibutramine and prescription-strength

orlistat typically cost over \$100 a month, which puts them out of reach for many patients who might benefit from their use. The older weight loss agents, such as phentermine, are typically more affordable because generic formulations are available.

As a result of adverse effects, contraindications, drug interactions, and costs, many patients who might benefit from pharmacotherapy for obesity do not receive this treatment. Additional treatment options are clearly needed. A relatively new class of agents, the glucagon-like peptide 1 (GLP-1) receptor agonist family, has garnered intense interest as a potential therapeutic agent for obesity management.

GLP-1 receptor agonist class

In recent years, there has been an increased understanding and appreciation of the role of gastrointestinal hormones in the control of glucose metabolism and body weight. One such hormone, GLP-1, is produced primarily by enteroendocrine L-cells located in the ileum, although these cells are also present throughout the small intestine and colon.^{13,14} GLP-1 is secreted in response to food intake and the presence of nutrients in the intestinal lumen.¹⁵ GLP-1, along with other gut peptides, is responsible for the phenomenon known as the incretin effect, in which the insulinemic response to an oral glucose load exceeds that elicited by an equivalent amount of glucose delivered intravenously. GLP-1 also plays a role in the ileal brake mechanism, in which the presence of nutrients in the ileal lumen leads to a decrease in gastric motility.

The GLP-1 receptor belongs to the G-protein coupled family of receptors, and it is known to be present in the pancreas, gastrointestinal tract, brain, and other tissues, including the heart.¹⁶ GLP-1 receptors have also been identified in vagal afferent neurons in the rat nodose ganglion, and studies suggest that GLP-1 may act on target organs not only through classic hormonal mechanisms but also through neural pathways.^{17,18} In the pancreas, important actions of GLP-1 include the enhancement of glucose-dependent insulin synthesis and secretion, and stimulation of beta-cell proliferation.¹⁹ GLP-1 also inhibits inappropriate alpha-cell glucagon secretion, which occurs despite hyperglycemia in patients with type 2 diabetes.²⁰ This reduction of glucagon secretion lessens hepatic glucose output and contributes to the antidiabetic effects of GLP-1. Important gastrointestinal effects of GLP-1 include reductions in gastric acid secretion and gastrointestinal motility, both of which are mediated primarily through the vagus nerve.¹⁸ In the brain, GLP-1 receptors are found in the paraventricular nucleus and other hypothalamic regions involved in the regulation of appetite

and body weight.²¹ GLP-1 appears to cross the blood–brain barrier,^{22,23} and postprandial increases in circulating GLP-1 are temporally associated with neural activation in areas of the hypothalamus and prefrontal cortex that are involved in the regulation of feeding behavior.²⁴ However, in rats, the GLP-1-induced increase in hypothalamic neural activity is attenuated by vagotomy, suggesting that the vagus nerve plays a role in the central nervous system response to peripheral GLP-1.²⁵

GLP-1 clearly plays a role in regulating satiety, feeding behavior, and body weight. In rodents, intracerebroventricular administration of GLP-1 reduces food intake.^{26,27} In humans, peripheral administration of GLP-1 has been shown to increase satiety and reduce energy intake.^{28,29} Studies suggest that chronic administration of GLP-1 can reduce body weight in both rats³⁰ and humans.³¹ However, GLP-1 receptor knockout mice exhibit normal feeding behaviors and body weights, suggesting that GLP-1 plays a supporting rather than a primary role amidst the complex and overlapping neurohormonal pathways regulating body weight.³²

In addition to its effects on appetite and food intake, GLP-1 may also play a role in energy metabolism. Studies in rodents suggest that administration of GLP-1 may increase energy expenditure and alter fuel utilization, favoring the oxidation of fat over carbohydrate.^{27,33} These findings are supported by a small ($n = 46$) cross-sectional study in humans, which suggested that higher fasting GLP-1 levels are associated with higher rates of resting energy expenditure and fat oxidation.³⁴ Exogenous administration of GLP-1 was shown to increase resting energy expenditure in a small clinical trial involving 13 healthy adults.³⁵ However, it has also been suggested that GLP-1 administration reduces diet-induced thermogenesis (ie, the energy expended as a direct result of food consumption, digestion, and absorption), potentially because of its effects on gastrointestinal motility.^{36,37}

As compared with lean controls, obese individuals have been shown to have an attenuated secretion of GLP-1 in response to either an oral carbohydrate load³⁸ or a mixed meal.³⁹ Furthermore, Verdich et al demonstrated that diet-induced weight loss increases postprandial GLP-1 secretion in obese volunteers.³⁹ These findings, as well as the observed effects of GLP-1 administration on appetite, food intake, and body weight, as discussed above, stimulated interest in the use of GLP-1 in the treatment of obesity. Data about the antidiabetic effects of GLP-1 (ie, enhancement of beta-cell responsiveness to elevated glucose levels, promotion of beta-cell proliferation, and inhibition of inappropriate

glucagon release during hyperglycemia) also made it an attractive target for the treatment of diabetes. However, native GLP-1 is rapidly metabolized by the enzyme dipeptidyl peptidase-4 (DPP-4), so it has a half-life of 1–2 minutes when administered intravenously or around 1 hour when injected subcutaneously.⁴⁰ As a result, the therapeutic utility of the peptide is limited.

Fortunately, a number of potent GLP-1 receptor agonists have been identified. Two such agents, exenatide and liraglutide, have already been approved by the FDA for the treatment of diabetes, and other agents, including taspoglutide and albiglutide, are in various stages of development.

Exenatide

Exenatide (Byetta[®]) is an injectable GLP-1 receptor agonist that is currently approved by the FDA for the treatment of type 2 diabetes, either as monotherapy or as an adjunct to the use of oral antidiabetic agents. It is a synthetic form of exendin-4, a peptide hormone found in the saliva of the lizard *Heloderma suspectum*, also known as the Gila monster.⁴¹ Exenatide and the naturally occurring exendin-4 are not full GLP-1 analogs, but they are potent agonists of the human GLP-1 receptor, exhibiting the same antidiabetic effects as native GLP-1. Unlike GLP-1, however, exenatide is not metabolized by the enzyme DPP-4, and its reported half-life is 2.4 hours. Exenatide undergoes renal clearance, and its half-life is therefore prolonged in patients with kidney disease.⁴²

Effects on HbA_{1c} and body weight in diabetes

Exenatide has clearly been shown to improve glycemic control in patients with type 2 diabetes while reducing body weight. In numerous randomized trials lasting up to 52 weeks, treatment with exenatide as monotherapy or as an adjunct to oral antidiabetic agents produced mean reductions in HbA_{1c} of up to 1.4% and mean weight losses of up to 3.6 kg, as shown in Table 1.^{43–53} Improvements in both HbA_{1c} and body weight appear to be dose-dependent.^{43–45}

In each of the randomized trials shown in Table 1, exenatide-associated weight loss was progressive for the duration of the study, up to 52 weeks. Buse et al recently published interim analyses of two- to three-year data gathered in open-label extension trials following three 30-week double-blind, placebo-controlled trials.^{53,54} In 238 subjects treated with exenatide for at least two years, HbA_{1c} decreased significantly by 1.1% and body weight decreased significantly by 4.7 kg, on average.⁵⁴ In 217 subjects treated with exenatide for at least three years, HbA_{1c} declined by

Table 1 Summary of randomized trials investigating the effects of twice-daily exenatide on HbA_{1c} and body weight in patients with uncontrolled type 2 diabetes

Study	n	Study design			Duration of study (weeks)	Concomitant diabetes medications	Mean change in HbA _{1c} (%)		Mean change in body weight (kg)	
		Blinding	Control	Design			5 µg bid	10 µg bid	5 µg bid	10 µg bid
*Buse et al ⁴³	377	Triple	Placebo	Parallel	30	SU	-0.5	-0.9	-0.9	-1.6
*Kendall et al ⁴⁴	733	Double	Placebo	Parallel	30	Met + SU	-0.6	-0.8	-1.6	-1.6
*DeFronzo et al ⁴⁵	336	Triple	Placebo	Parallel	30	Met	-0.4	-0.8	-1.6	-2.8
*Heine et al ⁴⁶	551	None	Insulin glargine	Parallel	26	Met + SU	NA	-1.1	NA	-2.3
*Nauck et al ⁴⁷	501	None	Biphasic insulin aspart	Parallel	52	Met + SU	NA	-1.0	NA	-2.5
*Zinman et al ⁴⁸	233	Double	Placebo	Parallel	16	TZD ± Met	NA	-0.9	NA	-2.1
*Barnett et al ⁴⁹	138	None	Insulin glargine	Crossover	16	Met or SU	NA	-1.4	NA	-0.4 (on SU) -2.6 (on Met)
*Moretto et al ⁵⁰	232	Double	Placebo	Parallel	24	None	-0.7	-0.9	-2.8	-3.1
§Bunck et al ⁵¹	69	None	Insulin glargine	Parallel	52	Met	NA	-0.8	NA	-3.6
*Davies et al ⁵²	235	None	Insulin glargine	Parallel	26	2 or 3 oral agents (Met, SU, or TZD)	NA	-1.2	NA	-2.7
*Buse et al ⁵³	464	None	Liraglutide	Parallel	26	Met, SU, or both	NA	-0.8	NA	-2.9

Notes: *Exenatide was administered at a dose of 5 µg bid for 4 weeks and then 5 or 10 µg bid for the duration of the study; §Exenatide was 5 to 20 µg bid or tid, depending upon glycemic control and tolerance; 7% of volunteers received 5 µg bid, 62% received 10 µg bid, and 31% received doses above 20 µg daily.

Abbreviations: HbA_{1c}, glycosylated hemoglobin; Met, metformin; NA, not available; SU, sulfonylurea; TZD, thiazolidinedione.

1.0% and body weight decreased by 5.3 kg, on average.⁵⁵ As in the original placebo-controlled Phase III trials,^{43–45} significant weight loss occurred in the extension trials despite a lack of specific counseling regarding diet, physical activity, and weight management. Interestingly, there was no apparent weight plateau during follow-up, suggesting that exenatide-associated weight loss is progressive for up to three years.

Other benefits

A variety of other beneficial metabolic effects have occasionally but inconsistently been observed in diabetic patients treated with exenatide, particularly with longer-term use. These include improvements in systolic and diastolic blood pressure,^{50,55} LDL-cholesterol,^{43,55} HDL-cholesterol, and triglycerides.⁵⁵ Off-label use of exenatide in patients with the metabolic syndrome (but not diabetes) has been reported; in clinical practice, improvements in waist circumference, blood pressure, total cholesterol, and triglycerides have been seen in these patients.⁵⁶

There are little published data about the effects of exenatide on body weight in nondiabetic patients with obesity. At the 2009 Endocrine Society annual meeting, Trautmann et al presented preliminary data from the first randomized, double-blind, placebo-controlled trial of

exenatide for weight reduction in nondiabetic adults.⁵⁷ In this study, 152 subjects followed a diet and exercise program and were randomized to receive either exenatide 10 µg twice daily or placebo for 24 weeks. At the end of 24 weeks, exenatide-treated subjects experienced a mean weight loss of 5.1 kg (approximately 4.7% of initial weight), which was significant compared with a mean loss of 1.6 kg in placebo-treated subjects. Weight loss was progressive throughout this study, with no apparent weight plateau observed at 24 weeks. Several other clinical trials are now underway to investigate the effects of exenatide in nondiabetic patients, including patients with obesity and polycystic ovary syndrome.

Dosing and administration

The recommended dose of exenatide is 5–10 µg injected subcutaneously twice a day before meals. The manufacturer recommends starting at 5 µg twice a day for one month (to improve tolerability) and then increasing to 10 µg twice a day based on clinical response. Exenatide is currently available as either 5 µg or 10 µg fixed dose prefilled pens, with each pen containing 60 doses. A long-acting release (LAR) formulation of exenatide has been developed for weekly use and is currently in clinical trials but is not yet approved by the FDA.^{58,59} Initial research suggests that

2 mg of exenatide LAR, administered weekly, may improve glycemic control more than twice-daily exenatide, with comparable reductions in body weight.^{58,60} Other formulations of exenatide that are in early phase development include a transdermal patch and nasal spray.

Adverse events

The most common adverse events experienced with exenatide treatment are gastrointestinal in nature. In the Phase III trials of exenatide for type 2 diabetes, nausea was the most common adverse event, occurring in up to 51% of subjects treated with 10 µg bid.^{43–45} Vomiting and diarrhea occurred in up to 14% and 17% of exenatide-treated subjects, respectively. In most patients, these gastrointestinal effects are mild or moderate and rarely lead to drug discontinuation. In the Phase III trials, less than 6% of subjects experienced severe nausea, and less than 4% of subjects discontinued treatment due to nausea. Typically, the incidence of nausea is greatest during the first two months of therapy and declines thereafter. Interestingly, nausea does not seem to contribute significantly to the drug's effects on body weight, because patients who never experience nausea lose similar amounts of weight as those who do.^{43–45} Nausea appears to occur less frequently with the LAR formulation in development, and patient satisfaction may be greater with once-weekly rather than twice-daily dosing.^{58,61} Exenatide is not recommended for use in patients with gastroparesis or other disorders that significantly reduce gastrointestinal motility.

Since the approval of exenatide by the FDA in 2005, there have been postmarketing reports of pancreatitis in exenatide-treated patients.^{62–64} Most cases were apparently mild or moderate in severity, resolving completely upon cessation of the drug. However, rare cases of fatal and nonfatal hemorrhagic or necrotizing pancreatitis have also been reported. Therefore, upon initiation or dose escalation, all patients should be informed about the potential risks and symptoms of pancreatitis. Furthermore, the use of exenatide should be avoided in patients with a history of pancreatitis or significant risk factors for pancreatitis, such as active alcohol abuse, severe hypertriglyceridemia, or symptomatic gallstones.

Coadministration of exenatide and sulfonylureas has been associated with an increased risk of hypoglycemia. In a Phase III trial, up to 36% of patients treated with both exenatide and a sulfonylurea experienced mild to moderate hypoglycemia, compared with just 3% in the placebo group, who continued to have poor glycemic control on a sulfonylurea alone.⁴³ However, when used either as monotherapy or as an adjunct to metformin, exenatide does not increase the risk

of hypoglycemia.^{45,50} In these circumstances, hypoglycemia would not be expected to occur, because GLP-1 receptor agonism modulates insulin and glucagon secretion in a glucose-dependent manner.

Development of antiexenatide antibodies has been observed in up to 49% of subjects treated with exenatide for 30 weeks.^{43–45} Fortunately, antibody formation does not affect glycemic control and does not appear to increase the risk of adverse events. Other common but typically mild adverse events observed in the Phase III trials include dizziness, jitteriness, and headaches.

Contraindications

Exenatide is not recommended for use in patients with severe renal impairment (ie, creatinine clearance < 30 mL/min), including those requiring dialysis, and caution is advised in patients with a history of renal transplant or moderate renal impairment (creatinine clearance 30–50 mL/min). There have been postmarketing reports of increased serum creatinine, renal impairment, acute renal failure, and worsening of chronic renal failure, sometimes requiring dialysis or transplantation.^{64,65} In some cases, affected patients were taking other pharmacologic agents known to affect renal function, such as angiotensin-converting enzyme inhibitors, diuretics, or nonsteroidal anti-inflammatory agents. In some cases, affected patients had nausea, vomiting, or decreased fluid intake, which may have contributed to their worsening renal function.

Drug interactions

Significant drug interactions are relatively rare with exenatide. There have been postmarketing reports of prolonged prothrombin time and increased International Normalized Ratio, sometimes associated with bleeding, in patients on warfarin and exenatide.⁶⁴ Since exenatide delays gastric emptying, it may affect the extent and rate of absorption of oral medications. Therefore, medications that require a threshold concentration for efficacy, such as oral contraceptives and antibiotics, should be taken at least one hour before administration of exenatide. Exenatide has not been studied for use with insulin, and the manufacturer does not recommend concomitant use of these agents. However, off-label use of the combination has been reported.^{66–68}

Patient satisfaction and adherence

Patient adherence to exenatide therapy is generally good, but route of administration, side effects, cost, and insurance coverage can impact on adherence. Some patients may

initially be reluctant to use injectable medications, but the fixed-dose prefilled pen makes administration simple and convenient. Furthermore, many patients report that injections using fine-gauge pen needles are less painful than finger sticks for home blood glucose monitoring. Studies suggest that patients treated with twice-daily exenatide experience significant improvements in treatment satisfaction and reductions in diabetes-related symptoms, including fatigue and symptoms of hypo- and hyperglycemia.^{61,69} However, in the Phase III clinical trials of 30 weeks' duration, 4%–10% of exenatide-treated subjects withdrew due to treatment-emergent adverse events, such as nausea.^{43–45} In clinical practice, discontinuation due to adverse events may be slightly more common.⁷⁰ Cost may be another barrier to treatment, because the retail price of exenatide can approach \$300 per month. Fortunately, in recent years, more third-party payers have included exenatide in their formularies, but some require prior authorization, documentation of inadequate glycemic control with oral agents, or higher patient co-pays. Off-label use (such as with concomitant insulin therapy or in patients without type 2 diabetes) may not be a covered benefit.

Liraglutide

Liraglutide (Victoza[®]) is an injectable GLP-1 receptor agonist currently approved by the FDA for the treatment of type 2 diabetes not controlled by lifestyle modification or oral antidiabetic therapy. Unlike exenatide, liraglutide is a GLP-1 analog, sharing 97% amino acid sequence homology

with native GLP-1. Important modifications to the peptide structure serve to delay its absorption from subcutaneous tissue, make it resistant to DPP-4 degradation, and enable reversible binding to albumin.⁷¹ Over 98% of liraglutide is bound to albumin, and free liraglutide is metabolized by endogenous peptidases. Liraglutide does not undergo significant renal or hepatic clearance. As a result, its reported half-life after subcutaneous administration is 13 hours.

Effects on HbA_{1c} and body weight in diabetes

Liraglutide has been shown to improve glycemic control in patients with type 2 diabetes while reducing body weight. In randomized trials lasting up to 52 weeks, treatment with 1.2–1.8 mg of liraglutide daily as monotherapy or as an adjunct to oral antidiabetic agents produced mean reductions in HbA_{1c} of up to 1.5% and mean weight losses of up to 3.2 kg, as shown in Table 2.^{53,72–77} Earlier trials utilizing lower doses of liraglutide typically reported smaller improvements in HbA_{1c} and body weight.^{78,79} In a head-to-head randomized trial sponsored by Novo Nordisk, 1.8 mg liraglutide once daily produced significantly greater reductions in HbA_{1c} than 10 µg exenatide twice daily.⁵³

In the clinical trials shown in Table 2, weight loss occurred with liraglutide despite a lack of specific counseling regarding diet, physical activity, and weight management. In some of these trials, weight loss appears to have reached a plateau by 12–20 weeks of treatment,^{73,75,77} whereas in another study,

Table 2 Summary of randomized trials investigating the effects of once-daily liraglutide on HbA_{1c} and body weight in patients with uncontrolled type 2 diabetes

Study	n	Study design			Duration of study (weeks)	Concomitant diabetes medications	Mean change in HbA _{1c} (%)		Mean change in body weight (kg)	
		Blinding	Control	Design			1.2 mg daily	1.8 mg daily	1.2 mg daily	1.8 mg daily
*Vilsboll et al ⁷²	165	Double	Placebo	Parallel	14	None	-1.4	-1.45	NA	-3.0
**Garber et al ⁷³	746	Double	Glimepiride	Parallel	52	0–1 oral agents	-0.8	-1.1	-2.0	-2.5
~Nauck et al ⁷⁴	1091	Double	Placebo or glimepiride	Parallel	26	Met	-1.0	-1.0	-2.6	-2.8
**Zinman et al ⁷⁵	533	Double	Placebo	Parallel	26	Met + rosiglitazone	-1.5	-1.5	-1.0	-2.0
~Marre et al ⁷⁶	1041	Double	Placebo or rosiglitazone	Parallel	26	Glimepiride	-1.1	-1.1	+0.3	-0.2
**Buse et al ⁵³	464	None	Exenatide	Parallel	26	Met, SU, or both	NA	-1.1	NA	-3.2
**Russell-Jones et al ⁷⁷	581	Mixed [§]	Placebo or insulin glargine	Parallel	26	Met + glimepiride	NA	-1.3	NA	-1.8

Notes: *Liraglutide doses were 0.65 mg, 1.25 mg or 1.9 mg daily (0.65 mg results not reported here); ** In these trials, liraglutide was initiated at a dose of 0.6 mg daily for 1 week and then increased over 1–2 weeks to a dose of 1.2 or 1.8 mg daily; [§]Estimated mean change in body weight was obtained from a figure in this manuscript, as the mean value was not reported; ~Liraglutide was administered at doses of 0.6, 1.2, or 1.8 mg daily. Results from the 0.6 mg arm are not shown here. Subjects in the 1.2 and 1.8 mg dose arms underwent a dose-escalation period for 2–3 weeks after randomization; § In this trial, patients were randomly assigned to liraglutide, placebo, or open-label insulin glargine.

Abbreviations: HbA_{1c}, glycosylated hemoglobin; Met, metformin; SU, sulfonylurea.

weight loss was progressive for up to 26 weeks.⁵³ Treatment with liraglutide has been shown to reduce visceral as well as subcutaneous adiposity in patients with type 2 diabetes.⁸⁰

Other benefits

In addition to improvements in glycemic control and body weight, liraglutide may have other metabolic benefits in patients with diabetes. Significant reductions in systolic blood pressure^{73–75} and triglycerides^{53,72} have been observed with liraglutide in some studies. A recent meta-analysis of six Phase III clinical trials, reported at the 2009 annual meeting of the Endocrine Society, suggests that liraglutide also lowers total and LDL-cholesterol levels and reduces the prevalence of the metabolic syndrome in patients with diabetes.⁸¹ Furthermore, reductions in plasminogen activator inhibitor 1, an inflammatory biomarker, and B-type natriuretic peptide, a biomarker associated with cardiovascular risk, have been observed in liraglutide-treated patients with diabetes.⁸²

Liraglutide is currently being studied as a potential treatment for obesity in patients without diabetes, although it is not yet FDA-approved for this indication. In a Phase II trial of 20 weeks' duration, 564 nondiabetic obese subjects were randomly assigned to one of four doses of liraglutide (1.2, 1.8, 2.4, or 3.0 mg daily), placebo, or orlistat 120 mg three times daily.⁸³ Approximately one-third of subjects had prediabetes at the time of randomization. During the trial, subjects were instructed to consume a low-fat, 500 kcal/day deficit diet and to increase physical activity as measured using pedometers. Subjects randomized to liraglutide lost significantly more weight than those assigned to either placebo or orlistat. Mean weight loss was 4.8, 5.5, 6.3, and 7.2 kg for the 1.2, 1.8, 2.4, and 3.0 mg doses of liraglutide, respectively, as compared with 2.8 kg with placebo and 4.1 kg with orlistat. In addition, the prevalence of prediabetes was significantly reduced in liraglutide-treated subjects, as compared with those on placebo or orlistat. Improvements in blood pressure were also seen with liraglutide, although these were not consistently greater than improvements seen with placebo or orlistat. In an interim analysis of data from an ongoing 84-week, open-label extension of this Phase II trial, Finer et al reported similar findings, including a reduced prevalence of prediabetes and some improvements in blood pressure with liraglutide.⁸⁴

Dosing and administration

For the treatment of type 2 diabetes, the recommended dose of liraglutide is 1.2 to 1.8 mg injected subcutaneously once daily at any time of day. The manufacturer recommends

starting at 0.6 mg daily for one week to reduce gastrointestinal symptoms during initial titration. The dose should then be increased to 1.2 or 1.8 mg daily, based on clinical response. Liraglutide is currently available as a fixed-dose, prefilled pen delivering doses of 0.6, 1.2, or 1.8 mg.

Adverse events

As with exenatide, the most common adverse events experienced with liraglutide treatment are gastrointestinal in nature. In Phase III trials, nausea was the most common adverse event, occurring in up to 40% of subjects treated with liraglutide.^{53,72–77} Data from one head-to-head trial suggest that nausea is less persistent with liraglutide than with exenatide.⁵³ Researchers reported that the incidence of nausea is greatest during the first month of therapy and declines thereafter. Vomiting and diarrhea occurred in up to 12% and 21% of liraglutide-treated subjects, respectively. In most subjects, these gastrointestinal effects were mild or moderate, typically leading to drug withdrawal in less than 4% of subjects on 1.2 mg daily or up to 11% of subjects on 1.8 mg daily.

Small but statistically significant increases in heart rate (eg, 2–4 beats per minute) have been observed in some of the Phase III clinical trials.^{73,76} In the head-to-head study of liraglutide versus exenatide, increases in heart rate occurred in both groups, although the change was significant only for liraglutide.⁵³ Development of anti-liraglutide antibodies has been observed in up to 13% of treated subjects.^{76,77} Antibody formation does not appear to affect drug efficacy in most patients, but efficacy may be compromised in rare patients with extremely high antibody levels.⁷¹ Patients who develop anti-liraglutide antibodies may be slightly more likely to experience upper respiratory tract infections than antibody-negative patients. Other common but typically mild adverse events observed in the Phase III trials include headaches and fatigue.

Pancreatitis has been observed in the Phase III clinical trials of liraglutide, although it is rare.⁷¹ Therefore, liraglutide should be used cautiously in patients with a history of pancreatitis or significant risk factors for pancreatitis, such as active alcohol abuse, severe hypertriglyceridemia, or symptomatic gallstones.

Combination therapy with liraglutide and an insulin secretagogue may increase the risk of hypoglycemia. In clinical trials, up to 33% of patients treated with both liraglutide and a sulfonylurea experienced mild to moderate hypoglycemia.^{53,76,77} However, when used either as monotherapy or as an adjunct to metformin, liraglutide does not increase the risk of hypoglycemia.^{72,74}

Contraindications

Treatment with liraglutide has been associated with an increased risk of benign and malignant thyroid C-cell tumors in rodents.⁷¹ The clinical relevance of this finding is unknown, because there has been no reported increase in thyroid C-cell tumors, such as medullary thyroid carcinoma, in human subjects. Nevertheless, liraglutide is contraindicated for use in patients with a personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2. Rare cases of papillary thyroid carcinoma have been reported in liraglutide-treated subjects. In most cases, these were reportedly small tumors discovered as a result of protocol-specified thyroid surveillance testing, which is not routinely recommended in clinical practice.

Since liraglutide does not undergo significant renal or hepatic clearance, no dose adjustment is recommended in patients with renal or hepatic impairment. However, there are limited safety data regarding the use of liraglutide in these patients, so it should be used cautiously.

Drug interactions

Like exenatide, liraglutide delays gastric emptying, so may affect the extent and rate of absorption of oral medications. However, no clinically significant effects have been found in clinical pharmacology trials conducted by the manufacturer.⁷¹ Liraglutide has not been studied for use with insulin, and concomitant use of these agents is not recommended.

Patient satisfaction and adherence

As with exenatide, the route of administration, side effects, cost, and insurance coverage would be expected to impact patient adherence with liraglutide treatment. In the head-to-head trial of once-daily liraglutide versus twice daily exenatide, treatment satisfaction was significantly greater in the liraglutide group.⁵³ Liraglutide's dosing schedule (once daily at any time of day) is certainly more convenient than exenatide's current dosing schedule (twice daily before meals). However, approval of an LAR formulation of exenatide for weekly use would likely increase patient satisfaction even more. Since liraglutide has only recently been approved by the FDA, insurance coverage is likely to be an issue for some patients. The retail price of liraglutide can approach \$400 a month for the highest dose.

Other GLP-1 receptor agonists in development

In the future, other GLP-1 receptor agonists may also be available, besides exenatide and liraglutide. Taspo-

glutide is a GLP-1 analog that is currently under study by Roche for the treatment of type 2 diabetes.⁸⁵ A sustained-release formulation has been developed for weekly use. Albiglutide is a long-acting GLP-1 receptor agonist which is under study by GlaxoSmithKline for the treatment of type 2 diabetes.⁸⁶ If approved by the FDA, it would likely be administered once weekly.

Another intriguing strategy in the early phase of development is the employment of peptides which act as dual agonists of both GLP-1 and glucagon receptors, like the naturally-occurring peptide, oxyntomodulin. In rodents, GLP-1 and glucagon receptor coagonists appear to increase energy expenditure, decrease food intake, reduce body weight, improve dyslipidemia, reduce hepatic steatosis, and improve glycemic control.^{87,88}

Conclusion

GLP-1 receptor agonists have proven to be a very useful option in the treatment of type 2 diabetes, particularly in overweight and obese patients. Treatment-associated weight loss can be significant, which sets this class of medications apart from most other antidiabetic agents. In the future, GLP-1 receptor agonists may also play a role in the management of nondiabetic patients with obesity. Given the recent increase in the prevalence of obesity and the paucity of effective pharmacologic therapies, the development of new agents to treat obesity is of critical importance. GLP-1 receptor agonists may have utility, either alone or as part of a multipronged approach to the pharmacologic management of obesity. Unfortunately, the same issues that limit the use of currently approved weight loss medications (ie, adverse effects, contraindications, limited coverage by third-party payers, and cost) may affect GLP-1 agonists as well.

Disclosure

The authors report no conflicts of interest in this work.

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