

Comparison of liraglutide versus other incretin-related anti-hyperglycaemic agents

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The two classes of incretin-related therapies, dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1 RAs), have become important treatment options for patients with type 2 diabetes. Sitagliptin, saxagliptin, vildagliptin and linagliptin, the available DPP-4 inhibitors, are oral medications, whereas the GLP-1 RAs—twice-daily exenatide, once-weekly exenatide and once-daily liraglutide—are administered subcutaneously. By influencing levels of GLP-1 receptor stimulation, these medications lower plasma glucose levels in a glucose-dependent manner with low risk of hypoglycaemia, affecting postprandial plasma glucose more than most other anti-hyperglycaemic medications. Use of GLP-1 RAs has been shown to result in greater glycaemic improvements than DPP-4 inhibitors, probably because of higher levels of GLP-1 receptor activation. GLP-1 RAs can also produce significant weight loss and may reduce blood pressure and have beneficial effects on other cardiovascular risk factors. Although both classes are well tolerated, DPP-4 inhibitors may be associated with infections and headaches, whereas GLP-1 RAs are often associated with gastrointestinal disorders, primarily nausea. Pancreatitis has been reported with both DPP-4 inhibitors and GLP-1 RAs, but a causal relationship between use of incretin-based therapies and pancreatitis has not been established. In clinical trials, liraglutide has shown efficacy and tolerability and resulted in certain significant benefits when compared with exenatide and sitagliptin.

Keywords: DPP-4 inhibitor, GLP-1, linagliptin, liraglutide, saxagliptin, sitagliptin, vildagliptin

Date submitted 1 January 2012; date of final acceptance 11 January 2012

Introduction

Incretin-related therapies have become established as important treatment options for patients with type 2 diabetes (T2D) [1] and the number of available options will increase in the near future. Knowledge about how the current incretin-related anti-hyperglycaemic therapies compare to each other can help health care professionals make informed treatment choices for individual patients.

Patients with T2D have an impaired incretin effect, which appears to be the result of reductions in the insulinotropic and glucagon-suppressive actions of the incretin hormones glucagon-like peptide (GLP-1) and glucose-dependent insulinotropic peptide (GIP) [2,3], although declines in the release of these hormones have also been reported among patients with T2D [2,4]. When these patients receive infusions of GLP-1 to supraphysiological levels, the insulin secretory response improves, glucagon secretion is suppressed and plasma glucose levels can be significantly improved. These effects occur in a glucose-dependent manner, that is, only when glucose levels are elevated, resulting in a low risk of hypoglycaemia [2,5,6].

In addition to improving glucose control, raising GLP-1 levels can provide additional benefits such as slowed gastric emptying, decreased acid secretion, increased feeling of satiety and reduced energy intake [5,7]. In humans, endothelial dysfunction, cardiovascular function and β -cell function also appear to improve with a GLP-1 infusion [8–11], while animal studies suggest that GLP-1 can stimulate expansion of β -cell mass [12], and reduce high blood pressure [13].

As native GLP-1 is degraded rapidly by the enzyme dipeptidyl peptidase-4 (DPP-4), resulting in a half-life of approximately 2 min following intravenous administration [14], its therapeutic use is impractical. Two strategies have been employed to produce incretin-related therapies. One approach is to inhibit the DPP-4 enzyme, resulting in an extended half-life and an increase in circulating endogenous GLP-1 and GIP [3]. The other approach involves the use of agents resistant to the breakdown of DPP-4 that bind to and activate the GLP-1 receptor, thus producing glucoregulatory effects similar to those of GLP-1. This article discusses the clinical profiles and compares the available agents in these two classes.

Pharmacological Differences Between the Incretin-Related Therapies

The GLP-1 receptor agonists (GLP-1 RAs) exenatide, exenatide once weekly (currently only approved in Europe) and liraglutide are peptides, and so they must be given by

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subcutaneous injection: twice daily (BID) for exenatide, within 60 min before the two main meals and at least 6 h apart; once a week on the same day for exenatide once weekly, with or without meals; and once a day for liraglutide, independent of meals. Although both exenatide and liraglutide are GLP-1 RAs, exenatide is a mimetic, discovered in the saliva of the Gila monster (*Heloderma suspectum*), with 53% amino acid sequence identity to the chemical structure of native GLP-1, while liraglutide is an analogue of human GLP-1 with 97% sequence identity [15,16]. Exenatide once weekly is a long-acting formulation of exenatide in which exenatide is encapsulated in microspheres of poly(D,L lactic-co-glycolic acid) for gradual drug delivery [17]. Liraglutide differs from human GLP-1 by the attachment of a palmitic acid via a glutamic acid spacer to lysine at position 26 and by the replacement of lysine at position 34 with arginine [18]. It is thought that the addition of a fatty acid chain to liraglutide's structure allows it to form heptamers when injected, which delay its absorption and binding to albumin, increasing its resistance to DPP-4 degradation and allowing the maximum concentration to be reached at 8–12 h after dosing [19,20]. In contrast, exenatide reaches its median peak concentration in 2 h [21]. Exenatide once weekly takes much longer than either liraglutide or exenatide BID to reach maximum concentrations. After 2 weeks of administering exenatide once weekly, serum concentrations exceed minimal efficacy levels and continue to increase over the next 4–5 weeks if treatment is maintained [22]. Clinical studies have confirmed that administration of exenatide and liraglutide results in dose-dependent decreases in hyperglycaemia through insulinotropic activity and suppression of glucagon secretion, both occurring in a glucose-dependent manner [23–25]. It is probable that there is a greater degree of GLP-1 receptor stimulation with GLP-1 RAs than that resulting from the two- to threefold increase in GLP-1 levels with DPP-4 inhibitors [3,26].

DPP-4 inhibitors are small molecule oral medications. There are presently three available in the USA: sitagliptin (also produced in a single pill combination tablet with metformin), saxagliptin (also produced in a single pill combination tablet with metformin extended release) and linagliptin. All are administered once a day at any time, except for the sitagliptin combination tablet with metformin, which should be taken BID with meals. In Europe, another twice-daily DPP-4 inhibitor can be prescribed: vildagliptin (also produced in a single pill combination tablet with metformin). Sitagliptin is a phenethylamine type of DPP-4 inhibitor, saxagliptin and vildagliptin are cyanopyrrolidines [27] and linagliptin is xanthine-derived [28]. As saxagliptin has been observed in the laboratory to have strong interactions with the DPP-4 residues Ser⁶³⁰, Glu²⁰⁵ and Glu²⁰⁶, which are essential to the enzyme's catalytic activity, its potency for inhibiting DPP-4 activity is considered more robust than that of both sitagliptin and vildagliptin [29]. However, linagliptin has demonstrated more potent inhibition of DPP-4 when compared to the three other DPP-4 inhibitors under identical *in vitro* conditions [28]. Despite the variable selectivity of the currently approved DPP-4 inhibitors, it is not clear that there is much clinical difference between them. When the recommended dosages for each agent

are administered, the median time to maximum concentration (T_{max}) ranges from 1.7 h for vildagliptin, 2 h for saxagliptin, 1–4 h for sitagliptin and 1.5 h for linagliptin [30–33]. The duration of DPP-4 inhibition is claimed to be 24 h with each agent; however, the terminal half-life ($t_{1/2}$) for saxagliptin is 2.5 h, vildagliptin 3 h and sitagliptin 12.4 h [30–32]. Although the $t_{1/2}$ for linagliptin is more than 100 h, the effective half-life is approximately 12 h [33]. Only saxagliptin appears to have a pharmacologically active metabolite, 5-hydroxy saxagliptin, which has a $t_{1/2}$ of 3.1 h [31]. Following an oral glucose load or meal in patients receiving DPP-4 inhibitors, there is an increase in the circulating levels of GLP-1, a reduction in glucagon concentration and an enhancement of glucose-dependent insulin secretion [30–33].

In the USA, all FDA-approved incretin-related therapies can be used as monotherapy (although liraglutide is not recommended as first-line therapy) [33–37], whereas in Europe, only sitagliptin and linagliptin are approved as monotherapy [32,33]. In the USA, all incretin therapies can also be used in dual- or triple-combination therapy with metformin, sulphonylureas (SUs) and/or thiazolidinediones (TZDs) [33–37]. However, the approved combined uses for these medications are slightly more restrictive in Europe, where liraglutide is approved for use in dual combination with metformin or SUs, and exenatide, exenatide once weekly, saxagliptin, sitagliptin and vildagliptin can be used in dual combination with metformin, SUs or TZDs [20–22,30–32]. Exenatide, exenatide once weekly, liraglutide and sitagliptin are the only medications approved for triple combination with metformin and a SU or metformin and a TZD in Europe [20–22,32]. In both the USA and Europe, sitagliptin is approved for use with insulin [32,34]. The efficacy and safety of exenatide and liraglutide in conjunction with insulin have been studied, but only limited approval has been obtained for any combined use [38,39]. In one 52-week trial, the addition of insulin detemir to liraglutide 1.8 mg and metformin in patients not achieving glycaemic targets led to decreases in HbA1c, sustained weight loss and a small increase in minor hypoglycaemic events [40,41]. In Europe, insulin detemir may be used as add-on therapy with liraglutide [41]. The addition of liraglutide in patients already treated with insulin has not been evaluated. The addition of exenatide following insulin optimisation led to reduction in HbA1c, modest weight decrease, and no change in hypoglycaemic rates [38], and in the USA, exenatide may be added on to therapy with insulin glargine [37]. No clinical data exist regarding the combination of GLP-1 RAs with DPP-4 inhibitors in treatment, and it is not currently recommended, although data in minipigs have suggested pharmacokinetics are unlikely to be altered by the combination [42].

As expected from the glucose-dependent pharmacokinetic/pharmacodynamic profiles of incretin-related therapies, these treatments lead to improvements in controlling postprandial glucose (PPG) excursions [43,44]. Twice-daily exenatide is dosed to peak with PPG concentrations, unlike the other incretin-related therapies, which can be administered without regard for meals, and provides control of postprandial excursions. In head-to-head trials, exenatide taken BID lowered PPG to a greater degree than did sitagliptin and liraglutide [15,45].

Improvements in HbA1c demonstrated by incretin-related therapies when added to metformin are shown in Table 1.

Effect on Gastric Emptying and Weight Loss

Patients with T2D often have accelerated gastric emptying, which may contribute to postprandial hyperglycaemia [51,52]. Native GLP-1 can slow accelerated emptying of the stomach, and slow acid secretion, contributing to its effectiveness at lowering postprandial hyperglycaemia [5,7]. Clinical studies have shown that GLP-1 RAs produce the same effect as native GLP-1 [23,25], while DPP-4 inhibitors do not [3,53]. The slowed gastric emptying observed with GLP-1 RAs may contribute to the most common gastrointestinal adverse event reported for these therapies in clinical trials—nausea [15,26,43,54–58]. Gastrointestinal problems are infrequent with DPP-4 inhibitors [43].

In clinical studies, GLP-1 RAs have been associated with dose-dependent weight loss [49,59], which has generally not been seen with DPP-4 inhibitors as the latter appear to be weight neutral [60,61]. The higher levels of GLP-1 receptor stimulation achieved with GLP-1 RAs compared to DPP-4 inhibitors are probably the most important factor responsible for the difference in weight effect observed between the two kinds of incretin-related therapies. The weight loss is not primarily related to gastrointestinal symptoms such as nausea, as many patients using GLP-1 RAs lose weight without experiencing any nausea, and the nausea is typically transient [3]. Preclinical and clinical studies have shown that these agents can dose-dependently increase the feeling of satiety, reduce meal size and lower energy intake in a manner similar to that of native GLP-1 [7,62–65]. The slowed gastric emptying by GLP-1 RAs may also contribute to increased satiety, reduced food intake and the resultant clinically significant weight loss shown in many studies with these agents [3,15,49,55–59]. Another possible explanation for the lack of DPP-4 inhibitor effect on weight may be that they inhibit cleavage of the gut hormone peptide YY (PYY). Thus, levels of intact PYY1-36, which stimulates food intake, may be increased while levels of the active form PYY3-36, which reduces food intake, may be reduced [66]. In a recent 12-week, randomised, placebo-controlled clinical study, sitagliptin decreased PYY3-36 while increasing intact PYY1-36. The depression of PYY3-36 levels with DPP-4 inhibitor treatment may thus contribute to the difference in weight response between the two classes of incretin therapies [67]. Lastly, in animal studies, GIP has been linked with obesity through over-nutrition [68]. Although T2D is a GIP-resistant state [2], DPP-4 inhibitors raise GIP, as well as GLP-1 levels, by blocking the activity of the DPP-4 enzyme. This effect might also have a role in the weight neutrality (rather than weight loss) that is seen with DPP-4 inhibitor therapy.

Blood Pressure, Lipids and Other Cardiovascular Risk Factors

GLP-1 RAs have been shown to potentially improve multiple cardiovascular risk factors, but the mechanisms for these additional benefits are not yet clear. Reductions in systolic

blood pressure (SBP) that range from 2 to 7 mmHg over 26 weeks [15,54–58] have been shown to precede any significant weight loss [69,70]. Nevertheless, weight loss due to GLP-1 RAs may be responsible for some of the observed improvements in blood pressure and lipids. After 3.5 years of exenatide twice-daily treatment in an open-label study, the quarter of patients who experienced the largest mean weight loss (12.8 kg) also had the greatest mean changes in SBP (–8.1 mmHg), high-density lipoprotein cholesterol (HDL-C) (+10.6 mg/dl) and triglycerides (–104.2 mg/dl) [71], despite a minimal correlation in the overall results between weight loss and lipid changes [71]. Further research is necessary to determine the actual mechanism for the improvements in blood pressure and the modest but significant reductions in triglycerides, free fatty acids and low-density lipoprotein cholesterol (LDL-C) levels that result with GLP-1 RA treatments [54,72]. Furthermore, a significant increase in HDL-C has also been observed in some studies [71,73]. In addition, liraglutide treatment has been associated with significant decreases in levels of plasminogen activator inhibitor-1 (PAI-1) and B-type natriuretic peptide (BNP), both of which are considered as biomarkers for cardiovascular risk [74]. The mechanisms for these effects also remain to be shown.

Although blood pressure reductions and improved lipid profiles similar to those experienced with GLP-1 RAs have not been seen in clinical trials of DPP-4 inhibitors, a modest reduction in blood pressure has been reported for sitagliptin and vildagliptin in some studies [75–77]. A retrospective study of a large cohort database that found an association between sitagliptin treatment, slight weight loss and a small decrease in blood pressure suggests that the improvement in blood pressure is connected to weight loss [75], but more study of the underlying mechanism is warranted because DPP-4 inhibitors are generally considered weight neutral [60,61]. A few studies have also recorded modest beneficial effects on lipid profiles with sitagliptin and vildagliptin [75,78,79]. One clinical trial concluded that vildagliptin may counteract postprandial hyperlipidaemia by either decreasing chylomicron production, increasing chylomicron clearance or both [79]. However, more study is needed to confirm whether DPP-4 inhibitors have any clinically significant effect on lipid levels and, if so, what the possible mechanisms would be.

Metabolism and Tolerability

Sitagliptin and saxagliptin are eliminated from the body primarily through renal excretion; in Europe, sitagliptin is therefore not recommended for patients with moderate and severe renal insufficiency, while saxagliptin can be used in these populations with dose reductions. In the USA, lower dosages should be used with both treatments in these populations [31,32,34,35]. Exenatide is also eliminated by the kidneys, and both exenatide twice daily and once weekly are contraindicated in patients with severe renal impairment or end-stage renal disease (CrCl <30 ml/min) [21,22,37]. Caution should also be applied when initiating or escalating doses of exenatide BID in patients with moderate renal impairment (CrCl 30–50 ml/min) and in patients with renal transplantation [21,37]. Exenatide once

Table 1. Study results of incretin-related therapies among patients inadequately controlled with metformin in randomised trials. Except for the Pratley study comparing sitagliptin and liraglutide, results shown come from separate trials with different patient population characteristics and unique study designs, and do not support direct comparison.

	Trial duration (weeks)	Met dosage (mg/day)	Therapy addition	Participants (n)	Duration of diabetes (years)	Baseline HbA1c (%)	Baseline BMI (kg/m ²)	Δ HbA1c from baseline (%)	Δ weight from baseline (kg)	Frequency of mild or moderate hypoglycaemia (%)	Three most common AEs per therapy reported	Rescue medication if allowed
Linagliptin [46]	24	≥1500	5 mg OD	523	>5 years n = 285 (56%)	8.1	29.9	-0.5	All changes similar to placebo effect	0.4*	Hyperglycaemia, nasopharyngitis, influenza	SU
Saxagliptin [47]	24	≥1500	2.5 mg OD	192	6.7	8.1	31.7	-0.6	All changes similar to placebo effect	7.8†	Diarrhoea, nasopharyngitis, headache	Patients immediately enrolled in trial extension and received open-label pio 15 mg (which could be titrated upward to 45 mg) in addition to blinded study medication plus open-label met
			5 mg OD	191	6.4	8.1	31.2	-0.7		5.2†	Nasopharyngitis, diarrhoea, headache	
			10 mg OD	181	6.3	8.0	31.1	-0.6		3.9†	Nasopharyngitis, headache, URTI	
			Placebo OD	179	6.7	8.1	31.6	+0.1		5.0†	Diarrhoea, nasopharyngitis, headache/influenza	NS
	26	≥1500	100 mg OD	219	6.3	8.5	32.6	-0.9‡	-1.0	5% minor§	Nasopharyngitis, headache, nausea/diarrhoea	
Vildagliptin [48]	52	≥1500	50 mg BID	1396	5.7	7.3	31.8	-0.4	-0.2	1.7§	Nasopharyngitis, headache, dizziness	Pio
			Glimepiride ≤6 mg/day	1393	5.8	7.3	31.7	-0.5	+1.6	16.2† (included are 10 severe hypoglycaemic incidents requiring assistance)	Tremor, hyperhidrosis, hypoglycaemia	
Exenatide [49]	30	≥1500	5 µg BID	110	6.2	8.3	34	-0.4	-1.6	4.5¶	Nausea, URTI, diarrhoea	NS
			10 µg BID	113	4.9	8.2	34	-0.8	-2.8	5.3¶	Nausea, diarrhoea, vomiting	
			Placebo BID	113	6.6	8.2	34	+0.1	-0.3	5.3¶	Nausea, URTI, diarrhoea	

Table 1. Continued.

Trial duration (weeks)	Met dosage (mg/day)	Therapy addition	Participants (n)	Duration of diabetes (years)	Baseline HbA1c (%)	Baseline BMI (kg/m ²)	Δ HbA1c from baseline (%)	Δ weight from baseline (kg)	Frequency of mild or moderate hypoglycaemia (%)	Three most common AEs per therapy reported	Rescue medication if allowed
Exenatide once weekly [50]	26	Stable doses throughout study	160	6	8.6	32	-1.5	-2.3	1	Nausea, diarrhoea, vomiting	NS
Liraglutide [26]	26	2 mg once weekly	166	5	8.5	32	-0.9	-0.8	3	Nausea, diarrhoea, headache	NS
		100 mg sitagliptin 45 mg pio	165	6	8.5	32	-1.2	2.8	1	URTIs, peripheral oedema, diarrhoea	
Liraglutide [26]	26	1.2 mg OD	225	6.0	8.4	32.6	-1.2	-2.9	5% minor§ (in addition one major hypoglycaemic event requiring assistance occurred)	Nausea, nasopharyngitis, headache	NS
		1.8 mg OD	221	6.4	8.4	33.1	-1.5	-3.4	5% minor§	Nausea, nasopharyngitis, headache/diarrhoea	

AE, adverse event; BG, blood glucose; BID, twice daily; BMI, body mass index; met, metformin; NS, not specified; OD, once daily; pio, pioglitazone; SU, sulphonylurea; UTI, urinary tract infection; URTI, upper respiratory tract infection.

* Plasma glucose ≤3.9 mmol/l.

† Mild or moderate reported hypoglycaemia did not require treatment or medical intervention.

‡ The relative high efficacy of sitagliptin in comparison to the efficacy of the other DPP-4 inhibitors occurred in patients who were not treatment naive.

§ Plasma glucose <3.1 mmol/l.

¶ Symptoms reported consistent with possibly confirmed plasma glucose <3.3 mmol/l.

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