review article

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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

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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].

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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

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 Ser^{630}, Glu^{205} and Glu^{206}, 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].

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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

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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
			Placebo OD	177	>5 years n = 93 (53%)	8.0	30.1	+0.2		2.3*	Hyperglycaemia, nasopharyngitis, UTI/headache/BG increased	
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	
	26	≥1500	100 mg OD	219	6.3	8.5	32.6	−0.9‡	−1.0	5% minor§	Nasopharyngitis, headache, nausea/diarrhoea	NS
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	

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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	2 mg once weekly	160	6	8.6	32	−1.5	−2.3	1	Nausea, diarrhoea, vomiting	NS
			100 mg sitagliptin	166	5	8.5	32	−0.9	−0.8	3	Nausea, diarrhoea, headache	
			45 mg pio	165	6	8.5	32	−1.2	2.8	1	URTI, peripheral oedema, diarrhoea	
Liraglutide [26]	26	≥1500	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 DDP-4 inhibitors occurred in patients who were not treatment naïve.

§Plasma glucose <3.1 mmol/l.

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

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weekly is not recommended in patients with moderate renal impairment [22]. Vildagliptin, which is eliminated primarily by the kidneys, is not recommended in patients with moderate, severe or end-stage renal disease [30], nor should it be used in patients with hepatic impairment, including those who have alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels three times the normal upper limit. Liver function tests for ALT and AST should be performed before treatment, and periodically thereafter [30].

In contrast to the other incretin-related therapies, linagliptin is mainly eliminated unchanged via faeces, so no dose reduction is recommended in the case of renal or hepatic impairment [33,80]. Liraglutide degrades in the body by enzymatic activity like GLP-1, only much more slowly [81], and should therefore pose a lower risk of accumulation in the case of renal disease.

In a study of 30 patients who were given a single dose of liraglutide 0.75 mg, no clear change in pharmacokinetics was evident among the 24 patients with varying degrees of renal dysfunction compared with the 6 patients with normal renal function [82]. In a meta-analysis of 2783 patients, of whom 486 receiving liraglutide treatment had mild renal impairment, similar decreases in HbA1c occurred in patients with mild renal impairment (60 ml/min $\leq$ CrCl $\leq$ 89 ml/min), compared with patients with normal renal function (CrCl > 89 ml/min) who received either liraglutide 1.2 or 1.8 mg as monotherapy or in combination with an oral anti-hyperglycaemic for 26 weeks [83]. Changes in serum creatinine were not significantly different from baseline for either treatment groups [83]; however, there is limited experience with liraglutide in patients with moderate renal impairment and no experience in patients with severe renal impairment. Consequently, liraglutide is not recommended for these two patient groups in Europe [20]. In the USA, there have been post-marketing reports of acute renal failure and worsening of chronic renal failure, usually in association with nausea, vomiting, diarrhoea or dehydration, which may sometimes require haemodialysis, so caution is warranted when initiating or escalating doses in patients with renal impairment [36].

Very few drug interactions have been noted with incretin therapies [84]. When used with an SU, a reduction in the dosage of the SU should be considered to reduce the risk of hypoglycaemia with most incretin-related therapies [20–22,31–33]. In the case of vildagliptin, dosage should be reduced when combined with a SU [30]. When saxagliptin is used concurrently with a strong cytochrome P450 3A4/5 (CYP3A4/5) inhibitor, for example, ketoconazole, plasma concentrations of saxagliptin will increase, so a dosage reduction of saxagliptin is recommended in the USA, although none is advised in Europe [31,35]. Linagliptin's efficacy may be reduced by a strong P-gp or CYP3A4 inducer, such as rifampicin, so an alternative treatment is advised [33]. Unlike some other pharmacologic treatments for diabetes, particularly SUs and insulin, hypoglycaemia is less common with incretin-related therapies [40,85]. Use of DPP-4 inhibitors may be associated with an increased risk of infections, such as urinary tract infections, nasopharyngitis, upper respiratory tract infections and headaches [33–35,43]. With exenatide and liraglutide a few cases of angiooedema have been reported [20,21]. More common with GLP-1 RAs are gastrointestinal adverse events (primarily nausea), which are usually transient and occur mostly during the first 4 weeks of treatment [54,56]. A phase 2 study that used a validated scale system, the Gastrointestinal System Rating Scale (GSRS), to evaluate the quantity and intensity of gastrointestinal adverse events from the patients' perspective confirmed that such disorders are usually transient and of mild-to-moderate severity [86]. Titrating the dosage of GLP-1 RAs according to instructions can help to reduce the incidence of gastrointestinal effects. Pancreatitis has been reported with both DPP-4 inhibitors and GLP-1 RAs [20–22,32,33]; however, patients with T2D have a nearly three-times greater risk of developing pancreatitis than individuals without diabetes [87], and a causal relationship between use of incretin-based therapies and pancreatitis has not been established. The evidence regarding the risk for pancreatitis with incretin-related therapies compared with non-incretin-related therapies is, at present, conflicting [88–91].

In rodent studies, thyroid C-cell tumours have resulted from exposure to high doses of exenatide and liraglutide [20–22,92], but the relevance of these findings for humans is not yet known [84]. The ability of GLP-1 RAs to stimulate calcitonin release appears to be species-dependent. In studies with non-human primates exposed for up to 87 weeks with doses 60-fold greater than recommended for humans and in clinical trials with up to 2 years' exposure, increased calcitonin release did not occur with liraglutide treatment [92]. In a meta-analysis of clinical trials lasting no more than 2 years with over 5000 patients receiving either liraglutide or control therapy, 3-month measurements of serum calcitonin showed that mean serum calcitonin concentrations were at the low end of the normal range in all treatment groups at baseline and remained low throughout the trials [93]. The European label for liraglutide cautions patients against possible thyroid adverse events [20], while the US prescribing instructions state that liraglutide is contraindicated in patients who have a personal or family history of medullary thyroid carcinoma or of Multiple Endocrine Neoplasia syndrome type 2 (MEN 2) [36]. Monitoring with serum calcitonin tests or thyroid ultrasounds is not advised by the American Association of Clinical Endocrinologists (AACE) because it may increase unnecessary procedures, because of low test specificity for serum calcitonin and a high background incidence of thyroid disease. AACE also does not recommend obtaining baseline serum calcitonin levels or thyroid ultrasounds unless thyroid nodules are detected on initial physical examination, or if nodules occur during administration of liraglutide [94]. Thyroid nodules in liraglutide-treated patients should be managed in the usual manner [94].

Clinical Trials Comparing DPP-4 Inhibitors and GLP-1 RAs

So far, few trials have been conducted directly comparing the two classes of incretin-related therapies. The available data are included here.

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Exenatide taken BID was compared with sitagliptin in a 4-week, randomised, crossover study in 61 patients with T2D with an average HbA1c of 8.5 ± 1.2% and an average 2-h PPG of 245 ± 65 mg/dl [45]. Patients received exenatide (5 µg BID for 1 week, then 10 µg BID for 1 week) or sitagliptin [100 mg once every morning (QAM)] for 2 weeks. After 2 weeks, patients crossed over to the alternate therapy. At the end of the study, the change in fasting plasma glucose (FPG) was similar with the two therapies (−15 ± 4 mg/dl for exenatide vs. −19 ± 4 mg/dl for sitagliptin; $p = 0.3234$), but the 2-h PPG levels were significantly lower with exenatide (−133 ± 6 mg/dl vs. −208 ± 6 mg/dl, respectively; $p < 0.0001$). When patients switched from exenatide to sitagliptin, 2-h PPG rose by 73 ± 11 mg/dl, and when patients switched from sitagliptin to exenatide, 2-h PPG decreased by 76 ± 10 mg/dl. Compared to sitagliptin, exenatide showed greater improvement in the insulinogenic index of insulin secretion (ratio 1.50 ± 0.26; $p = 0.0239$), produced a greater reduction in postprandial glucagon [$AUC_{0-240\ min}$ (pg min/ml) geometric LS mean ratio 0.88 ± 0.03; $p = 0.0011$] and total caloric intake (−134 ± 97 kcal vs. +130 ± 97 kcal; $p = 0.0227$), and slowed gastric emptying to a greater extent [acetaminophen $AUC_{0-240\ min}$ (mg min/dl) LS mean ratio 0.56 ± 0.05; $p < 0.0001$]. With both treatments, mild-to-moderate gastrointestinal symptoms were the most common adverse events reported.

In a double-blind comparison of exenatide once weekly with sitagliptin or the TZD treatment pioglitazone, patients were randomised to 2 mg exenatide as a once-weekly injection plus oral placebo once daily (n = 160), 100 mg sitagliptin once daily plus once-weekly placebo injection (n = 166), or 45 mg pioglitazone once daily plus once-weekly placebo injection (n = 165) for 26 weeks [50]. Baseline HbA1c levels were 8.6, 8.5 and 8.5%, respectively. At trial end, the reduction in HbA1c was −1.5% with exenatide once weekly, −0.9% with sitagliptin and −1.2% with pioglitazone with treatment differences of −0.6% (95% CI [−0.9; −0.4]; adjusted $p < 0.0001$) for exenatide once weekly vs. sitagliptin, and −0.3% (95% CI [−0.6; −0.1]; adjusted $p = 0.0165$) vs. pioglitazone. Weight change with exenatide once weekly was −2.3 kg, compared to −0.8 kg with sitagliptin ($p = 0.0002$) or +2.8 kg with pioglitazone ($p < 0.0001$) [50]. There was also a significant difference in reduction of SBP between exenatide once weekly and sitagliptin (−4 mmHg; $p = 0.0055$), but none between exenatide once weekly and pioglitazone [50]. The most common adverse events patients experienced for exenatide once weekly and sitagliptin were nausea (24 and 10%, respectively) and diarrhoea (18 and 10%, respectively). With pioglitazone the most common events were upper-respiratory tract infections (10%) and peripheral oedema (8%) [50].

The other direct comparison between GLP-1 RAs and DPP-4 inhibitors occurred in a 26-week trial in which 658 patients inadequately controlled with 1500 mg or more of metformin were randomised to receive, in addition, 1.2 mg liraglutide, 1.8 mg liraglutide or 100 mg sitagliptin, all administered once daily [26]. Daily dosages of liraglutide were escalated at 0.6 mg intervals weekly, from a 0.6 mg starting dose to the final dose of either 1.2 or 1.8 mg. The mean HbA1c baselines

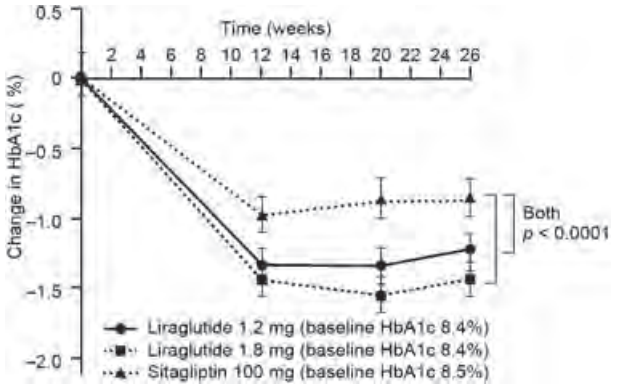

Figure 1. Change in HbA1c values from baseline over 26 weeks for 1.2 and 1.8 mg liraglutide, both once daily, and 100 mg sitagliptin once daily. Adapted with permission from Ref. [26].

in each of the three groups were 8.4% (liraglutide 1.2 and 1.8 mg) and 8.5% (sitagliptin). Liraglutide produced greater reductions in overall HbA1c and FPG than sitagliptin. HbA1c levels declined −1.50% for liraglutide 1.8 mg, −1.24% for liraglutide 1.2 mg and −0.90% for sitagliptin ($p < 0.0001$ for both liraglutide doses vs. sitagliptin; figure 1). The estimated treatment difference (ETD) in comparison to sitagliptin was −0.60% (95% CI [−0.77; −0.43]) for liraglutide 1.8 mg and −0.34% (95% CI [−0.51; −0.16]) for liraglutide 1.2 mg (both $p < 0.0001$). FPG declined more with liraglutide 1.2 and 1.8 mg (−1.87 mmol/l [−34 mg/dl] and −2.14 mmol/l [−39 mg/dl], respectively) than with sitagliptin (−0.83 mmol/l [−15 mg/dl]; $p < 0.0001$ for both liraglutide doses vs. sitagliptin). Weight loss was also greater with liraglutide (−3.4 and −2.9 kg for 1.8 and 1.2 mg, respectively, and −1.0 kg for sitagliptin; $p < 0.0001$ for both liraglutide doses vs. sitagliptin). The most common adverse events experienced with liraglutide were gastrointestinal, primarily nausea, which lasted for a median of 13 days with liraglutide 1.2 mg and 8 days with liraglutide 1.8 mg. Infections, primarily nasopharyngitis, were the most common adverse events in the sitagliptin group, but occurred with similar frequency in both sitagliptin- and liraglutide-treated patients.

Results of the Diabetes Treatment Satisfaction Questionnaire (DTSQ) administered to a subgroup of study participants (n = 505) showed treatment satisfaction increased in all three groups. Compared with the sitagliptin group (n = 170), treatment satisfaction was significantly greater in the liraglutide 1.8 mg group (n = 171; $p = 0.03$), despite the fact that liraglutide is an injectable therapy while sitagliptin is an oral one. Treatment satisfaction was similar between sitagliptin and the liraglutide 1.2 mg group (n = 164; $p = 0.4$) [95]. In a 26-week extension of this study, weight, FPG and HbA1c changes during the prior 26 weeks were generally maintained at 52 weeks [96]. After the 52-week study, 419 patients previously on sitagliptin therapy were switched to liraglutide 1.2 or 1.8 mg for an additional 26 weeks [97], and additional improvements in HbA1c, FPG and weight loss were observed. HbA1c decreased by 0.24% in the liraglutide 1.2 mg group ($p = 0.006$) and by 0.45% in the liraglutide 1.8 mg group

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($p = 0.0001$); FPG declined by -0.84 ± 0.2 mmol/l ($p = 0.0004$) and -1.42 ± 0.3 mmol/l ($p < 0.0001$), respectively, and weight change was -1.64 ± 0.37 kg ($p < 0.0001$) and -2.48 ± 0.44 kg ($p < 0.0001$), respectively. DTSQ scores for the 26-week extension also rose for 102 analysed patients who switched to liraglutide 1.2 ($n = 54$) or 1.8 mg ($n = 48$), indicating a greater treatment satisfaction with the injectable therapy [98]. The increase in DTSQ scores for patients who transferred to liraglutide 1.2 mg treatment was significant ($p = 0.0170$).

The results of similar studies comparing the currently available GLP-1 RAs and DPP-4 inhibitors when added to the regimen of patients with T2D with inadequate glycaemic control on metformin are summarised in Table 1. It is worth noting that the greatest reductions in HbA1c observed with DPP-4 inhibitors have been reported in combination with metformin among treatment-naïve patients [99,100]. The higher efficacy of DPP-4 inhibitors plus metformin in these studies is probably related to some additional increment effect of metformin on GLP-1. Algorithms for the treatment of T2D developed by a panel convened by AACE and the American College of Endocrinology and by writing groups from the American Diabetes Association and the European Association for the Study of Diabetes can assist with prescribing of GLP-1 RAs and DPP-4 inhibitors in a clinical setting [1,101].

Clinical Trials Comparing GLP-1 RAs

A few trials have compared the efficacy and tolerability of the two formulations of exenatide. In the first part of the 30-week Diabetes Therapy Utilization: Researching Changes in A1C, Weight and Other Factors Through Intervention with Exenatide Once Weekly (DURATION-1) study, 148 patients were randomised to 2 mg exenatide once weekly and 147 were randomised to 5 µg exenatide BID for 4 weeks, then 10 µg for the remaining 26 weeks [17]. Concurrent T2D treatments were allowed during the study: metformin was used by 77 and 69%, an SU by 37 and 37%, and a TZD by 15 and 17% of patients in each group, respectively [17]. Mean HbA1c at baseline was 8.3% in both groups. After 30 weeks, HbA1c had declined significantly more with exenatide once weekly (1.9 vs. 1.5%; $p = 0.0023$). Reductions in weight (−3.7 kg vs. −3.6 kg) and SBP (−4.7 mmHg vs. −3.4 mmHg) were similar. Nausea was the most common adverse event in either group (26.4 vs. 34.5%), while injection site pruritus was the second most common event with exenatide once weekly (17.6%), and vomiting with exenatide twice daily (18.6%). Withdrawals due to adverse events during the trial were 6.1 and 4.8%, respectively.

After the first 30-week stage of the DURATION-1 trial, 258 patients continued into a 22-week open-label extension: 128 patients remained on exenatide once-weekly treatment, whereas 130 switched from exenatide BID to once weekly [102]. At the end of 52 weeks, patients in the first group maintained their improvement in HbA1c and the other group made further progress. The change from baseline HbA1c for patients who remained on exenatide once weekly at 30 weeks was −2.1% [102]. At 52 weeks, the change in baseline was −2.0%. For patients who switched treatments, change in baseline HbA1c at 30 weeks was −1.8%. At 52 weeks, their change from baseline HbA1c was also −2.0%. Change from baseline in weight (−4.1 kg vs. −4.5 kg) and SBP (−6.2 mmHg vs. −3.8 mmHg) continued to be comparable between groups [102]. Treatment-related adverse events in the extension were similar to those in the first stage.

Following the 22-week extension, a 52-week open-label extension was added onto the DURATION-1 trial. Of the 295 patients, 216 (73%) were randomised during the first stage and followed for a total of 2 years [103]. At the end of that period, these patients maintained improvements from baseline of −1.7% in HbA1c, −2.6 kg in weight and −3.0 in SBP.

The efficacy and tolerability between exenatide once weekly and exenatide BID were also compared in a 24-week trial, known as DURATION-5 [104]. Mean HbA1c at baseline for the 129 patients randomised to exenatide once weekly was 8.5% and was 8.4% for the 123 patients randomised to exenatide BID. Mean change in HbA1c after 24 weeks was significantly greater for the exenatide once-weekly group (−1.6 vs. −0.9%; $p < 0.0001$). Similar reductions in weight occurred in both groups (−2.3 kg vs. −1.4 kg). Only the exenatide once-weekly group had a significant change in SBP from baseline (−2.9 mmHg). Nausea was the most frequently reported adverse event in both groups, and it occurred with more frequency in patients taking exenatide twice daily (35 vs. 14%).

Results directly comparing the efficacy and tolerability of exenatide and liraglutide have been published from only one trial and its extension [15,105]. In the 26-week study, known as the Liraglutide Effect and Action in Diabetes 6 (LEAD-6) trial, patients with T2D who were failing treatment with metformin, SU, or both were randomly assigned to liraglutide 1.8 mg once daily ($n = 233$) or exenatide 10 µg BID ($n = 231$) [15]. At study end, overall HbA1c values decreased by 1.12% with liraglutide and 0.79% with exenatide, for an ETD of −0.33% (95% CI −0.47; −0.18; $p < 0.0001$; figure 2).

Liraglutide decreased FPG significantly more than exenatide [ETD −1.01 mmol/l (18.18 mg/dl; 95% CI −1.37; −0.65 mmol/l); $p < 0.0001$], but exenatide decreased PPG

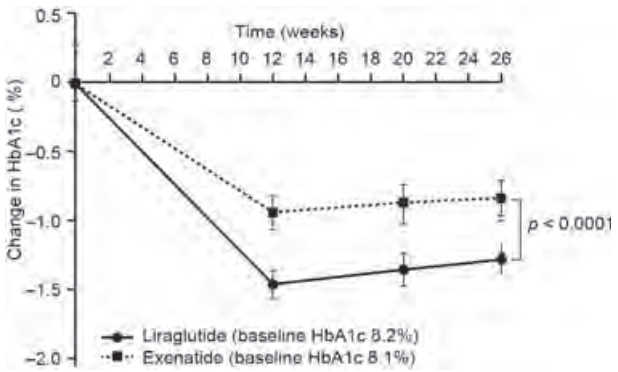

Figure 2. Change in HbA1c values from baseline over 26 weeks between 1.8 mg liraglutide once daily and 10 µg exenatide twice daily. Adapted with permission from Ref. [15].

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more than liraglutide after breakfast [ETD 1.33 mmol/l (23.94 mg/dl; 95% CI 0.80; 1.86 mmol/l); $p < 0.0001$] and dinner [ETD 1.01 mmol/l (18.18 mg/dl; 95% CI 0.44; 1.57 mmol/l); $p = 0.0005$], when its plasma concentrations would be highest. Weight loss was not statistically significantly different between treatments (−3.24 kg for liraglutide and −2.87 kg for exenatide; $p = 0.22$), nor were reductions in blood pressure. Decrease in SBP was 2.51 mmHg for liraglutide and 2.00 mmHg for exenatide ($p = 0.64$). Minor hypoglycaemia was less common with liraglutide than with exenatide (26 vs. 34%) and occurred mainly in patients treated with SUs. Both drugs were well tolerated, and the most common adverse event, nausea, occurred initially in a similar percentage of patients treated with liraglutide and exenatide. However, nausea was less persistent in patients treated with liraglutide and was present among a smaller proportion of liraglutide-treated patients at the end of the study compared with exenatide-treated patients (3 vs. 9%; $p < 0.0001$). The homeostasis model assessment of β-cell function (HOMA-β) increased significantly more with liraglutide vs. exenatide (32.12 vs. 2.74%, ETD 29.37% [95% CI 16.81; 41.93]; $p < 0.0001$).

All patients who completed the 26-week trial ($n = 389$) enrolled in the 14-week trial extension during which patients originally randomised to liraglutide continued treatment ($n = 202$), while those previously using exenatide were switched to liraglutide ($n = 187$) [105]. At the end of the 14-week extension, significant improvements were observed among patients switched to liraglutide in HbA1c values (−0.32%; $p < 0.0001$), SBP (−3.8 mmHg; $p < 0.0001$), weight (−0.9 kg; $p < 0.0001$) and HOMA-β (14.5%; $p \leq 0.001$) [105]. A post-hoc analysis of the 14-week extension showed that even patients who responded well to exenatide could benefit from switching to liraglutide. During the extension, 93% of patients who reached the AACE HbA1c target of ≤6.5% with exenatide remained at target after switching to liraglutide and experienced a further mean HbA1c reduction of 0.3%. Among patients who failed to reach this target with exenatide, 25% achieved it after switching to liraglutide and had an HbA1c reduction of 0.7% [106]. Treatment satisfaction, as measured by the DTSQ, improved significantly among patients switched from exenatide to liraglutide ($p = 0.0131$) [107], in agreement with DTSQ results from the main study in which 94% of liraglutide-treated patients expressed satisfaction with their treatment compared with 86% of those receiving exenatide ($p = 0.0176$) [107].

The greater efficacy and tolerability demonstrated by liraglutide 1.8 mg in comparison with exenatide could relate to the duration of action difference between the compounds. Liraglutide has been shown to possess a longer duration of action and a more steady pharmacokinetic and pharmacodynamic profile than exenatide [108], which could result in prolonged duration of GLP-1 receptor activation.

The efficacy and safety of exenatide once weekly in comparison with liraglutide have been tested in only one trial (DURATION-6). In a 26-week, open-label, randomised trial, 450 patients received liraglutide and 461 patients received exenatide once weekly [109]. Mean HbA1c at baseline was 8.5%. At end of trial, reduction in HbA1c was greater among patients receiving liraglutide (−1.48% vs. −1.28%). Patients on liraglutide therapy also experienced more weight loss (−3.58 kg vs. −2.68 kg). There were similar decreases in SBP in each group (−3.5 mmHg vs. −2.5 mmHg). The most common adverse events in the trial were nausea, which was more frequent with liraglutide (20.4 vs. 9.3%), diarrhoea (13.1 vs. 6.1%) and vomiting (10.7 vs. 3.7%). Slightly more patients receiving liraglutide discontinued the study because of adverse events (5.3 vs. 2.6%).

The formation of antibodies is an issue of potential concern with GLP-1 RAs. Anti-liraglutide antibodies have been reported in trials at a rate of up to 13% [54], with an average of 9% [20], compared with a rate of 38% for anti-exenatide antibodies in studies of that agent [21]. Antibodies do not appear to alter the glycaemic efficacy of liraglutide [20]; however, high levels of anti-exenatide antibodies may reduce the glycaemic response to exenatide BID [21,110].

Conclusions

Incretin-based agents represent a valuable addition to anti-hyperglycaemic therapy by offering glycaemic efficacy with low risk for hypoglycaemia because of their glucose-dependent enhancement of insulin secretion and suppression of glucagon secretion. Clinical trial results suggest that GLP-1 RAs may provide more effective glucose-lowering than DPP-4 inhibitors. They are also associated with weight loss and evidence of some blood pressure reduction. DPP-4 inhibitors, on the other hand, are orally administered and are generally not associated with the increase in gastrointestinal adverse events, mainly nausea, observed with GLP-1 RAs. To date, tolerability of DPP-4 inhibitors has been quite good, although there have been reports of hypersensitivity reactions and an increased risk for some infections. Patients with renal or hepatic insufficiency should not use vildagliptin, and exenatide is not recommended in patients with severe renal impairment or end-stage renal disease.

The LEAD programme regulatory clinical trials demonstrated liraglutide's efficacy and tolerability in combination therapy with up to two oral anti-hyperglycaemic medications. Liraglutide 1.2 and 1.8 mg treatment achieved and maintained HbA1c reductions of 0.84–1.5% across the LEAD-1-6 trials [111], in addition to significant reductions in FPG and PPG after three daily meals. Hypoglycaemia risk was low with liraglutide, and its use resulted in weight loss that appeared to increase with increasing baselinebody mass index (BMI). Liraglutide was also found to be associated with SBP reductions.

Liraglutide 1.8 mg, administered with a once-daily meal-independent injection, was shown in the LEAD-6 trial to reduce HbA1c more effectively than exenatide with a lower risk for hypoglycaemia and a more rapid decrease in the frequency of nausea. However, exenatide showed greater reduction in post-breakfast and post-dinner glycaemic excursions. When compared with exenatide once weekly in DURATION-6, liraglutide treatment resulted in greater glycaemic control and weight loss. In the study by Pratley et al. liraglutide 1.2 and 1.8 mg produced significantly greater reductions in HbA1c, FPG and weight loss than sitagliptin [26]. Treatment satisfaction was also greater in patients treated with liraglutide (1.8 mg) than in patients treated with sitagliptin.

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Conflict of Interest

Dr Blonde's institution has received grant or research support from Eli Lilly, Novo Nordisk and sanofi-aventis; he has been a speaker for AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Merck, Novo Nordisk and Santarus and has been a consultant for Amylin, AstraZeneca, Bristol-Myers Squibb, GlaxoSmithKline, Johnson & Johnson, Merck, Novo Nordisk, Orexigen, sanofi-aventis, Santarus and VeroScience. Dr Blonde's late wife's estate contains shares of Amylin and Pfizer stocks.

Dr Montanya has participated in advisory panels for Intartis and Novo Nordisk and has been a speaker for AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Merck Sharpe & Dohme and Novo Nordisk.

Drs Blonde and Montanya both wrote and amended the manuscript comprehensively prior to submission.

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