GLP-1 receptor agonists vs. DPP-4 inhibitors for type 2 diabetes: is one approach more successful or preferable than the other?

S. Brunton

SUMMARY

Background: In patients with type 2 diabetes (T2D), incretin-based therapies improve glycaemic control with low incidence of hypoglycaemia and without weight gain, both advantages over traditional add-ons to metformin. Dipeptidyl peptidase-4 (DPP-4) inhibitors are administered orally and provide a physiological increase in glucagon-like peptide-1 (GLP-1) levels, while GLP-1 receptor agonists (GLP-1RAs) are injectable and deliver pharmacological levels of GLP-1RA. This review aims to distinguish between GLP-1RAs and DPP-4 inhibitors, and discuss when each may be favoured in clinical practice. **Methods:** A MEDLINE search, limited to human clinical trials and using the search criteria 'GLP-1RA' or 'DPP-4 inhibitor', identified seven head-to-head studies and one relevant post hoc analysis (all a GLP-1RA vs. the DPP-4 inhibitor sitagliptin). In combination with treatment algorithms, product prescribing information and personal clinical experience, these studies were used to compare the efficacy and suitability of GLP-1RAs and DPP-4 inhibitors in patients with T2D. **Results:** In head-to-head clinical trials, GLP-1RAs provided greater glycaemic control, weight loss and overall treatment satisfaction vs. the DPP-4 inhibitor sitagliptin. Transient nausea was more frequent with GLP-1RAs and should be addressed through patient education and an incremental dosing approach. Current treatment algorithms recommend incretin-based therapy use after metformin failure, but local guidance may restrict their use. **Conclusion:** GLP-1RAs provide superior glycaemic control and weight loss vs. DPP-4 inhibitors in patients with T2D. DPP-4 inhibitors may sometimes be preferred to a GLP-1RA if weight is not a concern, oral administration is a desirable feature or when a GLP-1RA cannot be tolerated.

Primary Care Metabolic Group, Charlotte, NC, USA

Correspondence to:
Stephen Brunton, Primary Care Metabolic Group, 15603 McCullers Ct, Charlotte, NC 28227, USA
Tel.: +1 704 752 6663
Fax: +1 704 752-9441
Email: ozdoc@aol.com

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Introduction

Traditional therapies available to patients with type 2 diabetes (T2D) after metformin failure [sulphonylureas (SUs), thiazolidinediones (TZDs)] are often associated with drawbacks such as weight gain, hypoglycaemia or poor long-term efficacy. The incretin-related therapies dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists (GLP-1RAs) not only improve glycaemic control with a low risk of hypoglycaemia but can also have beneficial non-glycaemic effects such as avoidance of weight gain, reduced blood pressure and improvements in beta-cell function and cardiovascular risk biomarkers (1–3).

From personal experience, it appears that there is a misconception among some clinicians that DPP-4 inhibitors are essentially orally administered GLP-1RAs. This review aims to distinguish between the two treatment classes.

Incretin physiology

The incretins are a group of hormones produced by the gastrointestinal system that enhance insulin secretion in a glucose-dependent manner; the combined incretin response accounts for 50–70% of total postprandial insulin production (4,5). The two main human incretins are GLP-1 and glucose-dependent insulinotropic peptide (GIP). In addition to direct insulinotropic action, animal data suggest that incretin hormones may also have protective effects on the beta-cell by enhancing proliferation and resistance to apoptosis (6). GLP-1 also promotes satiety and inhibits glucose-dependent glucagon secretion, as

well as reducing hepatic glucose production (6,7). Within the gut, GLP-1 exerts a motility-inhibiting effect and slows gastric emptying (6).

In patients with T2D, the response to GIP is impaired. Unlike GLP-1, GIP infusion in patients with T2D does not amplify the late-phase insulin response to glucose (8,9). Furthermore, the addition of GIP to a concurrent GLP-1 infusion not only provides no further glycaemic benefit but also antagonises GLP-1-induced glucagon suppression (9). Therefore, incretin-based therapeutic intervention has focused on GLP-1. However, native GLP-1 has limited pharmacological value because of its short half-life (1–2 min), attributable to degradation by the peptidase enzyme DPP-4 (10). Two strategies have been employed to elevate and sustain GLP-1-mediated effects over prolonged periods: inhibition of DPP-4, which extends the half-life of endogenous GLP-1, and is therefore dependent on endogenous GLP-1 production (DPP-4 inhibitors); and use of GLP-1RAs resistant to DPP-4 degradation that can provide supraphysiological stimulation of the GLP-1R. The therapeutic potential of DPP-4 inhibitors and GLP-1RAs is dependent on their different modes of action.

DPP-4 inhibitors and GLP-1RAs: what is the difference?

DPP-4 inhibitors are small molecular-weight drugs that inhibit ≥ 90% of DPP-4 activity and are orally administered on a once-daily (OD) basis [vildagliptin twice daily (BID)] (11,12). There are currently three Food and Drug Administration (FDA)-approved DPP-4 inhibitors: sitagliptin, saxagliptin and linagliptin. In the European Union (EU), a fourth, vildagliptin, is also available.

The GLP-1RAs are peptide-based therapies and therefore, such as insulin, require subcutaneous injection to avoid degradation by gastrointestinal enzymes. There are currently three approved DPP-4-resistant GLP-1RA therapies: exenatide, a GLP-1-like xenopeptide and two GLP-1RAs – liraglutide, a human GLP-1 analogue, and the recently approved exendin-4-based agent lixisenatide. Exenatide and lixisenatide are synthetic forms of the naturally occurring peptide exendin-4 and both share approximately 50% sequence identity with native GLP-1 (13,14). Exenatide is available as a BID or once-weekly (OW) formulation where the latter comprises exenatide encapsulated in microspheres of poly (D,L lactic-co-glycolic acid) for gradual drug delivery (15). Lixisenatide is administered OD (16). Liraglutide is a human GLP-1 analogue that shares 97% amino acid sequence identity with native GLP-1. Liraglutide reversibly binds to albumin, increasing plasma half-life and allowing OD dosing (17). Unlike exenatide and lixisenatide, which are predominantly eliminated by glomerular filtration with subsequent proteolytic degradation, liraglutide is largely metabolised prior to excretion, with no specific organ identified as a major route of elimination (16,18,19).

The main patient-perceived difference between DPP-4 inhibitors and GLP-1RAs is likely to be their mode of administration: oral (DPP-4 inhibitors) vs. injection (GLP-1RAs). Although it is believed that patients generally oppose injectable therapies, evidence suggests that this is not always the case, especially if the injectable therapy has greater efficacy (20–22).

Efficacy of DPP-4 inhibitors and GLP-1RAs in clinical trials

In clinical trials, comparable HbA1c reductions of 0.4–0.7% have been reported with sitagliptin (100 mg OD), vildagliptin (50 mg BID), saxagliptin (5 mg OD), or liniagliptin (5 mg OD) monotherapy for 26 weeks (23). GLP-1RAs (liraglutide 1.2 or 1.8 mg OD, exenatide 10 μg BID, exenatide OW, or lixisenatide 20 μg OD), by comparison, result in HbA1c reductions of 0.6–1.9% following 24/26/30 weeks of treatment as dual (+metformin) or triple (+metformin + SU/TZD) therapy (24–29). Comparing the individual GLP-1RAs, liraglutide 1.8 mg has been shown to provide greater reductions in HbA1c than both exenatide BID (−1.12% vs. −0.79%; $p < 0.0001$) and exenatide OW (−1.48% vs. −1.28%) in head-to-head studies (30,31).

GLP-1RAs are typically associated with weight loss (1–3 kg after 26/30 weeks), whereas DPP-4 inhibitors are generally weight-neutral, again possibly reflecting the limited increase in GLP-1R stimulation with DPP-4 inhibitors (23,25,32,33). Direct comparisons of the GLP-1RAs have suggested that liraglutide 1.8-mg treatment may result in greater weight loss than exenatide BID [−3.24 vs. −2.87 kg; estimated treatment difference (ETD) −0.38 kg (95% CI −0.99 to 0.23); $p = 0.22$] and exenatide OW [−3.58 vs. 2.68 kg; ETD 0.90 kg (95% CI 0.39–1.40); $p < 0.001$] (30,31). Because of their glucose-dependent mechanism of action, the risk of hypoglycaemia is low with both GLP-1RAs and DPP-4 inhibitors. However, the risk of hypoglycaemia is higher when either is used in combination with a SU (24,34–38).

Studies of GLP-1RAs in Asian populations have shown reductions in HbA1c that are comparable to or greater than those seen in global large randomised trials (39). Likewise, clinical evidence suggests that DPP-4 inhibitors exhibit greater HbA1c-lowering efficacy in Asians than in other ethnic populations (40). The mechanisms underlying these effects

remain unclear, although they may potentially be caused by differences in pathophysiology of T2D among Asian patients, particularly in relation to body weight (39,40). However, as yet, no head-to-head studies have been conducted that compared the use of GLP-1RAs and DPP-4 inhibitors in Asian populations.

Aim of the review

Numerous clinical trials have compared the efficacy and safety of GLP-1RAs and DPP-4 inhibitors with placebo or oral antidiabetic drugs (OADs); however, few trials directly compare the two treatment classes. This review will focus on the results of trials directly comparing GLP-1RAs and DPP-4 inhibitors with the aim of distinguishing between the two treatment classes, and will also discuss clinical situations when each of the drug classes might be preferable.

Methods

Clinical trials directly comparing GLP-1RAs and DPP-4 inhibitors in patients with T2D were identified through a MEDLINE search using the search criteria 'GLP-1RA' or 'DPP-4 inhibitor'. Nine relevant studies were identified, one of which was excluded because it compared the use of exenatide OW vs. sitagliptin, both as monotherapy, and exenatide OW is not licensed for monotherapy. Trial data, in combination with treatment algorithms, product prescribing information and personal clinical experience, were used to compare the efficacy and safety of GLP-1RAs and DPP-4 inhibitors in patients with T2D.

Results

Seven head-to-head studies and a *post hoc* analysis met the inclusion criteria. At the time of writing, the one study comparing lixisenatide with sitagliptin (NCT00976937) had not yet reported results.

Clinical performance: head-to-head studies of DPP-4 inhibitors and GLP-1RAs

Few studies have directly compared GLP-1RAs and DPP-4 inhibitors (41). In fact, of the DPP-4 inhibitors, only sitagliptin has been studied in comparison with GLP-1RAs. However, as individual agents within the DPP-4 inhibitor class have achieved similar efficacy in clinical trials, these head-to-head data should represent a fair comparison of GLP-1RAs and DPP-4 inhibitors in general (23,24).

Direct comparisons of exenatide BID with sitagliptin have been limited to two short cross-over clinical studies, a 4-week and 8-week study (Table 1) (42,43). In patients with T2D uncontrolled on met-

formin, exenatide BID treatment provided significantly greater improvements in 24 h and postprandial glucose (PPG) levels vs. sitagliptin (Table 1) (42,43). Switching from sitagliptin to exenatide BID reduced 2-h PPG, while switching from exenatide BID to sitagliptin increased 2-h PPG (42). Exenatide BID treatment also significantly slowed gastric emptying and reduced total daily caloric intake vs. sitagliptin, reflected by greater weight loss (Table 1). No major hypoglycaemia was reported with either treatment, and common adverse events were mild-to-moderate gastrointestinal complaints (nausea, vomiting, diarrhoea), which were more frequent with exenatide treatment than sitagliptin (42,43).

Exenatide OW has been compared with sitagliptin in a longer 26-week randomised trial of patients with T2D inadequately controlled on metformin alone, in which exenatide OW resulted in significantly greater reductions in HbA1c and body weight compared with sitagliptin (Table 1) (44). Again, there were no episodes of major hypoglycaemia and the most common adverse events with both treatments were gastrointestinal. As part of a 26-week study extension, patients were switched from sitagliptin to exenatide OW, resulting in significant further incremental decreases in HbA1c and body weight (Table 1) (45).

A 26-week randomised, open-label trial compared the safety and efficacy of liraglutide (1.2 and 1.8 mg) with sitagliptin in patients with T2D uncontrolled on metformin (46). Significantly greater reductions in HbA1c and body weight were achieved with liraglutide 1.8 mg and liraglutide 1.2 mg compared with sitagliptin (Table 1). Nausea was more frequent with liraglutide, but was transient in nature, and the proportion of patients experiencing minor hypoglycaemia was low (5%) in all groups. Liraglutide (1.2 and 1.8 mg) provided greater reduction in HbA1c than sitagliptin across the continuum of HbA1c (Figure 1) (47). Following a 26-week extension period, during which prior improvements in HbA1c and weight were generally maintained (22), 419 patients switched from sitagliptin to liraglutide 1.2 or 1.8 mg for a further 26 weeks, resulting in significant improvements in HbA1c and body weight (Table 1) (48).

Based on these trial data, the GLP-1RAs show a consistently superior blood glucose-lowering effect and result in greater weight loss than sitagliptin, with both classes carrying a low risk of hypoglycaemia; this is in accordance with our understanding of the mode of action of the two drug classes. This must be balanced against the requirement to inject a GLP-1RAs and their greater tendency to cause nausea, at least during treatment initiation.

A *post hoc* analysis of data from the LIRA-DPP-4 and LEAD-6 studies, which compared the efficacy of liraglu-

Table 1 Summary of glycaemic control and weight change data from GLP-1RA vs. DPP-4 inhibitor trials

Study	Duration (n)	Treatment	Change in glycaemic control	Change in body weight
DeFronzo et al. (42)	2 weeks (61)	Exen BID + Met	2-h PPG: −6.2 mmol/l; $p < 0.0001$*	−0.8 kg; $p = 0.006$*
		Sita + Met	2-h PPG: −2.1 mmol/l	−0.3 kg
	Switch 2 weeks (61)	Exen BID → Sita	2-h PPG: +4.1 mmol/l	N/A
		Sita → Exen BID	2-h PPG: −4.2 mmol/l	N/A
Berg et al. (43)	4 weeks (86)	Exen BID + Met/TZD	24-h glucose: −2.3 mmol/l; $p < 0.001$* 2-h PPG: −6.0 mmol/l; $p < 0.001$*	−1.37 kg; $p < 0.05$*
		Sita + Met/TZD	24-h glucose: −1.6 mmol/l 2-h PPG: −2.5 mmol/l	−0.89 kg
Bergenstal et al. (44)	26 weeks (342)	Exen OW + Met	HbA1c: −1.5%; $p < 0.0001$*	−2.3 kg; $p = 0.0002$*
		Sita + Met	HbA1c: −0.9%	−0.8 kg
Wysham et al. (45)	Switch 26 weeks (130)	Sita → Exen OW	HbA1c: −0.3%; $p = 0.001$[†]	−1.1 kg; $p = 0.0006$[†]
Pratley et al. (46)	26 weeks (665)	Lira 1.2 mg + Met	HbA1c: −1.24%; $p < 0.0001$ vs. Sita	−2.9 kg; $p < 0.0001$ vs. Sita
		Lira 1.8 mg + Met	HbA1c: −1.5%; $p < 0.0001$ vs. Sita	−3.4 kg; $p < 0.0001$ vs. Sita
		Sita + Met	HbA1c: −0.9%	−1.0 kg
Pratley et al. (22)	52 weeks (665)	Lira 1.2 mg + Met	HbA1c: −1.29%; $p < 0.0001$ vs. Sita	−2.8 kg; $p < 0.0001$ vs. Sita
		Lira 1.8 mg + Met	HbA1c: −1.51%; $p < 0.0001$ vs. Sita	−3.7 kg; $p < 0.0001$ vs. Sita
		Sita + Met	HbA1c: −0.88%	−1.2 kg
Pratley et al. (48)	Switch 26 weeks (419)	Sita → Lira 1.2 mg	HbA1c: −0.24%; $p = 0.006$[†]	−1.64 kg; $p < 0.0001$[†]
		Sita → Lira 1.8 mg	HbA1c: −0.45%; $p = 0.0001$[†]	−2.48 kg; $p < 0.0001$[†]

Exenatide BID: 10 μg BID following incremental dosing (5 μg BID for first week). Sitagliptin: 100 mg each morning. Exenatide OW: 2 mg OW. Liraglutide: incremental dosing; 0.6 mg OD for 2 weeks, 1.2 mg OD for 2 weeks, then 1.8 mg at week 4 if required. BID, twice daily; Exen, exenatide; Met, metformin; N/A, data not available; PPG, postprandial glucose; OD, once daily; OW, once weekly; Sita, sitagliptin; TZD, Thiazolidinedione. *Versus comparator treatment arm; [†]versus baseline (preswitch) value.

tide 1.8 mg with that of exenatide BID and sitagliptin when used as add-on to metformin in patients already close to target [baseline HbA1c > 8.0% (63.9 mmol/mol)], supports early liraglutide use as an alternative to sitagliptin (49). Following 26 weeks of treatment, the mean reduction in HbA1c was significantly greater with liraglutide than sitagliptin (−1.01% vs. −0.48%; $p < 0.0001$), reflected by more than twice as many patients achieving HbA1c targets with liraglutide 1.8 mg [HbA1c < 7.0% (53.0 mmol/mol): 78% vs. 37%, $p < 0.0001$; HbA1c ≤ 6.5% (47.5 mmol/mol): 53% vs. 19%, $p < 0.0001$]. Substantially more patients also achieved HbA1c targets with liraglutide 1.8 mg compared with exenatide BID [HbA1c < 7.0% (53.0 mmol/mol): 84% vs. 62%, $p = 0.03$; HbA1c ≤ 6.5% (47.5 mmol/mol): 65% vs. 35%, $p = 0.01$] (49).

Patient selection: guidelines and future trends
Clinical guidelines provide criteria to assist medical professionals in determining the most appropriate therapeutic intervention for T2D management. Cur-

rent recommendations are based on the data available at the time of publication. However, with increasing data supporting the earlier use of incretin therapies, these guidelines may change in the future.

What do the current guidelines recommend?
Treatment algorithms for the management of T2D have been published by the American Association of Clinical Endocrinologists (AACE) and the American Diabetes Association/European Association for the Study of Diabetes (ADA/EASD) (50,51). Clinicians must also consider local guidance when prescribing therapies. For example, in England and Wales, the National Institute for Health and Clinical Excellence (NICE) publishes guidelines that are strongly influenced by the cost effectiveness of a drug.

The AACE has recently released a comprehensive diabetes management algorithm (51). The algorithm includes 11 major classes of medications with therapeutic pathways based on three entry HbA1c ranges
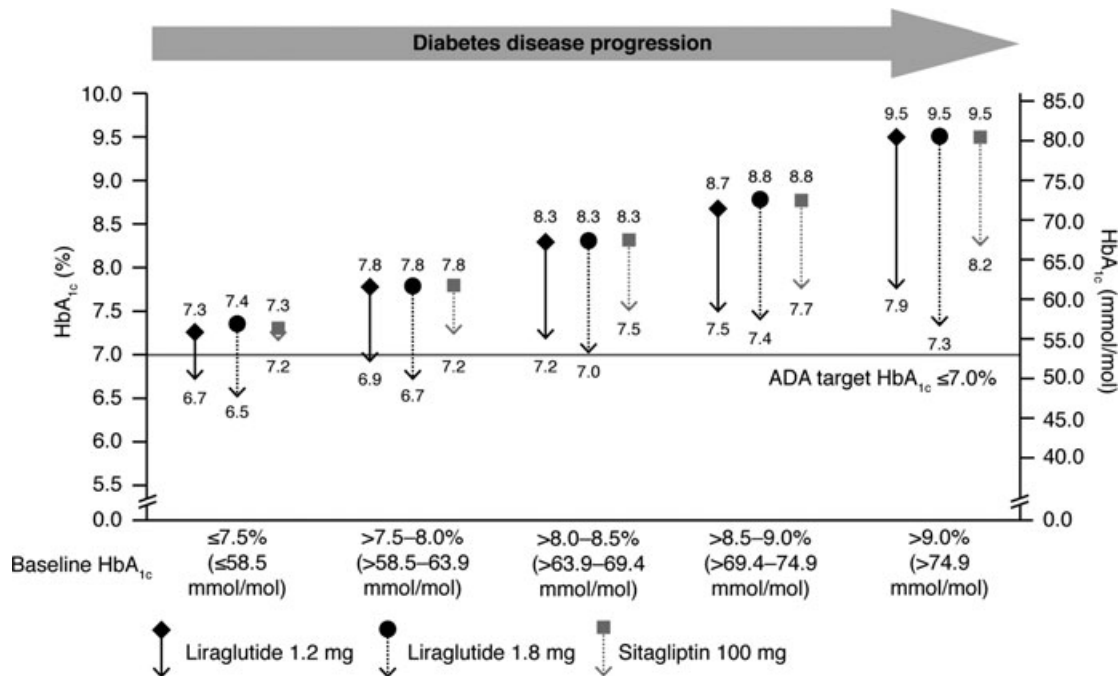
Figure 1 Effect of liraglutide and sitagliptin on HbA1c according to baseline HbA1c following 26 weeks' treatment. Data from (47), originally presented as an oral at ADA 2010. Data are mean, LOCF, ITT analysis

[> 7.5% or 58.5 mmol/mol (monotherapy); ≥ 7.5% or 58.5 mmol/mol (dual/triple therapy); > 9.0% or 74.9 mmol/mol (dual, triple or insulin therapy)]. The AACE panel positions GLP-1RAs ahead of DPP-4 inhibitors (but behind metformin) as monotherapy for patients in the lowest HbA1c category. When considering the addition of a second- or third-line agent, GLP-1 RAs are positioned at the top of the hierarchy of agents to use; DPP-4 inhibitors are positioned second for dual therapy and fifth for use in triple therapy (Figure 2). In patients on basal insulin who require additional prandial control, GLP-1RAs are again positioned ahead of DPP-4 inhibitors in the AACE algorithm (51). The EASD/ADA position statement recommends GLP-1RA or DPP-4 inhibitor use following the failure of metformin monotherapy (50).

NICE recommends the use of DPP-4 inhibitors as second-line therapy after metformin failure [HbA1c ≥ 6.5% (47.5 mmol/mol)] when SU use is either contraindicated or not tolerated, or there is a significant risk of hypoglycaemia or its consequences (52). NICE prioritises GLP-1RA use in patients where body weight or weight-related comorbidities are a particular concern. For example, liraglutide 1.2 mg and exenatide BID are recommended for use in triple therapy with metformin and SU/TZD if HbA1c ≥ 7.5%, body mass index (BMI) ≥ 35 kg/m^2 and the patient has psychological or medical problems associated with high body weight, or if BMI < 35 kg/m^2,

but weight loss would benefit other significant obesity-related comorbidities (52,53).

In summary, the EASD/ADA position statement and the AACE consensus guidelines support the frequent use of incretin-based therapies (particularly GLP-1RAs) following metformin failure (1,50). However, clinicians should also consider local guidance, which may prioritise incretin-based therapies only in specific patient groups.

DPP-4 inhibitors and GLP-1RAs: contraindications, safety concerns and special populations

Contraindications
The DPP-4 inhibitors and the GLP-1RAs exenatide BID and lixisenatide are only contraindicated in patients with hypersensitivity to any of their excipients, while exenatide OW (US) and liraglutide (US) are also contraindicated in patients with a personal or family history of medullary thyroid carcinoma or in patients with multiple endocrine neoplasia syndrome type 2 (MEN-2) (16,18,19,54–64). There have been postmarketing reports and published case studies relating to skin lesions in patients treated with DPP-4 inhibitors (59,60,62,63,65). Skin lesions have not been reported in an increased incidence in clinical trials with DPP-4 inhibitors, although experience is limited in patients with diabetic skin complications. Therefore, it is recommended that patients
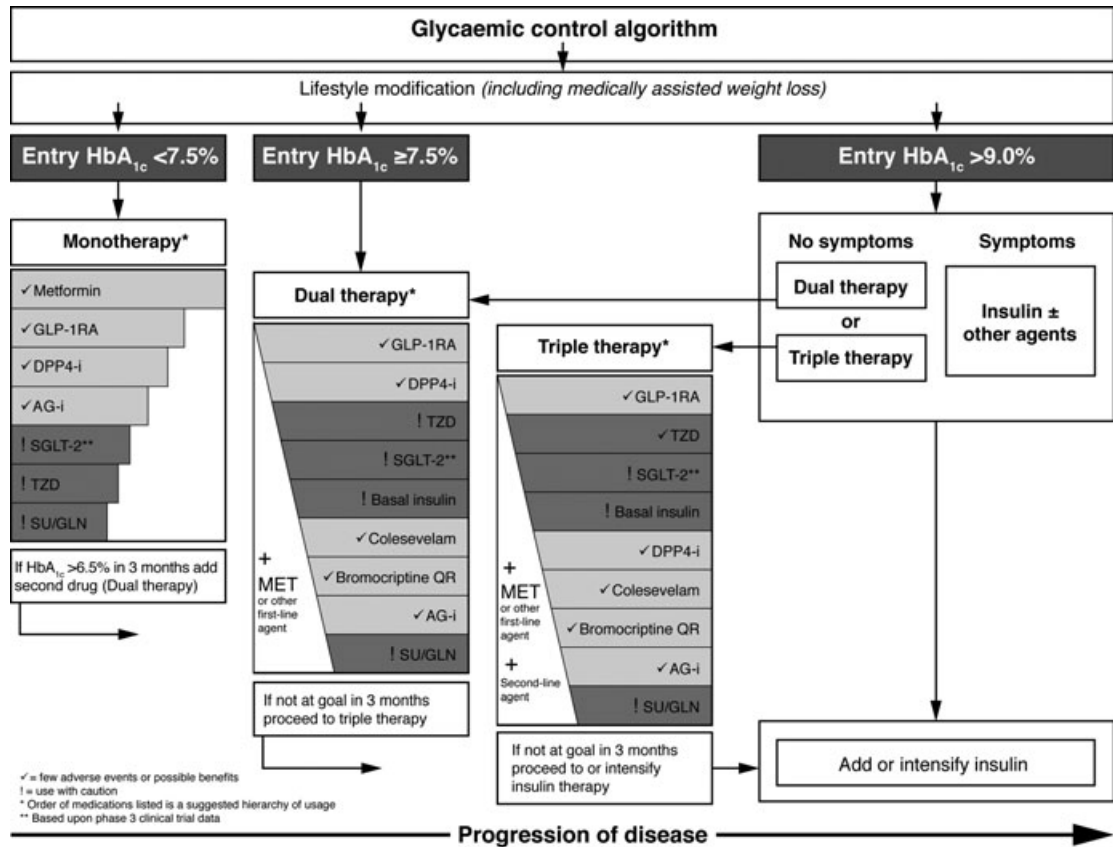
Figure 2 Glycaemic control algorithm for the management of type 2 diabetes developed by the AACE. ©Reprinted with permission from American Association of Clinical Endocrinologists (51). AG-I, alpha-glucosidase inhibitors; DPP-4-i, DPP-4 inhibitor; GLN, glinides; GLP-1-RA, GLP-1 receptor agonist; MET, metformin; SGLT-2, sodium-glucose transporter-2 inhibitors; SU, sulphonylurea; TZD, thiazolidinedione. HbA1c correspondent mmol/mol values: 6.5% = 47.5 mmol/mol; 7.5% = 58.5 mmol/mol; 9.0% = 74.9 mmol/mol

treated with DPP-4 inhibitors are monitored for skin disorders (59,60,62,63). Skin and tissue reactions are also an uncommon adverse event observed with GLP-1RAs (16,18,19).

Pancreatitis and pancreatic cancer

There has been concern regarding the risk of pancreatitis with GLP-1RAs and DPP-4 inhibitors, particularly with their long-term use, which may initiate histological changes leading to chronic pancreatitis and, potentially, pancreatic cancer (66). In the liraglutide Phase 3 clinical programme, the rate of pancreatitis was slightly increased compared with comparators, although still lower than expected in a background population with T2D (54,67), and there have been postmarketing reports of acute pancreatitis with sitagliptin, vildagliptin, saxagliptin and exenatide BID (18,59,60,62). Therefore, both DPP-4 inhibitors and GLP-1RAs should be discontinued promptly if pancreatitis is suspected (18,19,54–64). Recently, pancreatic safety with incretin therapies has come under further scrutiny following publication of

a report citing increased, potentially precancerous, pancreatic mass in patients treated with sitagliptin or exenatide BID (68). This study analysed a small number of donated human cadaveric pancreata and reported an approximately 40% increase in pancreatic mass. Because of a number of methodological flaws, these findings should be interpreted with caution. For example, substantial differences existed between the two diabetic groups: subjects in the control group were 18 years younger, 67% were female subjects (vs. 25%), two died of diabetic ketoacidosis and five were untreated (68). As such, an editorial in the same issue of the journal questioned whether the increase in pancreas mass in those receiving incretin-based therapy was attributable to their treatment or a function of some of the control group having type 1 diabetes (which is associated with a 48% decrease in pancreatic mass within 10 years of diagnosis) (69). Subsequently, the FDA has advised patients and healthcare practitioners to continue with treatment as before (70). More recently, following a thorough investigation, the European Medicines Agency has

stated that currently available data on GLP-1-based therapies do not confirm concerns of an increased risk of pancreatic adverse events (71).

Cardiovascular outcome studies for saxagliptin and alogliptin have recently been published, which together included ~11,000 DPP-4 inhibitor-treated subjects (72,73). In both the EXAMINE (Examination of Cardiovascular Outcomes with Alogliptin vs. Standard of Care) and the SAVOR-TIMI 53 (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction) randomised, double-blind, placebo-controlled clinical trials, low incidence of pancreatitis and pancreatic cancer was reported, with comparable rates in both active treatment and placebo groups (72,73).

Renal insufficiency and acute renal failure

Renal insufficiency is a common comorbidity in T2D patients and can complicate treatment by elevating plasma levels of therapeutic agents. Although, overall, there is low incidence of acute renal failure with GLP-1RAs, several cases have been reported (74–78). Conversely, cases of acute renal failure resulting from DPP-4 inhibitor therapy are extremely rare (79). Sitagliptin, saxagliptin and vildagliptin are largely renally excreted and a degree of drug accumulation has been reported in patients with renal insufficiency treated with sitagliptin and saxagliptin (58–62). Therefore, in patients with moderate-to-severe renal impairment, dosing adjustment is required when administering sitagliptin (US and EU), saxagliptin (EU and US) and vildagliptin (EU) (Table 2) (58–62). Linagliptin, however, has a largely non-renal route of excretion and can be used without dose adjustment in patients at all stages of renal disease (63,64). Exenatide (BID and OW) is predominantly renally excreted and is not recommended in patients with severe renal impairment (Table 2) (18,55–57). Lixisenatide may be prescribed without dose adjustment in mild renal impairment, but data are lacking in patients with more advanced disease, and lixisenatide should be used with caution (moderate renal impairment) or not at all (severe impairment) in these populations (16). Liraglutide is metabolised in a similar manner to large proteins and thus is not renally excreted. In the US, liraglutide is approved for use with caution in patients at all stages of renal disease, but is not recommended in patients with moderate-to-severe disease in the EU, because of limited data (Table 2) (19,54). The renal safety of incretin-based therapies is currently being assessed in a number of large prospective trials (e.g. NCT 01394341, NCT01744236, NCT01835678, NCT0 1664676).

Other considerations

Finally, again because of limited data, GLP-1RAs and DPP-4 inhibitors are either not recommended or should be used with caution in elderly (≥ 75 years old), paediatric (< 18 years old), pregnant or breast-feeding patients, or those with hepatic impairment (Table 2) (16,18,19,54–64).

When incretin choice may be subjective or based on patient choice

In general, when a patient is already within ~1.5% of HbA1c target, practitioners often prefer to prescribe DPP-4 inhibitors over GLP-1RAs in the first instance, largely because of ease of incorporation into existing therapy and lower cost. However, practitioners should consider that, in clinical trials, when DPP-4 inhibitors are used as monotherapy or added to existing metformin therapy, reductions in HbA1c are typically < 1% (23,46). A patient's willingness to lose weight may be an important additional factor when choosing an incretin therapy in patients already close to target. Obese or overweight patients with T2D may prefer a GLP-1RA, even when only a small reduction in HbA1c is required, as weight loss may improve their long-term outcomes (80–82). It is important to note that retrospective analyses have suggested that patients with heart failure who experience clinically significant weight loss are at increased risk of mortality. Consequently, because of the decrease in body weight seen with GLP-1RAs, obese patients with heart failure may represent a subset of individuals that requires more careful observation. Less risk for these patients is associated with DPP-4 inhibitors as they do not induce clinically significant weight loss (83).

When patients have very poor glycaemic control on OADs (> 1.5% from target), a GLP-1RA is often recommended over a DPP-4 inhibitor attributable to superior glycaemic efficacy, particularly if the patient is overweight. One major barrier to GLP-1RA treatment is the reluctance of some patients to inject; in such cases, a DPP-4 inhibitor is often the next choice.

Dealing with practical issues: injections and gastrointestinal tolerability

The main advantages of DPP-4 inhibitors compared with GLP-1RAs are less frequent nausea and oral administration. Nausea with GLP-1RAs often occurs early in GLP-1 RA therapy and can be limited using an incremental dosing approach (18,19,57); exenatide OW has only a single dose (2 mg), but it takes 6–10 weeks to achieve steady state plasma levels (55,56). Injecting GLP-RAs at mealtimes may also help some patients, and my personal experience sug-

Table 2 Summary of label information for DPP-4 inhibitor and GLP-1RA use in the US and EU in patients with renal and hepatic impairment. Please consult the respective SPC/PI for further information

		Ref	Renal impairment			Hepatic impairment
			Mild	Moderate	Severe	
DPP-4 inhibitors	Sitagliptin	EU (SPC) (59)	✓	✓ 50 mg	✓ 25 mg	✓ Mild to moderate. Not studied for severe
		US (PI) (58)	✓	✓ 50 mg	✓ 25 mg	✓ Mild to moderate. Not studied for severe
	Saxagliptin	EU (60)	✓	✓ 2.5 mg	✓ 2.5 mg with caution	✓ Mild to moderate ×Severe
		US (61)	✓	✓ 2.5 mg	✓ 2.5 mg	✓
	Vildagliptin	EU (62)	✓	✓ 50 mg	✓ 50 mg	×
		US	N/A	N/A	N/A	N/A
	Linagliptin	EU (63)	✓	✓	✓	✓ However, clinical experience is lacking
		US (64)	✓	✓	✓	✓
GLP-1RAs	Liraglutide	EU (19)	✓	×Limited clinical experience	×Limited clinical experience	× Limited clinical experience
		US (54)	✓	✓ With caution	✓ With caution	✓ With caution because of limited experience
	Exenatide BID	EU (18)	✓	✓ With caution*	×	✓
		US (57)	✓	✓ With caution*	×	✓ However, clinical experience is lacking
	Exenatide OW	EU (56)	✓	×Limited clinical experience	×	✓
		US (55)	✓	✓ With caution	×	✓
	Lixisenatide	EU (16)	✓	✓ With caution	×Limited clinical experience	✓
		US	N/A	N/A	N/A	N/A

BID, twice daily; OW, once weekly; SPC, summary of product characteristics; PI, prescribing information. ✓, recommended with no dose adjustment unless stated; ×, not recommended; N/A, not applicable. *Caution when escalating dose from 5 to 10 μg.

gests that nausea from liraglutide can often be obviated by eating smaller meals and stopping eating at the first sign of satiation; patients sometimes describe experiencing nausea after meals, but this may actually just be a feeling of 'fullness'. When nausea is a problem, returning the patient to a lower GLP-1RA dose for a week before repeating the incremental dosing steps can often prove successful. In patients who are reluctant to inject, practitioners can demonstrate that GLP-1RA injection pens are easy and relatively painless to use; a dummy 'dry' injection (to the patient and/or the clinician) can illustrate this very well. In addition, personal experience suggests that a patient is often reassured that, with their eyes closed, they often cannot differentiate between a soft pinch on the arm and a dry needle.

Treatment satisfaction data from patient-reported outcome studies suggest that patients are satisfied with injectable therapies if they provide advantages over orally administered treatments (84,85). Overall treatment satisfaction has been reported to be significantly greater for liraglutide 1.8 mg compared with sitagliptin, with similar treatment convenience and flexibility scores (85). Overall treatment satisfaction was also greater for exenatide OW compared with sitagliptin after 26 weeks' treatment (84). Switching from sitagliptin to liraglutide also improved overall treatment satisfaction ($p < 0.05$ for liraglutide 1.2 mg), while there was no significant change in treatment convenience and flexibility despite the different administration routes (48). In all these examples, the improved treatment satisfaction with the GLP-1RA was observed in concert with improved glycaemic control and greater weight loss compared with sitagliptin therapy.

Together, these results suggest that treatment efficacy is as important to patients as convenience. Patients appear satisfied with an injectable therapy if it provides additional clinical benefits.

Conclusions

The incretin-based therapies improve glycaemic control with a low incidence of hypoglycaemia and without weight gain, both advantages over traditional add-ons to metformin therapy.

DPP-4 inhibitors are simple to incorporate into existing therapy following metformin ± SU failure and are generally weight-neutral with few gastrointestinal side effects. GLP-1RAs offer superior glycaemic control and weight loss compared with sitagliptin, likely because of the supraphysiological levels of the GLP-1RA provided in comparison with the physiological concentrations of GLP-1 and GIP achieved with sitagliptin. Although DPP-4 inhibitors are oral agents, GLP-1RAs are easy to administer and performing the first injection in the office can often alleviate any needle anxiety. In addition, treatment satisfaction data suggest that patients are more satisfied with a GLP-1RA than with sitagliptin and do not mind switching from oral to injectable medication when efficacy is improved.

With this in mind, a GLP-1RA is usually my preferred choice ahead of a DPP-4 inhibitor. However, if weight loss is not particularly desirable and only a small decrease in HbA_{1c} is required to achieve glycaemic target, a DPP-4 inhibitor may be appropriate. Currently, GLP-1RAs are sometimes prioritised over DPP-4 inhibitors in specific patient groups, such as those with obesity-related comorbidities. However, wider use of GLP-1RAs early in disease progression may provide superior glycaemic control and weight loss, and therefore result in more favourable long-term outcomes.

Acknowledgements

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