GLP-1 receptor agonists or DPP-4 inhibitors: How to guide the clinician?

Agonistes des récepteurs du GLP-1 ou inhibiteurs de la DPP-4 : comment orienter le choix du clinicien ?

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Abstract

Pharmacological treatment of type 2 diabetes has been enriched during recent years, with the launch of incretin therapies targeting glucagon-like peptide-1 (GLP-1). Such medications comprise either GLP-1 receptor agonists, with short (one or two daily injections: exenatide, liraglutide, lixisenatide) or long duration (one injection once weekly: extended-released exenatide, albiglutide, dulaglutide, taspoglutide); or oral compounds inhibiting dipeptidyl peptidase-4 (DPP-4), the enzyme that inactivates GLP-1, also called gliptins (sitagliptin, vildagliptin, saxagliptin, linagliptin, alogliptin). Although both pharmacological approaches target GLP-1, important differences exist concerning the mode of administration (subcutaneous injection versus oral ingestion), the efficacy (better with GLP-1 agonists), the effects on body weight and systolic blood pressure (diminution with agonists versus neutrality with gliptins), the tolerance profile (nausea and possibly vomiting with agonists) and the cost (higher with GLP-1 receptor agonists). Both agents may exert favourable cardiovascular effects. Gliptins may represent a valuable alternative to a sulfonylurea or a glitazone after failure of monotherapy with metformin while GLP-1 receptor agonists may be considered as a good alternative to insulin (especially in obese patients) after failure of a dual oral therapy. However, this scheme is probably too restrictive and modalities of using incretins are numerous, in almost all stages of type 2 diabetes. Physicians may guide the pharmacological choice based on clinical characteristics, therapeutic goals and patient’s preference.

Résumé

Le traitement pharmacologique du diabète de type 2 s’est enrichi, ces dernières années, de l’apport des médicaments à effet incrétine ciblant le glucagon-like peptide-1 (GLP-1). Ces médicaments comprennent soit des agonistes des récepteurs au GLP-1, à courte (un ou deux injections par jour : exénatide, liraglutide, lixisénaïtide) ou longue durée d’action (injection hebdomadaire : exénatide à libération prolongée, albiglutide, dulaglutide, taspoglutide) ; soit des agents inhibant l’enzyme inactivant le GLP-1, la dipeptidyl peptidase-4 (DPP-4), actifs par voie orale, les gliptines (sitagliptine, vildagliptine, saxagliptine, linagliptine, alogliptine). Bien que ces approches pharmacologiques ciblent toutes deux le GLP-1, elles se différencient par leur mode d’administration (injection sous-cutanée versus prise orale), leur efficacité (meilleure avec les GLP-1 agonistes), leurs effets sur le poids corporel et sur la pression artérielle systolique (diminution avec les agonistes versus neutralité avec les gliptines), leur profil de tolérance (risque de nausées ou vomissements avec les agonistes) et leur coût (supérieur avec les agonistes du GLP-1). Toutes deux pourraient être bénéfiques sur le plan cardiovasculaire. Il apparaît qu’une gliptine est une excellente alternative à un sulfamide ou une glitazone après échec d’une monothérapie par metformine alors qu’un analogue des récepteurs au GLP-1 est une bonne alternative à l’insuline (surtout chez les sujets obèses) après échec d’une bithérapie orale. Ce schéma est sans doute trop restrictif et les modalités d’utilisation sont nombreuses, à quasi tous les stades du diabète de type 2. Le choix pourra s’orienter selon les caractéristiques cliniques, les objectifs fixés ou simplement les préférences du patient.

1. Glucagon-like peptide-1 receptor agonists or dipeptidyl peptidase-4 inhibitors: a clinician’s guide

Treatment for type 2 diabetes mellitus has become increasingly complex in recent years, particularly with the advent of incretin therapies [1,2]. The incretin effect can be defined as an enhanced insulin response to glucose, administered orally.
as opposed to intravenously, despite equivalent amplitude of the controlled glycemic excursion. This phenomenon can be explained by the action of gastrointestinal hormones called incretins that are secreted in response to food intake and enhance insulin secretion. Two of the hormones implicated in this process are glucagon-like-peptide-1 (GLP-1) and glucose-dependent-insulinotropic polypeptide (GIP) [3].

The incretin effect is blunted in patients with type 2 diabetes, proportionally with increasing plasma glucose level. The reasons behind this reduced response are poorly understood but a growing body of arguments suggest the phenomenon could be secondary rather than primary [4]. In any case, this defective incretin effect can contribute to hyperglycemia, first postprandially then secondarily in the fasting state, contributing to glucose imbalance. The pharmacological approaches currently available have focused on GLP-1 rather than GIP. There are two ways to increase the plasma levels and thus the action of GLP-1: either via exogenous GLP-1 by administering an analogue compound (a class of drugs called incretin mimetics) or via prevention of endogenous GLP-1 degradation by inhibiting the action of dipeptidyl peptidase-4 (DPP-4), an enzyme released by the endothelium which rapidly inactivates GLP-1 (these inhibitors constitute a class of drugs called incretin potentiators) (Fig. 1) [1,5]. Both of these pharmacological approaches have their advantages and disadvantages (Table 1), calling for an examination of their respective roles in the therapeutic armamentarium for type 2 diabetes [6–9].

The purpose of this article is to compare these two classes of drugs, incretin mimetics (GLP-1 receptor agonists) and incretin potentiators (DPP-4 inhibitors), in order to provide the clinician with a set of arguments for guiding therapeutic decision-making based on the individual characteristics of each patient.

2. Glucagon-like peptide-1 receptor agonists

For routine clinical practice, GLP-1 cannot be used directly because of its rapid degradation by DPP-4; the peptide would have to be administered intravenously as was initially done during the proof-of-concept studies [10]. GLP-1 has multiple effects, mainly:

- glucose-dependent enhancement of insulin secretion, action which gave rise to the name “incretin”, (the effect increases with high plasma glucose levels and disappears at normal or a fortiori low levels);
- inhibition of glucagon secretion, again in a glucose-dependent manner (the effect is observed at high plasma glucose levels but disappears at low levels, enabling normal feedback regulation);
- slowing of gastric emptying, an effect which contributes to lowering immediate postprandial hyperglycemia, but also favoring nausea and vomiting;
- direct and indirect central anorexigenic effects [11]. In addition, GLP-1 appears to have a protective effect on pancreas Langerhans islet B-cells (anti-apoptotic effect); evidence has however to date come only from animal studies and the clinical impact remains to be demonstrated.

In any case, all of these effects are a priori favorable for the type 2 diabetes patient since they could contribute to both improved glycemic control and weight regulation [3]. GLP-1 has direct effects on the vascular wall (endothelium) and on the myocardium, effects which could have a positive impact on protection against atherosclerosis and its complications, beyond the direct effects of glycemic control [12,13]. These findings have led the pharmaceutical industry to search for compounds prolonging the agonistic effect on GLP-1 receptors [1,14]. These compounds, GLP-1 agonists [15] or DPP-4 inhibitors [16], have been found effective for improving glycemic control in patients with type 2 diabetes. There is also hope for other positive effects, notably cardiovascular effects [12,13].

Exendin-4 (exenatide) is a natural compound (initially extracted from a lizard called the Gila monster), which exhibits about 50% structural identity with human GLP-1. Exendin-4 binds to the GLP-1 receptor producing an agonist effect, yet is resistant to DPP-4 (Fig. 1), which prolongs its action and authorizes subcutaneous administration [17]. Exenatide, marked under the trade name of Byetta®, should be administered twice daily; its efficacy and safety have been demonstrated in several clinical trials [18]. Liraglutide (Victoza®) is a human GLP-1 analog produced by the recombinant DNA technique [19]. It is obtained by substitution of one amino acid (lysine in position 34 replaced by arginine) and acylation by adjunction of a C16 fatty acid (palmitic acid on the lysine in position 26). This peptide retains 97% homology with human GLP-1 but exhibits characteristic resistance to DPP-4 (Fig. 1). In addition, coupling with the fatty acid enables binding with albumin (via the same principle as the insulin detemir), prolonging its duration of action and allowing a single daily injection [20]. Its efficacy (notable to control fasting glycemia) and gastrointestinal tolerance appear to be slightly better than for exenatide [21]. A third compound, lixisenatide (Lixumia®), has recently been awarded approval by the European Medicines Agency (EMA) and has already been marketed in certain countries [22]. A prolonged release form of exenatide (Bydureon®) has also been developed;
this formulation allows weekly injections, offering better patient comfort than the two daily injections yet with better efficacy and tolerance [23,24]. Other prolonged action compounds are also in the final stages of clinical investigation (albiglutide, dulaglutide, taspoglutide) [14]. Prolonged action GLP-1 receptor agonists have certain advantages compared with the rapid-action reference compound exenatide. The decline in the HbA1c level is greater, with better glycemic control in the fasting state and considerably improved gastrointestinal tolerance [24,25]. Conversely, skin reactions at the injection site appear to be more frequent [24].

In general, GLP-1 receptor agonists induce a 1–1.5% reduction in the HbA1c level, a reduction comparable with that observed when insulin is started after failure of oral treatment [15]. One potential advantage of GLP-1 receptor agonists is the fact that these drugs can trigger a certain degree of weight loss by a central and peripheral anorexigenic effect [11]. This weight loss is often desirable in the type 2 diabetes patient and contrasts with the weight gain usually observed with insulin, sulfonylureas or glitazones [26]. Nevertheless, in general and as compared with placebo, the weight loss is relatively modest, as demonstrated in two recent meta-analyses [27,28]. In patients with type 2 diabetes, the mean weight loss observed in 18 controlled clinical trials usually lasting 6 months to 1 year was 2.8 kg (95% CI 3.4–2.3). A fall in blood pressure, mainly systolic pressure, has been reported consistently in the clinical trials testing liraglutide or exenatide, but with a slight increase in heart rate [12]. A decrease in serum triglycerides and postprandial hyperlipidemia has also been reported [18]. These observations suggest that GLP-1 receptor agonists could have effects beyond glycemic control [13,29]. The data collected from clinical trials on GLP-1 receptor agonists do not show any cardiovascular safety problem and have even reported a trend towards fewer major cardiovascular events in treated patients compared with other medications, including placebo [30]. A possible cardiovascular protective effect remains to be specifically confirmed in large-scale prospective trials currently under way (Table 1).

The most common undesirable manifestation reported with GLP-1 receptor agonists is nausea, especially early after treatment onset, generally dictating a progressive titration when starting treatment. This effect is more pronounced with rapid-action exenatide (due to a more

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### Table 1
Comparison of common characteristics and differences between glucagon-like peptide-1 (GLP-1) receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors.

<table>
<thead>
<tr>
<th>Characteristics/Effects</th>
<th>GLP-1 receptor agonists</th>
<th>DPP-4 inhibitors</th>
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</thead>
<tbody>
<tr>
<td>Compounds</td>
<td>Exenatide (Byetta®, Bydureon®)</td>
<td>Sitagliptin (Januvia®)</td>
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<tr>
<td></td>
<td>Liraglutide (Victoza®)</td>
<td>Vildagliptin (Galvus®)</td>
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<td></td>
<td>Lisixenatide (Lyxumia®)</td>
<td>Saxagliptin (Onglyza®)</td>
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<td></td>
<td>Albiglutide</td>
<td>Linagliptin (Trajenta®)</td>
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<tr>
<td></td>
<td>Dulaglutide</td>
<td>Alogliptin (Nesina®, in Japan)</td>
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<tr>
<td></td>
<td>Taspoglutide</td>
<td></td>
</tr>
<tr>
<td>Administration</td>
<td>Subcutaneous injection</td>
<td>Oral</td>
</tr>
<tr>
<td>Mechanisms of action</td>
<td>Important increase in exogenous GLP-1 (or equivalent)</td>
<td>Moderate increase in endogenous GLP-1</td>
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<tr>
<td>Glucose-dependent effects</td>
<td>Increased insulin secretion (incretin effect)</td>
<td>Increased insulin secretion (incretin effect)</td>
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<tr>
<td></td>
<td>Decreased glucagon secretion</td>
<td>Decreased glucagon secretion</td>
</tr>
<tr>
<td>Extra-pancreatic effects</td>
<td>Slower gastric emptying (especially with exenatide)</td>
<td>Little or no effect on gastric emptying</td>
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<td></td>
<td>Central anorexigenic effect</td>
<td>Weak central anorexigenic effect</td>
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<tr>
<td>Lowering of HbA1c level</td>
<td>−1.1 to −1.6%</td>
<td>−0.6% to −1.1%</td>
</tr>
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<td>Weight loss</td>
<td>−2 to −4 kg</td>
<td>0 to −1 kg</td>
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<td>Hemodynamic effects</td>
<td>Lower systolic blood pressure</td>
<td>No effect on blood pressure</td>
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<tr>
<td></td>
<td>Increase heart rate</td>
<td>No effect on heart rate</td>
</tr>
<tr>
<td>Lipidic effects</td>
<td>Lower postprandial lipid and triglyceride levels</td>
<td>Slight decrease in cholesterol</td>
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<tr>
<td>Hypoglycemic risk</td>
<td>Nil (except when combined with insulin or sulfonylurea)</td>
<td>Nil (except when combined with insulin or sulfonylurea)</td>
</tr>
<tr>
<td>Adverse effects</td>
<td>Nausea, vomiting</td>
<td>Good tolerance</td>
</tr>
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<td></td>
<td>Antibodies (exenatide &gt; liraglutide)</td>
<td>Respiratory infections?</td>
</tr>
<tr>
<td></td>
<td>Risk of pancreatitis?</td>
<td>Risk of pancreatitis?</td>
</tr>
<tr>
<td>Official indications*</td>
<td>All stages of type 2 diabetes mellitus (from monotherapy to combination with insulin)</td>
<td>All stages of type 2 diabetes mellitus (from monotherapy to combination with insulin)</td>
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<td>Use if renal insufficiency</td>
<td>Caution if creatinine clearance &lt; 60 mL/min</td>
<td>Dose reduction if creatinine clearance &lt; 50 mL/min (except linagliptin)</td>
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<td>Ongoing cardiovascular trials</td>
<td>Excel (prolonged release exenatide)</td>
<td>Tecos (sitagliptin)</td>
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<td>Leader (liraglutide)</td>
<td>Savor-Timi 53 (saxagliptin)</td>
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<td>Elixa (lisixenatide)</td>
<td>Carolina (linagliptin)</td>
</tr>
<tr>
<td></td>
<td>Rewind (dulaglutide)</td>
<td>Examine (alogliptin)</td>
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* All official indications are not accepted for reimbursement in all countries for all marketed compounds.
pronounced effect on gastric emptying) than with liraglutide or prolonged release exenatide. A higher risk of pancreatitis has been suggested [31] but this point remains controversial [32]. The same can be said for medullary thyroid cancer, particularly for liraglutide [31]. In any case, the very long-term safety profile of these drugs still remains to be determined [33,34]; the future will tell the appropriate place for these drugs in our increasingly complex therapeutic armamentarium for type 2 diabetes [23]. There have also been reports of antibody production, more often against exenatide than liraglutide (in agreement with the homology difference with human GLP-1), but any impact of these antibodies on the drug’s efficacy or safety has not been formally demonstrated [34]. The risk of drug interactions with GLP-1 receptor agonists would be relatively limited, even if retarded absorption of certain other drugs due to the slower gastric emptying cannot be excluded (notably with rapid-action exenatide) [35]. Finally, there are certain limitations on prescription of exenatide (to be used cautiously in patients with a creatinine clearance <60 mL/min and contraindicated at <30 mL/min) and liraglutide (not to be used if the creatinine clearance <60 mL/min).

3. Dipeptidyl peptidase-4 inhibitors (gliptins)

DPP-4 inhibitors, also called gliptins, are the only oral antidiabetic drugs whose anti-hyperglycemic action results primarily from an incretin effect. Gliptins are associated with an increasingly important drug class for the treatment of type 2 diabetes. Several compounds have been marketed: sitagliptin (Januvia®), vildaglaptin (Galvus®), saxagliptin (Onglyza®), linagliptin (Trajenta®), alogliptin (only in Japan) [36]. The increased plasma levels of GLP-1 induced by these drugs (about 3-fold) is sufficient to stimulate insulin secretion and inhibit glucagon secretion, both effects being glucose-dependent. These modifications improve both postprandial and fasting glycemic control, and thus HbA1c levels. DPP-4 inhibitors have an anti-hyperglycemic effect comparable to that of sulphonylureas or pioglitazone, when combined with metformin [16]. Comparing with these two drugs, DPP-4 inhibitors have the advantage of not inducing weight gain and, compared with sulphonylureas, have the obvious benefit of not inducing hypoglycemia, especially severe episodes [16]. Compared with GLP-1 receptor agonists, DPP-4 inhibitors have the advantage of easy administration, generally with a single daily oral dose, without titration. In addition, many of these compounds are also available in combined formulations with metformin, further limiting the number of medicines to take and increasing therapeutic adherence [36]. Finally, unlike GLP-1 receptor agonists, the GLP-1 levels reached with DPP-4 inhibitors is insufficient to inhibit gastric emptying, explaining their better gastrointestinal tolerance [1].

DPP-4 inhibitors do not affect blood pressure or heart rate significantly and the impact on the lipid profile is relatively limited, although a slight decrease in cholesterol levels has been reported [37]. One encouraging reduction found to be statistically significant is the incidence of major cardiovascular events, observed in patients treated in phase 3 gliptin trials (odds ratio versus comparator: 0.689 [C195% 0.825–0.899]) (P = 0.006) [38]. These data will have to be confirmed in large-scale prospective clinical trials currently under way where the main endpoint is precisely cardiovascular morbidity and mortality (Table 1) [12,36].

Globally, DPP-4 inhibitors have an excellent tolerance and safety profile with an incidence of adverse effects non-significantly different from placebo; it is even lower compared with metformin (fewer gastrointestinal disorders), sulfonylureas (fewer episodes of hypoglycemia) or thiazolidinediones (fewer cases of edema and weight gain) [39]. Unlike glitazones, gliptins do not increase the risk of bone fractures and might even be associated with a decreased risk [40]. A trend for higher incidence of benign upper airways infections has also been reported [41], but not confirmed in most of the controlled clinical trials [39,42]. The suspected higher risk of pancreatitis, or even pancreas cancer, was based on evidence exposed to potential bias [31]. The data collected in clinical trials on this point have been reassuring [43]. As for GLP-1 receptor agonists, the long-term safety of gliptins remains to be determined [33]. The risk of drug interactions with DPP-4 inhibitors would appear to be relatively low, at least lower than expected with sulfonylureas, glinides or glitazones [44].

DPP-4 inhibitors share the same mechanism of action, but with distinctive pharmacodynamic properties (DPP-4 specificity), and even greater differences for their pharmacokinetic properties [45]. The greatest difference is probably the elimination route which is mainly renal for sitagliptin, saxagliptin (and its active metabolite) and vildaglaptin, while it is almost exclusively biliary for linagliptin [46]. Thus administered doses have to be adjusted in patients with moderate to severe kidney failure (half or even quarter doses for sitagliptin), excepting linagliptin which can be used at the same daily dose irrespective of the glomerular filtration rate.

4. Comparing glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors

Although both pharmacological approaches involve GLP-1, there are considerable differences in terms of efficacy and tolerance as well as ease of administration and cost (Table 1) [9,42]. A pair of articles recently published in the “for debate” section has presented the arguments in favor of one or other of these two pharmacological approaches for the treatment of type 2 diabetes [6,7]. Most of the studies have analyzed the effects of a GLP-1 receptor agonist and DPP-4 inhibitors in patients already treated with metformin [47].

A recent meta-analysis compared the effects of GLP-1 receptor agonists and DPP-4 inhibitors in type 2 diabetes patients who did not achieve perfect glycemic control with metformin alone [48]. The conclusion was that GLP-1 receptor agonists are more effective in lower the HbA1c level. In addition, they induce a moderate weight loss (0–1 kg). Inversely, they exhibit less satisfactory gastrointestinal tolerance, requiring subcutaneous injections, and cost more. In another meta-analysis, the decline in the HbA1c level with GLP-1 receptor agonists ranged from −1.1% to −1.6% while it reached −0.6% to −1.1% with DPP-4 inhibitors [49]. Globally, the difference in terms of reduced
HbA1c level was 0.49% (95% CI 0.31–0.67) between the two types of incretins [16]. There have been very few clinical trials directly comparing a DPP-4 inhibitor (incidentally all of which were conducted with sitagliptin) versus a GLP-1 receptor agonist [6,50]. The main results are summarized in Table 2 [51–56]. These studies confirm the indirect data assembled in the meta-analysis, i.e. that the reduction in HbA1c, fasting glycemia, and body weight is greater with GLP-1 agonists than with 100 mg sitagliptin; conversely, the differences in terms of blood pressure are not consistent between the different trials. Considering the available studies, lixisendtide compares favorably with the other types of incretin, including both exenatide and sitagliptin [21].

5. Guiding the therapeutic choice

The consensus statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) published early in 2009 offered a place for GLP-1 receptor agonists after failure of metformin treatment, as an alternative to sulfonylureas or a basal insulin (considered as the first choice) or as an alternative to pioglitazone (as a second-choice), while no place was retained for DPP-4 inhibitors [57]. These recommendations have been criticized because they seem to be more a reflection of the opinion of a few experts than peremptory proof provided by factual evidence [58]. In addition, gliptins were awarded a place of choice for single, dual, or triple drug therapy in the decision-making algorithm proposed, nearly at the same time, by the American Association of Clinical Endocrinologists/American College of Endocrinology [59].

The new guidelines for type 2 diabetes published jointly by the ADA and the EASD early in 2012 specifically emphasized the importance of defining a patient-centered approach to treatment [60]. This time, the DPP-4 inhibitors were mentioned as a pharmacological alternative after failure of metformin monotherapy, at the same level as GLP-1 receptor agonists, a glucose lowering sulfonylureas, a thiazolidinedione (pioglitazone), an intestinal alpha-glucosidase inhibitor (acarbose) or a basal insulin. The authors emphasized several elements useful for guiding the clinician’s choice. Thus, if there is a risk of hypoglycemia, the choice should focus on incretins, pioglitazone or acarbose. If the patient is obese or wants to lose weight (or at least would like to avoid gaining weight), preference should be given to GLP-1 receptor agonists, the only treatment triggering weight loss, or a gliptin, or acarbose, which have a neutral effect on weight. Finally, if the cost of the treatment is in the forefront, adding a sulfonylurea would certainly be a less costly solution (but with the risk of hypoglycemia and weight gain); it should be noted that from a cost standpoint, gliptins are less expensive than GLP-1 receptor agonists. In these guidelines, it is also mentioned that GLP-1 receptor agonists have a “high” quality efficacy, comparable with sulfonylureas, while the efficacy of gliptins is termed “intermediate”. There could be some discussion concerning this difference in gliptins and sulfonylureas efficacy since the published meta-analyses and the available direct-comparison clinical trials have shown comparable efficacy for DPP-4 inhibitors and sulfonylureas [50,61].

Finally in the guidelines published by the International Diabetes Federation (IDF), DPP-4 inhibitors are mentioned as second-choice drugs, after failure, and as a complementary treatment of metformin, with as an alternative glitzone or an alpha-glucosidase inhibitor; conversely, a third position is assigned to GLP-1 receptor agonists, on the same level as oral triple therapy or adjunction of basal or pre-mixed insulin, probably due to the higher cost and the more complex administration [62].

Thus the comparison of the different guidelines shows a certain number of differences in terms of the relative positions given to GLP-1 receptor agonists and DPP-4 inhibitors, reflecting the most difficult task of choosing the appropriate drug. The advantages of DPP-4 inhibitors [6] and those of GLP-1 receptor agonists [7] were recalled in two papers published this year in 2012 in a “for debate” series. We emphasized the fact that attempting to determine which class of incretins is superior to the other is probably a moot question due to the differences in the two approaches and to the markedly heterogeneous nature of type 2 diabetes, which offers a place of choice for both options depending on the individual patient’s particular situation [6]. A possible proposition for a decision-making algorithm is summarized in Fig. 2 and can provide, as an example, a guide for the clinician reflecting on the orientation of the appropriate therapeutic choice. As in the algorithm proposed by the IDF, we feel

Fig. 2. Place of drugs with an incretin effect in the treatment of type 2 diabetes. Warning: the proposals presented here are designed as a useful guide for clinicians; they are not official guidelines. (+) Pioglitazone, a meglintid or acarbose can be used as an alternative to sulfonylureas in certain countries, but globally are prescribed much less. Insulin therapy could also be proposed at this stage, but is not often prescribed.
that gliptins should be preferred over GLP-1 receptor agonists in most patients after failure of metformin. This is the specific case of type 2 diabetes patients with a risk of hypoglycemia (an important advantage from this point of view compared with sulfonylureas) and in the elderly population where DPP-4 inhibitors would appear to have a particularly interesting efficacy/safety ratio and also the advantage of ease of administration [63]. A GLP-1 receptor agonist might however be the appropriate choice if weight loss is a major objective or if the HbA1c has reached a level such that the probability that gliptins would bring it into the target range (for example < 7%) is unlikely. The British National Institute for Health and Clinical Excellence (NICE) guidelines state that a body mass index greater than 35 kg/m² is an important criterion for preferential prescription of a GLP-1 receptor agonist, such as liraglutide [26].

If oral bitherapy is unsuccessful, adding a GLP-1 receptor agonist has demonstrated value, retarding the point where insulin has to be used [26, 64]. This solution is undoubtedly more effective than oral triple therapy including a gliptin in patients whose type 2 diabetes has already reached an advanced stage, even though evidence from a direct-comparison controlled clinical trial is still lacking (available trials have to date concerned patients treated with metformin alone) [52, 53, 55, 56] (Table 2). This option would also favor weight loss, in contrast with the weight gain generally observed with insulin or a glitazone [26]. Finally, recent studies indicate the usefulness of associating a DPP-4 inhibitor or a GLP-1 receptor agonist for type 2 diabetes patients who start requiring insulin, with an insulin-sparing goal, reduced risk of hypoglycemia, and less weight gain [26]. Thus there is little doubt that in the future the field of action of incretins will broaden still further among the therapeutic modalities for type 2 diabetes [2].

6. Conclusion

Considering available data, there is no evidence that GLP-1 receptor agonists are superior to DPP-4 inhibitors [7], or vice-versa [6]. In fact, the two incretin classes each have their advantages and disadvantages if one considers the parameters of importance for routine clinical management, i.e. efficacy, tolerance, ease of use, and cost. Furthermore, individual profiles of type 2 diabetes patients are quite variable such that treatment should be patient-centered, i.e. whenever possible, adjusted to individual patient characteristics, therapeutic objectives (to be discussed and determined in agreement with the patient), available resources, and patient preferences [60]. This article provides a few key elements, which may be useful for guiding the clinician managing an increasingly complex disease, type 2 diabetes, and its evolving cohort of complications, particularly cardiovascular complications.

Table 2

<table>
<thead>
<tr>
<th>Reference</th>
<th>Duration (wk)</th>
<th>Intervention</th>
<th>n</th>
<th>Baseline HbA1c (%)</th>
<th>ΔHbA1c (%)</th>
<th>HbA1c &lt; 7% (%)</th>
<th>Fasting glycaemia (mmol/l)</th>
<th>Δ weight (kg)</th>
<th>Blood pressure syst/dia (mmHg)</th>
<th>Heart rate bpm</th>
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<tr>
<td>DeFronzo et al., 2008 [51]</td>
<td>2</td>
<td>Sitagliptin</td>
<td>61</td>
<td>8.5</td>
<td>nd</td>
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<td>−0.03</td>
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<td>Exenatide 2 × 5 µg — 2 × 10 µg</td>
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<td>Exenatide 2 mg weekly</td>
<td>160</td>
<td>8.6</td>
<td>−0.31</td>
<td>+17</td>
<td>−0.7</td>
<td>−1.1</td>
<td>−2.7/nd</td>
<td>nd</td>
</tr>
<tr>
<td>Wysham et al., 2011 [53]</td>
<td>52</td>
<td>From sitagliptin to exenatide (26–52 weeks)</td>
<td>116</td>
<td>7.5</td>
<td>−1.15</td>
<td>43</td>
<td>−1.1</td>
<td>−0.8</td>
<td>−1.8/nd</td>
<td>+0.5</td>
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<tr>
<td>Russel-Jones et al., 2012 [54]</td>
<td>26</td>
<td>Sitagliptin</td>
<td>163</td>
<td>8.8</td>
<td>−1.53</td>
<td>63</td>
<td>−2.3</td>
<td>−2.0</td>
<td>−1.3/nd</td>
<td>+1.5</td>
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<tr>
<td></td>
<td></td>
<td>Exenatide 2 mg weekly</td>
<td>248</td>
<td>8.5</td>
<td>−0.83</td>
<td>21</td>
<td>−0.96</td>
<td>−1.78/−0.64</td>
<td>−0.64</td>
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</tr>
<tr>
<td>Pratley et al., 2010 [55]</td>
<td>26</td>
<td>Sitagliptin</td>
<td>219</td>
<td>8.5</td>
<td>−1.24</td>
<td>44</td>
<td>−1.87</td>
<td>−2.86</td>
<td>−0.55/−0.71</td>
<td>+2.32</td>
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<td>Liraglutide 1.2 mg</td>
<td>225</td>
<td>8.4</td>
<td>−1.50</td>
<td>55</td>
<td>−2.14</td>
<td>−3.38</td>
<td>−0.72/0.07</td>
<td>+3.94</td>
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<tr>
<td></td>
<td></td>
<td>Sitagliptin</td>
<td>221</td>
<td>8.4</td>
<td>−1.51</td>
<td>63</td>
<td>−1.51</td>
<td>−2.87/−0.53</td>
<td>+1.72</td>
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<tr>
<td>Pratley et al., 2011 [56]</td>
<td>52</td>
<td>Sitagliptin</td>
<td>151</td>
<td>8.5</td>
<td>−1.29</td>
<td>50</td>
<td>nd</td>
<td>−1.16</td>
<td>−1.03/−1.47</td>
<td>+0.09</td>
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<tr>
<td></td>
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<td>Liraglutide 1.2 mg</td>
<td>135</td>
<td>8.4</td>
<td>−1.39</td>
<td>50</td>
<td>nd</td>
<td>−2.78/−0.53</td>
<td>+1.72</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>Liraglutide 1.8 mg</td>
<td>150</td>
<td>8.4</td>
<td>−1.51</td>
<td>63</td>
<td>nd</td>
<td>−3.68/−0.87</td>
<td>+3.09</td>
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</tr>
</tbody>
</table>

Δ: change versus baseline; nd: not done; sys/dia: systolic/diastolic; bpm: beats per minute.

a Short-duration cross-over study.

b Same study as preceding with one year follow-up.
Disclosure of interest

The author declares that he has no conflicts of interest concerning this article.

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References


