Dipeptidyl peptidase-4 inhibitors in the treatment of type 2 diabetes: a comparative review

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The dipeptidyl peptidase (DPP)-4 inhibitors are a new class of antihyperglycaemic agents which were developed for the treatment of type 2 diabetes by rational drug design, based on an understanding of the underlying mechanism of action and knowledge of the structure of the target enzyme. Although they differ in terms of their chemistry, they are all small molecules which are orally available. There are some differences between them in terms of their absorption, distribution, metabolism and elimination, as well as in their potency and duration of action, but their efficacy, both in terms of inhibiting plasma DPP-4 activity and as antidiabetic agents, appears to be similar. They improve glycaemic control, reducing both fasting and postprandial glucose levels to lower HbA1c levels, without weight gain and with an apparently benign adverse event profile. At present, there seems to be little to distinguish between the different inhibitors in terms of their efficacy as antidiabetic agents and their safety. Long-term accumulated clinical experience will reveal whether compound-related characteristics lead to any clinically relevant differences.

Keywords: alogliptin, antidiabetic drug, diabetes mellitus, DPP-4, GLP-1, glycaemic control, incretin, linagliptin, saxagliptin, sitagliptin, vildagliptin

Introduction

Therapies for type 2 diabetes (T2DM) based on the actions of the incretin hormone, glucagon-like peptide-1 (GLP-1), were first introduced in 2005. GLP-1 is an intestinal hormone, which has been shown to play an important role in the normal regulation of glucose homeostasis. It has a number of effects that contribute to the maintenance of glucose tolerance, such as improvements in α- and β-cell function, including the glucose-dependent stimulation of insulin and suppression of glucagon secretion, as well as non-pancreatic effects such as delaying gastric emptying and suppression of appetite [1]. These actions are preserved in patients with T2DM, and the first clinical-proof-of-concept study, published in 2002, showed that GLP-1 could reduce HbA1c levels in T2DM patients when given by continuous subcutaneous infusion [2].

GLP-1 is, however, a labile peptide and is rapidly removed from the circulation by a combination of degradation and renal clearance. The enzyme that is responsible for the initial cleavage of GLP-1 (whereby it loses its insulinotropic action) in vivo is the serine protease dipeptidyl peptidase (DPP)-4. The identification of its key role in the metabolic clearance of GLP-1 in humans provided the rationale for inhibiting the enzyme (in order to increase the levels of endogenous intact GLP-1) as a therapy of T2DM [3]. Preclinical studies showing that DPP-4 inhibition could prevent the degradation of GLP-1 in vivo, leading to increased insulinotropic activity [4], were followed by the first demonstration in humans, that a DPP-4 inhibitor could improve glycaemic control in subjects with T2DM [5].

The principle of using DPP-4 inhibitors as therapy of T2DM [1,6] is now firmly established, and numerous inhibitors are in varying stages of clinical development, with four already approved: sitagliptin in 2006, vildagliptin in 2007 and more recently, saxagliptin in 2009 and alogliptin in 2010 (presently only in Japan). The purpose of this article is to review briefly the five leading compounds in the DPP-4 inhibitor class (sitagliptin, vildagliptin, saxagliptin, alogliptin and linagliptin, currently in phase 3 clinical development), with special emphasis on any features which may help to distinguish between them.

Chemistry

As a therapeutic class, the DPP-4 inhibitors comprise a diverse group of compounds, which can be broadly divided into those that mimic the dipeptide structure of DPP-4 substrates and those which are non-peptidomimetic. Compounds such as sitagliptin (β-amino acid based) [7–9], and vildagliptin [10–12] and saxagliptin [13,14], which are nitrile-containing inhibitors, belong to the former class, whereas alogliptin (modified pyrimidinedione) [15,16] and linagliptin (xanthine-based) [17,18] are members of the latter (figure 1, Table 1).

The compounds which have been developed for therapeutic use are all competitive reversible inhibitors, which display high affinity for DPP-4, resulting in inhibition constants ($K_i$) in the low nanomolar range [13,19–21]. There are, however, differences in the way in which they interact with the enzyme.
Thus, sitagliptin, alogliptin and linagliptin form non-covalent interactions with residues in the catalytic site [7,15,17]. In contrast, inhibition of DPP-4 by vildagliptin and saxagliptin has been described as a two-step process that involves the formation of a reversible covalent enzyme–inhibitor complex in which there is a slow rate of inhibitor binding and a slow rate of inhibitor dissociation, resulting in the enzyme slowly equilibrating between the active and inactive forms [22–24]. This means that the catalytic activity will be inhibited even after the free drug has been cleared from the circulation and may help to explain why vildagliptin and saxagliptin inhibit DPP-4 activity for longer than their relatively short half-lives would suggest. This may have repercussions in terms of their durations of action and dosing frequencies (see below).

**Potency and DPP-4 Inhibitory Efficacy**

Although the described DPP-4 inhibitors are all competitive reversible inhibitors, it can be difficult to compare them using data reported in individual studies, because these are influenced by differences in the assay conditions used to estimate the extent of DPP-4 inhibition. However, one study in which the inhibitors were directly compared under identical experimental conditions reported that all five inhibitors showed similar efficacy (i.e. maximal effect) for inhibition of DPP-4 in vitro, but that there were differences in potency (i.e. amount of compound needed; IC$_{50}$ = $\sim$1 nM for linagliptin vs. 19, 62, 50 and 24 nM, for sitagliptin, vildagliptin, saxagliptin and alogliptin, respectively) [19]. With regard to half-life, there are also differences between the various inhibitors. Vildagliptin [12,25] and saxagliptin [14,26] are cleared from the plasma relatively quickly, whereas sitagliptin [9,27], alogliptin [28] and linagliptin [29] have much longer survival times (Table 2, figure 2). These differences are reflected in the therapeutic doses, which range from 5 mg for saxagliptin to 100 mg for sitagliptin, and in the dosing frequency (once daily for most of them, twice daily for vildagliptin; Table 2). Nevertheless, despite the differences in potency, when used at their therapeutic doses, the effects of the inhibitors, in terms of the extent of DPP-4 inhibition *in vivo*, are broadly

**Table 1.** Chemistry, metabolism and elimination of dipeptidyl peptidase (DPP)-4 inhibitors.

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>Chemistry</th>
<th>Metabolism</th>
<th>Elimination route</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitagliptin [7–9]</td>
<td>β-amino acid-based</td>
<td>Not appreciably metabolized</td>
<td>Renal (~80% unchanged as parent)</td>
</tr>
<tr>
<td>Vildagliptin [10–12]</td>
<td>Cyanopyrrolidine</td>
<td>Hydrolysed to inactive metabolite (P$_{450}$ enzyme independent)</td>
<td>Renal (22% as parent, 55% as primary metabolite)</td>
</tr>
<tr>
<td>Saxagliptin [13,14]</td>
<td>Cyanopyrrolidine</td>
<td>Hepatically metabolized to active metabolite (via P$_{450}$ 3A4/5)</td>
<td>Renal (12–29% as parent, 21–52% as metabolite)</td>
</tr>
<tr>
<td>Alogliptin [15,16]</td>
<td>Modified pyrimidineone</td>
<td>Not appreciably metabolized</td>
<td>Renal (&gt;70% unchanged as parent)</td>
</tr>
<tr>
<td>Linagliptin [17,18]</td>
<td>Xanthine-based</td>
<td>Not appreciably metabolized</td>
<td>Biliary (&gt;70% unchanged as parent); &lt;6% via kidney</td>
</tr>
</tbody>
</table>
**Table 2.** Half-life, potency (dose) and dipeptidyl peptidase (DPP-4) inhibitory efficacy of DPP-4 inhibitors.

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>Compound $t_{1/2}$ (h)</th>
<th>Dosing</th>
<th>DPP-4 inhibition*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitagliptin [9,27]</td>
<td>8–24</td>
<td>100 mg qd</td>
<td>Max ~97%; &gt;80% 24 h postdose</td>
</tr>
<tr>
<td>Vildagliptin [12,25]</td>
<td>1 $\frac{1}{2}$–4 $\frac{1}{2}$</td>
<td>50 mg bid</td>
<td>Max ~95%; &gt;80% 12 h postdose</td>
</tr>
<tr>
<td>Saxagliptin [14,26]</td>
<td>2–4 (parent) 3–7 (metabolite)</td>
<td>5 mg qd</td>
<td>Max ~80%; &gt;70% 24 h postdose</td>
</tr>
<tr>
<td>Alogliptin [28]</td>
<td>12–21</td>
<td>25 mg qd</td>
<td>Max ~90%; ~75% 24 h postdose</td>
</tr>
<tr>
<td>Linagliptin [29]</td>
<td>10–40</td>
<td>5 mg qd (anticipated)</td>
<td>Max ~80%; ~70% 24 h postdose</td>
</tr>
</tbody>
</table>

* DPP-4 activity measured in human plasma *ex vivo*; not corrected for sample dilution in the assay.

Similar. Over 90% inhibition is attained within 15 min of inhibitor administration, with around 70–90% inhibition being sustained at 24 h postdose (Table 2, figure 2); for vildagliptin, although the extent of plasma DPP-4 inhibition drops to around 50% after 24 h with the 50 mg dose, the weekly therapeutic dosing regimen maintains plasma DPP-4 inhibition at >80% over the full 24-h period. However, it should be pointed out that plasma DPP-4 activity is assessed *ex vivo* (i.e. in plasma samples taken after *in vivo* dosing) and is generally not corrected for the inherent dilution of the sample in the assay. Hence, the true extent of DPP-4 inhibition *in vivo* is probably higher than the measured values suggest.

**Selectivity**

DPP-4 is a member of a family of proteases, two of which (DPP-8 and -9) have been implicated in preclinical toxicities and suppression of T-cell activation and proliferation in some [30,31], but not all [20] studies; in order to minimize any potential off-target side effects, the inhibitors intended to be used therapeutically have, therefore, been chosen with this in mind (Table 3). Thus, in this respect, sitagliptin and alogliptin can both be described as being highly selective; they essentially show no inhibitory activity against other members of the DPP-4 family when tested *in vitro* [7,15]. Vildagliptin and saxagliptin are somewhat less selective with regard to inhibition of DPP-8/9 *in vitro* [20,21], although whether this has any significance *in vivo* is questionable because DPP-8/9 are located intracellularly. Linagliptin, while being selective with regard to DPP-8/9, is less selective with regard to fibroblast activation protein-$\alpha$ (FAP-$\alpha$)/seprase [19]. FAP-$\alpha$ is an extracellular enzyme which is not generally present in normal adult tissue (although it is expressed in stromal fibroblasts and upregulated during tissue remodelling) [32]. However, the extent of any FAP-$\alpha$ inhibition *in vivo* with the therapeutic dose of linagliptin in humans has not been reported.

**Table 3.** *In vitro* selectivity of dipeptidyl peptidase (DPP)-4 inhibitors (fold selectivity for DPP-4 vs. other enzymes).

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>Selectivity</th>
<th>QPP/DPP-2</th>
<th>PEP</th>
<th>FAP-$\alpha$</th>
<th>DPP-8</th>
<th>DPP-9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitagliptin [7]</td>
<td>High</td>
<td>&gt;5550</td>
<td>&gt;5550</td>
<td>&gt;5550</td>
<td>&gt;2660</td>
<td>&gt;5550</td>
</tr>
<tr>
<td>Vildagliptin [10,20]</td>
<td>Moderate</td>
<td>&gt;100 000</td>
<td>60 000</td>
<td>285</td>
<td>270</td>
<td>32</td>
</tr>
<tr>
<td>Saxagliptin [21]</td>
<td>Moderate</td>
<td>&gt;50 000</td>
<td>Not reported</td>
<td>&gt;4000</td>
<td>390</td>
<td>77</td>
</tr>
<tr>
<td>Alogliptin [15]</td>
<td>High</td>
<td>&gt;14 000</td>
<td>&gt;14 000</td>
<td>&gt;14 000</td>
<td>&gt;14 000</td>
<td>&gt;14 000</td>
</tr>
<tr>
<td>Linagliptin [19]</td>
<td>Moderate</td>
<td>&gt;100 000</td>
<td>&gt;100 000</td>
<td>89</td>
<td>40 000</td>
<td>&gt;10 000</td>
</tr>
</tbody>
</table>

QPP, quiescent cell proline dipeptidase; PEP, prolyl endopeptidase; FAP-$\alpha$, fibroblast activation protein-$\alpha$.
Absorption

The DPP-4 inhibitors are all orally available and are rapidly absorbed (figure 2), with significant inhibition of plasma DPP-4 activity being seen within 5 min of administration. Oral bioavailability in humans is generally high (~87% for sitagliptin [33], 85% for vildagliptin [34] and ~67% for saxagliptin [35]), although somewhat lower for linagliptin (~30%) [36].

Distribution

Where available, data indicate that the volume of distribution of the various inhibitors in humans is greater than the total body water (~70 l for vildagliptin [12], 198 l for sitagliptin [9], 300 l for alogliptin [28] and ~2.7 l/kg for saxagliptin [35]), suggesting that these compounds distribute widely into the tissues. However, although their chemistries suggest that they are unlikely to diffuse freely over the cell membrane, whether or not they actually cross the cell membrane has not been studied in detail and no information is available for sitagliptin, alogliptin or linagliptin. The intrinsic membrane permeability of saxagliptin is reported to be very low, and neither saxagliptin nor its major metabolite (BMS-510849) is a prominent substrate for multidrug resistance P-glycoprotein (Pgp) transporters or for cellular uptake transporters [26]. There is some indirect evidence that vildagliptin may be able to cross the cell membrane. Thus, it has been reported that at very high doses (>600 times the human dose), vildagliptin inhibits DPP-8/9 in vivo in rats [20]; because DPP-8/9 are located in the cytosol, this would suggest that vildagliptin does have some access to the intracellular compartment, but it is unclear whether this occurs in humans with the therapeutic dose.

In the plasma, most of the inhibitors display low, reversible protein binding (38% for sitagliptin [33], 10% for vildagliptin [11,12] and negligible for saxagliptin [14]). In contrast, linagliptin binds extensively to plasma proteins in a concentration-dependent manner and it has been calculated that at the therapeutic dose (5 mg) most of the drug will be protein bound (primarily to DPP-4) [37].

Preclinical studies have revealed that the highest concentrations of the drugs are found in the intestines, kidney and liver [9,12,14,38], which, notably, are also the tissues with the highest expression of DPP-4. Available information indicates that very low levels of the inhibitors are found in the brain (saxagliptin and its primary metabolite [35], vildagliptin [12] and linagliptin [38]), suggesting that the compounds may not cross the blood–brain barrier. However, they do appear to be able to cross the placenta freely (saxagliptin [14], vildagliptin [12] and sitagliptin [9]).

Metabolism

Sitagliptin, alogliptin and linagliptin do not undergo appreciable metabolism in vivo in humans; around 80% of the dose is eliminated unchanged as the parent compound (Table 1). For sitagliptin, the limited metabolism produces six metabolites in trace amounts (each accounting for <1% to 7% of sitagliptin-related material in plasma), with in vitro studies indicating that the primary enzyme responsible is CYP3A4 with a lesser contribution from CYP2C8 [8]. Three of these metabolites (M1, M2 and M5) are active, but are not expected to contribute to the pharmacodynamic profile of sitagliptin because of the combination of low plasma concentration and low affinity for DPP-4 [8,9]. For alogliptin, the parent molecule accounts for >80% of alogliptin-related material in plasma and two minor metabolites have been identified, N-demethylated (active) and N-acetylated (inactive) alogliptin, accounting for less than 1% and approximately 5%, respectively [16]. In the case of linagliptin, the parent compound made up around 70% of drug-related material in plasma, while exposure to the major metabolite (CD1790, identified as S-3-hydroxyperipendinyl derivative of linagliptin) was around 18% of that of the parent compound. Formation of CD1790, which is pharmacologically inactive, is dependent upon CYP3A4. In addition, seven minor metabolites (each accounting for 0.3 to <5% of linagliptin-related material in plasma) were identified [18].

In contrast, both vildagliptin and saxagliptin undergo extensive metabolism in humans (Table 1). The major metabolic pathway for vildagliptin is hydrolysis at its cyano moiety, which occurs in the liver and other tissues via a CYP450-independent mechanism, to produce a carboxylic acid metabolite (M20.7/LAY151) and four minor metabolites. The parent molecule and the major metabolite, which is pharmacologically inactive, account for the majority of vildagliptin-related material in the plasma (approximately 72% and 55%, respectively) [11,12]. Saxagliptin is heptatically metabolized by CYP3A4/5 to produce a major metabolite (5-hydroxy saxagliptin; BMS-510849), which is also a competitive, reversible inhibitor of DPP-4 with approximately 50% of the potency of the parent drug. Systemic exposure to saxagliptin-related material is accounted for by the parent molecule (22%) and BMS-510849 plus other unidentified minor monohydroxylated metabolites (76%) [14].

Excretion

Generally, the DPP-4 inhibitors are eliminated primarily via the kidney, with the rate of renal clearance exceeding glomerular filtration, suggesting that active transport is involved. For sitagliptin, around 70% of the dose is excreted as the parent molecule and active transport has been shown to account for around 50% of its clearance [39]; the human organic anion transporter (OAT)-3, organic anion transporting polypeptide (OATP)-4C1 and Pgp transporters in the proximal tubule have been indicated to be involved [40]. Alogliptin (and its minor metabolites) is renally eliminated, with around 60–70% of the dose appearing in the urine as the parent compound [28,41]. Clearance of alogliptin is greater than normal glomerular filtration, but the renal transporters involved have not been identified, although drug-interaction studies suggest that Pgp is unlikely to be involved [28]. Similarly, both saxagliptin and its primary metabolite (BMS-510849) are primarily renally eliminated, accounting for 24 and 36% of the dose, respectively [14]. Again, renal clearance of the parent compound is greater than the glomerular filtration rate, indicating the involvement of active renal secretion, but the mechanism is unknown; saxagliptin is reported not to be a substrate for OAT1, OAT3, OATPA, OATPC, OATP8, organic cation transporter
alogliptin, were reported to be associated with adverse skin toxicity in monkeys. However, this may be a finding which is specific to monkeys, as it has not been observed in other preclinical species, and importantly, there have been no reports of skin problems in the clinical trials with any of the inhibitors [12,14,55–57].

For saxagliptin, small, reversible, dose-dependent reductions in absolute lymphocyte count have been noted in some of the clinical trials, but this has not been reported for the other DPP-4 inhibitors. The effect was more apparent at saxagliptin doses ≥20 mg (which is greater than the therapeutic dose), but values still remained within normal limits [14,58]. There was no effect on white blood cell or neutrophil count and no evidence of altered immune function. At present, the clinical significance of this (if any) remains unknown.

At the time of initial registration of vildagliptin (in EU), a meta-analysis of the clinical trial data revealed that the 100 mg qd dose was associated with small numerical elevations in liver transaminases compared to placebo or 50 mg bid. For this reason, the recommended therapeutic dose was changed to 50 mg bid, with the recommendation that liver function tests be performed before initiation and at three monthly intervals for the first year of treatment and periodically thereafter [12,59]. Subsequently, the trend for mild increases (greater than three times the upper limit of normal) in liver enzymes was confirmed in the larger pooled safety analysis, but notably, this was not associated with any increased incidence of actual hepatic adverse events [56]. Nevertheless, liver function tests are still recommended and vildagliptin is not approved for use in patients with hepatic insufficiency (see later).

Despite the above observations, overall, the DPP-4 inhibitors as a class appear to be very well tolerated, and rates of adverse effects have been low, and generally not different to placebo or comparator. An early meta-analysis of incretin-based therapies (in which inhibitor data were available only for sitagliptin and vildagliptin) did, however, suggest that there was an increased risk of some infections (urinary tract infections with both inhibitors and nasopharyngitis more evident with sitagliptin) and headache (more evident with vildagliptin) [60,61]. Since then, updated safety analyses (each >10 000 patients, exposed for up to 2 years) of the sitagliptin and vildagliptin clinical trials have been published, showing no increased risk for urinary tract or respiratory infections or headache (and indeed, no increased risk of any other adverse effect) with the DPP-4 inhibitors compared to placebo or comparator [55,56]. Notably, recent debate over potential links between some antidiabetic medications and cancer [62] or bone fracture [63] does not seem to extend to the DPP-4 inhibitors, with no evidence for increased signals being observed in the safety analyses [55,56]. Cardiovascular safety of new drugs, including antihyperglycaemic agents, has also been the focus of concern, with the FDA requiring pharmaceutical companies to show that new agents to not increase the risk of adverse cardiovascular events. Retrospective analyses of data from the clinical development programmes of sitagliptin, vildagliptin and saxagliptin do not appear to indicate any increased cardiovascular risk with the DPP-4 inhibitors relative to comparators [55,64,65], but large prospective trials, designed specifically to evaluate the effect of sitagliptin, saxagliptin and
renal insufficiency, with the rate of adverse events being similar.

vildagliptin is reported to be well tolerated in patients with mild

jects with impaired renal function [12,14], and as for sitagliptin,

to vildagliptin and saxagliptin is also similarly increased in sub-

trol over 1 year and was generally well tolerated [71]. Exposure

ESRD on dialysis), sitagliptin provided effective glycaemic con-

cate or severe chronic renal insufficiency (including those with

§Dose reduction (2.5 mg) when saxagliptin co-administered with strong cytochrome P450 3A4/5 inhibitors (e.g. ketoconazole).

†Not studied/no clinical experience.

∗CrCl, creatinine clearance; ESRD, end-stage renal disease.

Table 4. Prescribing characteristics of dipeptidyl peptidase (DPP)-4 inhibitors.

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>Renal insufficiency*</th>
<th>Hepatic insufficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mild (CrCl ≥50 ml/min)</td>
<td>Moderate (CrCl ≥30–&lt;50 ml/min)</td>
</tr>
<tr>
<td>Sitagliptin (launched EU, USA)</td>
<td>✓</td>
<td>Presently not recommended (EU) 1/2 dose (USA)†</td>
</tr>
<tr>
<td>Vildagliptin† (launched EU)</td>
<td>✓</td>
<td>Presently not recommended†</td>
</tr>
<tr>
<td>Saxagliptin§ (launched EU, USA)</td>
<td>✓</td>
<td>Presently not recommended†</td>
</tr>
<tr>
<td>Alogliptin (launched Japan)</td>
<td>✓</td>
<td>1/2 dose</td>
</tr>
<tr>
<td>Linagliptin (not yet approved)</td>
<td>✓ (likely)</td>
<td>✓ (likely)</td>
</tr>
</tbody>
</table>

CrCl, creatinine clearance; ESRD, end-stage renal disease.

*Assessment of renal function recommended prior to initiation of treatment and periodically thereafter.
†Not studied/no clinical experience.
‡Assessment of hepatic function recommended prior to initiation of vildagliptin and periodically thereafter.
§Dose reduction (2.5 mg) when saxagliptin co-administered with strong cytochrome P450 3A4/5 inhibitors (e.g. ketoconazole).

alogliptin on cardiovascular outcomes are underway. There has also been some debate over whether incretin-based therapies, including the DPP-4 inhibitors, are associated with elevated risk of pancreatitis [66]. This does not seem to be borne out by the pooled safety analyses [56,67] or retrospective analyses of large healthcare data bases [68,69]. Continued vigilance and longer term reports are still needed to confirm these observations.

Use in Patient Subpopulations

Renal Insufficiency

Because most of the described DPP-4 inhibitors are eliminated renally, it might be expected that their pharmacokinetic profile would be influenced by impairments in renal function. In line with this, exposure to sitagliptin increased proportionately to the degree of renal failure, but the drug was well tolerated, even in patients with end-stage renal disease (ESRD), including those on dialysis; the fraction removed by dialysis was small (∼13% for haemodialysis started at 4 h postdose) [70]. Based on this study, it was concluded that no dose adjustment was necessary in subjects with mild renal insufficiency [creatinine clearance (CrCl) 50–80 ml/min]. However, in order to maintain plasma sitagliptin exposure comparable to that in subjects with normal renal function, in subjects with moderate renal insufficiency (CrCl 30–50 ml/min) or severe renal insufficiency (CrCl <30 ml/min)/ESRD, dose reductions of 50 and 75%, respectively, are required [70]. In T2DM patients with moderate or severe chronic renal insufficiency (including those with ESRD on dialysis), sitagliptin provided effective glycaemic control over 1 year and was generally well tolerated [71]. Exposure to vildagliptin and saxagliptin is also similarly increased in subjects with impaired renal function [12,14], and as for sitagliptin, vildagliptin is reported to be well tolerated in patients with mild renal insufficiency, with the rate of adverse events being similar to comparators [56]; no data are yet available in patients with moderate or severe renal impairment (Table 4).

On the basis of these observations, sitagliptin, vildagliptin and saxagliptin have been approved for use in subjects with mild renal insufficiency without dose adjustment, and where the indication is approved, sitagliptin and saxagliptin can be used in patients with moderate or severe renal insufficiency/ESRD with appropriate dose adjustment (Table 4). Alogliptin is also eliminated renally and can be used in subjects with moderate or severe renal impairment with dose reduction (Table 4). Because linagliptin is not predominantly eliminated via the kidneys, it could be anticipated that this drug might be able to be used in renal disease patients, including those with severe renal insufficiency/ESRD without the need for any dose adjustment [72].

Hepatic Insufficiency

The DPP-4 inhibitors generally appear to be well tolerated in patients with hepatic impairment and there seems to be no clinically meaningful impact of hepatic insufficiency on their pharmacokinetics. Thus, in subjects with moderate hepatic impairment, exposure to sitagliptin was slightly, but non-significantly increased [73], whereas exposure to alogliptin was slightly decreased [74]. For vildagliptin, exposure to the parent drug showed non-significant trends to decrease in patients with mild or moderate hepatic impairment and to increase in patients with severe hepatic impairment, whereas exposure to the primary (inactive) metabolite (M20.7) increased non-significantly in all groups, compared with healthy subjects [75]. In line with its hepatic metabolism, saxagliptin exposure increased and that of the active metabolite (BMS-510849) decreased in subjects with hepatic impairment [14].

Overall, these studies suggested that no dose adjustment will be necessary in patients with hepatic impairment. Vildagliptin
is, however, not recommended for use in patients with hepatic insufficiency or those with pretreatment alanine aminotransferase or aspartate aminotransferase at greater than three times the upper limit of normal (because of the association of vildagliptin with mild increases in hepatic transaminases; see above). The other DPP-4 inhibitors which have been approved can be used in patients with mild/moderate hepatic insufficiency without dose adjustment (Table 4), although because hepatic impairment increases exposure to saxagliptin (in accord with its hepatic metabolism; see above), caution is required if used in subjects with moderate hepatic insufficiency [14]. At present, limited data in subjects with severe hepatic impairment mean that the DPP-4 inhibitors are currently not recommended for use in this patient group. Because the liver is the primary route of elimination for linagliptin, it could be anticipated that linagliptin may require dose adjustment or may not be recommended for use in subjects with hepatic impairment.

**Antidiabetic Efficacy**

As might be expected from their similar efficacy in inhibiting DPP-4 activity (see above), broadly speaking, the DPP-4 inhibitors all seem to show similar efficacy in lowering HbA1c levels, although it must be stressed that these are observations made in different studies and so must be interpreted with some caution (figure 3). At present, data are available only from one direct head-to-head comparison between the inhibitors, in which the efficacy of saxagliptin and sitagliptin as add-on therapy in metformin-treated patients was compared [76]. This showed non-inferiority of saxagliptin to sitagliptin in terms of HbA1c lowering (−0.5 vs. −0.6% from a baseline of ~7.7%; i.e. from 60 to 55 mmol/mol for saxagliptin vs. from 61 to 54 mmol/mol for sitagliptin) at week 18, with similar proportions of subjects (26 vs. 29%) reaching target HbA1c levels of <6.5% (<48 mmol/mol). However, in terms of the reduction in fasting plasma glucose, it did appear that there might be a small difference, with sitagliptin being more efficacious (−0.6 vs. −0.9 mmol/l; difference 0.30 ± 0.115 mmol/l, 95% confidence interval: 0.08–0.53); this could potentially be related to differences in the half-life of the compounds (Table 2, figure 2). In other direct head-to-head studies, the DPP-4 inhibitors have shown similar efficacy to metformin [77,78], the sulphonylureas [79,80], the glitazones [81,82] and the alpha-glucosidase inhibitors [83]. In line with other antidiabetic agents [84], greater reductions in HbA1c are seen in subjects with higher baseline levels (figure 3).

**Figure 3.** HbA1c lowering efficacy of dipeptidyl peptidase (DPP)-4 inhibitors in relation to baseline HbA1c levels, as monotherapy or add-on therapy (open symbols) or initial combination therapy (closed symbols) in studies of ≥12 weeks duration (see Appendix for references). Triangle, sitagliptin (100 mg qd); circle, vildagliptin (50 mg bid or 100 mg qd); square, saxagliptin (5 mg qd); diamond, alogliptin (25 mg qd) and star, linagliptin (5 mg qd).

**Conclusions**

The DPP-4 inhibitors are the first new therapeutic class of oral antihyperglycaemic drug for T2DM for many years. They were designed for the treatment of the disease based on prior knowledge of the physiology of the incretin hormone GLP-1 and an understanding of the target (DPP-4), contrasting with the development of other antidiabetic agents whose blood glucose-lowering effects were initially discovered more by chance than by design without fully knowing the underlying mechanisms (e.g. metformin, sulphonylureas and glitazones). Identification of the 3-dimensional/tertiary structure of the DPP-4 protein allowed the rational design of small molecule inhibitors which interact only with the catalytic site without interfering in any of the other functions of the DPP-4/CD26 molecule. This, together with the understanding of the role of GLP-1 in glucose homeostasis and its unique susceptibility to cleavage by DPP-4, probably accounts for the remarkable lack of adverse effects so far associated with the therapeutic use of the DPP-4 inhibitors.

As a class, the DPP-4 inhibitors comprise of a group of chemically diverse compounds, which differ in terms of their potency to inhibit the DPP-4 enzyme, their duration of action and their metabolism and elimination, as well as isolated compound-specific characteristics (Table 5). They are all apparently well tolerated (side-effect profile resembles placebo) and result in clinically meaningful reductions in blood glucose (fasting and postprandial) and HbA1c levels, with minimal risk of hypoglycaemia and without weight gain—in this latter respect, they are better than all other agents except metformin and the incretin mimetics. They are used without the need for dose titration and give broadly similar HbA1c lowering efficacy to other oral antidiabetic agents; they are compatible with first-line therapy and they give predictable additivity to other agents, where they can be used without dose adjustment of either agent.

At present, although there are some practical differences between the different DPP-4 inhibitors with respect to dosing frequency and their ability to be used in different patient subpopulations, there seems to be little to distinguish between them in terms of their efficacy as antidiabetic agents and their safety. Only long-term accumulated clinical experience will reveal whether compound-related characteristics lead to any clinically relevant differences.
**Table 5.** Differences and similarities between dipeptidyl peptidase (DPP)-4 inhibitors.

<table>
<thead>
<tr>
<th>Differences</th>
<th>Similarities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical structures</td>
<td>Efficacy (HbA1c lowering)</td>
</tr>
<tr>
<td>In vitro selectivity</td>
<td>Safety</td>
</tr>
<tr>
<td>Metabolism (changed/unchanged, active/inactive metabolite)</td>
<td>Tolerability</td>
</tr>
<tr>
<td>Elimination (renal/hepatic)</td>
<td></td>
</tr>
<tr>
<td>Preclinical toxicities</td>
<td></td>
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<tr>
<td>Potency (therapeutic dose)</td>
<td></td>
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<tr>
<td>Dosing frequency (once/twice daily)</td>
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<tr>
<td>Use in patient subpopulations (e.g. impaired renal/hepatic function)</td>
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</tr>
</tbody>
</table>

**Conflict of Interest**

As this is a single author review, C. F. Deacon was responsible for all aspects of the manuscript. CFD has received consultancy/lecture fees from companies with an interest in developing and marketing incretin-based therapies for the treatment of type 2 diabetes (Astra Zeneca/BMS, Lilly, Merck, Novartis, Novo Nordisk, Servier). Spouse is employed by Merck and holds stock options in Merck and Novo Nordisk.

**References**

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review article


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Appendix

List of references to studies where HbA1c lowering efficacy is included in figure 3.

Sitagliptin


Saxagliptin


Alogliptin


Linagliptin


