Vildagliptin for the treatment of diabetes

The prevalence of Type 2 diabetes (DM2) has reached epidemic proportions in essentially all industrialized nations. The burgeoning population of DM2 has been attributed to parallel increases in obesity, sedentary lifestyle and less healthy dietary component choices (e.g., high glycemic index foods). By the time DM2 is diagnosed, at least 50% of β-cell function has been lost; this loss appears to progress inexorably, despite treatment. Because control of glucose has been shown to reduce diabetic microvascular complications, and improve quality of life, tools that enhance this process are valuable to clinicians and patients alike. We have evolved in our understanding of DM2 to recognize that multiple metabolic defects contribute to this disorder. Accordingly, it is uncommon that any monotherapy can consistently provide durable control of DM2. Pharmacotherapies that address the multiple metabolic derangements now identified in DM2, especially amongst the incretin class, may also be helpful as they have often been found to be more 'user friendly' because they result in less weight gain, less hypoglycemia, and have the utility to be particularly useful for addressing postprandial glucose excursions. Our discussion will focus upon vildagliptin, an oral dipeptidyl peptidase type 4 inhibitor, one of the earliest oral incretin enhancers to be trialed in clinical use, and will be restricted to DM2, rather than Type 1 diabetes in which no role for noninsulin therapies has been clearly defined. Salutary metabolic effects of glucagon like peptide (GLP)-1 and glucose-dependent insulinotropic peptide or gastric inhibitory peptide have been difficult to capture, since their half-life is very brief (12 min). For GLP-1 and gastric inhibitory peptide, the enzyme responsible for degradation is DPP-4; hence, DPP-4 inhibitors delay GLP-1 degradation, prolonging the therapeutic effect. The two currently available novel therapeutic approaches to capture incretin effects are DPP-4 inhibition, and parenteral GLP-1 agonism (i.e., exenatide, liraglutide). As DM2 can uncommonly be controlled with monotherapy, it is important to evaluate add-on treatments. In a meta-analysis of 27 randomized controlled trials (mean duration 32 weeks) addressing DM2 inadequately controlled with metformin, comparable degrees of improved glucose control were achieved with various pharmacotherapeutic classes including α-glucosidase inhibitors, DPP-4 inhibitors, glinides, GLP-1 agonists, sulfonylurea and thiazolidinediones (TZD). Incretins and α-glucosidase inhibitors were associated with weight neutrality; as has been consistently noted in multiple trials, sulfonylurea and thiazolidinedione had a significant incidence of weight gain; hypoglycemia was more frequent with sulfonylurea.

KEYWORDS: dipeptidyl peptidase type 4 inhibitor ▪ gastric inhibitory peptide ▪ glucagon-like peptide 1 ▪ glucose-dependent insulinotropic polypeptide ▪ incretins ▪ Type 2 diabetes ▪ vildagliptin

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Vildagliptin is an oral incretin enhancer that acts to increase active levels of the incretin hormone glucagon-like peptide (GLP)-1 by inhibiting the dipeptidyl peptidase type 4 enzyme responsible for the rapid deactivation of GLP-1 *in vivo* [1]. This activity results in improved glucose-dependent functioning of pancreatic islet-β and α-cells, addressing two central deficits in Type 2 diabetes (DM2). Vildagliptin treatment improves β-cell sensitivity to glucose, producing increased insulin secretory rate relative to glucose in both postprandial and fasting states. Improved α-cell function is shown as restoration of appropriate glucose-related suppression of glucagon and, therefore, reduced endogenous glucose production during both postprandial and fasting periods. There is evidence that long-term vildagliptin treatment may slow underlying deterioration of β-cell function in DM2. There is also a potential synergistic effect of vildagliptin and metformin in increasing active GLP-1 levels, and this activity may contribute to the long-term improvements in β-cell function observed in patients with DM2 who have vildagliptin added to ongoing metformin therapy. Vildagliptin treatment has also been associated with beneficial extra pancreatic effects, including improved peripheral insulin sensitivity and improved postprandial triglyceride-rich lipoprotein metabolism. Vildagliptin is used

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as a combination therapy with other agents [2]. Improvement of β- and α-cell function through incretin enhancement with vildagliptin results in more physiologic meal-related and fasting glycemia profiles [3].

Type 2 diabetes is a complex progressive metabolic dysregulation disorder with multiple etiologies. The National Diabetes Fact Sheet (2011) indicates that 25.8 million people (8.3% of the population) in the USA, 60 million in Europe (2004) and 220 million in the world are suffering from diabetes [201]. Approximately 26.9% of adults in the USA over the age of 65 years of age suffer from DM2. Equally concerning is that more than 35% of adults over the age of 20 have prediabetes, that number is increasing to more than 50% of adults over 65. DM2 is a major cause for kidney failure, nontraumatic amputations, blindness, heart disease, stroke and mortality (seventh leading cause) among adults in the USA.

Among the adults with diabetes (Type 1 diabetes and DM2), it is estimated that 58% take oral agents, 12% take insulin only, 14% take both, with a small cohort managed with diet/exercise alone [202]. Clinical trials have demonstrated, in both DM2 and Type 1 diabetes, that improved A1C is associated with a reduction in the major microvascular complications. Nonetheless, problematic adverse effects of the most commonly used oral agents include hypoglycemia and weight gain, either of which can lead to noncompliance, as well as personal distress. Additionally concerning is the observational data that some commonly used DM2 pharmacotherapies might actually have an adverse effect on cardiovascular (CV) risk. For instance, a recent retrospective cohort study using the UK general practice research database with 91,521 patients found that all-cause mortality was 24–61% higher in subjects receiving a sulfonylurea (SU) than metformin. Chronic heart failure was increased 18–30%. In this same database, pioglitazone was associated with decreased (31–39%) all-cause mortality when compared to metformin. According to this analysis, not all thiazolidinediones (TZDs) share the same beneficial CV effects: rosiglitazone was associated with increased (34–41%) all-cause mortality when compared to pioglitazone [4–6].

Metformin has significant limitations in patients with renal disease and gastrointestinal (GI) side effects.

Why CV outcomes with pioglitazone are so different from rosiglitazone is not completely understood. However, lipid effects of the former have been consistently shown to be more favorable [4]. SU is associated with severe hypoglycemia and most likely to affect the elderly, those with worsening renal function, and those with irregular meal schedules [7]. Weight gain is a common side effect of SU. Some patients fail to respond after a few years of continued therapy (secondary failure) [8,9].

Incretins

It has been recognized for over a decade that oral administration of glucose induces a more prominent secretory response of insulin than when the same amount of glucose is given intravenously. This augmented insulin response has been termed the 'incretin effect', since it is attributed to intestinal incretins GLP-1 and gastric inhibitory peptide (GIP), which appear to be the mediators of this enhanced insulin secretion [10].

GIP/GLP activity at their respective receptors increases the intracellular cAMP in pancreatic β-cells and increases glucose-dependent insulin secretion. An additional favorable attribute of GLP is its effects upon glucagon. Although DM2 has been traditionally perceived solely as a β-cell disorder, recent recognition that α-cells (the source of glucagon) are also dysfunctional helps to explain both the observation of problematic postprandial hyperglycemia (persistent secretion of glucagon from dysfunctional α-cells resulting in continued gluconeogenesis despite hyperglycemia), and the recognition that incretins might be particularly useful to address postprandial hyperglycemia since they tend to reduce postprandial glucagon. There is reduced incretin secretion in DM2 and this is thought to be a secondary effect rather than a primary effect [11].

These receptors (GIP/GLP-1) are also represented in other tissues and organs including fat, bone and the brain. Although not yet confirmed in humans, it is thought provoking that animal studies show not only β-cell function preservation, but also actually β-cell proliferation under the stimulus of dipeptidyl peptidase (DPP)-4 inhibitors. GIP has been shown to have an antiapoptotic function in pancreatic β-cells GIP, enhances glucagon secretion and GLP-1 suppresses it. Other observational studies have revealed that the GIP and GLP-1 act on β-cells and act as a stimulant that leads to the proliferation of β-cells and/or progenitor cells [12].

Glucagon-like peptide-1 is released after an oral meal and this lowers the postprandial

hyperglycemia significantly inhibiting glucagon release without affecting gastric emptying [13]. In the bone, GIP enhances bone growth and GLP-1 reduces bone resorption. In the brain, both incretins may control appetite [12].

In DM2, there is decreased efficacy of GIP, with preserved normal efficacy of GLP-1 where its postprandial secretion and the β-cell responsiveness to hyperglycemia is significantly reduced [14–20].

Pharmacology

Vildagliptin (identified as 'LAF 237' in early clinical trials) selectively inhibits DPP-4 and prevents the degradation of incretin hormones GLP-1 and GIP (incretin enhancer). Vildagliptin (available in the EU and other countries) is a potent reversible and competitive inhibitor of DPP-4, an effect that is not species specific. Vildagliptin has two phases of binding: an initial rapid phase and subsequent slow phase of binding, providing both prompt and persistent DPP-4 inhibition. Vildagliptin has some inhibitory effect on DPP-8 and DPP-9, but the clinical relevance of this remains uncertain [21–23].

In clinical trials of DM2 patients, DPP-4 inhibition by vildagliptin is demonstrated within 45 min, and reaching a maximum at 24 h [24]. In DM2 patients, 50 mg of vildagliptin is associated with 50% DPP-4 inhibition within 0.5 h; at 12 h, approximately 80% DPP-4 inhibition is still evident, allowing once- or twice-daily administration [25]. Durable, dose-dependent DPP-4 inhibition by vildagliptin has been demonstrated by documentation of up to 90% inhibition after 28 days continuous treatment [26].

Other DPP-4 inhibitory (DPP-4i) agents are approved for use in DM2 patients in various regions and countries. This includes sitagliptin (EU, USA), saxagliptin (EU, USA), alogliptin (Japan), and linagliptin (USA). There are some differences in the pharmacology and pharmacokinetics of these agents; DPP-4 inhibition and therapeutic benefits in reducing HbA1C, postprandial plasma glucose (PPG), fasting plasma glucose (FPG) and side-effect profiles are similar [27].

Pharmacokinetics

Vildagliptin exhibits dose-proportional pharmacokinetics. It's high bioavailability provides rapid absorption resulting in C_{max} (at least 85% absorption) in 1.1 h. Less than 10% is protein bound. Although not studied in humans, in animals (in whom metabolism appears similar to humans) vildagliptin did not cross the blood–brain barrier. It is excreted mainly through urine (85.4%) and feces (4.5%). The half-life is 2.8 h. It is metabolized into metabolically inactive compounds via four major pathways. Vildagliptin is neither metabolized by, nor inhibits, or induces hepatic CYP enzymes [28]. Absorption studies did not reveal any clinically significant differences among Caucasian and Asian patients (preferred maximum dose of vildagliptin is 100 mg/daily [50 mg twice daily, BID, better than once a day] to possibly reduce the potential LFT abnormalities) [29,203]. Food is known to decrease vildagliptin absorption by a nonclinically significant less than 20%, hence it may be administered without consideration of meal times [30].

Special population

Kidney disease

Various DPP-4i have different pathways for metabolism and elimination. As urinary excretion is the primary metabolic fate of vildagliptin, changes in renal function do affect pharmacokinetics: C_{max} increases (8–66%) and area under the curve (AUC; 32–134%) are seen with worsening of kidney function [31]. With kidney failure, the primary metabolite of vildagliptin (LAY 151) is increased significantly in proportion to the degree of chronic kidney disease: 1.6-times (mild), 2.4-times (moderate), 5.4-times (severe), and 6.7-times end-stage renal disease. As vildagliptin undergoes renal tubular secretion and renal hydrolysis in addition to glomerular filtration, simply using glomerular filtration rate may underestimate the impact of chronic kidney disease upon vildagliptin elimination. Hence, vildagliptin is not recommended in patients with moderate or more severe chronic kidney disease [204].

Hepatic disorders

Vildagliptin metabolism is not altered in patients with mild-to-moderate hepatic impairment [32]. However, with severe hepatic impairment, the AUC of LAY151 is increased twofold. European labeling indicates that as long as hepatic dysfunction is mild (e.g., aspartate aminotransferase/alanine aminotransferase [AST/ALT] <3-times upper limit of normal [ULN]) no dose adjustment of vildagliptin is necessary, but vildagliptin is not recommended when liver function tests (LFTs) are over 3-times ULN [204]. Rare cases of hepatic dysfunction have been reported in association with vildagliptin. In each case, patients were asymptomatic and LFTs returned to normal after drug discontinuation. In the EU it is recommended to test LFTs at baseline, every 3 months

for the first year, and periodically thereafter. Patients who develop abnormal LFTs should be closely monitored: if the AST or ALT increases over 3-times ULN, or if there is evidence of hepatic dysfunction or jaundice, the drug should be withdrawn. Following the recovery of LFT, vildagliptin should not be reinitiated [204].

Hepatic side effects of vildagliptin were evaluated in a meta-analysis of 38 (Phase II or III) clinical trials. There were no statistically significant differences in the incidence of hepatic enzyme elevations (ALT or AST >3-times ULN) or hyperbilirubinemia with vildagliptin up to 50 mg once a day; at 50 mg BID, the incidence of LFT elevations were comparable with vildagliptin (three per 5905) and other gliptins (three per 6595). More prominent LFT elevations (AST or ALT >10-times ULN) were similarly distributed as compared with other gliptins (0 per 2091 with vildagliptin 50 mg QD, and one per 5917 with vildagliptin 50 mg BID, two per 6695 with other gliptins) [31,33,34].

Geriatric population & vildagliptin

Age, gender and BMI have little clinically relevance on the pharmacokinetics and clinical efficacy of vildagliptin [35]. No dose adjustment is needed in the elderly. Various populations are also studied without notable changes in the pharmacokinetics [29,36].

For example, in a clinical trial of 40 healthy older volunteers who received 100 mg of oral vildagliptin, the peak plasma concentration increased 17%, and the AUC was 31% higher. In this same population, renal clearance was 32% lower in the elderly than in younger subjects [35]. Such pharmacokinetic differences are typically not associated with pharmacodynamic effects; hence, there is no change in DPP-4 efficacy in the elderly. The caution about its use in persons aged over 75 years noted in the European guidelines, is based upon the lack of clinical trial data, not evidence of adverse effects [37,204].

Elderly patients have a higher incidence of DM2-related morbidity and mortality. Additionally, hypoglycemia – especially if symptomatic – can be a great barrier to achievement of glycemic goals. DPP-4i (including vildagliptin) improves the adaptability of α- and β-cells to hyper- and hypo-glycemia through the control of PPG and glucagon, which may contribute to their low incidence of hypoglycemia [38]. A systematic review of DPP-4i (including vildagliptin) found comparable effectiveness for A1C reduction (0.7–1.2%) and safety amongst various members of the class. Hypoglycemia risk was low (e.g., 2.32 events/pt-year on vildagliptin 100 mg/day vs 2.64 events/pt-year on placebo), and was similar in younger as well as older (>65 years) patients [39].

Pregnancy & lactation

Animal studies have shown reproductive toxicity, however, there are no adequate human data on the use of vildagliptin in pregnancy or during lactation. Accordingly, vildagliptin is not advised during pregnancy or lactation [204].

Drug interactions

The main metabolic pathway for vildagliptin is hydrolysis (60%). Minor pathways involved in vildagliptin include glucuronidation (4.4%), oxidation (1.6%), CYP450, and P-glycoprotein [31,204]. None of these metabolic pathways is of sufficient intensity to produce concern about drug interactions. For instance, digoxin clearance reduction of 19% has been reported (not clinically relevant). Various CYP enzyme pathways are not meaningfully impacted by vildagliptin, including simvastatin (CYP3A4), and pioglitazone (CYP2C8). Similarly, there is no warfarin (CYP2C9) interaction: when warfarin was administered with vildagliptin, there was no notable change in INR [40,41].

Coadministration of antidiabetic agents (glyburide, pioglitazone, metformin) did not indicate any negative interactions [42,43].

Similarly, cardiovascular drugs including amlodipine, valsartan, ramipril and simvastatin [44,45] do not demonstrate negative interaction with vildagliptin.

Incretins, bradykinin and substance-P are indirect substrates (after processing by aminopeptidase P) of DPP-4. There are reports that combining an ACE inhibitor with vildagliptin increases the incidence of angioedema. In this series, the angioedema incidence was too low to confirm whether it is clinically important. Fortunately, the angioedema observed when vildagliptin was combined with ACE inhibitor was mild and transitory in the majority of cases, in spite of the continuation of both agents [46–48].

As the physiologic effects of drugs such as thiazides, corticosteroids and thyroids may include increases in blood glucose, the efficacy of numerous antidiabetic agents, including vildagliptin, may be antagonized [31,204].

Dose

Vildagliptin is approved for use in the EU and other countries. It is approved to be used as a monotherapy (50 mg daily [QD] or BID), combination therapy with metformin or pioglitazone

(up to 50 mg BID), and combination with SU (50 mg QD). Although the daily dose of 100 mg is efficacious, 50 mg BID is preferred because the 100 mg QD dose has been associated with infrequent LFT abnormalities. Although not within European labeling, anecdotal reports of vildagliptin use with insulin suggest that it is a rational combination. Commercially available vildagliptin entities in Europe and some Latin American countries include vildagliptin monotherapy (Galvus®, Jalra®, Xiliarx®), and a fixed-dose combination of vildagliptin/metformin (Eucreas®, Icandra®, Zomarist®) [48].

Clinical benefits

Glucose

Vildagliptin has effects on fasting, intraprandial and postprandial glucose through multiple mechanisms, whether used as monotherapy [49] or in combination with other agents (e.g., metformin) [50]. By enhancing the response of islet cells, it favorably impacts both hyper- and hypoglycemia [51]. Vildagliptin, like all DPP-4i agents, elevates and sustains GLP-1 levels. Enhanced glucose-dependent insulin secretion improves postprandial glucose control; during hyperglycemia, dose-dependent glucagon suppression improves both fasting and postprandial glucose levels. During hypoglycemia, vildagliptin increases the glucagon response [52]. Vildagliptin has demonstrated in a long-term (2 years) randomized, placebo-controlled trial of mildly hyperglycemic drug-naive patients, the potential to attenuate the otherwise progressive loss of glucose control typically observed in DM2 [53]. Various studies indicate the HbA1C reduction with vildagliptin (50 mg BID) as monotherapy was approximately 1% (0.8–0.92% from the baseline) and the fasting glucose reduction is 14.5–25 mg/dl [48]. Greater degrees of glucose reduction are observed when used in combination with metformin [54].

Postprandial glucose effects

The mechanisms of action of vildagliptin (and all DPP-4i) target primarily prandial phenomenon, hence greatest glucose efficacy is observed in postprandial glucose levels. Both short- (12 week) and long-term (52 week) efficacy trials with vildagliptin monotherapy confirm reductions in PPG, which are confirmed with add-on therapy trials [55–58].

Fasting glucose effects

Vildagliptin also has been shown to improve FPG. A 4-week trial in DM2 patients demonstrated FPG lowering attributed to enhanced GLP-1 and GIP levels compared to baseline [23,59,60].

Intraprandial glucose effects

Rapid glucose fluctuations are thought to play a major role in the development of diabetic complications. To that end, vildagliptin (50 mg BID) was compared to sitagliptin (100 mg/day) in DM2 patients uncontrolled with metformin. Interprandial glycemia (IPG) was studied over 2 days, monitoring 24 h acute glucose fluctuation. In this trial, glucose fluctuation was more favorably impacted by vildagliptin than sitagliptin [61].

Modulation of intraprandial glucose fluctuation may be related to glucagon suppression induced by vildagliptin [62].

Effects on insulin & insulin sensitivity

The preponderance of data suggests that insulin sensitivity is improved with vildagliptin in DM2 patients [62–65]. The mechanism of improved insulin sensitivity by the DPP-4i agents are unclear. One possible speculative mechanism for improved insulin resistance by DPP-4i agents is suppression of glucagon dependent hepatic gluconeogenesis.

A single dose of vildagliptin 100 mg in DM2 patients increased postprandial insulin secretion. presumed mechanisms of which are post-meal elevation of GLP-1 and GIP and improved β-cell function demonstrated by an enhanced glucose-induced insulin secretion [62]. In a two-step glucose clamp study vildagliptin improved glucose responsiveness of insulin secretion by 50%, glucose clearance and insulin sensitivity [66].

As a member of the incretin class, it has been presumed that vildagliptin effects would be primarily in response to oral administration of carbohydrate. Nonetheless, in a clinical trial involving 21 metformin-treated patients, augmentation of insulin secretion was found after both oral and during isoglycemic intravenous glucose infusion, suggesting that there may be additional mechanisms of action with vildagliptin not heretofore identified [67,68].

This observation is not supported by other studies. Mean insulin levels rise on vildagliptin. The insulinogenic index (change in insulin secretion rate divided by the change in plasma glucose during a 6 h meal tolerance test) was significantly improved with vildagliptin [58,69,70].

The adaptation index (insulin secretion multiplied by insulin sensitivity) was used in some studies to demonstrate the insulin secretion and sensitivity in relation to the plasma glucose levels.

The adaptation index was significantly increased in vildagliptin treated patients when compared to placebo [64].

Effects in prediabetes

Improvement in insulin sensitivity was noted in prediabetic patients who were treated with vildagliptin. A study of vildagliptin in prediabetes found improved insulin sensitivity, β-cell function and postprandial glycemia [71].

Glucagon & α-cell function

Glucagon, through enhancement of hepatic glucose production, plays a major role in glucose homeostasis. Glucagon is secreted by the α-cells of the pancreas. When blood glucose drops to suboptimal levels, glucagon secretion restores euglycemia by induction of hepatic glucose production. Once euglycemia is restored (or hyperglycemia occurs), and any time insulin levels rise (which should be at times of plasma glucose elevations), glucagon (in healthy individuals) should be shut off. In nondiabetic individuals, postprandial glucose elevations stimulate insulin secretion, which suppresses glucagon. Hypoglucogonemia is attributed to the suppression of hepatic glucose production and maintenance of the postprandial glucose tolerance. Administration of all DPP-4i, including vildagliptin, suppresses, meal-related glucagon secretion in DM2 patients. DM2 is characterized by inappropriate continuation of postmeal hyperglucogonemia in the face of hyperglycemia, reflecting an α-cell insensitivity to insulin (insulin should normally suppress α-cell activity). The mechanism of glucagon suppression by DPP-4i may be enhancement of pancreatic α-cells' sensitivity to insulin [25,62].

For instance, a placebo-controlled study of 28-day treatment comparing vildagliptin and placebo in DM2 patients demonstrated enhanced α-cell responsiveness to both the suppressive effects of hyperglycemia and the stimulatory effects of hypoglycemia [23].

A placebo-controlled study revealed that vildagliptin decreased the glucagon levels, even though insulin levels were actually lower (which would tend to allow glucagon levels to rise) [72–75].

In a study in which vildagliptin 50 mg, BID or glimeperide 6 mg/day was added to metformin for uncontrolled DM2, only vildagliptin reduced the postprandial glucagon levels, providing evidence for possible improvement of α-cell function [76].

It has been observed that vildagliptin does not increase risk of hypoglycemia when added to SU, perhaps due to preservation of counter-regulatory mechanisms. There are reports regarding increased hypoglycemia when DPP-4i is used in combination with high-dose SU. Vildagliptin could also produce hypoglycemia in the elderly and patients with reduced renal function.

DPP-4i reduces glucagon secretion by increasing GLP-1 levels in DM2 patients. It is well known that the hyperglycemia (postprandial glucose surge) is controlled by DPP-4i through GLP-1. α-cell response to hypo- and hyper-glycemia were studied in a randomized, double-blind, placebo-controlled trial. In this study vildagliptin demonstrated the improvement in the α-cell responsiveness to the suppressive effects of hyperglycemia and the stimulatory effects of hypoglycemia [51]. In another clinical study (add on to metformin) glucagon response to a standard meal was measured at baseline and study end point (mean 1.8 years) with vildagliptin and SU, noted that vildagliptin (not SU) improved the postprandial α-cell function, which persists for at least 2 years [76]. The improvement of fasting islet cell function improvement was noted in another study [77].

Lipids

In general, DPP-4i, including vildagliptin, are felt to be lipid neutral. A long-term trial (2 years) with vildagliptin monotherapy has confirmed this. Vildagliptin treatment for 4 weeks (when compared to placebo) improved postprandial plasma triglyceride, and apolipoprotein B-48-containing triglyceride-rich lipoprotein particle metabolism [78].

Vildagliptin, when used in combination with other therapies, may have lipid effects, although results have been inconsistent [79,80].

For instance, in a placebo-controlled trial comparing postprandial lipid effects of vildagliptin or pioglitazone added to metformin, modest lipid improvement was noted in the vildagliptin group, however the results were not statistically significant [81]. In a randomized, double-blind, crossover study with vildagliptin or placebo, there was no change in glycerol, triglycerides, and free fatty acid concentrations over 7 days of treatment. There was some evidence that vildagliptin augmented postprandial lipid mobilization and oxidation [82].

Weight

Vildagliptin is weight neutral as a monotherapy agent in many clinical studies. With add-on therapy with metformin, there is a slight increase in weight (1.24 kg) when compared to metformin. Clinically add-on therapy

with metformin is considered weight neutral. There was a modest increase in weight with SU. Vildagliptin in combination with pioglitazone resulted in a dose dependent increase in weight up to 2.69 kg compared to the effect of pioglitazone (1.41 kg) [204].

Islet cell function

Islet cells play the vital role in the pathogenesis of DM2. Vildagliptin has been studied in animal models and clinical trials. Improvement in both α- and β-cell function during periods of hypo- or hyper-glycemia has been observed [66,77,83].

β-cell function

There is some evidence that DPP-4i administration in DM2 patients improves β-cell function, as demonstrated by a variety of metrics, including insulin secretion rate and other surrogates. The insulin secretion rate is estimated by measuring C-peptide. The C-peptide response is measured with fasting mixed-meal tolerance test. A liquid (Sustacal/Boost) meal (liquid meal tests are used in some studies) is ingested and C-peptide is measured in 2–4 h. The glucagon stimulation test is performed by intravenous glucagon administration with measurement of C-peptide over the subsequent 10 min [68,84–86].

The improvements in insulin secretion have been observed not only in monotherapy trials, but in some combination trials. For instance, vildagliptin, when added to metformin, showed durable increases in insulin secretion through the 1-year conclusion of the trial [75]. Meal-related improvement of β-cell function was observed in other studies. The 'adaptation index' (insulin secretion × insulin sensitivity – measures the ability of the β-cells to adapt insulin secretion to the ambient insulin sensitivity) is reduced in DM2 patients and it was augmented with coadministration of vildagliptin in metformin-treated patients [75,83].

Monotherapy trials

Vildagliptin has been studied as monotherapy as well as add-on therapy. Both short- and long-term (up to 52 weeks) studies of vildagliptin have been reported [51,87–89].

Subjects of diverse age (18–80 years) have been included in clinical trials [90–92].

Monotherapy studies commonly enrolled recently diagnosed DM2 patients.

Clinical efficiency

The 24-week monotherapy studies showed reductions in A1C (0.8–1.1%) and FPG (~20 mg/dl or 11 mmol/l). Whether in

Table 1. Side effects of vildagliptin.

Symptoms	Vildagliptin	Placebo
Monotherapy		
Infections and infestations (influenza, bronchitis, nasopharyngitis)	1.4%	0.3%
Nervous system disorders	0.9%	0.6%
Combination therapy		
Peripheral edema	VIL + pioglitazone = 7.0% VIL + pioglitazone 30 mg = 6.1%	2.5% Pioglitazone + placebo Pioglitazone 9.3%
Weight gain	1.5 kg with 50 mg and 2.7 kg with 100 mg/day	1.4 kg
Angioedema	Normal	Higher with added ACEi
Cardiac	Normal – health volunteers	Increased first degree AV block in trials; relationship not established
Hypoglycemia (monotherapy)	0.4% (VIL 100 mg/day)	0
Skin disorders: blister, skin lesion, exfoliation, ulcer and diabetic foot complications	Similar to placebo	Similar to placebo
Serious adverse events and deaths	No death directly related to VIL	
AST/ALT >3×	0.5% VIL	0.6% (TZD)

ACEi: Angiotensin-converting enzyme inhibitor; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; AV: Atrioventricular; TZD: Thiazolidinedione; VIL: Vildagliptin.
Data taken from [99,100,203,204].

Table 2. Dipeptidyl peptidase-4 inhibitors.

Drug	Chemical structure	Metabolism	Elimination	Fraction bound to protein	Compound $t_{1/2}$ (h)	Dose	DPP-4 inhibition	Potential drug interactions	Co-administration with CYP3A4 dose adjustment	Safety concerns
Vildagliptin	Cyanopyrrolidine	Hydrolyzed to inactive metabolite (P450-independent)	Renal (22% as parent, 55% as primary metabolite)	Low	1.5–4.5	50 mg BID	Max approximately 95%; >80% 12 h postdose	No	No	100 mg QD dose was associated with small numerical elevations in liver transaminases compared to placebo or 50 mg BID
Sitagliptin	β-amino acid-based	Not appreciably metabolized	Renal (~80% unchanged as parent)	Intermediate	8–24	100 mg QD	Max ~97%; >80% 24 h postdose	No	No	
Saxagliptin	Cyanopyrrolidine	Hepatically metabolized to active metabolite (via P450 3A4/5)	Renal (12–29% as parent, 21–52% as metabolite)	Very low	2–4 (parent) 3–7 (metabolite)	5 mg QD	Max ~80%; ~70% 24 h postdose	Yes	Half recommended dose	Dose-dependent (higher doses) reductions in absolute lymphocyte count in some clinical trials – clinical significance unknown
Linagliptin	Xanthine-based	Not appreciably metabolized	Eliminated via the enterohepatic system (80%) or urine (5%)	High	10–40	5 mg QD	Max ~80%; ~70% 24 h postdose	Possibly	Minor importance with CYP3A4, caution	
Alogliptin	Modified pyrimidinedione	Not appreciably metabolized	Renal (>70% unchanged as parent)	Very low	12–21	25 mg QD	Max ~90%; ~75% 24 h postdose	No	No	

BID: Twice daily; CKD: Chronic kidney disease; CV: Cardiovascular; LFT: Liver function tests; QD: Once daily; URI: Upper respiratory infection; UTI: Urinary tract infection.
Adapted from [10,64,65,108,111,206–209].

Table 2. Dipeptidyl peptidase-4 inhibitors (cont.).

Drug	Monitoring	Hepatic insufficiency	CV risk	Renal disease mild (CrCl >50 ml/min), moderate CKD (>30–<50 ml/min)	Severe CKD CrCL <30 ml/min	Side effects >5 %	URI	UTI	Hypoglycemia – elderly patients vs placebo
Vildagliptin (cont.)	LFT before and 3 monthly intervals for a year and periodically	Not recommended	No added risk noted	Not recommended (EU)	Not recommended		5–11%	2–5.1%	2.32 events placebo 2.64 events per patient-year
Sitagliptin (cont.)	No routine monitoring	Mild-to-moderate: OK Severe: not recommended	No added risk noted	Not recommended (EU), 50% dose (USA)	Not recommended (EU), 25% dose (USA)	Headache, URI	2.2–8.3%	2–5.4%	0% events placebo 0% events
Saxagliptin (cont.)	No routine monitoring	Mild-to-moderate: OK Severe: not recommended	No added risk noted	Not recommended (EU), 50% dose (USA)	Not recommended (EU), 50% dose (USA)		4.3–8.3%	5.2–10%	6.3% events placebo 8.0% events
Linagliptin (cont.)	No routine monitoring	No dose adjustment	No added risk noted	No dose adjustment	No dose adjustment				
Alogliptin (cont.)		Mild-to-moderate: OK Severe: not recommended		50% dose	25% dose				8% events placebo 10.5%

BID: Twice daily; CKD: Chronic kidney disease; CV: Cardiovascular; LFT: Liver function tests; QD: Once daily; URI: Upper respiratory infection; UTI: Urinary tract infection.
Adapted from [10,64,65,108,111,206–209].

combination or monotherapy, A1C reductions from vildagliptin are proportional to the pretreatment A1C. In patients inadequately controlled on metformin, SU, insulin or pioglitazone, vildagliptin as an add-on therapy reduced A1C by 0.51–0.97%. The EMAs 2007 report indicates that vildagliptin is statistically inferior to metformin 1000 mg BID, and trends towards being inferior to rosiglitazone 8 mg/day. Vildagliptin demonstrated improved β-cell function including Homeostasis Model Assessment (HOMA)-b, proinsulin to insulin ratio, and measures of β-cell responsiveness [204]. A 52-week multicenter, randomized, parallel-group study extension study in drug-naive DM2 patients compared vildagliptin (100 mg/day) with metformin (2000 mg/day). At the 1-year end point of the extension phase, both agents enjoyed favorable A1C reductions: vildagliptin (1%), and metformin (1.5%). Both drugs were weight neutral, but vildagliptin had fewer GI adverse effects (vildagliptin 25% and metformin 45.6%) in this trial [80].

Combination therapy

There are several multicenter, randomized, double-blinded studies comparing vildagliptin as an add-on medication and as combination therapy. The duration of studies ranged from 12 to 104 weeks (12 weeks [93] 24 weeks [94–96] 52 weeks [55,79] and 104 weeks [97]).

The age of the patients ranged from 18–80 years. Comparisons were made with metformin, voglibose, acorbose, rosiglitazone, and SU. The noninferiority of vildagliptin (100 mg/day) monotherapy with metformin was established in 12-week trials and not established for metformin, glicazide in a prolonged duration study. Vildagliptin was superior to voglibose in 12-week therapy in reducing HbA1C. The noninferiority was not established with acarbose. The HbA1C reduction was higher with vildagliptin 50 mg BID or 100 mg once daily. Clinically significant reduction of FPG was obtained with BID dosing. In the majority of the cases vildagliptin with combination therapy was weight neutral except when added to metformin (dose-dependently increased weight up to 1.24 kg) and pioglitazone (dose-dependent increase in weight up to 2.69 kg compared to the effect of pioglitazone alone ~1.41 kg). With SU, the weight gain was insignificant (+0.31 kg). The add-on therapy reduced HbA1C (mean reductions from baseline of 0.51–0.97% from the baseline) and FPG (mean reductions of 0.441–0.13 mmol/l). The addition of vildagliptin to insulin resulted in a modest reduction in HbA1C (-0.27% and in a subpopulation of elderly patients -0.70%) [98,204].

Vildagliptin (50 mg BID) was added to insulin in a 24-week, double-blind, randomized, placebo-controlled, parallel-group study in patients with DM2 whose hyperglycemia was inadequately controlled. This study revealed improvement in hyperglycemia with a reduced incidence of hypoglycemia when compared with placebo.

Vildagliptin was well tolerated and showed improvement in glycemic control and was associated with a reduced incidence of hypoglycemia relative to placebo. Meta-analysis of pooled data from 25 Phase III trials of vildagliptin (either as single dose or multiple dose as mono- or combination-therapy lasting 12 weeks–2 years) were evaluated for cardio and cerebrovascular mortality and found to be similar to other gliptins [99]. As add-on therapy to metformin, clinical efficacy of vildagliptin at 3 months has been shown to be comparable to TZDs, regardless of age, race or BMI [99,100].

Adverse reactions

The adverse events in monotherapy studies were comparable to placebo. The common side effects noted are listed. The side effects were dose dependent. Monotherapy: dizziness, headache, peripheral edema, constipation, nasopharyngitis, upper respiratory tract infection and arthralgia are reported similar to placebo. In combination therapy, tremor, headache, dizziness, fatigue and nausea asthenia, nasopharyngitis and constipation are reported [203,204]. Common (≤1/100) symptoms with vildagliptin are tremor, headache, dizziness, fatigue, nausea, and edema. Uncommon (≤1 in 1000) include hypoglycemia, asthenia, arthralgia, constipation and nasopharyngeal infections are very rare (≤1 in 10,000). A meta-analysis of pooled data from 25 Phase III trials of vildagliptin (either as single dose or multiple dose as mono- or combination-therapy lasting 12 weeks–2 years) were evaluated for cardio and cerebrovascular mortality and found to be similar to other gliptins (Table 1) [100].

In a meta-analysis of pooled data of 38 Phase II and III clinical trials, adverse events of vildagliptin (50 mg BID = 6116 patients) was compared to comparators (6210 patients from these groups: placebo (23.7%), SUs (41.7%), metformin (18.8%), TZDs (12.3%) and acarbose (3.5%). This comparison revealed 5.7% (comparators 6.7%) discontinued vildagliptin

due to side effects and the overall drug-related adverse events were 15.7% with vildagliptin and 21.7% with comparators [101]. It does not increase the hypoglycemia produced by SU [73,74]. Recent case reports raise some concerns for acute pancreatitis and possible thyroid problems with the administration of vildagliptin or sitaglptin (DPP-4i) and GLP-1-based therapies [102–104]. A large retrospective cohort database study (786,656 patients) revealed an increase in pancreatitis with DM2 patients and did not reveal any association between the use of sitagliptin or exenatride and acute pancreatitis [105,106]. In the USA there is a US FDA safety alert in place for sitagliptin [107,205].

Role of vildagliptin in the management of DM2

Approximately half of DM2 patients achieve the ADA currently recommended A1C goal of less than seven. Among the factors that contribute to insufficient goal attainment are clinician inertia, patient inertia, system obstacles and patient noncompliance. Pancreatic β-cell failure occurs early in DM2. By the time a diagnosis of DM2 has been made, it is estimated that 50% of β-cell function has been lost [103,106,108]. Although both postprandial and fasting glucose provide important contribution to excess glucose burden, postprandial glucose becomes progressively more important as the A1C approaches a threshold of 8.4 or less. Choices for treatment of postprandial glucose as a specific target are often limited by expense or adverse effects. Although the most recent ADA Consensus Statement for management of DM2 recommends metformin as the preferred initial treatment (in combination with lifestyle modification), not all patients may be able to take metformin due either to renal disease or GI intolerance. Even in patients who tolerate metformin well, because DM2 is a progressive disorder, essentially all patients will eventually progress to require more than monotherapy with metformin. DPP-4i including vildagliptin is well tolerated by patients and can be administered once or twice a day irrespective of meal intake. See Tables 2 & 3 for DPP-4i comparisons and Tables 3 & 4 for glycosylated hemoglobin and FPG changes.

When monotherapy is no longer sufficient to control the hyperglycemia, an additional agent will be added to the regime. The majority of the patients will prefer to use oral agents to injectable agents. Although insulin and GLP-1 agonists are appropriate considerations when advancing therapy beyond metformin (and advocated as appropriate next-step treatment by the ADA Consensus document), many patients are reticent or frankly unwilling to employ parenteral therapy. Among the oral agents to be added to metformin, a number of considerations must be weighed prior to selection of treatment. First, it is important to add medications with complementary mechanisms to take best advantage of medication synergy. Once medications with synergistic effects are elected, tolerability issues should be reviewed with patients, since hypoglycemia (most common with SU or insulin), weight gain (most common with SU, insulin and TZD), and expense (most problematic with TZD, DPP-4, and GLP-1 agonists) may be essential 'deal-breakers' to patients. GI adverse effects during initial treatment may be problematic with GLP-1 agonists. From the risk–benefit consideration, some concerns remain about the CV safety profile of SU, and rosiglitazone; clinical studies do not show any CV complications with vildagliptin. In all the clinical studies vildagliptin was well tolerated and had less hypoglycemia than the comparators.

The NICE guidelines suggest to add a DPP-4 inhibitor such as sitagliptin or vildagliptin to

Table 3. HbA1C changes with dipeptidyl peptidase-4 inhibitors.

Drug	Monothererapy vs placebo	+ Metformin HbA1C	+ SU HbA1C	+ TZD HbA1C	+ AGI HbA1C	+ Insulin HbA1C
Vildagliptin 50 mg BID	0.8–0.92%	1–1.8%	1%	0.63–1%		
Sitagliptin 100 mg/day	0.5–0.6%	0.7%	0.6%	0.9%		0.6%
Saxagliptin 2.5–10 mg/day	2.5–10 mg/day, 0.4–0.5%	5–10 mg/day dose, 2.5%	0.5–0.6%	0.7–0.9%		
Linagliptin 5–10 mg/day vs placebo	0.60%	0.5%	1.1%			
Alogliptin	0.6%	0.6%	0.7%			0.6%

PDR for linagliptin, saxagliptin, sitagliptin [65,110,111].
AGI: α-glucosidase; SU: Sulfonylurea; TZD: Thiazolidinedione.

Table 4. Fasting plasma glucose changes with various dipeptidyl peptidase-4 inhibitor agents.

Therapy/trial	Vildagliptin 50 mg twice daily	Sitagliptin 100 mg/day	Saxagliptin 2.5–10 mg/day	Linagliptin 5–10 mg/day	Alogliptin
Monotherapy	14.5–25 mg	17–20 mg	15–17 mg	5–20 mg	10.3 mg
DPP-4i + metformin 100 mg twice daily	18–46 mg	17 mg	60–62 mg	12.7 mg	17 mg
DPP-4i + SU	21.6 mg	19 mg	7–10 mg	8.2 mg	4.4 mg
DPP-4i + TZD	15 mg	23 mg	–	32.6 mg	19.7 mg

DPP-4i: Dipeptidyl peptidase type 4 inhibitor; SU: Sulfonylurea; TZD: Thiazolidinedione.
Adapted from [64,110,111,207–209].

metformin when the patient is older. However, this has greater risk of hypoglycemia, or SU intolerance. A DPP-4i may be used instead of TZD in a patient when weight gain or being overweight is a problem. A DPP-4i may be added to metformin and SU when the patient is not able to achieve the target glycemic control and the administration of parenteral treatment (insulin, liraglutide, exenatide) is not acceptable [104,109,203,205,206].

Vildagliptin may be administered with mild renal disease and may be used in mild hepatic insufficiency (AST/ALT <3× ULN) with LFT monitoring. Administration of vildagliptin as a monotherapy or in combination with another agent (e.g., metformin) reduces hyperglycemia. In DM2, vildagliptin is effective in reducing HbA1C (~1% from baseline) and FPG (0.8–1.4 mmol/l–14.5–25 mg) as a monotherapy agent [48,49].

Future perspective

Unless there is a fundamental change in lifestyle on a global basis or insight into the prevention and modulation of DM2 undergoes a dramatic therapeutic evolution, clinicians in all specialties will continue to see an ever-growing population of people with diabetes and its long-term consequences. Based upon the observation that management of DM2 is limited by the complexity of the disorder, need for multiple medications, necessity of meeting multiple therapeutic goals concomitantly (lipids, blood pressure, glucose and healthy body weight), the only way to make meaningful inroads for our patients will be to become both more creative and more sensitive in our therapeutic choices. Easily accessible and affordable comprehensive multidisciplinary healthcare delivery systems and innovative healthcare delivery models such as 'Medical Home' or other effective chronic disease management models are essential in improving diabetic care.

Diabetes prevention trials have convincingly shown that a healthy lifestyle can be employed, but requires a sustained and intensive team effort (i.e., diet, exercise and behavioral advisors). This evidence should direct clinicians to emphasize and invest a greater portion of their clinical time to involve patients in successful long-term lifestyle modification programs. Treatments that achieve one sought-after goal (e.g., glucose control), at the expense of an equally important undesirable outcome (e.g., weight gain), will either become a thing of the past or 'second tier' choices. As some of the tissue damage of diabetes often occurs well before the diagnosis is evident, screening and early intervention will be increasingly emphasized. No distinct glycemic control parameters are found for prevention of all diabetic related complications and; therefore, it is important to achieve euglycemia (including control of FPG, PPG and HbA1C) as possible without the untoward effects of hypoglycemia.

Clinicians will move away from the recognition of diabetes as a disorder of the pancreatic β-cells to embrace consideration of dysfunction in multiple tissue compartments, particularly the GI tract. Based upon observations that diabetic patients undergoing bypass bariatric surgery enjoy essential resolution of diabetic derangements prior to a point in time at which improvement could be attributed to weight loss, clinicians will usher in the gastrointestinal epoch of diabetes management, in which the critical participation of the small bowel in glucose regulation will be recognized. Because of the failure of today's foundation treatments (metformin, insulin, SUs) to improve cardiovascular outcomes, as well as their risks of hypoglycemia (for the latter two), clinicians will restructure therapy with an initiative to provide treatments that reduce – or at least do not worsen – CV outcomes, that are weight neutral (or favorable), and that minimize the incidence of hypoglycemia. The DPP-4i agents available today have affinity towards other DPP group of proteins (DPP-8, DPP-9). DPP-4 is also involved in the metabolism of several peptides, such as GLP-1, GIP and other peptides such as GHRH, GLP-2, PACAP, GRP, other neuropeptides and chemokines.

In the future, DPP-4i agent's role beyond the metabolic control may be identified and highly selective DPP-4i agents may be developed. It is possible to develop new groups of medications based upon the new understanding of the complex metabolism of glucose and the roles played by various organs such as the kidney, liver, heart, GI tract and brain. Future antidiabetic agents may prevent diabetic complications as well as treat diabetes. Physiological ways to replace insulin may be developed. Advances in technology, biomedical research and engineering may lead to the development of artificial implantable pancreatic chips (artificial pancreas), which will monitor glucose and administer insulin every minute as needed (significant improvement to present day insulin pumps). Stem cell research, genetic engineering and advances in regenerative medicine may lead to the development of a biological pancreas and prevent the destruction (or replacement) of the pancreatic β-cells.

Diabetes may ultimately be discerned as a disorder in which pancreatic β-cells are a target of another dysfunction, rather than a fundamental culprit.

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Executive summary

Mechanism of action

- Vildagliptin (and other dipeptidyl peptidase-4-inhibitors) inhibits the degradation of dipeptidyl peptidase-4, leading to an increased insulin production and control of glucagon secretion.

Pharmacokinetics

- Well-absorbed orally and excreted mainly through the kidney.
- Does not inhibit or induce hepatic CYP enzymes.

Clinical activity

- Reduce HbA1C by approximately 1%.
- Reduces postprandial plasma glucose, fasting glucose and glucagon.

Dosing

- 501–100 mg daily
- Monotherapy: 50–100 mg/day
- Combination therapy:
  - Metformin: 50 mg twice daily (BID)
  - Sulfonylurea: 50 mg BID. Caution with high doses of sulfonylurea
  - Thiazolidinedione: 50 mg BID
  - Insulin: 50 mg BID

Special population & monitor

- Not recommended in moderate-or-severe kidney failure.
- Not recommended in liver failure.
- Test liver function before initiation and follow-up with liver function tests every 3 months.
- Discontinue vildagliptin if there is more than three-times increase in aspartate aminotransferase or alanine aminotransferase.
- Do not re-challenge after vildagliptin-induced increased liver function test returns to normal.
- No dose adjustment for geriatric population.

Adverse effects

- Dizziness, headache, peripheral edema, constipation, nasopharyngitis, upper respiratory tract infection and arthralgia are reported similar to placebo.

Role as an antidiabetic agent

- Weight neutral as monotherapy.
- Hypoglycemia incidence is low.
- Lipid neutral.
- Well tolerated, significantly reduced gastrointestinal side effects.
- May be used in cardiovascular and mild renal disorder with adjusted dose.

Future developments

- Possible development of highly selective dipeptidyl peptidase-4 inhibitors.
- Long-term outcome studies.
- Long-term study on cardiovascular benefits and possible side effects.

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