

Dipeptidyl Peptidase-4 Inhibitors and the Management of Hyperglycemia

Pamela M Katz, MD¹ and Lawrence A Leiter, MD²

1. Resident, Division of Endocrinology and Metabolism, University of Toronto;

2. Head, Division of Endocrinology and Metabolism, St Michael's Hospital, and Professor of Medicine and Nutritional Sciences, University of Toronto

DOI: 10.17925/USE.2009.05.1.63

Abstract

Incretin-based therapies, including both glucagon-like peptide 1 (GLP-1) analogs and dipeptidyl peptidase-4 (DPP-4) inhibitors, are increasingly being used for the treatment of type 2 diabetes. GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) are gut-derived incretin hormones that regulate glucose through co-ordinated effects on pancreatic alpha and beta cells. DPP-4 inhibitors enhance the effects of endogenous, active GLP-1 and GIP by inhibiting the enzyme responsible for their degradation. These agents lower glycated hemoglobin (HbA_{1c}) and help patients achieve glycemic targets, yet are weight-neutral and, due to their glucose-dependant mechanism of action, carry minimal risk of hypoglycemia. Furthermore, incretin-based therapies may alter disease progression through preservation of beta-cell mass and function. Although initially recommended for use in the early stages of type 2 diabetes, DPP-4 inhibitors appear to maintain their glycemic efficacy across the continuum of disease. They can be used either as monotherapy or in dual or triple combination therapy with other oral antihyperglycemic agents, and potentially also in combination with insulin. This review will focus on DPP-4 inhibitors and current clinical trial evidence to support their use in the management of hyperglycemia in type 2 diabetes.

Keywords

Type 2 diabetes, incretin, DPP-4 inhibitors, dipeptidyl peptidase-4, sitagliptin, vildagliptin, saxagliptin

Disclosures: Pamela M Katz, MD, has no conflicts of interest to declare. Lawrence A Leiter, MD, has received research funding from, provided continuing medical education (CME) on behalf of, and acted as a consultant to AstraZeneca, BMS, Bi, Eli Lilly, GSK, Merck, Novartis, Novo Nordisk, Roche, sanofi-aventis, and Servier.

Received: November 15, 2009 **Accepted:** December 8, 2009

Correspondence: Lawrence A Leiter, MD, Head, Division of Endocrinology & Metabolism, St Michael's Hospital, 61 Queen St East #6121, Toronto, Ontario, Canada M5C 2T2.
E: leiterl@smh.toronto.on.ca

The global prevalence of diabetes has increased dramatically in recent years and is predicted to rise substantially further to 440 million by 2030.^{1,2} Patients with type 2 diabetes face an increased risk of microvascular and macrovascular complications leading to significant morbidity and mortality and enormous healthcare expenditures. Despite the proven benefits of intensive glycemic control, particularly with respect to microvascular disease,³ the evidence-based goals are frequently not achieved.⁴

The progressive nature of type 2 diabetes, largely driven by a relentless decline in beta-cell function, leads to an inevitable need for escalation of treatment strategies.⁵⁻⁷ Persistent hyperglycemia may hasten this decline through an effect known as glucotoxicity. Unfortunately, intensification of therapy has often led to undesirable side effects, including hypoglycemia and weight gain, and may not adequately control post-prandial glucose excursions.⁸ These and other factors contribute to clinical inertia, resulting in unnecessary and disadvantageous delays to initiation of appropriate therapy.⁹⁻¹¹ Understanding of incretin physiology has led to the development of novel agents that successfully address several of these barriers. In this review, we will present the evidence for three DPP-4 inhibitors currently in clinical use: sitagliptin, saxagliptin, and vildagliptin

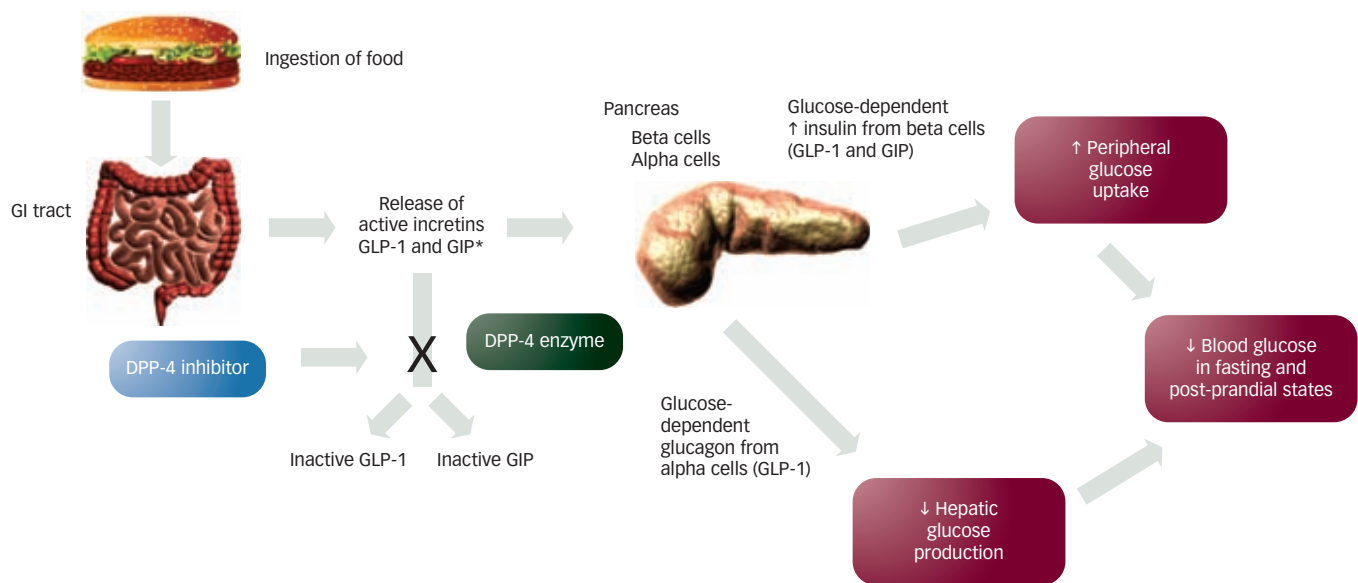
(not approved in the US at present). Caution must be employed when comparing efficacy between trials, as the degree of glucose lowering achieved depends in large part on baseline glycated hemoglobin (HbA_{1c}).

Incretin Physiology

The incretin effect refers to the augmentation of glucose-stimulated insulin secretion by intestinally derived peptides that are released in the presence of nutrients or glucose in the gut.¹² Two gastrointestinal peptide hormones mainly mediate this response: glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1).^{13,14}

GLP-1 and GIP activate G-protein-coupled receptors on pancreatic beta cells to stimulate insulin secretion.¹⁵ GLP-1 also acts on alpha cells to inhibit the secretion of glucagon, thereby decreasing hepatic glucose production. Effects on alpha and beta cells are glucose-dependent, therefore incretin-based therapies carry minimal risk for hypoglycemia.¹⁵ Further effects of GLP-1 include inhibition of gastric emptying and a sense of satiety, which may contribute to reduced caloric intake.¹³⁻¹⁵ The incretin effect is impaired in patients with type 2 diabetes, mainly due to reduced levels of active GLP-1, as well as defective GIP activity despite normal or increased levels.¹⁶⁻²⁰

Figure 1: Dipeptidyl Peptidase-4 (DPP-4) Inhibitors Enhance Incretin Levels Through Inhibition of DPP-4



DPP-4= dipeptidyl peptidase-4; GI = gastrointestinal; GIP = glucose-dependent insulinotropic peptide; GLP-1 = glucagon-like peptide 1. *Incretin hormones GLP-1 and GIP are released by the intestine throughout the day, and their levels increase in response to a meal. In persons with type 2 diabetes, incretin response to caloric intake is severely impaired or diminished.

Dipeptidyl Peptidase-4 Inhibitors

Intact, biologically active GLP-1 represents only 10–20% of total plasma GLP-1.¹⁴ GLP-1 and GIP are renally cleared and rapidly inactivated by the enzyme dipeptidyl peptidase-4 (DPP-4), a widely expressed serine protease.¹⁵

DPP-4 inhibitors are reversible competitive inhibitors of DPP-4 (see *Figure 1*). Currently available DPP-4 inhibitors appear similar in their ability to inhibit DPP-4 activity and give rise to comparable increases in intact hormone concentrations. Levels of GLP-1 achieved are generally sufficient to cause increased insulin secretion and decreased glucagon production, although not sufficient to induce the decreased appetite and food intake or the subsequent weight loss typically seen with GLP-1 analogs.²¹ By contrast, these orally administered DPP-4 inhibitors are generally considered weight-neutral and are less commonly associated with the gastrointestinal side effects of the GLP-1 analogs such as nausea, vomiting, or diarrhea.

A potential long-term concern with this class of agents is the unknown consequences of affecting DPP-4 activity on substrates other than GLP-1 and GIP.

There may be other important compound-related differences that ultimately differentiate between the DPP-4 inhibitors. For example, these agents vary in their routes of metabolism and elimination.²² Sitagliptin does not undergo appreciable metabolism and is primarily excreted unchanged by the kidney. By contrast, saxagliptin is hepatically metabolized to an active metabolite via CYP450 3A4/5; both parent compound and metabolite are renally excreted. Vildagliptin is hydrolyzed, to a large extent, by the liver to an inactive compound that is excreted in the urine.

Inhibitors may also differ in their selectivity for DPP-4 over other related enzymes, such as DPP-8 and DPP-9.^{22,23} The exact functions of these enzymes are unknown and the clinical significance of their inhibition in human subjects, if any, is unclear. Another potential concern is the specificity of agents for the catalytic activity of DPP-4 over other functions of the DPP-4/CD26 molecule.²³ CD26 is a cell-surface molecule on immune cells and is an important co-stimulatory molecule in immune activation. Thus, close surveillance of these agents must continue for potential effects on the immune system, although there have been no real concerns to date. Finally, there may also be compound-specific properties unrelated to DPP-4 inhibition that could result in unwanted side effects from a particular agent.

Implications for Type 2 Diabetes

In animal models, GLP-1 has been shown to expand beta-cell mass by stimulating beta-cell proliferation and inhibiting beta-cell apoptosis.^{15,24–27} Similarly, GLP-1 added to freshly isolated human islets improves glucose responsiveness and protects against apoptotic beta-cell death.²⁸ In a rodent model of type 2 diabetes, administration of a DPP-4 inhibitor increased pancreatic beta-cell mass and improved glucose-stimulated insulin secretion in isolated islets.²⁹ Thus, incretin-based therapies may address the issue of beta-cell failure, a key mechanism underlying disease progression in type 2 diabetes.

While preliminary results are encouraging, it is important to recognize that the significance of these findings to human subjects remains to be established. Recent studies also suggest GLP-1 may have protective effects on the cardiovascular system.^{30–33} These observations are particularly interesting given the high rates of cardiovascular disease among patients with diabetes; however, a detailed discussion of this topic is beyond the scope of the current review.

In a systematic review and meta-analysis of the early clinical trials on the use of incretin-based therapy for type 2 diabetes, these agents lowered HbA_{1c} compared with placebo: weighted mean difference -0.97% (95% confidence interval [CI] -1.13 to -0.81%) for GLP-1 analogs and -0.74% (95% CI -0.85 to -0.62%) for the DPP-4 inhibitors sitagliptin and vildagliptin.³⁴ DPP-4 inhibitors were associated with an increased risk of infections such as nasopharyngitis and urinary tract infection. Headaches were also reported more commonly, particularly with vildagliptin.

In 2008, a Cochrane review was published that included 25 studies ranging from 12 to 52 weeks in duration with a total of 6,743 patients randomized to sitagliptin and 6,121 patients to vildagliptin.³⁵ Sitagliptin and vildagliptin therapy resulted in an HbA_{1c} reduction compared with placebo of approximately 0.7 and 0.6%, respectively. Treatment did not result in weight gain and was generally well tolerated with no severe hypoglycemia. Of note, all-cause infection was significantly increased with sitagliptin therapy, but did not reach statistical significance for vildagliptin. Importantly, the majority of trials included in both of these reviews were of short duration, and therefore long-term safety and efficacy could not be assessed.

Sitagliptin

Sitagliptin (Januvia) is a potent, orally available, highly selective DPP-4 inhibitor. It was the first agent of its class to be available in the US and is approved for use as an adjunct to diet and exercise alone or in combination with another oral antihyperglycemic agent.

Monotherapy

Several studies have evaluated sitagliptin for use as monotherapy in patients with type 2 diabetes and inadequate glycemic control despite diet and exercise.^{36–38} Two studies examined the efficacy of sitagliptin 100 and 200mg compared with placebo and showed clinically and statistically significant reductions in HbA_{1c} ranging from -0.48 to -0.94%.^{36,37} As is typically seen in trials of glucose-lowering agents, patients with a higher baseline HbA_{1c} (>9%) experienced greater reductions in HbA_{1c} than those with better glycemic control at enrolment. Treatment with sitagliptin also resulted in significant improvements in markers of insulin secretion and beta-cell function compared with placebo. Key efficacy parameters did not differ significantly between sitagliptin doses, and subsequent studies have used 100mg daily. There does not appear to be a significant difference between once-daily (100mg once daily) and twice-daily (50mg twice daily) dosing regimens.³⁹ In a pooled cohort of 147 patients in two monotherapy trials, sitagliptin decreased mean HbA_{1c} from 8.5% at baseline to 6.9% at two years.⁴⁰ Compared with initial therapy with metformin titrated to a maximum of 2,000mg/day, sitagliptin 100mg daily was found to be non-inferior with respect to the primary endpoint (reduction in HbA_{1c} at 24 weeks).⁴¹

Add-on Dual Combination Therapy

In a pooled cohort of 852 patients in two trials of sitagliptin added to ongoing metformin therapy, HbA_{1c} decreased from a baseline of 8.0 to 6.9% at two years.⁴⁰ At 24 weeks, the addition of sitagliptin to ongoing metformin therapy led to a significant, -0.65% reduction in HbA_{1c} compared with placebo; 47% of patients achieved an HbA_{1c}

<7% with sitagliptin compared with 18.3% in the placebo-treated arm.⁴² Similarly, when added to ongoing treatment with pioglitazone, sitagliptin resulted in a significant reduction in HbA_{1c} at 24 weeks (-0.70%) and a greater proportion of patients reaching glycemic target with no increased risk of hypoglycemia compared with placebo.⁴³

Sitagliptin has similar glycemic efficacy to other oral agents such as rosiglitazone or glimepiride as add-on therapy to metformin.^{44,45} However, the addition of rosiglitazone resulted in a significant increase in bodyweight (+1.5kg) compared with sitagliptin (-0.4kg) or placebo (-0.8kg) over 18 weeks.⁴⁴ In addition, the incidence of hypoglycemia was significantly higher with glipizide (32%) than with sitagliptin (5%), and sitagliptin led to weight loss (-1.5kg) rather than the weight gain (+1.1kg) seen with glipizide (p<0.001) over 52 weeks.⁴⁵

Add-on Triple Combination Therapy

When combined with glimepiride, with or without metformin, the overall reduction in HbA_{1c} at 24 weeks by sitagliptin was -0.74% (95% CI -0.90 to -0.57; p<0.001) relative to placebo, with the greatest improvement, -0.89%, seen in those patients receiving the triple therapy.⁴⁶ In this study, an increase in adverse events was seen in the sitagliptin group, largely due to a higher incidence of hypoglycemia. Therefore, sulfonylurea dose adjustment may be required when adding sitagliptin to ongoing therapy. Another study of triple therapy showed a significant reduction in HbA_{1c} with sitagliptin compared with placebo on background metformin and rosiglitazone. At 18 weeks, sitagliptin lowered HbA_{1c} by -0.7% compared with placebo, an effect that continued out to 54 weeks.⁴⁷

Add-on Therapy to Insulin

Sitagliptin was recently evaluated as add-on therapy to stable-dose insulin with or without metformin in patients with type 2 diabetes.⁴⁸ The average duration of diabetes was 12 years, with a baseline HbA_{1c} of 8.7% at entry, suggesting a population with more advanced disease. Patients treated with sitagliptin achieved an additional reduction in HbA_{1c} of -0.6% at 24 weeks, and significantly more patients achieved target glycemic control. Interestingly, no increase in bodyweight from baseline was observed. However, the incidence of hypoglycemia was significantly greater with sitagliptin (15.5%) compared with placebo (7.8%). This was likely a result of the study design, as investigators were discouraged from making insulin dose adjustments during the study period unless the study subject had symptomatic hypoglycemia.

Initial Combination Therapy

Given what is known about the progressive nature of type 2 diabetes and the eventual need for multiple antihyperglycemic medications, a strategy of early combination therapy has been advocated, using agents that possess complimentary mechanisms of action to enable more patients to achieve and sustain glycemic control.^{49,50} Metformin and sitagliptin may have synergistic effects on the incretin axis; in a study of individuals with normal glucose tolerance, each agent alone increased post-meal active GLP-1 concentrations by 1.5- to two-fold, while their combination raised levels by greater than four-fold.⁵¹

In a 24-week study, 1,091 patients with a baseline HbA_{1c} of 8.8% were randomized to one of six daily treatments involving varying doses of

sitagliptin and metformin, alone or in combination.⁵² Indeed, initial combination therapy provided substantial and additive glycemic improvements with the most robust response—a placebo-subtracted reduction in HbA_{1c} from baseline of -2.07%—seen from maximum dose combination therapy. Glycemic response was generally sustained at 54 weeks and 104 weeks.^{53,54} However, an important limitation of these studies is that only patients who entered the 28-week continuation period following the initial 26-week trial without receiving glycemic rescue therapy were included in the analysis, while the subsequent 52-week extension study included only those subjects who chose to continue in the trial. Initial combination therapy was generally well tolerated, with low rates of hypoglycemia.

The combination of sitagliptin and metformin in a single fixed-dose combination tablet (Janumet) enhances convenience and may therefore improve adherence and overcome clinical inertia. Initial fixed-dose combination therapy resulted in a superior HbA_{1c} reduction and better glycemic goal attainment compared with metformin monotherapy at 18 and 44 weeks.^{55,56} Over the 44-week treatment period, HbA_{1c} reductions from a baseline of 9.9% were -2.3% for sitagliptin/metformin and -1.8% for metformin alone, favoring initial combination therapy. Interestingly, rates of certain gastrointestinal adverse experiences such as abdominal pain and diarrhea were lower with combination therapy, suggesting that the addition of sitagliptin may make metformin more tolerable, although a specific mechanism for this is lacking.⁵⁵

Initial combination therapy with sitagliptin and pioglitazone led to a reduction in HbA_{1c} at 24 weeks of -2.4% from a baseline of 9.5%, compared with -1.5% with pioglitazone monotherapy.⁵⁷ Fasting plasma glucose and measures of beta-cell function were also improved with initial combination therapy compared with pioglitazone alone.

Chronic Renal Insufficiency

Dose adjustments are recommended for sitagliptin in patients with moderate to severe renal insufficiency (RI) or end-stage renal disease (ESRD) (50mg daily if creatinine clearance (CrCl) ≥30 and <50ml/min and 25mg daily if CrCl <30ml/min).⁵⁸ Since the fraction of sitagliptin dose removed by dialysis is small, it can be administered without regard for timing of hemodialysis in patients with ESRD.

In a study of patients with moderate to severe RI and a baseline HbA_{1c} of 7.7%, patients were randomized to receive dose-adjusted sitagliptin 50mg (moderate RI, CrCl ≥30 and <50ml/min) or 25mg (severe RI, CrCl <30ml/min, including patients on dialysis) or initial treatment for 12 weeks with placebo followed by active treatment with glipizide.⁵⁹ At 12 weeks, the mean change in HbA_{1c} from baseline with sitagliptin was -0.7% (95% CI -0.9 to -0.4) compared with -0.2% (95% CI -0.4 to 0.1) in the group receiving placebo. The observed reduction in HbA_{1c} from baseline with sitagliptin was sustained at 54 weeks. Rates of adverse experiences were similar between groups, with the exception of hypoglycemia, which occurred at a lower rate with sitagliptin.

Safety

In a pooled analysis of 6,139 patients in 12 large, double-blind, randomized phase IIb and III studies of up to two years' duration, the

incidence rates of adverse experiences overall, serious adverse experiences, and discontinuation due to adverse experiences were similar between the sitagliptin and non-exposed groups (which included both placebo and active controls).⁶⁰ There was a higher rate of drug-related adverse experiences in the non-exposed group, primarily due to the increased incidence rate of hypoglycemia in studies in which a sulfonylurea was used as an active comparator.

Importantly, the small increases in nasopharyngitis and urinary tract infections observed in the earlier meta-analyses were not confirmed in this larger study. Overall incidence of cardiovascular- and gastrointestinal-related adverse experiences, including rates of pancreatitis, did not differ significantly between the sitagliptin and non-exposed groups. However, the US Food and Drug Administration (FDA) recently revised prescribing information for sitagliptin and Janumet (sitagliptin/metformin) due to 88 post-marketing cases of acute pancreatitis reported between October 2006 and February 2009 in patients using these agents.⁶¹ The nature of this association is not clear, particularly as diabetes itself may be a risk factor for pancreatitis. In a recent, large, retrospective cohort study, patients with type 2 diabetes had an almost three-fold greater risk of pancreatitis compared with age- and sex-matched controls without diabetes.⁶²

Saxagliptin and Vildagliptin

Saxagliptin (Onglyza) and vildagliptin (Galvus) are members of the cyanopyrrolidine chemical class.^{63,64} Saxagliptin was recently approved for use in the US as an adjunct to diet and exercise in patients with type 2 diabetes.⁶⁵ Vildagliptin is available in Europe and some other countries around the world, but not yet in the US.

Saxagliptin Monotherapy

In a dose-ranging study (dose range 2.5–40mg once daily) in drug-naïve patients with type 2 diabetes, saxagliptin significantly reduced HbA_{1c} by -0.7 to -0.9% from an average baseline of 7.9% compared with a 0.3% reduction with placebo at 12 weeks.⁶⁶ Similar and clinically meaningful reductions in HbA_{1c} were achieved with all doses of saxagliptin, with no significant dose-response relationship. A subsequent trial of saxagliptin monotherapy demonstrated mean changes in HbA_{1c} (baseline 7.9%) over 24 weeks of -0.43, -0.46, and -0.54% for saxagliptin 2.5, 5, and 10mg, respectively, versus +0.19% for placebo.⁶⁷ Improvements were also seen in fasting plasma glucose, post-prandial glucose-area under the curve (AUC), and the proportion of patients achieving HbA_{1c} <7%. There was no weight gain and the occurrence of hypoglycemia was similar to that seen with placebo. The recommended dose of saxagliptin is 2.5 or 5mg once daily, although 5mg is the proposed usual clinical dose.⁶⁸

A dose of 2.5mg once daily is recommended for patients with moderate to severe renal impairment (CrCl ≤50ml/min) or ESRD and when co-administered with medications that strongly inhibit cytochrome P450 3A4/5 (CYP3A4/5), for example ketoconazole.⁶⁸

Add-on Dual Combination Therapy

When added to ongoing metformin therapy, saxagliptin 2.5, 5, and 10mg resulted in statistically significant adjusted mean decreases in

HbA_{1c} from a baseline of 8.0% of -0.59, -0.69, and -0.58%, respectively, compared with placebo (+0.13%).⁶⁹ Reductions were seen at week four, the earliest time-point assessed, reached a maximum at 12 weeks, and were sustained through 24 weeks of treatment. A greater percentage of patients achieved target glycemic control without an increase in hypoglycemia or weight gain. Clinically meaningful glycemic improvements were sustained up to 102 weeks.⁷⁰ The addition of saxagliptin to metformin remained well tolerated with an overall adverse event profile consistent with that seen at 24 weeks.

A study by Chacra et al. compared the safety and efficacy of adding saxagliptin to a submaximal dose of the sulfonylurea glyburide versus uptitration of sulfonylurea monotherapy in a group of subjects with a mean baseline HbA_{1c} of 8.4%.⁷¹ Patients received either saxagliptin 2.5 or 5mg plus glyburide 7.5mg or glyburide titrated to a maximum of 15mg/day as necessary. Combination therapy resulted in a significantly greater reduction in HbA_{1c} than maximum sulfonylurea monotherapy, with more than twice as many patients achieving an HbA_{1c} <7%. In fact, HbA_{1c} increased by 0.08% from baseline with uptitrated glyburide compared with decreases in HbA_{1c} of -0.54% and -0.64% with submaximal sulfonylurea plus saxagliptin 2.5mg and 5mg, respectively. An increased risk of hypoglycemia, often seen with combination therapy, particularly involving a sulfonylurea or insulin, was not observed despite greater glycemic efficacy.

In a recently published study conducted in patients inadequately controlled on thiazolidinedione monotherapy (baseline HbA_{1c} 8.3%), the addition of saxagliptin 2.5 or 5mg resulted in statistically significant reductions in HbA_{1c} at 24 weeks of -0.66 and -0.94%, respectively, compared with -0.30% with placebo ($p < 0.0001$).⁷²

Initial Combination Therapy

Initial combination therapy in treatment-naïve patients was evaluated using metformin 500mg plus saxagliptin 5 or 10mg compared with monotherapy with saxagliptin 10mg or metformin 500mg plus placebo. At 24 weeks, combination therapy resulted in statistically significant improvements in glycemic parameters such as HbA_{1c}, fasting plasma glucose, and post-prandial glucose AUC, and a similar tolerability profile to monotherapy with either agent.⁷³

Safety

Clinical trials have shown saxagliptin to be safe and well tolerated thus far; however, experience with this agent is more limited. Of note, small, reversible, dose-dependent reductions in mean absolute lymphocyte count have been observed in studies of saxagliptin. To date this has not been associated with adverse clinical consequences. Similar to vildagliptin, adverse skin toxicology was reported in studies of saxagliptin in monkeys, although not in human clinical trials. There are no published studies to date of saxagliptin in patients taking insulin.

Vildagliptin Monotherapy

Monotherapy trials of vildagliptin in drug-naïve patients have shown significant reductions in HbA_{1c}.⁷⁴⁻⁷⁷ Pooling of data from phase III monotherapy trials, including placebo or active comparator controls,

using vildagliptin 100mg daily in 1,469 patients produced an adjusted mean change in HbA_{1c} of -1.0% at 24 weeks, from a baseline of 8.6%.⁷⁸ Vildagliptin has similar glycemic efficacy whether given as 50mg twice daily or 100mg once daily.⁷⁶ An excess in abnormal liver function tests was observed with the 100mg daily dosage, however, and the current recommendation in Europe is 50mg twice daily.

In drug-naïve patients with type 2 diabetes and mild hyperglycemia (HbA_{1c} 6.2-7.5%), treatment with vildagliptin 50mg once daily resulted in a modest but significant reduction in HbA_{1c} compared with placebo of -0.3% at one year⁷⁹ and -0.5% at two years.⁸⁰ Improvements were also seen in fasting and post-prandial glucose, as well as insulin-secretory rate relative to glucose (ISR/G), a reflection of beta-cell function. Thus, vildagliptin appeared to attenuate the progressive deterioration in glycemic control seen in patients treated with lifestyle counseling only, possibly through protective effects on beta-cell function.

Comparative studies have examined the efficacy and tolerability of vildagliptin relative to monotherapy with acarbose, rosiglitazone, metformin, and gliclazide.⁸¹⁻⁸⁵ Vildagliptin and acarbose decreased HbA_{1c} to a similar extent during 24-week treatment, meeting criteria for non-inferiority.⁸¹ Although bodyweight decreased with acarbose, vildagliptin was weight-neutral (-1.7 versus -0.4kg; $p < 0.001$) and resulted in fewer gastrointestinal adverse events compared with acarbose. Vildagliptin was also found to be as effective as rosiglitazone, improving HbA_{1c} by -1.1 and -1.3%, respectively, at 24 weeks.⁸² However, rosiglitazone increased bodyweight and was associated with more edema than vildagliptin.

In a 52-week study comparing treatment with vildagliptin (100mg daily) versus metformin (titrated to 2,000mg daily) in drug-naïve patients, both agents produced rapid, sustained reductions in HbA_{1c} from a baseline of 8.7% of -1.0 and -1.4%, respectively; however, statistical non-inferiority of vildagliptin was not established.⁸³ These results were sustained in an extension study at 104 weeks, suggesting durability of response for both agents.⁸⁴ Of note, metformin resulted in weight loss compared with vildagliptin, but was associated with significantly worse gastrointestinal tolerability (45.6 versus 25.0%; $p < 0.001$). The incidence of hypoglycemia was similarly low in both groups (<1%).

Another study compared monotherapy with vildagliptin versus gliclazide in treatment-naïve patients over two years.⁸⁵ Although the mean reduction in HbA_{1c} from baseline to week 104 was similar, at -0.5% in the group receiving vildagliptin and -0.6% with gliclazide monotherapy, vildagliptin did not meet the criteria for non-inferiority as the upper limit of the associated 95% CI for the between-group difference in mean change HbA_{1c} of -0.13% (-0.06 to 0.33%) was just above the cut-off of 0.3%.

Add-on Dual Combination Therapy

When added to ongoing metformin therapy in patients with inadequate glycemic control, vildagliptin was well tolerated and produced clinically meaningful reductions in HbA_{1c} in studies of up to one year.⁸⁶⁻⁸⁸ In a 24-week study, patients with a baseline HbA_{1c} of 8.4% were treated with vildagliptin 50mg daily, 100mg daily, or placebo and continued a stable metformin dose regimen. Placebo-adjusted mean

change from baseline to end-point was -0.7 and -1.1% in patients receiving 50 and 100mg, respectively, suggesting a dose-response effect.⁸⁷ Improvements were also seen in fasting and post-prandial glucose levels. Gastrointestinal adverse events were significantly less frequent among patients who received vildagliptin 50mg daily in combination with metformin than in those receiving metformin and placebo,⁸⁷ again suggesting that the addition of a DPP-4 inhibitor may improve the tolerability of metformin.

Vildagliptin was non-inferior to pioglitazone as add-on therapy to stable-dose metformin over 24 weeks, with comparable HbA_{1c} reductions maintained in both groups during a 28-week extension period.^{89,90} Hypoglycemia occurred rarely in both groups; however, pioglitazone caused significant weight gain from a baseline of 2.4kg compared with vildagliptin. Vildagliptin demonstrated comparable glycemic efficacy to glimepiride when added to ongoing metformin and displayed favorable tolerability with reduced bodyweight relative to glimepiride and a 10-fold lower incidence of hypoglycemia at 52 weeks.⁹¹ Vildagliptin (50 or 100mg daily) was also well tolerated and improved glycemic control compared with placebo in patients failing monotherapy with a sulfonylurea⁹² or thiazolidinedione⁹³ in studies of 24 weeks duration.

Add-on Therapy to Insulin

Vildagliptin was studied in 296 patients with type 2 diabetes inadequately controlled on insulin monotherapy.⁹⁴ The mean diabetes duration on entry was 14.7 years, duration of insulin use six years, and mean insulin dose 82 units per day, indicating advanced disease. The adjusted mean change in HbA_{1c} from a baseline average of 8.4% to 24 weeks was -0.5 and -0.2% in patients receiving vildagliptin and placebo, respectively. Although somewhat modest, the between-treatment difference was significant. Hypoglycemic events were less common and less severe among patients receiving vildagliptin compared with placebo, which is in contrast to the previously mentioned study of sitagliptin added on to insulin, likely because this study design allowed adjustments of insulin dose.

Initial Combination Therapy

The efficacy and safety of initial combination therapy with vildagliptin/metformin (Eucreas) was studied in treatment-naïve patients with type 2 diabetes.⁹⁵ Patients were randomized equally to receive vildagliptin plus high-dose metformin combination therapy (50mg + 1,000mg twice daily), vildagliptin plus low-dose metformin (50mg + 500mg twice daily), vildagliptin monotherapy (50mg twice daily), or high-dose metformin monotherapy (1,000mg twice daily). Mean change in HbA_{1c} from baseline was greater with combination therapy than with either agent as monotherapy. Rates of hypoglycemia were low with all treatment strategies. However, vildagliptin plus low-dose metformin combination therapy resulted in better gastrointestinal tolerability than metformin monotherapy. First-line treatment with combination vildagliptin and pioglitazone also provided better glycemic control than either component monotherapy and was well tolerated with low risk of hypoglycemia.⁹⁶

Safety

In a large pooled safety analysis, a slightly higher risk of mild liver enzyme elevation (aspartate aminotransferase [AST]/alanine

sminotransferase [ALT] >3 x upper limit of normal [ULN]) was observed with vildagliptin relative to comparators, although this did not translate into an increased risk for hepatic adverse events.⁹⁷ Nonetheless, assessment of hepatic function is recommended prior to initiation of therapy and monitoring should continue while on treatment, consistent with the product label. Use of vildagliptin is not recommended in patients with moderate to severe renal impairment, including patients on hemodialysis, due to lack of clinical experience.

Vildagliptin 50mg once or twice daily was not associated with an increased risk of pancreatitis-related adverse experiences relative to comparators.⁹⁸ Another analysis showed no increased risk of infections and infestations with vildagliptin.⁹⁹

The cardiovascular safety of vildagliptin was assessed in a meta-analysis of 20 phase III double-blind clinical trials including 6,978 patients treated with vildagliptin compared with 4,773 patients in placebo or active-controlled treatment groups. Vildagliptin was not associated with an increased risk for adjudicated cardiovascular and cerebrovascular events: odds ratio 0.89 (95% CI 0.75–1.05) and 1.05 (95% CI 0.97–1.15) for vildagliptin 50mg once daily and 50mg twice daily, respectively.¹⁰⁰

Comparison of Agents

Although several studies are under way, at present little evidence exists from direct head-to-head studies to distinguish among the DPP-4 inhibitors or compare these agents with GLP-1 analogs with respect to efficacy or safety. One study compared the effectiveness of vildagliptin (50mg twice daily) and sitagliptin (100mg once daily) in just 63 patients using metformin and/or other hypoglycemic agents and/or insulin over six months.¹⁰¹ Baseline HbA_{1c} was 8.0% for sitagliptin and 7.9% for vildagliptin with reduction to 7.4 and 7.0%, respectively (p=0.28). Patients treated with vildagliptin presented with a higher post-prandial glucose; however, no differences were observed on comparison of the two drugs.

Conclusions

The development of novel incretin-based therapies has expanded our armamentarium of agents for the management of type 2 diabetes. DPP-4 inhibitors possess a mechanism of action complementary to currently existing therapies and have demonstrated efficacy across a broad range of treatment contexts. They effectively lower HbA_{1c} when used as monotherapy or in combination with other antihyperglycemic medications. Even in patients already on insulin, with more advanced disease, and the presence of significant beta-cell failure, DPP-4 inhibitors continue to lower glucose, likely due in part to beneficial effects on the pancreatic alpha cell and suppression of glucagon production.

Although head-to-head studies comparing existing DPP-4 inhibitors are lacking, they do not appear to differ significantly with respect to glycemic efficacy. Compound-related differences may ultimately differentiate between agents in this class.

Established benefits of DPP-4 inhibitors include their neutral effect on weight profile and a glucose-dependent mechanism of action, which minimizes the risk of hypoglycemia. DPP-4 inhibitors are also convenient to take due to their oral route of administration independent of meal

consumption. These favorable characteristics may help clinicians and patients overcome clinical inertia, thereby facilitating therapy intensification and achievement of recommended glycemic targets. Another encouraging feature is their potential disease-modifying effects, including preservation of pancreatic beta-cell mass and enhancement of beta-cell function.

Overall, these medications appear safe and well tolerated. However, the durability of their effects and the long-term safety profile of these agents remain to be established. In addition, data are as yet lacking for important patient-centered outcomes such as diabetes complications, cost of therapy, and health-related quality of life, although long-term outcome studies are being initiated.¹⁰² Further studies and clinical experience will help to clarify the precise role that DPP-4 inhibitors will play in the management of type 2 diabetes. ■



Pamela M Katz, MD, is a Resident in the Division of Endocrinology and Metabolism at the University of Toronto. Her clinical interests include treatment of type 2 diabetes, hyperlipidemia, and endocrine disorders in pregnancy. Her research interests include quality improvement in the management of dyslipidemia and iodine nutrition in pregnancy.



Lawrence A Leiter, MD, is Head of the Division of Endocrinology and Metabolism at St Michael's Hospital in Toronto and a Professor in the Departments of Medicine and Nutritional Sciences at the University of Toronto. His research interests include clinical trials on the prevention of atherosclerosis, especially in diabetes, and the dietary and pharmacological treatment of diabetes, hyperlipidemia, hypertension, and obesity.

- King H, et al., *Diabetes Care*, 1998;21:1414–31.
- International Diabetes Federation, Available at: www.idf.org/president-international-diabetes-federation-calls-concerted-action-stop-diabetes-epidemic, (accessed November 27, 2009).
- Holman RR, et al., *N Engl J Med*, 2008;359:1577–89.
- Resnick HE, et al., *Diabetes Care*, 2006;29(3):531–7.
- Kahn SE, et al., *N Engl J Med*, 2006;355:2427–43.
- UKPDS Group, *Diabetes*, 1995;44(11):1249–58.
- Butler AE, et al., *Diabetes*, 2003;52:102–10.
- Van Gaal LF, et al., *Eur J Endocrinol*, 2008;158:773–84.
- Triplitt C, et al., *J Manag Care Pharm*, 2007;13(9):S2–16.
- Nicolucci A, et al., *Acta Biomed*, 2008;79:184–91.
- Brown JB, et al., *Diabetes Care*, 2004;27:1535–40.
- Habener JF, *Diabetes Mellitus: A Fundamental and Clinical Text*, 2nd ed, Philadelphia, PA, Lippincott Williams & Wilkins, 2000.
- Lovshin JA, et al., *Nat Rev Endocrinol*, 2009;5:262–9.
- Drucker DJ, et al., *Lancet*, 2006;368:1696–1705.
- Drucker DJ, *Cell Metab*, 2006;3:153–65.
- Nauck M, et al., *Diabetologia*, 1986;29:46–52.
- Elahi D, et al., *Regul Pept*, 1994;51:63–74.
- Vilsbøll T, et al., *Diabetes*, 2001;50:609–13.
- Nauck MA, et al., *J Clin Invest*, 1993;91:301–7.
- Vilsbøll T, et al., *Diabetologia*, 2002;45:1111–19.
- Holst JJ, et al., *Trends Mol Med*, 2008;14(4):161–8.
- Ahrén B, *Best Pract Res Clin Endocrinol Metab*, 2009;23(4):487–98.
- European Medicines Agency, Available at: www.emea.europa.eu/humandocs/PDFs/EPAR/eucreas/H-807-en6.pdf (accessed November 26, 2009).
- Li Y, et al., *J Biol Chem*, 2003;278:471–8.
- Drucker DJ, *Endocrinology*, 2003;144(12):5145–8.
- Tourrel C, et al., *Diabetes*, 2001;50:1562–70.
- Xu G, et al., *Diabetes*, 1999;48:2270–76.
- Farilla L, et al., *Endocrinology*, 2003;144(12):5149–58.
- Mu J, et al., *Diabetes*, 2006;55:1695–1704.
- Nikolaidis LA, et al., *Circulation*, 2004;109(8):962–5.
- Bose AK, et al., *Diabetes*, 2005;54:146–51.
- Sokos GG, et al., *J Card Fail*, 2006;12(9):694–9.
- Timmers L, Henriques JPS, et al., *J Am Coll Cardiol*, 2009;53:501–10.
- Amori RE, et al., *JAMA*, 2007;298(2):194–206.
- Richter B, et al., *Cochrane Database Syst Rev*, 2008;(2):CD006739.
- Scott R, et al., *Int J Clin Pract*, 2007;61(1):171–80.
- Aschner P, et al., *Diabetes Care*, 2006;29:2632–7.
- Raz I, et al., *Diabetologia*, 2006;49:2564–71.
- Hanefeld M, et al., *Curr Med Res Opin*, 2007;23(6):1329–39.
- Williams-Herman D, Seck T, Golm G, et al., Poster 754, presented at the 45th Annual Meeting of the European Association for the Study of Diabetes (EASD), September 27 – October 1, 2009, Vienna, Austria.
- Aschner P, et al., *Diabetes Obes Metab*, 2009; in press.
- Charbonnel B, et al., *Diabetes Care*, 2006;29(12):2638–43.
- Rosenstock J, et al., *Clin Ther*, 2006;28(10):1556–68.
- Scott R, et al., *Diabetes Obes Metab*, 2008;10(10):959–69.
- Nauck MA, et al., *Diabetes Obes Metab*, 2007;9(2):194–205.
- Hermansen K, et al., *Diabetes Obes Metab*, 2007;9(5):733–45.
- Arjona Ferreira JC, et al., *Diabetologia*, 2008;51(Suppl. 1):S365.
- Vilsbøll T, et al., *Diabetes Obes Metab*, 2009; in press.
- Bailey CJ, et al., *Int J Clin Pract*, 2005;59(11):1309–16.
- Del Prato S, et al., *Int J Clin Pract*, 2005;59(11):1345–55.
- Migoya EM, et al., Abstract 0286-OR, Diabetes Abstract Book, American Diabetes Association 67th Scientific Sessions, Chicago, IL, US, June 22–26, 2007.
- Goldstein BJ, et al., *Diabetes Care*, 2007;30:1979–87.
- Williams-Herman D, et al., *Curr Med Res Opin*, 2009;25(3):569–83.
- Qi, Daniel et al., *Diabetologia*, 2008;51(Suppl. 1):S36.
- Reasner C, et al., Poster 610-P, Presented at 69th Scientific Session of the American Diabetes Association, June 5–9, 2009, New Orleans, LA.
- Olansky L, et al., Abstract 0-0535, Presented at International Diabetes Federation/20th World Diabetes Congress in Montreal, Quebec, Canada, October 18–22, 2009.
- Yoon K, et al., Poster 747, Presented at the 45th Annual Meeting of the EASD, September 27 – October 1, 2009, Vienna, Austria.
- Bergman AJ, et al., *Diabetes Care*, 2007;30(7):1862–4.
- Chan JC, et al., *Diabetes Obes Metab*, 2008;10(7):545–55.
- Williams-Herman D, et al., *BMC Endocr Disord*, 2008;8:14.
- US Food and Drug Administration, Available at: www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHealthcareProfessionals/ucm183764.htm (accessed November 27, 2009).
- Noel RA, et al., *Diabetes Care*, 2009;32(5):834–8.
- Augeri DJ, et al., *J Med Chem*, 2005;48(15):5025–37.
- Vilhauer EB, et al., *J Med Chem*, 2003;46(13):2774–89.
- Traynor K, *Am J Health Syst Pharm*, 2009;66:1513.
- Rosenstock J, et al., *Diab Obes Metab*, 2008;10:376–86.
- Rosenstock J, et al., *Curr Med Res Opin*, 2009;25(10):2401–11.
- Bristol-Myers Squibb, Available at: packageinserts.bms.com/pi/pi_onglyza.pdf (accessed November 27, 2009).
- DeFronzo RA, et al., *Diabetes Care*, 2009;32:1649–55.
- DeFronzo RA, et al., Poster 547-P, Presented at American Diabetes Association 69th Scientific Sessions, June 5–9, 2009, New Orleans, Louisiana.
- Chacra AR, et al., *Int J Clin Pract*, 2009;9:1395–1406.
- Hollander P, et al., *J Clin Endocrinol Metab*, 2009 Oct 28 (Epub ahead of print).
- Jadzinsky M, et al., *Diab Obes Metab*, 2009;11:611–22.
- Ristic S, et al., *Diab Obes Metab*, 2005;7:692–8.
- Pratley RE, et al., *Horm Metab Res*, 2006;38(6):423–8.
- Pi-Sunyer FP, et al., *Diab Res Clin Pract*, 2007;76:132–8.
- Dejager S, et al., *Horm Metab Res*, 2007;39:218–23.
- Rosenstock J, *Int J Clin Pract*, 2008;62(Suppl. 159):15–23.
- Scherbaum WA, et al., *Diabetes Obes Metab*, 2008;10(8):675–82.
- Scherbaum WA, et al., *Diab Obes Metab*, 2008;10:1114–24.
- Pan C, et al., *Diabet Med*, 2008;25:435–41.
- Rosenstock J, et al., *Diabetes Care*, 2007;30:217–23.
- Schweizer A, et al., *Diabet Med*, 2007;24:955–61.
- Goke B, et al., *Horm Metab Res*, 2008;40:892–5.
- Foley JE, et al., *Horm Metab Res*, 2009 (Epub ahead of print).
- Goodman M, et al., *Horm Metab Res*, 2009;41:368–73.
- Bosi E, et al., *Diabetes Care*, 2007;30:890–95.
- Ahrén B, et al., *Diabetes Care*, 2004;27:2874–80.
- Bolli G, et al., *Diab Obes Metab*, 2008;10:82–90.
- Bolli G, et al., *Diab Obes Metab*, 2009;11:589–95.
- Ferrannini E, et al., *Diab Obes Metab*, 2009;11:157–66.
- Garber AJ, et al., *Diab Obes Metab*, 2008;10:1047–56.
- Garber AJ, et al., *Diab Obes Metab*, 2007;9:166–74.
- Fonseca V, et al., *Diabetologia*, 2007;50:1148–55.
- Bosi E, et al., *Diab Obes Metab*, 2009;11:506–15.
- Rosenstock J, et al., *Diab Obes Metab*, 2007;9:175–85.
- Kothny W, et al., Poster 764, Presented at the 45th Annual Meeting of the EASD, September 29 – October 2, 2009, Vienna, Austria.
- Ligueros-Saylan M, et al., Presentation 765, at the 45th Annual Meeting of the EASD, September 29 – October 2, 2009, Vienna, Austria.
- Foley J, et al., Presentation 773 at the 45th Annual Meeting of the EASD, September 29 – October 2, 2009, Vienna, Austria.
- Schweizer A, et al., Presentation 763 at the 45th Annual Meeting of the EASD, September 29 – October 2, 2009, Vienna, Austria.
- Gama, M et al., P1413, Presented at IDF/World Diabetes Congress, October 18–22, 2009, Montreal, Quebec, Canada.
- Bethel MA, et al., Presentation 1245 at the 45th Annual Meeting of the, September 29–October 2, 2009, Vienna, Austria.