Safety of dipeptidyl peptidase 4 inhibitors: a perspective review

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Abstract: Dipeptidyl peptidase 4 (DPP-4) inhibitors are a relatively new class of oral antihyperglycemic agent that enhance insulin secretion by reducing degradation of endogenous glucagon-like peptide 1. Currently, sitagliptin, vildagliptin, saxagliptin, linagliptin and alogliptin have been approved by the US Food and Drug Administration or the European Medicines Agency for use in patients with type 2 diabetes. Their glycemic efficacy has been well documented; however, data regarding their long-term safety are as yet inconclusive. While preclinical studies have indicated a potential cardioprotective effect of DPP-4 inhibitors, current clinical data from cardiovascular safety trials suggest a neutral effect on cardiovascular outcomes. Moreover, postmarketing experience has given rise to concerns about specific adverse events, including pancreatitis and hypersensitivity reactions. This review summarizes available evidence regarding safety of DPP-4 inhibitors. Overall, DPP-4 inhibitors appear to be a safe option for patients with type 2 diabetes. However, close pharmacovigilance is necessary to address the uncertainty regarding pancreas-related adverse events, while their potential impact on cardiovascular outcomes will be further elucidated after completion of more long-term studies.

Keywords: adverse effects, drug safety, dipeptidyl peptidase 4 inhibitors, pancreatitis, type 2 diabetes

Introduction

Dipeptidyl peptidase 4 (DPP-4) inhibitors are oral antihyperglycemic agents, introduced in 2006 for the treatment of type 2 diabetes. DPP-4 is a transmembrane glycoprotein located on the surface of most cell types and its pleiotropic actions may be associated with immune regulation, cell apoptosis and signal transduction [Golightly *et al.* 2012]. The prevailing and clinically relevant action of DPP-4 is the degradation of endogenous glucagon-like peptide 1 (GLP-1). By interrupting this effect, DPP-4 inhibitors enhance insulin secretion in a glucose-dependent manner [Nauck *et al.* 2009]. Sitagliptin was the first commercialized DPP-4 inhibitor, approved in 2006 by the US Food and Drug Administration (FDA) and in 2007 by the European Medicines Agency (EMA) at a dosage of 100 mg daily. Vildagliptin 50 mg twice daily was approved within the European Union in 2007. Saxagliptin and linagliptin received marketing authorization in 2009 and 2011 respectively, both at a dose of 5

mg once daily. Finally, alogliptin was approved in Japan in 2010 and by the FDA on January 2013.

The glycemic efficacy and weight-sparing effect of DPP-4 inhibitors have been documented in systematic reviews both against placebo and other antidiabetic medications [Fakhoury *et al.* 2010; Aroda *et al.* 2012; Deacon *et al.* 2012; Karagiannis *et al.* 2012]. However, their long-term safety remains inconclusive, while postmarketing experience has given rise to concerns about specific adverse events, including pancreatitis and hypersensitivity reactions. This review summarizes the evidence regarding the safety profile of the five commercially available DPP-4 inhibitors.

Hypoglycemia

DPP-4 inhibitors augment insulin secretion in a glucose-dependent manner, thus preventing hypoglycemia when used as monotherapy or in combination with antidiabetic agents which are

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known not to increase rates of hypoglycemia [Nauck *et al.* 2009]. Hypoglycemic risk was similar to placebo when a DPP-4 inhibitor was used as monotherapy or as combination therapy with metformin or a thiazolidinedione [Goossen and Graber, 2012; Gerrald *et al.* 2012]. However, incidence of hypoglycemia is increased when patients with background treatment with insulin or a sulfonylurea are treated with sitagliptin, saxagliptin, or linagliptin [Goossen and Graber, 2012; Bristol-Myers Squibb, 2011; Von Eynatten *et al.* 2013]. Of note, hypoglycemic risk was similar to placebo in patients treated with vildagliptin [Monami *et al.* 2010; Goossen and Graber, 2012] or alogliptin [Daily Med, 2013], even in patients already on insulin or a sulfonylurea.

Overall, DPP-4 inhibitors are not associated with a higher risk for hypoglycemia in comparison with metformin as monotherapy or with pioglitazone as second-line treatment [Karagiannis *et al.* 2012]. In a meta-analysis of patient-level data, incidence of hypoglycemia was similar between patients receiving sitagliptin and patients treated with metformin or a thiazolidinedione [Williams-Herman *et al.* 2010]. Consistently, hypoglycemic risk with vildagliptin was lower than with sulfonylureas [relative risk (RR) 0.25; 95% confidence interval (CI) 0.10–0.64] and similar to metformin, thiazolidinediones and α -glucosidase inhibitors [Cai *et al.* 2012].

Infections

The role of DPP-4 in immune functions [Reinhold *et al.* 2007; Ansorge *et al.* 2009], cell growth and apoptosis [Thompson *et al.* 2007] has raised concerns regarding a possible association with infections. Early meta-analyses suggested an increased risk for all-cause infections in patients receiving sitagliptin [Amori *et al.* 2007; Richter *et al.* 2008], but not in those treated with vildagliptin [Richter *et al.* 2008; Monami *et al.* 2010]. However, sitagliptin was not associated with upper respiratory tract or urinary tract infections in more recent analyses [Gerrald *et al.* 2012; Goossen and Graber, 2012]. Similarly, incidence of upper respiratory or urinary tract infections was similar to placebo in patients treated with vildagliptin [Ligueros-Saylan *et al.* 2010; Goossen and Graber, 2012], saxagliptin [Gerrald *et al.* 2012], linagliptin [Scherthaner *et al.* 2012] or alogliptin [Berhan and Berhan, 2013]. Regarding nasopharyngitis, a marginally increased risk was noted with sitagliptin (RR 1.35; 95% CI 1.03–1.77) [Goossen

and Graber, 2012], while a slight nonsignificant increase was recorded in patients treated with linagliptin as opposed to those receiving placebo [Goossen and Graber, 2012; Scherthaner *et al.* 2012]. Nasopharyngitis was recorded in 257 and 89 patients randomized to alogliptin 25 mg ($n = 5902$) and placebo ($n = 2926$) respectively [Daily Med, 2013].

Gastrointestinal adverse events

Sitagliptin was not associated with increased risk for diarrhea, nausea or vomiting [Williams-Herman *et al.* 2010; Gerrald and Graber, 2012]. Similarly, no increased incidence of gastrointestinal disorders was observed in patients treated with vildagliptin [Monami *et al.* 2010; Cai *et al.* 2012] or linagliptin [EMA, 2011]. Compared with other antidiabetic agents, gastrointestinal adverse events were more common in patients receiving metformin or a GLP-1 agonist than a DPP-4 inhibitor [Karagiannis *et al.* 2012].

Hypersensitivity and skin-related reactions

Postmarketing events of hypersensitivity reactions including anaphylaxis and angioedema are reported in the prescribing information of most DPP-4 inhibitors. Use of vildagliptin was associated with an increased incidence of angioedema ($n = 14/2754$) among individuals receiving an angiotensin-converting enzyme (ACE) inhibitor compared with a control group ($n = 1/1819$) [odds ratio (OR) 4.57; 95% CI 1.57–13.28] [Brown *et al.* 2009]. It is unclear whether this complication is specific to vildagliptin or is related to other DPP-4 inhibitors as well. It is probable that dual enzyme inhibition of DPP-4 and ACE may prolong half lives of bradykinin and substance P to a greater extent than use of ACE inhibitor alone [Byrd *et al.* 2011]. In animal studies, both bradykinin and substance P cause tracheal edema by increasing vascular permeability [Emanuelli *et al.* 1998]. Moreover, in a pooled analysis of 3749 patients, higher frequencies of skin and subcutaneous disorders were observed in the linagliptin group (4%) than in the placebo group (2.6%), while skin exfoliation and exfoliative dermatitis were reported in five and one patients receiving linagliptin, respectively [EMA, 2011].

However, in a pooled analysis of approximately 10,200 patients the incidence of angioedema did not differ between sitagliptin and placebo or other

antidiabetic medications [Williams-Herman *et al.* 2010]. Consistently, hypersensitivity or skin reactions were similar between saxagliptin and placebo in approximately 16,500 patients followed for a median of 2.1 years [Scirica *et al.* 2013]. Similarly, in a long-term randomized controlled trial, incidence of angioedema was low and did not differ significantly between alogliptin and placebo [White *et al.* 2013a]. Postmarketing safety of saxagliptin is investigated in a series of ongoing retrospective cohort studies, which are expected to provide important information regarding possible drug-related adverse events, including hypersensitivity reactions [Lo Re *et al.* 2012]. Furthermore, the FDA has requested a pharmacovigilance study to monitor for cases of severe hypersensitivity reactions associated with alogliptin [FDA, 2013b].

Pancreatitis

Pancreas-related adverse events reported after authorization of DPP-4 inhibitors have raised early concerns about their possible association with pancreatitis. Postmarketing events of acute pancreatitis including fatal hemorrhagic or necrotizing pancreatitis have been reported in patients receiving sitagliptin [Merck Sharp & Dohme Corp., 2012], vildagliptin [Girgis and Champion, 2011; Nakata *et al.* 2012; Saraogi *et al.* 2012; Kunjathaya *et al.* 2013], or saxagliptin [Bristol-Myers Squibb, 2011]. In an analysis based on data from the FDA adverse event reporting system (FAERS, formerly AERS) covering the first quarter of 2004 through the third quarter of 2009, use of sitagliptin increased the OR for pancreatitis more than sixfold compared with other therapies (6.74; 95% CI 4.61–10.0) [Elashoff *et al.* 2011]. Additionally, a case-control study suggests an association of sitagliptin with increased odds of hospitalization for acute pancreatitis [Singh *et al.* 2013]. However, these findings should be interpreted with caution in light of data from randomized controlled trials that did not verify an association of sitagliptin with acute pancreatitis ($n = 1$ event per 4709 patient-years of exposure) compared with a control group ($n = 4/3942$) [Engel *et al.* 2010]. Moreover, retrospective observational analyses from large databases did not demonstrate an increased incidence of acute pancreatitis in patients treated with sitagliptin compared with those receiving other antidiabetic medications [Dore *et al.* 2009; Garg *et al.* 2010]. Consistently, pancreatitis-related adverse events did not differ between patients receiving

vildagliptin and controls in pooled analyses (OR 0.70; 95% CI 0.26–1.88) [Ligueros-Saylan *et al.* 2010], while the incidence of acute or chronic pancreatitis was similar between patients receiving alogliptin and those on placebo in a randomized controlled trial of 18 weeks [White *et al.* 2013a].

Linagliptin was associated with an increased number of cases of pancreatitis compared with placebo [MHRA, 2012]. This was apparent in a large dataset of 4687 patients; 11 cases of pancreatitis among patients treated with linagliptin were recorded [EMA, 2011]. Based on data reported by the drug manufacturer, there were 15.2 cases of pancreatitis per 10,000 patient-year exposure in patients treated with linagliptin as opposed to 3.7 cases per 10,000 patient-year exposure in patients receiving placebo or active comparator [Boehringer Ingelheim International GmbH, 2012]. Furthermore, pancreatitis was reported in 11 of 5902 patients treated with alogliptin 25 mg and in 5 of 5183 patients in the control group during the drug's clinical program [Daily Med, 2013].

In September 2012, the Medicines and Healthcare Products Regulatory Agency (MHRA) in the UK commented on this topic, advising healthcare professionals to inform patients treated with DPP-4 inhibitors about symptoms of acute pancreatitis [MHRA, 2012]. In March 2013 both the FDA [FDA, 2013a] and the EMA [EMA, 2013a] raised additional concerns due to the findings of an independent academic group that suggested an increased risk not only for pancreatitis, but also for precancerous cellular changes in the pancreas of seven patients treated with sitagliptin and one with the GLP-1 analogue exenatide [Butler *et al.* 2013]. However, it should be noted that these findings were based on a small number of pancreatic tissue samples obtained from organ donors with or without type 2 diabetes ($n = 20$ and $n = 14$ respectively), who died due to causes other than diabetes. The ability to draw meaningful conclusions from this study is further attenuated by a number of methodological limitations, mainly due to mismatched cases and controls and use of poorly validated reagents [Engel *et al.* 2013a; Drucker, 2013; Kahn, 2013]. Thus, healthcare professionals are advised to continue following the prescribing recommendations of DPP-4 inhibitors [FDA, 2013a], while the Committee for Medicinal Products for Human Use considered even harmonizing the wordings

regarding pancreatitis in the product information of all incretin-based therapies [EMA, 2013b].

Cardiovascular safety

The effect of antidiabetic agents on cardiovascular outcomes has been a matter of uncertainty for the past four decades [Matthews and Tsapas, 2008]. Thus, in 2008 the FDA issued a guidance document calling for cardiovascular safety assessment of all new glucose-lowering therapies. Preclinical data have indicated a potential cardioprotective effect of DPP-4 inhibitors by increasing the concentration not only of GLP-1, but of other vasoactive peptides as well [Scheen, 2013]. However, data from cardiovascular safety trials suggest that DPP-4 inhibitors neither reduce nor increase cardiovascular morbidity or mortality in patients with type 2 diabetes [Scirica *et al.* 2013; White *et al.* 2013a]. In a dedicated cardiovascular study in approximately 5400 patients with a recent acute coronary syndrome, the incidence of major cardiovascular events (MACEs; death from cardiovascular causes, nonfatal myocardial infarction or nonfatal stroke) was similar between alogliptin and placebo [White *et al.* 2013a]. Similarly, in a placebo-controlled dedicated cardiovascular safety study on approximately 16,500 patients with cardiovascular risk factors followed for a median of 2.1 years, saxagliptin did not affect the rate of ischemic events; nevertheless it was associated with an increased rate of hospitalization due to heart failure [Scirica *et al.* 2013]. The study's authors could not provide a plausible explanation for the higher incidence of hospitalization for heart failure among patients treated with saxagliptin, yet suggest that this finding requires further investigation and confirmation. Long-term randomized controlled trials are underway for sitagliptin [Bethel *et al.* 2009] and linagliptin [Rosenstock *et al.* 2013] to provide conclusive evidence regarding their cardiovascular safety.

There are also additional data based on retrospective cohort studies or pooled analyses of randomized controlled trials regarding the effect of individual agents on cardiovascular outcomes. Use of sitagliptin was not associated with an increased risk of cardiovascular-related hospital admissions or deaths in comparison with other antidiabetic drugs in a retrospective population-based cohort study of approximately 72,740 newly treated patients with type 2 diabetes [Eurich *et al.* 2013]. The cardiovascular safety of

sitagliptin has also been assessed in a *post hoc* analysis utilizing a pooled population of 14,611 patients drawn by 25 studies up to December 2011 [Engel *et al.* 2013b]. The exposure-adjusted incidence per 100 patient-years for MACEs was similar in the sitagliptin group and the nonexposed group (adjusted incidence ratio 0.83; 95% CI 0.53–1.30). A subgroup analysis of the placebo-controlled studies yielded similar results (1.01; 95% CI 0.55–1.86). Similarly, the incidence of cardiovascular-related death did not differ between patients receiving sitagliptin and controls (0.95; 95% CI 0.40–2.30).

The results were similar for vildagliptin, based on a meta-analysis of 25 trials conducted by the drug manufacturer [Schweizer *et al.* 2010]. The risk for the composite outcome of acute coronary syndrome, transient ischemic attack, stroke and cardio-cerebrovascular death was similar between vildagliptin ($n = 6116$) and all comparators ($n = 6061$) (RR 0.84; 95% CI 0.62–1.14). The results were consistent in separate analyses for each component of the composite outcome and in subgroup analyses, including only patients at high cardiovascular risk.

In a pooled analysis of eight trials, the incidence of the composite cardiovascular event (cardiovascular-related death, nonfatal myocardial infarction, nonfatal stroke) was lower in patients randomized to saxagliptin ($n = 3356$) compared with patients randomized to placebo or an active comparator ($n = 1251$) [hazard ratio (HR) 0.44; 95% CI 0.2–0.82] [Frederich *et al.* 2010].

The impact of linagliptin on a composite outcome of cardiovascular death, nonfatal stroke, nonfatal myocardial infarction and hospitalization for unstable angina was assessed in a meta-analysis of eight trials, including 3319 patients randomized to linagliptin and 1920 randomized to comparators (placebo, $n = 977$; glimepiride, $n = 781$; voglibose, $n = 162$) [Johansen *et al.* 2012]. Cardiovascular events were recorded in 11 patients receiving linagliptin and 23 patients in the control group, resulting in a significantly lower cardiovascular risk with linagliptin (HR 0.34; 95% CI 0.16–0.70). Notably, 20 of the 23 events reported in the comparator group were observed with glimepiride. Subgroup analysis utilizing only placebo-controlled trials demonstrated a neutral effect of linagliptin on the cardiovascular composite endpoint [Johansen *et al.* 2012].

The cardiovascular safety of alogliptin has been evaluated in a pooled analysis of approximately 6000 patients randomized to alogliptin, placebo or an active comparator [White *et al.* 2013b]. A total of 13 and 10 MACE events were reported with alogliptin (2023 patient-years) and control treatments (966 patient-years) respectively, resulting in a similar cardiovascular risk (HR 0.63; 95% CI 0.0–1.41). Similarly, there was no difference in the incidence of non-MACE cardiovascular events, including angina, arrhythmias and heart failure, between alogliptin and comparators [White *et al.* 2013b].

Malignancies

Due to their mechanism of action, there have been concerns about a potential association of DPP-4 inhibitors with pancreatic malignancies. Observational data from the FAERS dataset suggest a more than twofold greater event rate for pancreatic cancer with sitagliptin than with other therapies [Elashoff *et al.* 2011]. Moreover, based on a recent *in vitro* study, precancerous cellular changes were observed in the pancreas of seven patients who had received sitagliptin for more than 1 year and died from causes other than diabetes [Butler *et al.* 2013]. Nevertheless, data from clinical trials do not indicate an increased risk for cancer with DPP-4 inhibitors. Meta-analyses demonstrate a similar risk of cancer between patients randomized to sitagliptin and patients receiving placebo or other antihyperglycemic treatment [Williams-Herman *et al.* 2010; Monami *et al.* 2011]. Furthermore, use of saxagliptin does not seem to be associated with increased incidence of pancreatic cancer or other malignancies as demonstrated by a long-term placebo-controlled trial [Scirica *et al.* 2013]. Similarly, there were no reports of pancreatic cancer in a long-term trial of 5380 patients randomized to alogliptin or placebo [White *et al.* 2013a].

Renal and hepatic toxicity

Renal excretion is the main elimination pathway for most DPP-4 inhibitors. It is therefore necessary to adjust their dose in patients with moderate or severe renal impairment. Sitagliptin has not been found to be nephrotoxic in clinical trials and was well tolerated at adjusted doses in patients with moderate or severe renal insufficiency, including those with end-stage renal disease treated with dialysis [Chan *et al.* 2008; Arjona Ferreira *et al.* 2013]. A retrospective analysis of a

large medical and pharmacy claims database revealed no association between sitagliptin and acute renal failure [Pendergrass *et al.* 2012]. However, there have been anecdotal postmarketing reports of worsening renal function among patients treated with sitagliptin [Merck Sharp & Dohme Corp., 2012]. Of note, a subset of these reports involved patients with chronic renal insufficiency who were prescribed inappropriately high doses of sitagliptin. Even though the mechanism of these renal adverse events and their potential association with sitagliptin remain unclear, it is recommended to monitor renal function in all patients receiving sitagliptin.

A meta-analysis of 38 studies did not reveal any difference in incidence of hepatic-related adverse events between vildagliptin and control groups (OR 0.87; 95% CI 0.64–1.19) [Ligueros-Saylan *et al.* 2010]. However, there have been rare cases of hepatic dysfunction (including hepatitis) in patients treated with vildagliptin which are reported in the drug's prescribing information [EMA, 2012]. While it is not possible to establish a causal relationship to drug exposure, its use is not recommended in patients with values of alanine aminotransferase or aspartate aminotransferase three times higher than the upper limit of normal. Moreover, liver function should be monitored prior to vildagliptin initiation and at 3-month intervals during the first year of treatment [EMA, 2012]. Similarly, for alogliptin hepatic adverse events including fatal and nonfatal hepatic failure have been described during its postmarketing use outside the United States. Although these reports contain insufficient information to establish a causative relationship, it is recommended that a liver test panel is obtained before initiating treatment with alogliptin [Daily Med, 2013].

Conclusion

In summary, hypoglycemia does not seem to be a main concern in patients receiving DPP-4 inhibitors. However, in patients with background treatment with insulin or a sulfonylurea it is advised to downtitrate the dose of these medications. Moreover, all patients initiating treatment with a DPP-4 inhibitor should be monitored for hypersensitivity reactions and skin disorders. Additionally, it is recommended to monitor renal function in patients receiving sitagliptin, while liver function should be checked in those treated with vildagliptin.

Dedicated cardiovascular studies suggest a neutral effect of alogliptin and saxagliptin on cardiovascular outcomes, while the safety profile of sitagliptin and linagliptin will be further illuminated through completion of relevant long-term studies. Finally, current evidence is insufficient to define a causative relationship between use of DPP-4 inhibitors and pancreatitis, and data from clinical trials do not suggest an increased risk for pancreatic cancer. Nevertheless, both the FDA and EMA are investigating all available data through pharmacovigilance evaluations in order to clarify the risk profile of DPP-4 inhibitors in relation to the pancreas and decide about necessary regulatory action.

In conclusion, DPP-4 inhibitors appear to be a safe option for patients with type 2 diabetes either as monotherapy or as add-on treatment. However, no robust conclusions can be drawn between individual DPP-4 inhibitors due to lack of head-to-head trials. Additionally, close pharmacovigilance monitoring plans are necessary in order to address the uncertainty regarding pancreas-related adverse events, while their potential impact on cardiovascular outcomes will be clarified in the near future after completion of more relevant long-term studies.

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