DPP-4 Inhibitors

Impact on glycemic control and cardiovascular risk factors

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The first dipeptidyl peptidase 4 (DPP-4) inhibitor sitagliptin was approved in 2006 as treatment for diabetes concurrently with lifestyle changes. A combined product of sitagliptin and glucophage was approved by the U.S. Food and Drug Administration in 2007. The second DPP-4 inhibitor, saxagliptin, was approved in the U.S. It was approved both as monotherapy as well as in combination with metformin, sulfonylurea, or thiazolidinedione. The use of a DPP-4 inhibitor called vildagliptin was approved in Europe and Latin America also as a combination with metformin, sulfonylurea, or thiazolidinedione. Two other DPP-4 inhibitors are also available (linagliptin and alogliptin). In this review, we will elaborate only on the first three drugs (sitagliptin, saxagliptin, and vildagliptin).

The different DPP-4 inhibitors are distinctive in their metabolism (saxagliptin and vildagliptin are metabolized in the liver and sitagliptin is not), their excretion, their recommended dosage, and the daily dosage that is required for effective treatment. They are similar, however, when comparing their efficacy regarding lowering HbA_{1c} levels, safety profile, and patient tolerance.

DPP-4 INHIBITORS AND PATIENT BLOOD GLUCOSE CONTROL—The influence of DPP-4 inhibitors on the blood levels of HbA_{1c} as monotherapy or in combination with other oral antidiabetes drugs was tested in multiple trials lasting 12–52 weeks. The results of these important trials were reviewed by Davidson (1) and will be summarized here briefly. Treatment with sitagliptin showed an average decrease in HbA_{1c} levels of 0.65% after 12 weeks of treatment, 0.84% after 18 weeks of treatment, 0.85% after 24 weeks of treatment, 1.0% after 30 weeks of treatment, and 0.67% after 52 weeks of treatment. Treatment with saxagliptin showed an average decrease in HbA_{1c} levels of 0.43–1.17%. Treatment with vildagliptin showed an average decrease in HbA_{1c} levels of 1.4% after 24 weeks as monotherapy in a subgroup of patients with no prior oral treatment and after a short period of time from the diagnosis of diabetes. In a meta-analysis that included information regarding treatment of type 2 diabetes with sitagliptin and vildagliptin for ≥12 weeks compared with placebo and other oral antidiabetic drugs, Amori et al. (2) showed a reduction of 0.74% in HbA_{1c} levels. This result proved DPP-4 inhibitors were only slightly less effective than sulfonylureas and as effective as metformin and thiazolidinediones in regard to reducing blood glucose. In studies with combination therapy of DPP-4 inhibitors and metformin in one pill, the results were even better because of two possible causes. First, metformin has an upregulating effect on the level of glucagon like peptide 1 (GLP-1), and therefore it enhances the incretin effect of the DPP-4 inhibitors. A second possible explanation for the improved results in the combined drug is the improved compliance of patients when taking one oral drug instead of two.

To date, there are no publications regarding the long-term combination therapy of these drugs and insulin injections.

DPP-4 INHIBITORS AND PATIENT WEIGHT—Studies on the influence of DPP-4 inhibitors on patient weight demonstrated variable results but are generally considered to be neutral. Studies regarding treatment with sitagliptin showed variability between 1.5 kg of weight loss in 52 weeks of therapy to 1.8 kg of weight gain in 24 weeks of therapy. Studies regarding treatment with vildagliptin showed variability between 1.8 kg of weight loss to 1.3 kg of weight gain in 24 weeks of therapy. Similar studies regarding saxagliptin showed variability between 1.8 kg of weight loss to 0.7 kg of weight gain in 24 weeks of therapy. In a meta-analysis of 13 studies regarding the treatment of all three DPP-4 inhibitors, the effect of this group of drugs on weight was neutral (2,3).

SAFETY PROFILE OF DPP-4 INHIBITORS—In controlled clinical studies of both monotherapy and combination therapy of sitagliptin, the overall incidence of adverse reactions in patients taking sitagliptin was similar to that reported with placebo. Discontinuation of therapy because of adverse reactions was also similar to placebo (4). The three most commonly reported adverse reactions in clinical trials were nasopharyngitis, upper respiratory tract infection, and headache. During postmarketing surveillance, acute pancreatitis was reported in 88 patients taking sitagliptin or metformin + sitagliptin between October 2006 and February 2009. In 19 of the 88 reported cases (21%), pancreatitis occurred within 30 days of starting sitagliptin or metformin + sitagliptin. Hospitalization was required in 58 (66%) of the patients. Upon discontinuation of sitagliptin, 47 of the 88 cases (53%) resolved. A causative relationship between sitagliptin and pancreatitis has not been established. Diabetes itself is a risk factor for pancreatitis. Other risk factors such as hypercholesterolemia, hypertriglyceridemia, and obesity were also present in 51% of the U.S. cases (5). In

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clinical trials, the incidence of pancreatitis did not differ significantly between the sitagliptin (0.1%) and nonexposed groups (0%) (4), although these data do not rule out the possibility of a rare adverse effect. During postmarketing surveillance, serious allergic reactions, including anaphylactoid reactions, angioedema, and exfoliate dermatologic reactions (such as Stevens-Johnson syndrome), were reported. These reactions have typically occurred within 3 months of sitagliptin initiation, with some occurring after the first dose. Among clinical trial recipients who received 2.5 or 5 mg saxagliptin daily, alone or in combination with metformin, a thiazolidinedione, or glyburide, 1.5% had a hypersensitivity-related event such as urticaria and facial edema (angioedema) compared with 0.4% in the placebo recipients. Saxagliptin may cause lymphopenia. Compared with data from placebo recipients, the mean decrease in the absolute lymphocyte count was 100 cells/μL among recipients of 5 mg saxagliptin daily. Lymphocyte count of ≤750 cells/μL occurred in 0.5% of patients receiving 2.4 mg saxagliptin, in 1.5% of patients receiving 5 mg saxagliptin, and in 0.4% of placebo recipients. Major adverse reactions reported by vildagliptin recipients included hypoglycemia cough and peripheral edema. In a pooled analysis of >8,000 patients, the incidence of elevations in liver enzymes (aspartate aminotransferase and alanine aminotransferase) to more than three times the upper limit of normal was higher in patients taking 100 mg vildagliptin PO once daily (0.86%) versus patients taking 50 mg vildagliptin PO once daily (0.21%) or 50 mg vildagliptin PO twice daily (0.34%). The placebo rate in this analysis was 0.4% (6).

Cardiovascular effects include hypertension (1.1–5.7%) and peripheral edema (3.8–5.9%). Headache and dizziness were also reported (1.9–12.9%). Nasopharyngitis and upper respiratory infection were reported similar to sitagliptin.

In a meta-analysis of clinical trials regarding treatment with sitagliptin and vildagliptin, there was no increased incidence of hypoglycemic events compared with the control group. An increased incidence rate of hypoglycemic events was observed in the sulfonylurea treatment group. Regarding the occurrence of other severe side effects, these studies showed no increased incidence in the DPP-4 inhibitor treatment group compared with the control group. In the group of patients treated with GLP-1 analogs, there was a slightly increased incidence of hypoglycemic events compared with the control group (7). No increased risk of cardiovascular events was found in any of the three DPP-4 inhibitor treatment groups (2,8).

DPP-4 INHIBITORS AND CARDIOVASCULAR EFFECT—In recent years, several trials were published about the protective effect of incretins on the heart (mostly GLP-1 analogs). A few studies were also published on the beneficial effect of DPP-4 inhibitors. In studies done on mice lacking the DPP-4 receptors that were treated with sitagliptin, the investigators induced acute myocardial infarction by left anterior descending coronary artery ligation (9). In these mice, an upregulation of cardio-protective genes and their protein products was shown. In another study in mice, it was shown that treatment with sitagliptin can reduce the infarct area and the protective effect of sitagliptin was protein kinase A dependent (10).

In diabetic patients who also suffer from coronary heart disease, it was demonstrated that treatment with sitagliptin improved their heart function and coronary artery perfusion, as observed in echo-debutamin tests (11). Frederich et al. (8) published a retrospective study regarding the influence of treatment with saxagliptin on cardiovascular morbidity and mortality. In this study, although there are many limitations, there was no increased risk of cardiovascular morbidity or mortality and perhaps a minimal nonsignificant advantage.

As for coronary heart disease risk factors, DPP-4 may contribute to a reduction in blood pressure. Mistry et al. (12) showed that sitagliptin produced small but statistically significant reductions of 2–3 mmHg systolic and 1.6–1.8 mmHg diastolic in 24-h ambulatory blood pressure measurements acutely (day 1) and at steady state (day 5), in nondiabetic patients with mild to moderate hypertension. Recently, a study by Marney et al. (13), in metabolic syndrome patients, showed that during placebo and low-dose ACE inhibition (5 mg enalapril), sitagliptin lowered blood pressure. However, this trend was reversed during higher-dose acute ACE inhibition (10 mg enalapril). They hypothesized that the combination of sitagliptin and high-dose ACE inhibition causes activation of the sympathetic tone, hence attenuating blood pressure reduction. Marney et al. suggested that high levels of substance P, because of the double blockade of ACE and DPP-4, caused the activation of the sympathetic system. Nevertheless, longer duration and prospective studies are needed to prove these novel findings and effects.

DPP-4 inhibitors have also been found to have an effect on postprandial lipid levels. Matikainen et al. (14) showed that treatment with vildagliptin for 4 weeks improves postprandial plasma triglyceride and apolipoprotein B-48–containing triglyceride-rich lipoprotein particle metabolism after a fat-rich meal in drug-naive patients with type 2 diabetes. Boschmann et al. (15) suggested that DPP-4 inhibition augments postprandial lipid mobilization and oxidation by activation of the sympathetic system rather than a direct effect on metabolic status. Another contribution to our understanding came recently from Hsieh et al. (16) that assessed postprandial lipid synthesis and secretion in normal and fructose-fed hamsters and in wild-type mice that were treated with or without sitagliptin. They found that DPP-4 inhibition, or pharmacological augmentation of GLP-1 receptor (GLP-1R) signaling, reduces intestinal secretion of triacylglycerol, cholesterol, and apolipoprotein B-48. Moreover, endogenous GLP-1R signaling is essential for the control of intestinal lipoprotein biosynthesis and secretion.

These studies and other similar ongoing studies are giving clinicians hope that the DPP-4 inhibitors as a group of drugs will have a beneficial effect not only on blood glucose levels but also on heart and coronary artery function.

COMPARISON BETWEEN GLP-1 ANALOGS AND DPP-4 INHIBITORS—In a trial comparing short-term treatment of 2 weeks with exenatide versus sitagliptin, the results were better after treatment with exenatide, as measured by several parameters: lowering postprandial glucose, increasing insulin levels, decreasing glucagon levels, and decreasing caloric intake (17). Pratley et al. (18) published the first long-term prospective trial comparing treatment with liraglutide versus sitagliptin in patients with type 2 diabetes who were not controlled after treatment with 1,500 mg/day metformin, as measured by their high HbA_{1c} levels (7.5–10%). Results of this trial showed a 1.5% decrease in HbA_{1c} levels when patients were treated with 1.8 mg liraglutide daily, 1.23% when treated

with 1.2 mg liraglutide daily, and 0.9% when treated with 100 mg sitagliptin daily. A 3.38-kg weight reduction was observed in patients treated with 1.8 mg liraglutide, a 2.86-kg weight reduction was observed in patients treated with 1.2 mg liraglutide, and a 0.96-kg weight reduction was observed in patients treated with 100 mg sitagliptin. Furthermore, the patients treated with liraglutide showed a decreased waist circumference but not a significant decreased waist-to-hip ratio. The three treatment groups showed decreased systolic and diastolic blood pressure measurements, but only in the liraglutide treatment group was an increase in heart rate observed. In the liraglutide treatment group, there was an increased incidence of minor side effects such as nausea and vomiting (21–27%) compared with the sitagliptin treatment group (5%). Incidences of hypoglycemic events were similar (5%) in all treatment groups.

SUMMARY—Treatment of diabetic patients with drugs from the incretin family is one of the basic and central treatment tools available to the clinician today. This treatment is as efficient as the other known oral antidiabetic drugs, and it is safer than sulfonylurea when comparing the incidence of hypoglycemic events and therefore can be considered as monotherapy as well as combination therapy with metformin. When considering which drug to choose between the GLP-1 analogs and the GPP-4 inhibitors, the clinician should consider parameters such as the patient's age, the time from initial diabetes diagnosis, body weight, compliance, and financial means.

In the older population, it is wise to consider DPP-4 inhibitors because of their confined effect on lowering blood glucose and neutral effect on caloric intake and therefore less negative effect on muscle and total body protein mass. In younger patients recently diagnosed with type 2 diabetes, abdominal obesity, and abnormal metabolic profile, one should consider treatment with GLP-1 analogs that would have a beneficial effect on weight loss and improve the metabolic profile. An additional factor to take into consideration when using these drugs is that DPP-4 inhibitors (in reduced doses) are safe for treating patients with moderate and severe renal failure, whereas GLP-1 analogs are contraindicated in these patients.

This group of new drugs is another step in our progress toward personalized medicine and tailoring the specific incretin prescribed to patients based on personal criteria.

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