Role of saxagliptin as monotherapy or adjunct therapy in the treatment of type 2 diabetes

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Abstract: Type 2 diabetes is associated with decreased incretin hormone response to an oral glucose load, and a progressive decline in postprandial glucagon-like peptide-1 (GLP-1) secretion. Incretin-based therapies offer a new option for treatment of type 2 diabetes. Saxagliptin, a potent, selective dipeptidyl peptidase-4 (DPP-4) inhibitor specifically designed for extended inhibition of the DPP-4 enzyme, causes increased endogenous GLP-1 concentration. In a phase 3 clinical trials program of 24 weeks duration, saxagliptin was studied in 6 multicenter, multinational, randomized, controlled studies and in combination with 3 of the most commonly administered oral antidiabetic drugs: metformin, glyburide and a thiazolidinedione (TZD). Saxagliptin provided significant reductions in hemoglobin HbA1c when given with metformin, glyburide, a TZD, or as monotherapy. Saxagliptin also reduced fasting plasma glucose and 2-hour post-prandial glucose in each of these studies, and was weight and lipid neutral. Saxagliptin was well tolerated and had a low risk of hypoglycemia when used as monotherapy.

Keywords: saxagliptin, incretins, type 2 diabetes, DPP-4 inhibitors

Introduction
Type 2 diabetes is a growing epidemic worldwide for which medical treatments are still actively sought. The nationwide incidence of diabetes has nearly doubled in the last decade. In the United States 17.9 million people have been diagnosed with type 2 diabetes, and another 5.7 million remain undiagnosed. Three landmark prospective, interventional studies – the Diabetes Control and Complications Trial (DCCT), the Kumamoto study, and the United Kingdom Prospective Diabetes Study (UKPDS) – showed significant reductions in the incidence of microvascular complications in patients with diabetes who were treated intensively, compared with conventional treatment. The DCCT, Kumamoto study, and UKPDS provide the accepted evidence that optimal glycemic control reduces the risk of complications. Yet glycemic control rates in the US and worldwide are poor and may be on the decline. After adjustment for age, ethnicity, sex, body mass index (BMI), medication use, and duration of diabetes, the odds of attaining glycemic control were 21% lower in the National Health and Nutrition Examination Survey (NHANES) 1999 to 2000 than in NHANES III (1988 to 1994; odds ratio, 0.79). Only 37.0% of those surveyed in 1999–2000 had hemoglobin HbA1c (HbA1c) levels of <7.0%, a proportion even smaller than the 44.3% reported for 1988 to 1994. This difference, although not statistically significant, shows a trend that must be reversed. 57.1% of patients with diagnosed diabetes have an HbA1c at or below the ADA guideline-recommended level of 7%.
The failure to achieve adequate glycemic control has led to further study of the pathogenesis of the disease and new drug discovery. We now understand that insulin demand increases in persons with increased caloric consumption, decreased physical activity, and increased age. Persons who are unable to compensate for increased insulin demand can develop prediabetes states, such as impaired glucose tolerance (IGT) and impaired fasting glucose (IFG), which can then progress to type 2 diabetes.

In patients who develop type 2 diabetes, beta-cell function appears to decline over time. Postprandial hyperglycemia develops gradually, later followed by a rise in fasting plasma glucose (FPG) levels. Hence, IGT and IFG represent intermediate steps in the progression to the clinical diagnosis of diabetes. Complications, including macrovascular and microvascular changes, begin well in advance of the clinical diagnosis of type 2 diabetes.

Incretin hormones play an important role in the regulation of blood glucose. Increased understanding of the glucoregulatory action of incretin hormones has yielded greater insight into the pathophysiology of diabetes and has led to the development of new treatments for patients with type 2 diabetes. Incretin hormone glucose-dependent insulinotropic peptide (GIP) is mainly secreted by the K cells in the duodenum and the proximal small intestine and glucagon-like peptide-1 (GLP-1) is secreted from the L cells of the distal gut. Specifically, it has been demonstrated that the endogenous human incretin hormone GLP-1 decreases blood glucose by several pathways—via the regulation of insulin and glucagon, inhibition of gastric emptying, and suppression of appetite, and that the normal physiologic response to GLP-1 is impaired in type 2 diabetes. GLP-1 stimulates insulin secretion in a glucose-dependent manner and suppresses glucagon secretion. In normal physiology, oral ingestion of nutrients stimulates GIP and GLP-1 secretion, which in turn increases insulin secretion from pancreatic beta-cells. Some studies have demonstrated a progressive decline in postprandial GLP-1 secretion, where individuals with normal glucose tolerance secrete more than those with impaired glucose tolerance, and individuals with type 2 diabetes demonstrate the greatest impairment in GLP-1 secretion. The clinical utility of native GLP-1 is limited by its short half-life (<2 minutes) due to its rapid degradation to inactive metabolites by the enzyme dipeptidyl peptidase-4 (DPP-4). Because of this limitation, new treatment approach has been developed to inhibit DPP-4 enzyme and thereby increase endogenous incretin hormone levels. They have shown a beneficial effect on beta-cell function in animal studies but there are no clinical trials to date showing preservation of beta-cell function.

The first DPP-4 inhibitor, sitagliptin, was approved by the Food and Drug Administration (FDA) in 2006 for use as monotherapy or in combination with metformin or thiazolidinediones (TZDs). Another DPP-4 inhibitor, vildagliptin, was approved in Europe in 2008. Saxagliptin (Onglyza®, Bristol-Myers Squibb) is also a potent, selective DPP-4 inhibitor specifically designed for extended inhibition of the DPP-4 enzyme causing increased endogenous GLP-1 concentration, and is now approved by the FDA.

**Pharmacology**

In patients with type 2 diabetes mellitus, administration of saxagliptin inhibits DPP-4 enzyme activity for a 24-hour period. The mean time to maximum concentration (T_{max}) following the 5 mg once daily dose is 2 hours for saxagliptin and 4 hours for its active metabolite 5-hydroxy saxagliptin. The maximum concentration (C_{max}) and area under the curve (AUC) values of saxagliptin and its active metabolite increase proportionally in the 2.5 to 400 mg dose range. The metabolism of saxagliptin is primarily by cytochrome P450 3A4/5 (CYP3A4/5). Therefore, strong CYP3A4/5 inhibitors and inducers alter the pharmacokinetics of saxagliptin and its active metabolite. Saxagliptin is excreted by both renal and hepatic pathways. 75% of saxagliptin is eliminated in the urine and 22% in the feces. Following a single oral dose of 5 mg saxagliptin to healthy subjects, the mean plasma terminal half-life (t_{1/2}) for saxagliptin and its active metabolite was 2.5 and 3.1 hours, respectively.

**Clinical studies**

Recent American Association of Clinical Endocrinologists (AACE) treatment guidelines have included incretin-based therapies such as DPP-4 inhibitors. The DPP-4 inhibitors are suggested to be used in the early stage of type 2 diabetes, with a main indication in combination with metformin in subjects with inadequate glycemic control when treated with metformin alone. DPP-4 inhibition may also be used in combination with sulfonylurea and TZDs. Sitagliptin was the first DPP-4 inhibitor to be approved in the United States. As monotherapy, sitagliptin 25 to 200 mg/day reduced HbA1c from baseline by −0.28% to −0.76% at 12 to 24 weeks. As initial therapy, sitagliptin–metformin combination therapy worked better than either sitagliptin or metformin monotherapy with an HbA1c reduction of 1.9% compared with 0.6% to 0.7%, and 1.13% after 24 weeks. As adjunct therapy, sitagliptin in combination with metformin, glipizide,
Saxagliptin was not associated with weight gain.19

Add-on studies

In another add-on trial, 768 inadequately controlled diabetic patients on submaximal dose of glyburide were randomized to receive either 2.5 or 5 mg of saxagliptin add-on to 7.5 mg glyburide or to placebo plus a 10 mg total daily dose of glyburide. Patients who failed to meet specific glycemic goals during the study were rescued with metformin treatment, added on to existing study medication. Compared to up-titrated glyburide, saxagliptin 5 mg plus 7.5 mg glyburide provided statistically significant reductions in HbA1c at 6 months (−0.6% vs +0.1%, P < 0.0001).22 An increase from baseline in body weight, of small magnitude and unclear clinical relevance, occurred in all treatment groups; however, weight gain was higher in the saxagliptin treatment groups. Improved glycemic control has been shown to promote weight gain in certain instances by decreasing glucosuria.22
Saxagliptin was also evaluated as add-on therapy with a TZD in 565 adult type 2 diabetes patients inadequately controlled on TZD alone. Patients were randomized to 2.5 or 5 mg of saxagliptin or placebo in addition to their current dose of TZD. At 6 months, HbA1c reduction with saxagliptin 2.5 mg plus TZD was −0.7% (P < 0.05 vs placebo plus TZD) vs placebo plus TZD, and −0.9% with 5 mg saxagliptin plus TZD vs placebo vs TZD (P < 0.0001).

**Safety and tolerability**

The most common adverse reactions reported in >5% of saxagliptin-treated patients and more commonly than in controls were upper respiratory tract infection (7.7%, 7.6%), headache (7.5%, 5.2%), nasopharyngitis (6.9%, 4.0%) and urinary tract infection (6.8%, 6.1%). Discontinuation of therapy due to adverse events occurred in 3.3% and 1.8% of patients receiving saxagliptin and placebo, respectively. There was a dose-related mean decrease in absolute lymphocyte count observed with saxagliptin. The clinical significance of this decrease is unknown. Hypersensitivity-related events such as urticaria and facial edema in the pooled analysis up to week 24 were reported in 1.5%, 1.5% and 0.4% of patients who received saxagliptin 2.5 mg, saxagliptin 5 mg, and placebo, respectively. Analysis of pooled data also showed no significant weight gain or effect on lipid profile compared to placebo.

The overall incidence of adverse events in medication-naive patients receiving saxagliptin 5 mg as initial combination with metformin compared with those receiving placebo plus metformin was 55% vs 59%, respectively. These adverse events included headache (7.5% vs 5.2% with metformin plus placebo) and nasopharyngitis (6.9% vs 4.0% with metformin plus placebo). When used as add-on combination therapy with a TZD, the incidence of peripheral edema for saxagliptin 2.5 mg, 5 mg, and placebo was 3.1%, 8.1% and 4.3%, respectively. The rates of peripheral edema for saxagliptin 2.5 mg and 5 mg vs placebo were 3.6% and 2% vs 3% when given as monotherapy, 2.1% and 2.1% vs 2.2% when given as add-on therapy to metformin, and 2.4% and 1.2% vs 2.2% when given as add-on therapy to glyburide. In the add-on to glyburide study, the incidence of reported hypoglycemia was higher in patients treated with saxagliptin 5 mg plus glyburide (14.6%) vs placebo plus uptitrated glyburide (10.1%). However, the incidence of confirmed hypoglycemia in this study was 0.8% for saxagliptin 5 mg plus glyburide and 0.7% for placebo plus up-titrated glyburide. The incidence of reported hypoglycemia with saxagliptin 5 mg vs placebo as add-on therapy to a TZD was 2.7% vs 3.8%, and the incidence of reported hypoglycemia with saxagliptin given as monotherapy was 5.6% compared to 4.1% for placebo.

**Summary**

Management of type 2 diabetes is difficult because none of the commonly prescribed oral therapies address the progressive decline in beta-cell function. Incretin-based therapies are associated with positive effects on beta-cell function, making them a potentially beneficial therapeutic option early in the disease when patients with type 2 diabetes still maintain some degree of beta-cell function. Although there are no head-to-head studies comparing the different DPP-4 inhibitors, sitagliptin, vildagliptin and saxagliptin have shown about equal efficacy of 0.4% to 0.8% HbA1c reduction. Saxagliptin is a potent DPP-4 inhibitor, which increases endogenous incretin levels. GLP-1 decreases glucose level by increasing insulin secretion in a glucose-dependent manner and by decreasing plasma glucagon concentrations. Thus saxagliptin may give adult type 2 patients the extra help they need in their struggle to gain glycemic control. In phase 3 clinical trials placebo-corrected HbA1c reductions with saxagliptin 5 mg were −0.8% when added to metformin, −0.7% when added to glyburide, −0.6% when added to a TZD and −0.6% as monotherapy at 6 months. The overall incidence of adverse events was similar between saxagliptin and placebo (72% vs 71%, respectively). Saxagliptin is weight and lipid neutral, offers once-daily dosing, and is now approved by the United States FDA for the treatment of adults with type 2 diabetes.

**Disclosures**

Dr Sharma is a speaker for Bristol-Myers Squibb and AstraZeneca.

**References**


