REVIEW

Saxagliptin: A Selective DPP-4 Inhibitor for the Treatment of Type 2 Diabetes Mellitus

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Abstract: The prevalence of type 2 diabetes mellitus is high and growing rapidly. Suboptimal glycemic control provides opportunities for new treatment options to improve the morbidity and mortality of this progressive disease. Saxagliptin, a selective DPP-4 inhibitor, increases endogenous incretin levels and incretin acitivty. In controlled clinical trials saxagliptin reduces both fasting and postprandial glucose and works in monotherapy and in combination with metformin, TZDs and sulfonylureas. Saxagliptin has a very favourable side effect profile and may have other beneficial non-glycemic effects. The authors review the current available evidence for the safety, efficacy and saxagliptin's place in therapy for type 2 diabetes mellitus. As understanding of the incretin hormones (GLP-1, GIP) expand we may see additional important non-glycemic effects that may affect the chronic management of type 2 diabetes mellitus.

Keywords: saxagliptin, incretin hormones, DPP-4 inhibitors

Introduction

Type 2 diabetes mellitus (T2DM) has an estimated worldwide prevalence of over 230 million people[1] and is projected to rise to 440 million people by 2030.[2] In the United States diabetes mellitus affects 24 million Americans with an additional 5,000 people diagnosed with diabetes each day.[3] By 2034 it is projected that 44.1 million Americans will have diabetes at an annual expense of $336 billion.[4] Ninety percent of people with diabetes have T2DM.[3] Diabetes is increasingly affecting the aging population. It has been estimated that nearly a quarter of Americans over the age of 60 have diabetes.[5] Given the number of people with this disease and the progressive nature of its course, aggressive and continuous management is paramount to improve the morbidity and mortality associated with this disease.

Many studies have demonstrated that tight glucose control can decrease the microvascular complications that accompany T2DM.[6–10] Yet, despite national guidelines providing treatment algorithms and even a wide array of agents to treat T2DM, tight glycemic control continues to be achieved in less than half of patients,[11,12] demonstrating the need for new treatment options. New pathophysiologic pathways including the altered incretin effect provide a novel mechanism to treat type 2 diabetes and may indeed help impact the relentless progression of this disease.

Pathophysiology of T2DM

T2DM is a progressive disorder in which there is cellular resistance to the action of insulin (mediated via acquisition of visceral obesity, lipotoxicity, impaired insulin signaling) and impaired beta cell secretion (initially first-phase insulin release followed by progressive beta cell loss and insulin deficiency). In addition to insulin resistance and impaired beta cell secretory function, deficient secretion of intestine-derived hormones (incretins), including glucose-dependent gastric inhibitory polypeptide (GIP) and glucagon-like peptide-1 (GLP-1), play an important role in the pathophysiology of T2DM. Glucagon-like peptide-1 (GLP-1) augments insulin secretion and suppression of glucagon while delaying gastric emptying. As a consequence glucagon is inappropriately released when it is normally suppressed during meals. This results in excessive hepatic glycogenolysis, gluconeogenesis, and post-prandial hyperglycemia.

The discovery of the incretin hormones and the "incretin effect" has led to the development of new classes of medications for the treatment of T2DM. These include the GLP-1 agonists and the DPP-4 inhibitors.

Introduction of the DPP-4 inhibitors

During a meal, incretin hormones such as glucagon-like peptide 1 (GLP-1) and glucose-dependent gastric inhibitory polypeptide (GIP) are released from the small intestine into the blood stream.[13,14] These hormones augment insulin secretion in a glucose-dependent manner. GLP-1 is the principal incretin involved in glucose metabolism. GLP-1 stimulates insulin biosynthesis and secretion by the beta cells, inhibits glucagon secretion thereby inhibiting excessive hepatic gluconeogenesis, slows gastric emptying, reduces appetite, and stimulates regeneration of islet β-cells. GIP and GLP-1 have extremely short plasma half-lives (less than 7 minutes and 2 minutes respectively) due to a very rapid inactivation by the enzyme dipeptidyl peptidase-4 (DPP-4). DPP-4 selectively cleaves two amino acids from GLP-1 and GIP which have proline or alanine in the second position and which are crucial for biological activity.[15,16] The DPP-4 enzyme is widely distributed in human organs and tissue. They include: the exocrine pancreas, sweat glands, salivary and mammary glands, thymus, lymph nodes, intestines and biliary tract, kidney, liver, placenta, uterus, prostate, brain, and skin. The capillary bed of the gut mucosa is where most GLP-1 is inactivated locally. DPP-4 is attached to the plasma membrane of the endothelia of almost all organs in the body. It is also present in body fluids such as blood plasma and cerebrospinal fluid. Inhibition of the DPP-4 enzyme leads to potentiation and prolongation of endogenous GIP and GLP-1 half-lives, and it is the mechanism of benefit in T2DM.

Prior to the introduction of the DPP-4 inhibitors the medications to treat T2DM were associated with undesirable side effects. Metformin has significant gastrointestinal side effects and should not be used in people with elevated creatinine (>1.5 in men and >1.4 in women). Sulfonylureas and metglitinides are associated with weight gain and hypogylcemia and have been shown to have significant secondary failure rates. The TZDs are associated with fluid retention causing edema and weight gain, have been linked to distal non-weight bearing fractures, and should not be used in Class III or IV congestive heart failure. Alpha glucosidase inhibi-

tors have significant lower gastrointestinal side effects such as flatulence and the GLP-1 agonists have been tied to nausea and vomiting.

The American Association of Clinical Endocrinologists Consensus Panel provided a treatment algorithm in 2009.[20] This guideline utilizes the baseline HgA1c to determine an optimal treatment regimen. A menu approach is provided based upon patient characteristics, co-morbid conditions, and glucose patterns. Lifestyle modification is recommended for all people regardless of HgA1c, but the type and number of medications offered are determined by baseline HgA1c. If a person has a HgA1c between 6.5%–7.5% then one agent with preference to metformin is recommended, but other acceptable agents include a TZD, DPP-4 inhibtor, glucosidase inhibitor, or a GLP-1 agonist. Treatment algorithms recommend automatic up titration if goals are not achieved in the next 2–3 months. If a person's HgA1c is between 7.5%–9% then the initial treatment should consist of lifestyle modification and 2 agents. The recommended combinations could include metformin, a DPP-4 inhibitor, TZD, or GLP -1 agonist with SU and glinide as alternatives. If the HgA1c is above 9% then intensive insulin therapy, insulin plus oral therapy or triple oral therapy, is recommended.

The treatment for type 2 diabetes has largely focused on glucose control without specific focus on the halting or slowing of disease progression. The results of UKPDS demonstrated that beta cell dysfunction progresses to beta cell failure with most treatment options.[21] Therefore, preserving islet cell function has become an important therapeutic target for disease progression and therapeutic intervention. GLP-1 has been shown to preserve beta cell function in animal studies. Agents that increase glucagon-like

petide-1 may also protect islet cell function and slow the progressive loss of beta cells.

The DPP-4 inhibitors are a new class of medications with a novel mechanism of action that may be able to change the course of progression of T2DM. These agents include sitagliptin and saxagliptin which are clinically available in the United States and vlidagliptin which is available in Europe and other countries. Other DPP-4 inhibitors still in development include linagliptin, dutogliptin, and melogliptin. Table 2 summarizes the current DPP-4 inhibitors in clinical trials and on the US market. This paper will review the current data available for saxagliptin.

Mechanism of Action of DPP-4 Inhibitors

There are three classes of DPP-4 inhibitors; substrate-like, non-substrate-like, and xanthine-based inhibitors. Substrate-like DPP-4 inhibitors usually have an electrophilic group that can interact either covalently or non-covalently with the active binding site of the enzyme.[15] Cyanopyrrolidines are competitive inhibitors of the DPP-4 enzyme and form reversible covalent bonds with the catalytically active serine hydroxyl (Ser630) site.[16,22] Examples of cyanoprirolidines are vildagliptin (Galvus®) and saxagliptin (Onglyza®). Non-substrate-like DPP-4 inhibitors are non-covalent inhibitors and usually have an aromatic ring that occupies the S1-pocket of the enzyme binding site.[23] Sitagliptin (Januvia®) is the principle compound from this class and was the first FDA approved DDP-4 inhibitor. Xanthine-based[24] compounds are believed to have higher potency, longer-lasting inhibition, and longer-lasting improvement of glucose tolerance. Alogliptin (Nesina®) is the first drug in this class. The DPP-4 inhibitors also interact with other DPP members

Table 1. Summary of AACE treatment algorithm.

A1c	6.5%–7.5%	7.6%–9%	>9%
Initial therapy	Metformin or: TZD DPP-4 inhibitor AGI GLP-1	Metformin + DPP4, TZD, GLP1 Or SU, Glinide	Insulin Insulin + orals Triple oral therapy
Next visit 2–3 m	Dual therapy	Triple therapy	
Next visit 2–3 m	Triple therapy	Insulin	
Next visit 2–3 m	Insulin		

AACE Diabetes Mellitus Clinical Practice Guideline Task Force. American Association of Clinical Endocrinologists Medical Guidelines for Management of Diabetes Mellitus. Available at www.aace.com/pub. Accessed 9-30-2010.

Table 2. DPP-4 inhibitors currently available (in US) and in clinical trials.

IUPAC name[1] Brand name (proprietor)	Available in US	Dosing (mg)	Stage of development
Sitaglitpin *Januvia* (Merck)	**Yes**	**25, 50, 100**	In clinical use
Saxagliptin *Onglyza* (Bristol-Myers-Squibb) (Astra-Zeneca)	**Yes**	**2.5, 5**	In clinical use
Vildagliptin *Galvus* (Novartis)	**No** (Investigational only)[2]		In Phase III clinical trials *Proprietor submitted approval letter to FDA*[3]
Alogliptin *Nesina* (Takeda)	**No** (Investigational only)		In Phase III clinical trials *Proprietor submitted approval letter to FDA*
Dutogliptin	**No**		In clinical trials
Melogliptin	**No**		In clinical trials
Linagliptin	**No**		In clinical trials

Notes: [1]International Union of Pure and Applied Chemistry Nomenclature; [2]In use clinically in the European Union where it has been approved; [3]Food and Drug Administration.

including DPP-8 and DPP-9, but the clinical significance of this interaction is not clear.

Metabolism

Saxagliptin and its active metabolite 5-hydroxy saxagliptin have similar pharmacokinetics in normal subjects and people with diabetes. It is well absorbed with oral administration and reaches peak concentration within 2 hours. There is negligible protein binding for both agents, and drug deposition is not affected by underlying disease state. Saxagliptin is excreted both by renal and hepatic clearance. Approximately 75% of the medication is excreted in the urine with active secretion noted. About 25% of the drug is excreted in the feces which is believed to be portion not absorbed in the GI tract.[25] Metabolism of saxagliptin is mediated via the CYP3A4/5. Co-administration of CYP3A4/5 inhibitors and enhancers has been shown to alter the pharmacokinetics of saxagliptin and 5-hydroxy saxagliptin.[25]

Pharmacokinetic Profile

Saxagliptin (in vitro) is a highly potent, selective and reversible competitive inhibitor of DPP-4.[26] It has been shown to be 10 times more potent at blocking DPP-4 than sitagliptin.[27] Saxagliptin has a greater than 4000 fold increased selectivity for DPP-4 compared to other proteases.[26,27]

Saxagliptin's active metabolite (5-hydroxysaxagliptin) is less potent but more selective than saxagliptin. Saxagliptin's binding to the DPP-4 enzymes is reversible with a half life of about 50 minutes. The 2.5 mg dose continued to inhibit DPP-4 50% at 24 hours.[28] As mentioned earlier, DPP-4 inhibitors block the proteolytic action of this enzyme, also known as CD26. In so doing, GLP-1 is prevented from degradation in the circulation and effectively extends the half-life of this hormone.[29] As a result, incretin levels are increased (GLP-1 and GIP) as much as 75%.[30] Early clinical trials have shown, DPP-4 inhibitors improve glycemic control by 1) increasing basal and postprandial GLP-1 plasma concentrations and, 2) by reducing postprandial glucagon secretion leading to a lowered plasma glucose concentration both fasting and postprandially.[31]

Two double blind studies were conducted to evaluate the safety and efficacy of saxagliptin as well as to develop pharmacokinetic/pharmacodynamic (PK/PD) data.[32] In the first, subjects age 18–70 years with type 2 diabetes were assigned to one of five dose panels. Within each panel, subjects (n = 6) were randomized to 2.5, 5, 15, 30, or 50 mg of saxagliptin or placebo (n = 2). In the second study, 50 age-matched healthy subjects (HS) were randomized to each of five dose panels. Within each panel, subjects were randomized to a higher doses of saxagliptin 100, 150, 200, 300, or

400 mg, 40 mg saxagliptin or placebo. All subjects underwent laboratory testing, ECG monitoring, and observation for adverse effects. No ECG aberrancies, abnormal labs, or hypoglycemic episodes were observed at any dose exposure. Systemic exposures were dose-proportional and similar on days 1 and 14. PK parameters were comparable between the two study groups (HS and T2DM). Saxagliptin inhibited, in dose-dependent fashion, plasma DPP-4 (pDDP-4) with doses ≥ 150 mg a day showing the same levels of inhibition. There was also a dose-related increase of 1.5–3.0 times the plasma GLP-1 concentration due to saxagliptin after breakfast, lunch, and dinner in both groups (T2DM and healthy subjects) on days 13 and 14.[32]

The authors concluded that saxagliptin was safe and effective at the doses tested. The effects were, in general, dose-related and the PKs were comparable in T2DM and healthy subject groups. Saxagliptin inhibited pDPP-4 and elevated pGLP-1 in a consistent manner using a once daily dosing regimen. Orally administered saxagliptin at doses from 2.5 to 400 mg a day for 2 weeks were safe, well-tolerated, and effective without causing hypoglycemia or changing the QT interval.[32]

Clinical Studies

Data was obtained by conducting searches on MED-LINE using the following search terms/key words: saxagliptin, type 2 diabetes, clinical trials, review, DPP-4 inhibitor, dipeptidyl peptidase, and GLP-1. The Cochrane Central Register of Controlled Trials[33] was searched for English language randomized-controlled trials including DPP-4 inhibitor therapy in adults having T2DM. The web-based site www.clinicaltrials.gov[34] was also searched focusing on saxagliptin. Finally, the ADA and EASD websites were reviewed for recent presentations with saxagliptin.

Saxagliptin as monotherapy

In a 24-week monotherapy study, saxagliptin was compared with placebo both as a fixed-dose and with dose titration: 2.5 mg QAM, 5 mg QAM, 5 mg daily after noon (QPM), and 2.5 mg titrated to 5 mg QAM (2.5/5 mg QAM) in 365 treatment-naive patients with Type 2 diabetes mellitus with inadequate glycemic control (mean baseline HbA1c 7.9%) using diet and exercise.[35] Statistically significant mean changes from baseline HbA1c were seen for 2.5 mg QAM (−0.71%; $P = 0.0023$), 5 mg QAM (−0.66%; $P = 0.0059$), 2.5/5 mg QAM (−0.63%; $P = 0.0119$), and 5 mg QPM (−0.61%; $P = 0.0157$) vs. placebo (−0.26%). Respective reductions in FPG were −0.63 ($P = 0.0204$), −0.59 ($P = 0.0271$), −0.69 ($P = 0.0130$), −0.44 ($P = $ NS), vs. 0.18 mmol-min/L. The percentages of patients achieving HbA1c <7% with 2.5 mg QAM, 5 mg QAM, 2.5/5 mg QAM, and 5 mg QPM, vs. placebo were 35.8, 44.9, 43.5, and 38.6% vs. 35.3%, respectively.[35]

Rosenstock et al[36] examined the safety and efficacy of saxagliptin in two cohorts (high and low dose) of antidiabetic drug naive type 2 diabetic patients with a baseline HbA1c ≥ 6.8 to 9.7%. This multi-center, randomized, parallel group, double-blind, placebo controlled trial examined a dose-response (anti-hyperglycemic effects) of six doses of saxagliptin following a 2 week dietary/placebo wash out phase. Patients were randomized in a 1:1 fashion, across doses, to 2.5, 5, 10, 20, 40 mg or placebo for a 12 week period. These were the low dose cohorts (n = 338). Results showed that, in all treatment arms, there was a 0.7%–0.9% reduction from the average baseline HbA1c of 7.9% vs. placebo (0.3% reduction). The low dose cohorts had a placebo-subtracted HbA1cs reduction of 0.45%–0.63%. Saxagliptin also showed significant placebo-subtracted reductions in fasting serum glucose (14–25 mg/dl) and 1 hour post-prandial glucose levels. Adverse effects, including hypoglycemia, were similar between all groups and saxagliptin was weight neutral. The incidence of confirmed hypoglycemia was of low incidence across dose-range.

In another study, Rosenstock et al[37] conducted a randomized, placebo-controlled, parallel-group, multi-centered trial that examined the effect of saxagliptin on a variety of endpoints concerning glucose control. The study used saxagliptin on a 24 week schedule with a 2 week run-in period. There were 401 treatment naive patients (baseline HgA1c 7%–10%) randomized into 2.5, 5.0 and 10 mg saxagliptin or placebo. An additional open label cohort (n = 66) had baseline HbA1c >10% but not <12%. Statistically significant lowering of HbA1c and FPG relative to baseline and PBO with saxagliptin treatment at all

Table 3. Saxagliptin glucose effects in monotherapy and combination therapy for type 2 diabetes.

Design	N	Treatment and dose	Study duration (weeks)	Baseline HbA1c	Outcome Adjusted mean change from baseline HbA1c (%)	Patients (%) reaching HbA1c <7.0%	Adjusted mean change from baseline FPG (mmol/L)	Adjusted mean change from baseline PPG-AUC (mmol*min/L)	Reference
Monotherapy	106	SAXA 5 mg	24	8.0	−0.5[a]	38[a]	−0.50[a]	−383[a]	Rosenstock, 2009
	95	PBO		7.9	0.2	24	0.33	−36	
Monotherapy	74	SAXA 5 mg QAM	24	7.9	−0.7[a]	45	−0.61	−456	CV181038
	72	SAXA 5 mg QPM		7.9	−0.6[a]	39	−0.44	−336	
	74	PBO		7.8	−0.3	35	0.17	−171	
With MET	191	SAXA 5 mg + MET	24	8.1	−0.7[a]	44[a]	−1.22	−532[a]	DeFronzo, 2009
	179	PBO + MET		8.1	0.1	17	0.07	−183	
With SU	253	SAXA 5 mg + GLY	24	8.5	−0.6[a]	23[a]	−0.56[a]	−278[a]	Chacra, 2009
	267	PBO + UP-GLY		8.4	0.08	9	0.06	66	
With TZD	186	SAXA 5 mg + TZD	24	8.4	−0.9[a]	42	−1.00	−514[a]	Hollander, 2009
	184	PBO + TZD		8.2	−0.3	26	−0.20	−149	
Initial combination with MET	320	SAXA 5 mg + MET	24	9.4	−2.5[a]	60[a]	−3.33[a]	−1170[a]	Jadzinsky, 2009
	328	PBO + MET		9.4	−2.0	41	−2.61	−823	
Long-term with MET[b]	191	SAXA 5 mg + MET	102	8.1	−0.40	30	−0.63	−323[a]	DeFronzo, 2009
	179	PBO + MET		8.1	−0.32	12	0.38	−64	
Long-term with SU[b]	253	SAXA 5 mg + GLY	76	8.5	0.03	10	0.44	−122	Clinicalstudy results.org 2009
	267	PBO + UP-GLY		8.4	0.69	5	0.23	181	

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doses. There was also significant lowering of the area under the curve (AUC) for fasting plasma glucose (FPG) and postprandial glucose (PPG). In addition, participants had increased postprandial insulin AUC and C-peptide levels. Adverse events (eg, hypoglycemia) were similar to that of placebo in all treatment groups, and there was associated weight gain attributable to saxagliptin. The authors concluded that saxagliptin was associated with greater reductions in HbA1c values for patients with worse control at baseline and was well-tolerated.

Saxagliptin in combination therapy

In a randomized placebo-controlled study[38] 743 patients with an average baseline HbA1c of 8.0% ± 0.9% with type 2 diabetes that were uncontrolled with metformin received saxagliptin in escalating doses of 2.5, 5, and 10 or placebo as well as metformin dosed between 1500–2550 mg/day. Patients in all saxagliptin plus metformin groups improved HbA1c's of 0.73%, 0.83%, and 0.71%, respectively at the end of 24 weeks ($P < 0.0001$). Saxagliptin added to metformin was also significantly more effective than metformin plus placebo in achieving HbA1c < 7.0%. Percentages of patients receiving saxagliptin 2.5, 5, and 10 mg vs. placebo added to metformin achieving this goal were 37, 44, and 44%, vs. 17%, respectively (all $P < 0.0001$).[38] Maximal FPG, and PPG-AUC reductions were observed with the saxagliptin 5-mg dose. Fasting plasma glucose was also shown to be lower (16 mg/dl–21 mg/dl) in the saxagliptin plus metformin group ($P < 0.0001$). Postprandial glucagon was also decreased, and there was an increase in C-peptide and postprandial insulin levels after OGTT versus placebo. Furthermore, no increase in hypoglycemia was observed in the saxagliptin group compared to placebo and add-on saxagliptin did not affect body weight compared with metformin plus placebo.[38]

In a subset of patients, beta-cell assessment was conducted via homeostatic model assessment-2 beta (HOMA-2B) and demonstrated that saxagliptin 2.5, 5, and 10 mg plus metformin improved beta-cell function. In addition, saxagliptin added to metformin significantly increased postprandial insulin ($P \leq 0.0001$, $P = 0.0063$, $P \leq 0.0001$, respectively), C-peptide ($P = 0.0003$, $P \leq 0.0001$, $P \leq 0.0001$,

respectively), and decreased postprandial glucagon ($P = 0.0090$, $P = 0.0025$, $P = 0.0010$, respectively) vs. metformin alone.[38]

Patients who completed all visits during the initial 24-week study period without need for hyperglycemia rescue therapy were eligible to enter a 78-week controlled long-term study extension. Patients who received saxagliptin in the initial 24-week study period maintained their current dosage in the long-term extension. At 102 weeks, treatment with saxagliptin 5 mg plus metformin was associated with a greater reduction in HbA1c than placebo plus metformin. At this time point, the placebo-corrected changes from baseline HbA1c for saxagliptin 2.5, 5, and 10 mg added to metformin were −0.62, −0.72, and −0.52%, respectively.[39]

Jadzinsky et al[40] completed a trial of a combination of metformin and saxagliptin as initial therapy for type 2 diabetes. In this multicenter randomized double blind study 1306 treatment naive patients who had uncontrolled T2DM with a HgA1c between 8%–12%. Patients were allocated to one of four treatment arms: saxagliptin 5 mg + metformin 500, saxagliptin 10 mg + metformin 500 mg, saxagliptin 10 mg + placebo, and metformin 500 mg + placebo. Saxagliptn was dosed once daily. Metformin groups had this dose titrated to 1000 mg after one week and this titration continued to a max of 2000 mg daily with split dosing or until the fasting glucose was <6.11 mmol.L. The initial combined therapy improved HgA1c (−2.5%) as well as fasting and PPG-AUC. The saxagliptin + placebo group saw a 1.7% reduction and the metformin + placebo group had a HgA1c reduction of 2.0%. In addition, 60.3% of patients reached a goal HgA1c <7%, significantly higher than saxagliptin alone (32.2%) and metformin alone (41.1%) with a $P < 0.0001$ for combination therapy compared to each monotherapy. Finally the saxagliptin and metformin combination provided significant improvements in B-cell function (HOMA-2B) compared to saxagliptin alone ($P < 0.0001$) and metformin alone ($P \leq 0.0004$).[40]

The efficacy of the addition of saxagliptin (2.5 or 5 mg once-daily) to glyburide (7.5 mg once-daily) compared with the incremental titration of glyburide (maximum dose = 15 mg daily) was assessed in 768 patients with a mean baseline HbA1c of 8.4%.[41] Patients enrolled in the trial started treatment on

saxagliptin 2.5 or 5 mg or placebo plus 7.5 mg or 10 mg glyburide. Incremental titration of glyburide to the maximum dose of 15 mg/day occurred at weeks two and four. Ninety two percent of patients in the glyburide only cohort were incrementally titrated to a daily dose of 15 mg at the end of the 24-week treatment period. The 2.5 and 5 mg saxagliptin plus 7.5 mg glyburide treatment groups had statistically significant adjusted mean decreases in HbA1c from baseline and FPG vs. the titrated glyburide group. Changes from baseline HbA1c with 2.5 and 5 mg saxagliptin plus glyburide vs. the titrated glyburide group were −0.54% and −0.64%, vs. 0.08%, respectively ($P < 0.0001$ for both combinations vs. titrated glyburide); the respective values for FPG were −0.39 mmol/L, −0.56 mmol/L, vs. 0.06 mmol/L ($P = 0.0218$ for 2.5 mg and $P = 0.002$ for 5 mg saxagliptin plus glyburide vs. titrated glyburide). Those patients achieving HbA1c < 7% were 22.4% and 22.8% vs. 9.1%, respectively (both $P < 0.0001$) and the values for PPG-AUC were −238 and −278, vs. 66 mmol·min/L, respectively (both $P < 0.0001$). Moreover, double the number of patients treated with 5 mg saxagliptin plus glyburide (10.4%) attained the HbA1c ≤6.5% treatment goal as opposed to the titrated glyburide group (4.5%) ($P = 0.0117$).[40] Increases in mean body weight in the saxagliptin treatment group (2.5 and 5 mg) vs. the titrated glyburide cohort were 1.5 lbs (0.7 kg; $P = 0.0381$) and 1.8 lbs (0.8 kg; $P = 0.0120$), vs. 0.7 lbs (0.3 kg), respectively. In the end, the 2.5 and 5 mg saxagliptin plus 7.5 mg glyburide treatment groups showed statistically significant adjusted mean decreases in baseline HbA1c and FPG compared with the titrated glyburide group.[41]

Patients meeting glycemic rescue criteria or completing all of their visits during the initial 24 week, short-term study period were eligible for inclusion in a 52-week study extension. Similar to the metformin long-term extension; those who received saxagliptin in the initial 24-week study period maintained their current dosage in the long-term extension. Treatment with 5 mg saxagliptin plus glyburide was associated with a greater reduction in HbA1c than placebo plus incrementally titrated glyburide that was sustained for up to 76 weeks.[42]

Another trial examined the effect of saxagliptin added to a group individuals with poorly controlled type 2 diabetes who were[43] using TZD as monotherapy. Patients on TZD therapy had HbA1c's ≥7.0% and ≥10.5% (mean 8.3%). Participant age varied from 18–77 yrs and included both genders. Results accrued after a TZD 2 week lead in period when patients were randomized to different groups of a dose-response curve of 2.5 mg/d; 5 mg/d, and placebo (PBO) in addition to the background TZD. Patients were treated for 24 weeks on this regimen. Patients randomized to saxagliptin 2.5 mg and 5 mg daily had improvements from baseline in endpoints measured when compared with PBO (ie, A1C values, AUC for FPG and PPG) and improved oral glucose tolerance and postprandial insulin surges as shown by AUC (area under the curve) modeling for HbA1c and C-peptide. Baseline reductions for 2.5 and 5 mg saxagliptin plus TZD vs. TZD alone were −436 and −514 vs. −149 mmol·in/L, respectively ($P < 0.0001$ for each comparison between saxagliptin plus TZD vs. TZD monotherapy). Compared to PBO (25.6%), a greater proportion of patients achieved a target HbA1c of <7% at 24 weeks on saxagliptin (42% at 2.5 mg, $P = 0.001$; 42% at 5 mg , $P = 0.005$%). Saxagliptin treatment increased postprandial insulin and C-peptide AUC compared with PBO ($P < 0.05$).

Overall rates of discontinuation and reported adverse events across all groups were similar to those rates found in the PBO group. Saxagliptin plus TZD also demonstrated significant improvements in beta-cell function (HOMA-2B assessment model), increases in postprandial insulin and C-peptide, and decreases in postprandial glucagon vs. TZD monotherapy. The authors concluded that the addition of saxagliptin to a TZD in those uncontrolled diabetics did not increase the risk of hypoglycemia and saw improved overall glycemic control.[43]

Safety

Saxagliptin is indicated in adults with type 2 diabetes as an adjunct to diet and exercise. After oral administration of saxagliptin and a glucose meal load there was a 2–3 fold increase in circulating levels of GLP-1 and GIP and increased glucose dependent insulin secretion due to DPP-4 inhibition.[25] The does is 5 mg once daily for most patients as there is no dose adjustment based on age, gender, race or hepatic impairment. Further there appears to be no significant drug interactions with other agents that treat hpyerglycemia or in hepatic impairment.[44–47]

Table 4. Adverse effects in clinical trials with saxagliptin.

	Monotherapy		With MET		With SU		With TZD		Initial combination with MET		Long-term combination with MET	
	SAXA 5 mg	PBO	SAXA 5 mg + MET	PBO + MET	SAXA 5 mg + GLY	PBO + UP-GLY	SAXA 5 mg + TZD	PBO + TZD	SAXA 5 mg + MET	PBO + MET	SAXA 5 mg + MET	PBO + MET
N	106	95	191	179	253	267	186	184	320	328	191	179
Headache	10 (9.4)	7 (7.4)	11 (5.8)	13 (7.3)	19 (7.5)	15 (5.6)	10 (5.4)	7 (3.8)	24 (7.5)	17 (5.2)	17 (8.9)	20 (11.2)
Peripheral edema	–	–	–	–	–	–	15 (8.1)	8 (4.3)	–	–	–	–
URTI	9 (8.5)	11 (11.6)	9 (4.7)	9 (5.0)	16 (6.3)	18 (6.7)	17 (9.1)	13 (7.1)	–	–	17 (8.9)	14 (7.8)
Urinary tract infection	9 (8.5)	4 (4.2)	10 (5.2)	8 (4.5)	27 (10.7)	22 (8.2)	12 (6.5)	12 (6.5)	–	–	15 (7.9)	12 (6.7)
Reported hypoglycemia (%)c	5 (4.7)	6 (6.3)	10 (5.2)	9 (5.0)	37 (14.6)	27 (10.1)	5 (2.7)	7 (3.8)	11 (3.4)	13 (4.0)	17 (8.9)	18 (10.1)
Confirmed hypoglycemia (%)d	0 (0)	0 (0)	1 (0.5)	1 (0.6)	2 (0.8)	2 (0.7)	0 (0)	0 (0)	0 (0)	1 (0.3)	2 (1.1)	1 (0.6)

Reprinted from core evidence, 5, Kalusa et Edelman, Saxagliptin: The evidence for its place in the treatment of type 2 diabetes mellitus, 23–37, 201, with permission from Dove Medical Press Ltd.[56]

Most common side effects to saxagliptin monotherapy in headache, back pain, diarrhea, upper respiratory tract infection, naspharyngitis and hypoglycemia. Adverse events are limited and are typically comparable to the control group both in monotherapy and in combination therapy.

The above clinical safety data was further supported by a study using pooled data from multiple studies. Saxagliptin, both as monotherapy (across the dose range of 2.5, 5, and 10 mg) and in combination with other oral hypoglycemic agents (SU, TZD, biguanide), had a low risk of hypoglycaemia.[48]

Saxagliptin is metabolized via the CYP3A4/5 enzyme. Because it is a CYP3A4/5 inhibitor the dose should be reduced to 2.5 mg per day for people who are taking ketoconazole, clarithromycin, nefazodone, telithromycin, itraconazole, indinavir, atazanavir, nelfinavir, ritonavir, saquinavir. However, no dose adjustment is needed for moderate CYP3A4/5 inhibitors such as diltiazem and verapamil.[25]

Acknowledging the ubiquitous nature of the enzyme these compounds may have more far reaching effects than have been currently identified. Further, other peptides may be affected, and other hormones and circulating peptides can have an indirect effect on how DPP-4 inhibitors actually work. For example, it has been suggested there may be non-incretin mechanisms of action at work affecting fasting/postprandial blood sugars.[30]

Renal dosing

In people with moderate to severe renal insufficiency (CrCl less than 50 ml/min) the dose should be reduced to 2.5 mg daily.[25] This dose can be used in patients who are on dialysis, but because it is removed by hemodialysis it should be administered after dialysis.[25]

Cardiovascular data

In light of recent warnings about additional cardiovascular risks with certain oral diabetes medications the FDA has recommended that all new agents to treat diabetes be evaluated for cardiovascular risk.[49] Cardiovascular risks were defined as MACE (major adverse cardiovascular events- cardiovascular death, non-fatal myocardial infarction, non-fatal stoke) and ACE (acute cardiovascular events-cardiovascular events needing revascularization interventions). For saxagliptin, a post-hoc meta-analysis

of phase 2 and 3 trials (4,607 participants, 3,206 who took saxagliptin) showed there was no additional cardiovascular risks for those who took saxagliptin compared to placebo or comparator.[50] To further meet the FDA guidelines a prospective cardiovascular outcome study has been initiated and should be completed sometime after 2015.[51]

Efficacy

Patients can see a 0.5%–0.7% reduction in HgA1c in monotherapy and a 0.6%–2.5% reduction in combination therapy. As with most medications reduction in glucose is relative to the initial glucose level. Saxagliptin can be co-administered with other oral agents, and efficacy appears to be synergistic.

Patient Preference

Saxagliptin (along with the other DPP-4 inhibitors currently available) has many features desirable to patients. It is efficacious as a once daily medication irrespective of meals and other daily medications. It has the ability to improve both fasting and postprandial control while being weight neutral. It has very few clinically significant drug to drug interactions. The starting dose is the effective dose and no titration is needed. Dosage is 5 mg except for those who have moderate to severe renal insufficiency or those who are taking strong CYP3A4/5 medications (2.5 mg). This medication is extremely well tolerated and has no significant risk of hypoglycemia. Albeit the data is currently limited, there appears to be no additional cardiovascular risk associated with this medication.

Place in Therapy

The addition of the DPP-4 inhibitors to the diabetes oral market reflects a significant advance. They appear to have excellent tolerability and may be able to be utilized in people who have co-morbid conditions that would exclude other agents. For example, the sulfonylureas and metformin are not recommended to be used in people with renal insufficiency, and TZDs have a black box warning in the presence of congestive heart failure. The available DPP-4 inhibitors can be used in both of these conditions.

Saxagliptin can be used as monotherapy in addition to lifestyle changes or in combination with metformin,

sulfonylureas, or pioglitazone. In comparison with other DPP-4 inhibitor available in the United States (sitagliptin) saxagliptin is a much more potent DPP-4 inhibitor, but it does not appear to be clinically significant when comparing duration of action or clinical efficacy. Currently saxagliptin will soon be available in combination with metformin which will make it more competitive with other DPP-4 inhibitors. The cardiovascular data appears to be very promising for saxagliptin.

The DPP-4 inhibitors may have a few unique niches where they will be the preferred oral treatment. These may include people of advanced age, those with newly diagnosed diabetes, and those reactive hypoglycemia. The authors have used DPP-4 inhibitors in people with reactive hypoglycemia. The mechanism of action for the DPP-4 inhibitors is that the effects of the medication are glucose driven, and the effect is greatest in people with significant hyperglycemia and less in people with mild hypoglycemia. Current studies show the safety of this class and virtually no hypoglycemia when used alone. The authors hypothesize that people with impaired glucose tolerance and reactive hypoglycemia would be candidates for this medication. However, this has not yet been formally studied.

Further, it has been identified that GLP-1 is produced in the central nervous system, and GLP-1 receptors are widely distributed in the brain. Animal studies suggest that GLP-1 may have neural protection effects and may actually protect the CNS from the effects of hyperglycemia.[51] If this proves to be accurate, this could have important effects on cognitive function and the long term treatment of hyperglycemia.

Since the natural history of T2DM results in eventual beta cell loss and insulin deficiency, intensive research has been directed at developing compounds to: 1) delay or prevent the onset of T2DM; and 2) to preserve beta cell function to prevent the inevitable requirement for exogenous insulin therapy. Incretin-based therapies including DPP-4 inhibitors have been evaluated for beta cell preservation.[53–55]

As the number of clinically available DPP-4 inhibitors increase the competition may help to control the cost of these agents which is a primary drawback to

this class. In addition, as the breadth of experience grows with this class we will be able to more clearly delineate the unique features of these medications and their place in the treatment of T2DM. Based upon on its excellent tolerability and few safety warnings saxagliptin is a good choice for many people with diabetes.

Conclusions

Saxagliptin is a once daily DPP-4 inhibitor that is safe and efficacious for the treatment of type 2 diabetes. Given its limited side effects, single day dosing independent of meals, its clean metabolic processing, and its limited drug interactions it is well placed as a new agent to treat type 2 diabetes. Future studies are needed to clarify its non-glycemic and potential beta cell preservation effects.

Disclosures

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