Saxagliptin: A dipeptidyl peptidase-4 inhibitor in the treatment of type 2 diabetes mellitus

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ABSTRACT

Type 2 diabetes mellitus (T2DM) is a metabolic disorder characterized by insulin deficiency or resistance. Management starts with single oral antidiabetic drug (OAD) but eventually switch over to combination therapy because of progressive β-cell dysfunction. Hypoglycemia, weight gain, and adverse cardiovascular events are major limitations of the available OADs (Sulfonylureas [SUs], thiazolidinediones [TZDs]). Saxagliptin, a reversible, competitive dipeptidyl peptidase-4 inhibitor, is recently approved agent in the treatment of T2DM. It acts by preventing the degradation of glucagon-like peptide – 1 and hence increases secretion of insulin and decreases secretion of glucagon. It is a well-tolerated agent with commonly reported adverse events which include upper respiratory tract infection, urinary tract infection, and headache. Hypoglycemia, weight gain, and adverse cardiovascular events are negligible as compared with other OADs. In clinical studies, saxagliptin was found to be effective and well tolerated when used as a monotherapy as well as in combination with metformin, SUs and TZDs. It is administered in the dose range of 2.5 to 5 mg once a day regardless of meal. Dosage reduction is required in patients having moderate to severe renal impairment as well as with concurrent administration of strong CYP3A4/5 inhibitors. To conclude, saxagliptin because of its novel mechanism of action (preserving beta cell function) and better tolerability profile seems to be a promising agent in the treatment of T2DM, especially in the early stage of the disease, but long-term clinical studies are required to prove its status in the management of T2DM.

Key words: Dipeptidyl peptidase-4, glycemic control, hypoglycemia, metformin

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic progressive metabolic disorder characterized by absolute or relative insulin deficiency. Diabetes has an estimated prevalence of around 220 million people worldwide and it is estimated to affect around 440 million by 2030.[1] Of these, around 90 to 95% of cases are of T2DM.[1] Expected rise in prevalence of diabetes is mainly due to increased life span because of better healthcare facilities and increase in diabetic risk factors, especially physical inactivity and obesity due to sedentary life style.[2] Pancreatic β-cell function is gradually deteriorated in patients of T2DM which is reflected into inadequate glycemic control on a long run.[3] Poorly achieved glycemic control leads to microvascular (retinopathy, nephropathy) and macrovascular (cardiovascular) complications. These are responsible for the tremendous burden of the diseases not only at an individual and social level, but also at an economic level.

Sulfonylureas (SUs), biguanides, and thiazolidinediones (TZDs) are the routinely used oral antidiabetic drugs (OADs)

Access this article online	
Quick Response Code:	Website: www.jpharmacol.com
	DOI: 10.4103/0976-500X.85934

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in the treatment of T2DM. Current treatment guidelines recommend metformin as the first agent to be added to diet and lifestyle changes for the majority of patients unless contraindicated.[4,5] Metformin monotherapy is capable of lowering HbA_{1C} by 1.5% and is generally well tolerated with lower risk of hypoglycemia.[5] Metformin provides either weight stability or modest weight loss in contrast to several other OADs.[5] The limitations of metformin are commonly seen gastrointestinal adverse effects and contraindication in renal insufficiency.[5] SUs are as effective as metformin in lowering HbA_{1C}, but its use is associated with hypoglycemia and weight gain up to 2 kg.[6] Though they are effective in lowering the blood glucose rapidly in the initial phase of therapy, it is difficult to sustain this effect with them.[6] Sulfonylurea therapy was implicated as a potential cause of increased cardiovascular disease mortality in the University Group Diabetes Program study.[7] TZDs, also known as insulin sensitizers, appear to have a more durable effect on glycemic control, particularly in comparison with SUs.[6] But their use is associated with weight gain, fluid retention with peripheral edema, and a two-fold increased risk for congestive cardiac failure.[8] Above mentioned treatments focus on reducing hyperglycemia and improving insulin sensitivity. These modalities are attractive in theory, as they appear to target the primary defects associated with T2DM. However, despite the wide array of treatment options available, glycemic control declines over time and eventually combination of OADs is required.[9] It is the progressive β-cell decline that determines the rate of disease progression,[10] and until recently, there were no means to deal with the chronic progressive β-cell dysfunction.[11] There is a need for new avenues of treatment targeting β-cell dysfunction and hence disease progression.

Incretin effect is responsible for up to 70% of insulin secretion following oral glucose ingestion,[12] and hence targeting incretin mimetic hormones seems to be promising but unexplored in the treatment of T2DM. Currently, GLP-1 (Glucagon-like peptide – 1) receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors are the available incretin-based therapies in the treatment of T2DM. As compared with GLP-1 receptor agonists, which are having parenteral route of administration and intolerable gastrointestinal adverse effects, DPP-4 inhibitors are administered orally and well tolerated.[13] In addition to improving β-cell function, stimulating insulin secretion, and inhibiting glucagon secretion, these agents reduce appetite, thereby stabilizing weight and/or promoting weight loss in patients with T2DM.[11] Because of glucose-dependent mechanism of action, they are more effective in reducing postprandial hyperglycemia, especially in the early stage of disease when patients of T2DM are still having functioning pancreatic β-cells.[11] AACE/ACE guidelines, published in late 2009, recommended DPP-4 inhibitors as an option for use as first-line monotherapy (HbA_{1C} – 6.5 to 7.5%) and in combination therapy (HbA_{1C} – 7.6 to 9%).[4] Sitagliptin was the first DPP-4 inhibitor approved by US FDA in 2006 as monotherapy or in combination with metformin or TZDs in the treatment of T2DM. Vildagliptin is the next DPP-4 inhibitor approved in Europe in 2008 and is under the regulatory review by United States. Saxagliptin is the recently approved agent in this class by US FDA in July 2009 as an adjunct to diet and exercise to improve glycemic control in adults with T2DM.[14]

CLINICAL PHARMACOLOGY OF SAXAGLIPTIN

It is a potent, reversible, and competitive inhibitor of DPP-4.

Mechanism of action

Saxagliptin and its active metabolite M2 (two-fold less potent than parent drug[15]) are DPP-4 inhibitors that improve glycemic control by preventing the inactivation of the incretin hormones GLP-1 and glucose-dependent insulinotropic polypeptide. This increases GLP-1 levels, stimulates insulin secretion, and reduces postprandial glucagon and glucose levels. Detailed actions of GLP-1 are depicted in Table 1. Saxagliptin and M2 are more selective for the inhibition of DPP-4 than DPP-8 (400- and 950-fold) or DPP-9 (75- and 160-fold) enzymes or a large panel of other proteases (>4000-fold).[15] It has been reported that inhibition of DPP-8/9 produced alopecia, thrombocytopenia, splenomegaly, thrombocytopenia, and multiorgan pathology, leading to death in rats and gastrointestinal toxicity in dogs.[16]

Pharmacokinetics

Saxagliptin is rapidly absorbed orally with bioavailability around 67%.[18] It is extensively distributed in extravascular tissue with highest concentrations found in the intestinal tissues and kidney.[18] It is principally hydrolyzed by CYP3A4/5 to major metabolite M2 and other minor metabolites[18] and hence dosage should be reduced in patients taking concurrent

Table 1: Actions of GLP-1 (Drucker DJ 2006)[17]

Organ	Effect
Endocrine pancreas	Increases insulin secretion, increases islet neogenesis, increases proliferation and decreases apoptosis of β cells, decreases glucagons secretion
Heart	Improves cardioprotection, increases cardiac output
Gastrointestinal tract	Delays gastric emptying, decreases gastric acid secretion, decreases small intestinal motility
Brain	Improves neuroprotection, decreases appetite (increase satiety level)
Liver	Decreases hepatic neoglucogenesis
Muscles and adipose tissue	Improves insulin sensitivity

GLP – 1 acts directly on the endocrine pancreas, heart, stomach, and brain, whereas actions on liver and muscles are indirect. GLP – 1 - glucagon-like peptide – 1

strong CYP3A4 inhibitors. Saxagliptin is excreted by both renal and hepatic pathways. 75% of saxagliptin is eliminated in the urine and 22% in the feces.[14] The renal clearance of saxagliptin (mean »230 ml/min) was greater than the estimated glomerular filtration rate (mean »120 ml/min), which suggests some active renal excretion of the drug.[19] As the primary route of elimination of both the parent drug and active metabolite M2 is renal,[20] dosage reduction is required in patient having moderate to severe renal impairment (Cr clearance <50 ml/min). Saxagliptin follows first order kinetics in dose range of 2.5 to 400 mg[19] and there was no appreciable accumulation after once daily dosing.[21] The median time to reach the peak plasma concentration of saxagliptin and its active metabolite M2 following 5 mg administration of single dose are 4 h and 2 h, respectively, while the mean plasma terminal elimination half-life are 2.5 h and 3.1 h, respectively.[3] It has been suggested that once bound, saxagliptin and its active metabolite would continue to inhibit DPP-4 during rapid increases of substrate *in vivo*, owing to their slow dissociation from the enzyme[15] which is responsible for 24-h glycemic control with single daily dosage despite having shorter half-life. None of the pharmacokinetic parameters were affected significantly by gender, body weight, age or race.[21]

Indication

Saxagliptin is approved as an adjunct to diet and exercise to improve the glycemic control in adults with T2DM. Saxagliptin should not be used for treatment of type 1 diabetes or diabetic ketoacidosis and the drug has not been studied in combination with insulin.[19] Saxagliptin has also been approved in combination with extended release metformin (500 mg and 1000 mg) as an adjunct to diet and exercise to improve glycemic control in adults with T2DM when treatment with both saxagliptin and metformin is appropriate.[22]

Dosage and administration

In patients with T2DM, the recommended dosage of saxagliptin is 2.5 or 5 mg once daily administered orally regardless of meals.[19] Dose should be reduced to 2.5 mg daily in patients with moderate to severe renal impairment or end-stage renal disease (CrCl < 50 ml/min) as well as with concurrent administration of strong CYP3A4/5 inhibitors (ketoconazole, clarithromycin, atazanavir, indinavir, itraconazole, nefazodone, nelfinavir, ritonavir, saquinavir and telithromycin).[19] Though alteration in the plasma concentration profile is expected when saxagliptin is coadministered with moderate CYP3A4/5 inhibitors (erythromycin, fluconazole, amprenavir) and with CYP3A4 inducer (rifampicin), dosage adjustment is not required.[3] Assessment of renal function is required prior to initiation of saxagliptin and periodically thereafter.[19] No dosage adjustment is required in patients with hepatic impairment.[19] Lower dosages of insulin secretagogues (e.g., SUs) are required when used in conjunction with saxagliptin to reduce the incidence of hypoglycemia.[19] Adequate and well-controlled clinical studies data are not available for the use in pregnant women as well as safety and effectiveness in pediatric patients (below 18 years of age) has not been established.[19] Hence, it is preferable not to use this drug in pregnant women and pediatric population until the long-term data are available. Secretion of saxagliptin in human milk is not known and hence caution should be exercised while using saxagliptin in a nursing mother.[19] Results of six double blind-controlled clinical studies had not shown any differences in safety and effectiveness between adult patients and patients ≥65 years of age.[19] But still, the parent drug as well as its active metabolite are primarily eliminated through kidney, and generally, in elderly having declining renal function, dose selection should be done after assessment of renal function.

Adverse effects

Saxagliptin as a monotherapy or in combination with other OADs is generally well tolerated, with most adverse events being of mild to moderate in severity. Most common adverse events (incidence ≥5%) with saxagliptin 5 mg (monotherapy or combination therapy) are upper respiratory tract infection, urinary tract infection, headache, and nasopharyngitis.[3] Substance P is the physiological substrate for DPP-4 which has a vasodilatory effect in the nasal tissue. DPP-4 inhibition and subsequent vasodilation in the nasal mucosa by substance P is the principal reason for development of nasopharyngitis which is commonly seen with saxagliptin, a DPP-4 inhibitor.[16] The results from the pooled analysis of the monotherapy study, as well as the initial combination and add-on therapy studies, concluded that saxagliptin had a low risk of hypoglycemia when used as a monotherapy or in combination with metformin, SUs, or TZDs.[1] Ability of saxagliptin to lower HbA_{1C} without increasing hypoglycemic episodes is due to its glucose-dependent action and is one of the main advantages as compared with other insulin secretagogues such as SUs.[21] Contrary to SUs and TZDs, saxagliptin monotherapy has a weight-neutral effect. Saxagliptin when used alone or in combination with metformin have not shown alternation in body weight in clinical studies up to 24-weeks duration.[3] However, statistically significant increase in body weight was observed when saxagliptin was combined with glyburide.[3]

US-FDA now requires that every investigational antihyperglycemic agent has to demonstrate that it does not have an adverse impact on cardiovascular risk. Saxagliptin was the first agent for T2DM to meet this FDA requirement.[13] A meta-analysis explored the impact of saxagliptin on major cardiovascular events (cardiovascular death, nonfatal MI, nonfatal stroke) showed that incidence of such adverse events was significantly lower among patients treated with saxagliptin than among control.[13] On the contrary,

study had raised the possibility that saxagliptin may have cardioprotective effect.[13]

Other infrequently reported adverse reactions are hypersensitivity-related events (rash, urticaria, facial edema) and increase in blood creatinine or creatine phosphokinase. Sharma MD had reported hypersensitivity-related events such as urticaria and facial edema in 1.5%, 1.5%, and 0.4% of patients who received saxagliptin 2.5 mg, saxagliptin 5 mg, and placebo, respectively in the pooled analysis of clinical trials up to 24 weeks of duration. Lymphopenia (0.1% and 0.5% with saxagliptin 2.5 or 5 mg/day *vs* 0% with comparators or placebo), rash (0.2% and 0.3% *vs* 0.3%), increase in blood creatinine (0.3% and 0% *vs* 0%) or blood creatine phosphokinase (0.1% and 0.2% *vs* 0%) levels were the most common (occurring in at least two patients receiving saxagliptin treatment) adverse events associated with discontinuation of therapy in the pooled analysis.[3] Though dose-related reduction in absolute lymphocyte count observed with saxagliptin was not associated with clinically relevant adverse drug reactions, caution and further exploration is required to elicit its clinical significance.

Comparison with other drugs of same class

Comparative evaluation of saxagliptin with sitagliptin or vildagliptin is very difficult as no such head-to-head studies have been conducted. But still, it has been found that saxagliptin was 10-fold more potent than either sitagliptin or vildagliptin for binding to DPP-4, although it does not translate clinically.[1] Saxagliptin was also found to be noninferior to sitagliptin when combined with metformin to achieve glycemic control in patients where metformin alone was ineffective.[24,25]

RESULT OF CLINICAL STUDIES

Summary of clinical studies of saxagliptin, either alone or in combination with other OADs, have been mentioned in Table 2.

In clinical studies up to 24-week duration, saxagliptin as a monotherapy was effective in lowering HbA_{1C} by 0.4 to 0.9%. It was well tolerated in the dose range of 2.5 up to 40 mg and adverse effects were comparable with that of placebo. Saxagliptin was found to be weight neutral and very low incidence of hypoglycemia was reported when used as a monotherapy. In treatment naïve patients as well as in patients inadequately controlled with metformin monotherapy, saxagliptin-metformin combination was found

Table 2: Summary of clinical studies of saxagliptin

Author	Study group	Duration	Study type	Result
Rosenstock *et al*. 2008[27]	Saxagliptin *vs* Placebo	12 weeks	Double-blind Multicentric Placebo-controlled Phase III	Saxagliptin effectively improved glycemic profile with adverse effects similar to placebo
Rosenstock *et al*. 2009[28]	Saxagliptin *vs* Placebo	24 weeks	Open label Placebo-controlled Phase III	Once daily saxagliptin monotherapy was well tolerated and effectively lowered glycemic parameters
Jadzinsky *et al*. 2009[29]	Saxagliptin + Metformin *vs* Metformin	24 weeks	Double blind Multicentric Active control Phase III	Saxagliptin metformin combination as initial therapy led to significant improvement in glycemic control as compared to metformin with similar tolerability profile
Hollander *et al*. 2009[30]	Saxagliptin + TZDs *vs* TZDs	24 weeks	Double blind Multicentric Placebo-controlled Phase III	Saxagliptin and TZDs combination was more effective to achieve glycemic control as compared to TZDs alone and combination was well tolerated
Chacra *et al*. 2009[31]	Saxagliptin + Glyburide *vs* Metformin	24 weeks	Double blind Multicentric Placebo-controlled Phase III	Saxagliptin addition to submaximal glyburide led to significant improvements in glycemic parameters as compared to uptitration of glyburide alone and was well tolerated
De Fronzo *et al*. 2009[32]	Saxagliptin + Metformin *vs* Metformin	24 weeks	Double blind Placebo-controlled Phase III	Saxagliptin addition to metformin was well tolerated and led to significant improvements in glycemic indexes as compared to metformin alone
Gokes *et al*. 2010[33]	Saxagliptin + Metformin *vs* Glipizide + Metformin	52 weeks	Double-blind Active-controlled Phase III	Saxagliptin was well tolerated and noninferior to glipizide when combined with metformin
Scheen *et al*. 2010[25]	Saxagliptin + Metformin *vs* Sitagliptin + Metformin	18 weeks	Double blind Multicentric Phase III	Saxagliptin addition to metformin was more effective in reducing HbA_{1C} than metformin alone and saxagliptin was noninferior to sitagliptin
Stenlöf *et al*. 2010[34]	Saxagliptin + Metformin XR *vs* Metformin	4 weeks	Double blind Multicentric Placebo-controlled Phase III	Saxagliptin effectively lowered plasma glucose concentrations through the 24 h dosing interval and was well tolerated

to be more effective in reducing glycemic parameters with no difference in adverse events as compared with metformin alone. Saxagliptin in combination with metformin was found to be well tolerated and noninferior to glipizide-metformin combination in reducing HbA_{1C} over a period of 52 weeks. Saxagliptin (2.5 to 5 mg) in combination with glyburide (7.5 mg) was found to be well tolerated and more efficient in reducing HbA_{1C} as compared with uptitration of glyburide (up to 15 mg) in poorly controlled T2DM patients with glyburide alone. Addition of saxagliptin to TZDs in patients not achieving glycemic control with TZDs alone had shown significant improvement in glycemic parameters and the combination was well tolerated with no significant difference in adverse effect profile. Saxagliptin as a monotherapy produces placebo-adjusted HbA_{1C} level reductions of 0.45 to 0.63% and greatest HbA_{1C} level reduction was observed in combination with metformin (around 2.53%). Nowicki *et al*. reported that saxagliptin was effective and well tolerated in patients with T2DM having moderate to severe renal impairment where metformin is contraindicated. Nowicki *et al*. had also reported that saxagliptin was not effective in patients with end-stage renal disease or on hemodialysis.

CONCLUSIONS

Saxagliptin, a competitive reversible inhibitor of DPP-4, is a recently approved drug for the treatment of T2DM. It has proven its efficacy in achieving glycemic control either alone or in combination with other OADs (especially metformin, SUs, and pioglitazone). Prolonged and selective inhibition of DPP-4 makes this agent more promising in its class. Its use is not associated with hypoglycemia, weight gain and adverse cardiovascular events which are the major limitations of existing OADs (TZDs, SUs). Despite all this, long-term clinical studies are required to confirm its promising status as an OAD in the treatment of T2DM.

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How to cite this article: Dave DJ. Saxagliptin: A dipeptidyl peptidase-4 inhibitor in the treatment of type 2 diabetes mellitus. J Pharmacol Pharmacother 2011;2:230-5.
Source of Support: Nil, **Conflict of Interest:** None declared.