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)
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. Metformin monotherapy is capable of lowering HbA\textsubscript{1c} by 1.5% and is generally well tolerated with lower risk of hypoglycemia. Metformin provides either weight stability or modest weight loss in contrast to several other OADs. The limitations of metformin are commonly seen gastrointestinal adverse effects and contraindication in renal insufficiency. SUs are as effective as metformin in lowering HbA\textsubscript{1c}, but its use is associated with hypoglycemia and weight gain up to 2 kg. 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. Sulfonlurea therapy was implicated as a potential cause of increased cardiovascular disease mortality in the University Group Diabetes Program study. TZDs, also known as insulin sensitizers, appear to have a more durable effect on glycemic control, particularly in comparison with SUs. But their use is associated with weight gain, fluid retention with peripheral edema, and a two-fold increased risk for congestive cardiac failure. 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. It is the progressive \( \beta \)-cell decline that determines the rate of disease progression, and until recently, there were no means to deal with the chronic progressive \( \beta \)-cell dysfunction. There is a need for new avenues of treatment targeting \( \beta \)-cell dysfunction and hence disease progression.

Incretin effect is responsible for up to 70% of insulin secretion following oral glucose ingestion, 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. In addition to improving \( \beta \)-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. 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 \( \beta \)-cells. AACE/ACE guidelines, published in late 2009, recommended DPP-4 inhibitors as an option for use as first-line monotherapy (HbA\textsubscript{1c} – 6.5 to 7.5%) and in combination therapy (HbA\textsubscript{1c} – 7.6 to 9%). Saxagliptin 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.

**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) 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). 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.

**Pharmacokinetics**

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

**Table 1: Actions of GLP-1 (Drucker DJ 2006)**

| Organ                          | Effect                                                                 |
|-------------------------------|------------------------------------------------------------------------|
| Endocrine pancreas            | Increases insulin secretion, increases islet neogenesis, increases proliferation and decreases apoptosis of \( \beta \) cells, decreases glucagon 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
The document discusses the pharmacokinetics and pharmacodynamics of saxagliptin, a DPP-4 inhibitor. Saxagliptin is excreted primarily through the kidney and is subject to dose adjustment in patients with renal impairment. It also interacts with other drugs, such as CYP3A4 inhibitors and insulin secretagogues. The medication is well-tolerated, with adverse effects primarily involving the respiratory system. The drug is approved for use in adults with type 2 diabetes as an adjunct to diet and exercise to improve glycemic control. The specific details about its dosage, administration, and adverse effects are highlighted.

**Indication**

Saxagliptin is approved as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. It is not indicated for type 1 diabetes or diabetic ketoacidosis and is not recommended for patients with end-stage renal disease.

**Dosage and administration**

The recommended dosage of saxagliptin is 2.5 or 5 mg once daily administered orally, regardless of meals. Dose reduction is required in patients with renal impairment or who are coadministered with strong CYP3A4 inhibitors.

**Adverse effects**

Saxagliptin is generally well tolerated, with the most common adverse effects being nasopharyngitis and upper respiratory tract infection. The drug is considered to have a low risk of hypoglycemia when used as a monotherapy or in combination with metformin, SUs, or TZDs.

**US-FDA requirement**

The US-FDA requires that every investigational antihyperglycemic agent must demonstrate that it does not have an adverse impact on cardiovascular risk. Saxagliptin was the first agent for T2DM to meet this requirement. A meta-analysis of major cardiovascular events showed that incidence was significantly lower among patients treated with saxagliptin than among controls. 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 0.1% and 0.5% with 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.[11] 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 HbA1c 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 to be well tolerated.

### Table 2: Summary of clinical studies of saxagliptin

| Author et al. | 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[34] | Saxagliptin + Metformin vs Sitagliptin + Metformin | 18 weeks | Double blind Multicentric Phase III | Saxagliptin addition to metformin was more effective in reducing HbA1c than metformin alone and saxagliptin was noninferior to sitagliptin |
| Stenlöf et al. 2010[35] | 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 HbA1C 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 HbA1C as compared with up titration 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 HbA1C level reductions of 0.45 to 0.63% and greatest HbA1C 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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