A systematic review of risks and benefits of sitagliptin and saxagliptin monotherapies and metformin combination therapies

Vishvas G*

University of New Mexico, College of Pharmacy, Department of Pharmacy Practice, 402 Cornell Dr. SE, Apt # 2, Albuquerque, NM, 87106, USA

ABSTRACT

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India has the highest prevalence of diabetes (50.8 million people). Sitagliptin and saxagliptin are the two newer drugs approved for the treatment of type 2 diabetes mellitus. The purpose of this paper is to conduct a systematic literature review of the pharmacological and pharmacoeconomical profiles of sitagliptin and saxaglitpin. Using the MeSH terms in PubMed, a total of four searches were conducted: only sitagliptin, only saxagliptin, and sitagliptin and saxagliptin combined with economics, separately. Various articles were found and analyzed: only sitagliptin (n=125), only saxagliptin (n=34), sitagliptin+economics (n=11), and saxagliptin+economics (n=3). These searches were then narrowed down using the inclusion and exclusion criteria: only sitagliptin (n=26), only saxagliptin (n=9), sitagliptin+economics (n=0), and saxagliptin+economics (n=0). The pooled results of clinical trials show that sitagliptin and saxaglitpin have a good general safety profile. However, no formal economic evaluation of sitagliptin and saxaglitpin in India were found during the search. Formal economic evaluations of sitagliptin and saxaglitpin costs and consequences are required.

INTRODUCTION AND BACKGROUND

According to the latest report by the International Diabetes Federation, India has the largest number of diabetes patients (50.8 million people) in the world. Following India on the diabetes prevalence are China (with 43.2 million people) and United States. According to the World Health Organization, between the years 2006 to 2015, the predicted loss of national income from diabetes is International Dollars (ID) 336.6 billion in India and ID 557.7 billion in China. Studies have demonstrated that the prevalence of diabetes in India are rising with the progression of time.

About 90-95% of all the diabetes patients are of the type 2 diabetes mellitus (T2DM). T2DM is a progressive disorder with an insidious onset. The most common precipitating cause of T2DM is the beta-cell dysfunction. The other metabolic disorders associated with T2DM are: chronic hyperglycemia, hepatic glucose production in the prandial state, and insulin insensitivity in fat and muscle cells. The common risk factors of T2DM are: impaired glucose intolerance, age over 45 years, family history of diabetes, polycystic ovarian syndrome, high blood pressure, obesity, physical inactivity, low high-density lipids or high triglycerides levels, being of certain racial and ethnic groups, and women who had gestational diabetes. T2DM also has various vascular complications associated with it, i.e. macrovascular complications (coronary artery disease, peripheral arterial disease, and stroke) and microvascular complications (diabetic nephropathy, neuropathy, and retinopathy).

A range of classes of oral therapeutic agents exists for the treatment of T2DM. Among these are biguanides (e.g. metformin), sulfonylureas (e.g., glipizide), alpha-glucosidase inhibitors (e.g., acarbose), thiazolidinediones (rosiglitazone), glinides (e.g., repaglinide), glucagon-like peptides-1 (GLP-1) (e.g. exenatide), and Dipeptidyl peptidase-4 (DPP-4) inhibitors (e.g. sitagliptin, saxagliptin, and vidagliptin). All of these classes of drugs have different mechanisms of actions, courses of treatments, safety profiles, and associated costs. Among these classes, the latestly approved drug therapeutic class by US FDA is that of DPP-4 inhibitors in which FDA approved sitagliptin and saxagliptin.

Sitagliptin and saxagliptin have demonstrated to offer substantial glycemic control in T2DM patients and offer substantial benefits when used. However, sitagliptin and saxagliptin come at increased costs. Thus, to inform healthcare providers about these two new drugs, a systematic review of their pharmacological and economic profiles is

Address for Correspondence:

Vishvas Garg, PhD Student, University of New Mexico, College of Pharmacy, Department of Pharmacy Practice, 402 Cornell Dr. SE, Apt # 2, Albuquerque, NM, 87106, USA

E-mail: Vishvas4588@gmail.com

required. Therefore, the purpose of this paper is to conduct a literature review of the pharmacological and economic profiles of saxagliptin and sitagliptin monotherapies and combination therapy with metformin.

RESEARCH DESIGN AND METHOD

Literature review of saxagliptin:

In an attempt to identify the current literature on the saxagliptin, especially the literature on the cost-effectiveness analysis and clinical trials, a search was carried out in Medline by querying PubMed search engine using the MeSH terms. The MeSH term "saxagliptin" was first searched alone by activating the following limits: clinical trial, randomized controlled trial, review, and English. "Saxagliptin" was then combined with the MeSH term "economics" using the Boolean combiner "AND" without activating any limits to obtain the query results. The references cited in all the above retrieved publications were also reviewed for relevance and were obtained when applicable.

Literature review of sitagliptin:

Similar to the objectives of the literature search for the saxagliptin, to identify the current literature on the sitagliptin, a search was carried out in Medline by querying PubMed search engine using the MeSH terms. The MeSH term "sitagliptin" was first searched alone using the following limits in the PubMed: clinical trials, meta-analysis, randomized control trial, review, English language, and humans. "Sitagliptin" was then combined with the MeSH term "economics" using the Boolean combiner "AND" without any limits to obtain the query results. The references cited in all the above retrieved publications were also reviewed for relevance and were obtained when applicable.

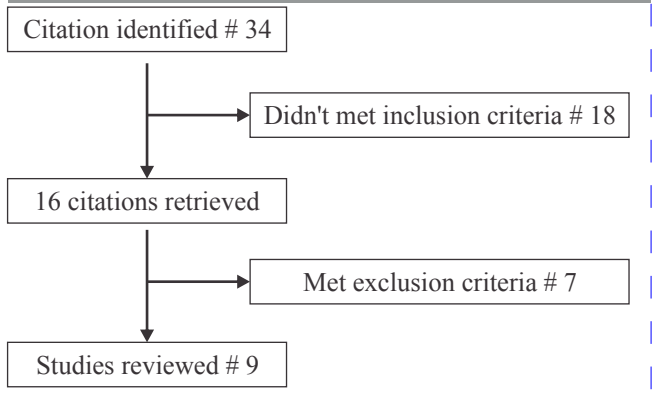
RESULTS AND DISCUSSION

Literature review of saxagliptin:

A total of 34 studies and 3 studies were obtained when the PubMed was searched for saxagliptin only and for saxagliptin and economics combined. These searched were examined in the following manner: For the first search which extracted 34 studies, these 34 studies were shortlisted to 16 studies (figure 1) on applying the following inclusion criteria to the abstracts of the 34 studies: studies describing the pharmacology, efficacy, safety, and dosage and administration of saxagliptin and/or saxagliptin combination therapy with metformin. Next, the following exclusion criteria were applied and the number of studies were shortlisted to 9: all clinical trials, presence of full-text, excluding reviews in which saxagliptin was not an area of primary discussion. The full text articles of these 9 studies were then retrieved and reviewed.

From the results of second PubMed search, which consisted of 3 studies, abstracts were reviewed for cost-effectiveness analysis of saxagliptin, especially studies describing the economic analysis of sitagliptin in India. However, all three studies were rejected as none of them met the above described inclusion criteria. This indicates that no economic evaluation of saxagliptin has been conducted till now.

Fig. 1: Roadmap for saxaglipin PubMed search



Pharmacology: saxagliptin is a selective and reversible DPP-4 enzyme inhibitor. DPP-4 enzymes cause enzymatic degradation of the GLP-1 into inactive metabolites. GLP-1 is required for the stimulation of glucose-dependent insulin secretion and reduction of glucagon secretion from the pancreas. The DPP-4 inhibitors (sitagliptin and saxagliptin), by acting on the beta-cells, inhibits the DPP-4 enzymes and prevents the deactivation of GLP-1. This in turn helps in secretion of insulin and reduction of glucagon levels in the body. This insulin then helps in maintaining the proper metabolic levels of glucose in the body.

Pharmacodynamics, dosage and administration, and clinical efficacy: currently, the saxagliptin is approved at once a daily dosage of 2.5 mg and 5 mg in individuals with normal renal functioning and at 2.5 mg in individuals with moderate-to-severe renal insufficiency or end stage renal disease (ESRD). Several clinical trials have shown the effectiveness of saxagliptin monotherapy and saxagliptin+metformin combination therapies: in a 12-week, multicentre, randomized, parallel-group, double-blind, placebo-controlled trial conducted at 152 out-patient US study centres, 338 (low-dose cohort) and 85 (high-dose cohort) drug-naive patients with T2DM and inadequate glycaemic control, saxagliptin resulted in a placebo-

subtracted statistically significant reduction in the HbA_{1C} levels ranging from 0.7%-0.9% and a placebo-subtracted statistically significant reduction in fasting serum glucose of range 14-25mg/dl.

In another 23 week randomized control trial with 401 patients (HbA_{1C} > or = 7% and < or =10%), participants were randomized and treated with oral saxagliptin 2.5, 5, or 10 mg once daily or placebo for 24 weeks and a separate open-label cohort with 66 patients (HbA_{1C} > 10% and < or =12%) who received saxagliptin 10 mg once daily for 24 weeks. It was found that saxagliptin demonstrated statistically significant decreases in adjusted mean HbA_{1C} changes from baseline (mean, 7.9%) to week 24 (-0.43%, -0.46%, -0.54%) for saxagliptin 2.5, 5, and 10 mg, respectively, vs. +0.19% for placebo (all $p < 0.0001$).

In another 24 week multicentre, randomized, double-blind, active-controlled phase 3 trial, 1306 treatment-naïve patients with T2DM and glycosylated haemoglobin (HbA_{1C}) >or=8 to <or=12% were randomized to receive saxagliptin 5 mg + metformin 500 mg, saxagliptin 10 mg + metformin 500 mg, saxagliptin 10 mg + placebo or metformin 500 mg + placebo for 24 weeks. At week 24, the saxagliptin 5 mg + metformin and saxagliptin 10 mg + metformin demonstrated statistically significant adjusted mean decreases vs. saxagliptin 10 mg and metformin monotherapies in HbA_{1C} (-2.5 and -2.5% vs. -1.7 and -2.0%, all $p < 0.0001$ vs. monotherapy).

Overall, saxagliptin monotherapy as well as the saxagliptin+metformin combination therapy demonstrated clinical efficacy in terms of HbA_{1C}, FPG, and PPG reductions. Other benefits of saxagliptin include weigh-neutrality and fewer gastrointestinal-related adverse events. However, as saxagliptin was approved recently in the year 2009, currently no long-term clinical trials data are available for it.

Adverse effects and tolerability: pooled data from various randomized clinical trials has shown that monotherapy and combination therapies of saxagliptin are generally well tolerated. In one of the trials, adverse events in the treatment group occurred with a similar frequency to that of the placebo group and no significant dose-related adverse events were identified at the tested dosage levels of saxagliptin. In a trial conducted by Jadzinsky and colleagues, skin-related adverse events were reported in 4.2% of the patients receiving 10mg saxagliptin monotherapy and 3.4-4.3% in patients receiving the combination therapy of saxagliptin with 5 or 10 mg metformin. Chen and colleagues conducted a literature review of clinical trials outcomes of the hypoglycemic events due to saxagliptin and found that the overall incidence of hypoglycemia was less than 2.5%. In a dose-ranging study, there were no cases of confirmed hypoglycemia with a dose of $\leqslant$ 40 mg. In another dose-ranging study, hypoglycemia was reported in 6.3% of the patients receiving 2.5-4.0 mg daily dose versus 1.5% receiving placebo. In another trial, after 102 weeks of treatment, 9-11% of patients receiving saxagliptin reported hypoglycemia versus 10% of those receiving metformin plus placebo. Furthermore, the cardiovascular safety (death, myocardial infarction, stroke, revascularization procedures, and cardiac ischemia) of saxagliptin was assessed using the post hoc analysis of eight trials, which included a total of 4607 patients. No increased risk of increased cardiovascular disorders saxagliptin monotherapy or combination therapy with metformin was found.

Literature review of sitagliptin:

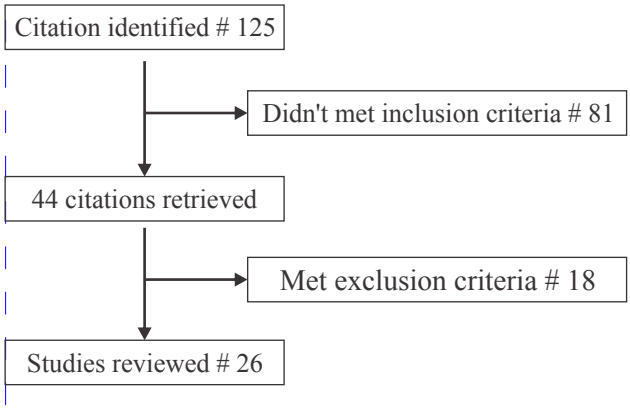
A total of 125 studies and 11 studies were obtained when the PubMed was searched for sitagliptin only and for sitagliptin and economics combined. These searches were examined as follows: the abstracts of 125 studies obtained from the first search were reviewed by applying the following inclusion criteria: pharmacology, efficacy, safety, and dosage and administration of sitagliptin and/or sitagliptin combination therapy with metformin. Based on this inclusion criteria, 44 studies were shortlisted (figure 2). On these 44 studies, the following exclusion criteria was applied: all clinical trials, presence of full-text, excluding reviews in which saxagliptin was not an area of primary discussion (figure 2). Based on this exclusion criteria, the number of studies shortlisted was 26. The full-text of these 26 studies was carefully examined.

From the results of second search, which consisted of 11 studies, abstracts were reviewed for cost-effectiveness analysis of sitagliptin, especially studies describing the economic analysis of sitagliptin in India. Based on this criteria, I found no studies.

Pharmacology: Belonging to the same class of oral hypoglycemic agents, i.e. DPP-4 inhibitors, both sitagliptin and saxagliptin has same mechanism of action; prevents the enzymatic degradation of GLP-1 proteins which in turn helps in increase in the secretion of insulin and decrease in the secretion of glucagon in the body to help maintain the appropriate metabolic levels of glucose in the body.

Pharmacodynamics, dosage and administration, and clinical efficacy: The recommended daily dosage of sitagliptin in the US is 100 mg once daily which may be taken

Fig. 2: Roadmap for sitaglipin PubMed search



without regard to food. Several clinical trials have shown the effectiveness of sitagliptin monotherapy and combination therapy with insulin secretagogues, like metformin.

The efficacy of sitagliptin monotherapy was well established in three large (n = 363 555 or 743) well designed, dose-ranging studies, which showed that treatment with sitagliptin improved glycaemic control in patients with inadequately controlled type 2 diabetes (HbA_{1c} levels of 6.5–10.0%). In these trials, HbA_{1c} levels were significantly ($p < 0.001$) reduced with sitagliptin 25–100 mg once daily or 50 mg twice daily (placebo-subtracted differences -0.39% to -0.56%) sitagliptin 25–200 mg once daily (-0.69% to -1.04%) or sitagliptin 5–50 mg twice daily (-0.38% to -0.77% versus -1.0% with glipizide 5–20 mg/day) relative to placebo after 12 weeks of therapy.

The efficacy of sitagliptin was also evaluated in several, ⩽24 week, randomized, double-blind, clinical trials. Oral sitagliptin 100mg once daily as monotherapy significantly improved glycaemic control relative to placebo in adult patients with inadequately controlled type 2 diabetes. The efficacy of sitagliptin was sustained in a 30-week extension of a 24-week double-blind trial.

The efficacy of sitagliptin as initial combination therapy with metformin was evaluated in a 24-week, randomized, double-blind, placebo controlled trial and a double blind 30-week, followed by a 50-week extension in patients with inadequately controlled type 2 diabetes. Oral sitagliptin as initial combination therapy with metformin significantly improved glycaemic control in adult patients with inadequately controlled type 2 diabetes; after 24 weeks of treatment, HbA1c, FPG and 2-hour PPG levels were significantly reduced with sitagliptin plus metformin compared with sitagliptin or metformin monotherapy or placebo. Furthermore, the efficacy of sitagliptin as add-on therapy to ongoing treatment with metformin was evaluated in several 12- to 52-week, randomized, double blind, placebo and active comparator, controlled trials. After up to 30 weeks of treatment, the HbA_{1c}, FPG and 2-hour PPG levels were significantly reduced with sitagliptin add-on treatment relative to existing treatment.

Adverse effects and tolerability: pooled data from clinical trials show that sitagliptin is generally well tolerated. Overall, the most common (incidence >6% in either group) treatment-emergent adverse events in the sitagliptin or comparator groups were upper respiratory tract infection (7.8% vs 8.4%), nasopharyngitis (7.1% vs 5.9%) and hypoglycaemia (3.4% vs 10.9%). Among patients receiving sitagliptin as add-on treatment to metformin, no adverse events occurred with an incidence ⩾ 5% and more frequently than with existing metformin therapy. In addition, the individual trials showed that sitagliptin monotherapy or combination therapy with metformin was associated with a low (0.3%) incidence of hypoglycaemia and gastrointestinal events. Sitagliptin was also found to be weight neutral in these clinical trials.

CONCLUSION

This literature review demonstrates that the new DPP-4 inhibitors, sitagliptin and saxaglipin, have a good general safety and efficacy profile. These drugs have been approved worldwide including in places such as India, USA, and Europe. However, from this literature review, it was found that no formal economic evaluation of sitagliptin and saxaglipin has been conducted till date in India. And, for saxagliptin, it was found that no economic evaluation has been conducted anywhere in the world, till date. Therefore, a systematic economic evaluation for accessing the costs and consequences of using sitagliptin and saxagliptin in the treatment of T2DM patients is required.

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