Saxagliptin: A Clinical Review in the Treatment of Type 2 Diabetes Mellitus

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ABSTRACT

Background: Some conventional therapies for type 2 diabetes mellitus (T2DM) fail to address the progressive nature of the disease, and as a result, they may become ineffective in maintaining normoglycemia. Antihyperglycemic agents have been developed to target incretin hormones, specifically glucagon-like peptide (GLP)-1. Incretin analogues and agents that delay GLP-1 degradation, the dipeptidyl peptidase (DPP)-4 inhibitors, offer mechanisms of action that may improve T2DM management. Saxagliptin was approved by the US Food and Drug Administration in July 2009 and by the European Medicines Evaluation Agency in October 2009 for use as monotherapy or in combination regimens for the treatment of T2DM.

Objective: The aim of this article was to review the mechanism of action, pharmacology, clinical efficacy, and tolerability associated with the use of saxagliptin in patients with T2DM.

Methods: MEDLINE, BIOSIS, International Pharmaceutical Abstracts, and Google Scholar were searched for English-only clinical trials and therapeutic reviews published between 1966 and June 15, 2011 (search term: *saxagliptin*). Additional trials and reviews were identified from the reference lists of published articles.

Results: Findings on efficacy and tolerability were obtained from 11 completed Phase III clinical trials. In trials in saxagliptin-naive patients, changes from baseline in glycosylated hemoglobin (HbA_{1c}) ranged from −0.72% to −0.90% in the saxagliptin treatment arms compared with −0.27% with placebo (all, $P < 0.007$). When saxagliptin was used in combination with metformin for 24 weeks, the adjusted mean reductions from baseline in HbA_{1c} and the proportions of patients achieving target HbA_{1c} (<7.0%) were significantly greater with saxagliptin + metformin compared with monotherapy with either drug (all, $P \leq 0.0001$). When saxagliptin was used in combination with a sulfonylurea or a thiazolidinedione, the changes in HbA_{1c} ranged from −0.54% to −0.64% and −0.66% to −0.94%, respectively, in a dose-dependent manner ($P \leq 0.0007$ vs monotherapies). Based on changes in HbA_{1c}, saxagliptin + metformin was reported to be noninferior to sitagliptin + metformin (−0.52% and −0.62%, respectively; difference, 0.09% [95% CI, −0.01% to 0.20%]). Saxagliptin was reported to have been well tolerated, with the most common adverse events being upper respiratory infection, urinary tract infection, headache, and nasopharyngitis. A systematic review of cardiovascular events in pooled trial results of saxagliptin use reported no increased cardiovascular risk compared with metformin, glyburide, or placebo (relative risk, 0.24 [0.09–0.63]).

Conclusions: Saxagliptin, used as monotherapy and in combination regimens, has been associated with significant reductions in HbA_{1c} and significant increases in the rate of achieving target HbA_{1c} in patients with T2DM. It has been reported to be well tolerated compared with other oral antihyperglycemic agents. Based on the findings from the studies in this review, the primary role of saxagliptin is expected to be in combination therapy with other antihyperglycemic agents. (*Clin Ther.* 2011;33:1005–1022)

Key words: dipeptidyl peptidase-4 inhibitors, glucagon-like peptide 1, saxagliptin, type 2 diabetes.

INTRODUCTION

According to the Centers for Disease Control and Prevention,[1] 8% of the US population has diabetes, and in

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2006, diabetes was listed as the 7th leading cause of death. In 2007, the economic cost burden of diabetes in the United States was conservatively estimated at >$174 billion.[2] Poorly treated hyperglycemia can lead to microvascular and macrovascular complications, including retinopathy, nephropathy, neuropathy, and cardiovascular disease. It is increasingly essential for health care providers to have an understanding of all diabetes treatment options to provide optimal care for the growing population of diabetic patients.

Unfortunately, only ~50% of diabetic patients in the United States meet the American Diabetes Association's recommended goal for glycosylated hemoglobin (HbA_{1c}), <7.0%.[3] Conventional treatment options help to improve insulin secretion, insulin sensitivity, and excess production of hepatic glucose, yet some do not maintain normoglycemia over time when used as monotherapy.[4] Some conventional therapies fail to address the progressive nature of diabetes and the pathophysiologic deterioration in β-cell function.[5,6] In addition, these therapies have been associated with an increased risk for hypoglycemia (sulfonylureas and insulin), weight gain (sulfonylureas, insulin, and thiazolidinediones [TZDs]), and gastrointestinal intolerance (metformin and α-glucosidase inhibitors), which may limit glycemic control.[7]

Over the past decade, antihyperglycemic therapies have been developed to target incretin hormones and their pathways. In individuals without diabetes, incretin hormones, such as glucagon-like peptide (GLP)-1, are released from the small intestine after the ingestion of a meal. In a glucose-dependent manner, GLP-1 causes insulin release from the β cells of the pancreas, decreases glucagon secretion from the α cells of the pancreas, and reduces hepatic glucose production. GLP-1 also slows gastric emptying and induces satiety.[8,9] Incretin analogues, specifically GLP-1, and agents that delay their degradation, the dipeptidyl peptidase (DPP)-4 inhibitors, offer mechanisms of action that may improve overall type 2 diabetes mellitus (T2DM) management.[10–12] Much interest has also been devoted to the effects of DPP-4 inhibitors on the preservation of β-cell function.[13]

In May 2009, the National Institute for Health and Clinical Excellence recommended DPP-4 inhibitors for use as second-line therapy behind metformin for patients at significant risk for hypoglycemia or if a sulfonylurea is not tolerated or is contraindicated.[14] Initially, the place of DPP-4 inhibitors in therapy is likely to parallel that of GLP-1 agonists (eg, exenatide, liraglutide) until more research on the potential benefits is available.[7]

The use of saxagliptin as monotherapy or in combination with other oral antihyperglycemic medications was approved by the US Food and Drug Administration (FDA) in July 2009 and by the European Medicines Evaluation Agency in October 2009 for the treatment of diabetes. Sitagliptin was the first agent in this class of medications to be approved by the FDA (October 2006). The combination product of sitagliptin/metformin was subsequently approved in March 2007. In November 2010, the combination product of saxagliptin/metformin was approved, and a third DPP-4 inhibitor, linagliptin, was approved in May 2011.[15] Vildagliptin and alogliptin are 2 DPP-4 inhibitors that have not been approved for use in the United States.[16] The use of saxagliptin in combination with insulin has not been extensively studied.[17]

The purpose of this review article was to discuss the mechanism of action, pharmacology, clinical efficacy, and tolerability associated with the use of saxagliptin in patients with T2DM. The potential place in therapy for saxagliptin among other oral antihyperglycemics and DPP-4 inhibitors is also discussed.

MATERIALS AND METHODS

MEDLINE, BIOSIS, International Pharmaceutical Abstracts, and Google Scholar were searched for English-only clinical trials and therapeutic reviews published between 1966 and June 15, 2011, using the search term *saxagliptin*. Additional trials and reviews were identified from the reference lists of published articles.

RESULTS

Sixty-one clinical trials and review articles were identified. Efficacy and tolerability results were obtained from 11 clinical trials of saxagliptin. Two of the 11 trials were extension studies, 1 of which was presented in abstract form.

Mechanism of Action

GLP-1 is rapidly degraded within minutes by the enzyme DPP-4, a member of the DPP enzyme family, which includes DPP-4, DPP-8, DPP-9, and fibroblast activation protein. Saxagliptin slows the rapid inactivation of GLP-1 through DPP-4 inhibition. This inhibition extends the activity of endogenous GLP-1, re-