New Drug Review

The Role of Sodium-Glucose Co-Transporter 2 Inhibitors in the Treatment of Type 2 Diabetes

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ABSTRACT

Purpose: Diabetes is a chronic metabolic disorder characterized by hyperglycemia that results from insulin resistance, diminished or absent insulin secretion, or both. Approximately one-half of patients with diabetes fail to achieve acceptable glycemic control. Consequently, morbidity and mortality associated with diabetes is high, resulting from complications such as cardiovascular disease and nephropathy. The sodium-glucose co-transporter 2 (SGLT2) inhibitors are a new class of medications for the treatment of type 2 diabetes. This article provides an overview of efficacy and safety data for the SGLT2 inhibitors and outlines their role in the management of diabetes.

Methods: Relevant articles were identified through searches of PubMed and International Pharmaceutical Abstracts by using the key terms *canagliflozin*, *dapagliflozin*, *empagliflozin*, and *sodium-glucose co-transporter 2 inhibitor*. A review of bibliographies of retrieved articles was also performed to identify additional references. All identified trials published in English and that involved the efficacy and safety of SGLT2 inhibitors in the treatment of type 2 diabetes were reviewed.

Findings: The SGLT2 inhibitors improve glucose control by increasing urinary glucose excretion. Effectiveness is decreased in the presence of renal dysfunction. These agents are efficacious as monotherapy and add-on therapy for patients with type 2 diabetes uncontrolled on metformin, sulfonylureas, insulin, and other antihyperglycemic combinations. The SGLT2 inhibitors lower glycosylated hemoglobin by 0.5% to 1% and fasting plasma glucose by ~15 to 35 mg/dL, depending on the agent and the dosage used, and are also associated with modest reductions in weight (−1.5 to −3.5 kg) and systolic blood pressure (−3 to −5 mm Hg). Genital mycotic infections and increased urination, owing to the mechanism of action, are the most common adverse effects. In general, the class is well tolerated, and the risk of hypoglycemia is low.

Implications: With their unique mechanism of action and good safety and tolerability profiles, the SGLT2 inhibitors are an important addition to existing treatments for type 2 diabetes. Because of the lack of data with this class of drugs when current treatment guidelines for diabetes were published, the SGLT2 inhibitors are recommended as second- or third-line therapies for diabetes. Forthcoming data on the long-term efficacy and safety profile of these agents should help to solidify the role of SGLT2 inhibitors in the management of diabetes. (*Clin Ther*. 2015;37:1150–1166)

Key words: canagliflozin, dapagliflozin, empagliflozin, sodium-glucose co-transporter 2 inhibitor.

INTRODUCTION

Diabetes is a chronic metabolic disorder characterized by hyperglycemia that results from insulin resistance, diminished or absent insulin secretion, or both. Diabetes is estimated to affect 29.1 million Americans and close to 350 million people worldwide.[1,2] The most common form of diabetes, accounting for 90% to 95% of cases, is type 2 diabetes mellitus (T2DM), or

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diabetes attributed to insulin resistance. Chronic complications of diabetes include both microvascular complications such as nephropathy, neuropathy, and retinopathy and macrovascular complications such as heart disease and stroke. Cardiovascular (CV) risk is significant in T2DM, with heart disease or stroke claiming the lives of 2 of 3 patients.[2,3] Substantial evidence indicates that controlling blood glucose prevents the risk or reduces progression of microvascular complications.[4,5] Furthermore, controlling other risk factors such as hypertension and dyslipidemia reduces the risk of both nephropathy and retinopathy and is paramount to decreasing the occurrence of CV disease in diabetes.

First-line therapy for the management of T2DM generally involves lifestyle modifications, including diet and exercise, along with metformin.[6] Other oral medications for the treatment of T2DM have traditionally included sulfonylureas, meglitinides, thiazolidinediones (TZDs), dipeptidyl-peptidase-4 inhibitors, α-glucosidase inhibitors, bromocriptine, and colesevelam. Injectable agents such as various forms of insulin, glucagon-like peptide-1 (GLP-1) receptor agonists, and amylin analogs are also used for the treatment of T2DM. Despite the availability of a wide variety of medications, almost one-half of patients with diabetes fail to achieve acceptable glycemic control.[7] Thus, the search for effective medications for diabetes continues. In 2013 a new class of antihyperglycemic medications, the sodium-glucose co-transporter 2 (SGLT2) inhibitors, entered the market. Canagliflozin was the first of these agents to obtain approval by the US Food and Drug Administration (FDA) in March 2013. Subsequently, the FDA approved dapagliflozin in January 2014 and empagliflozin in August 2014. Each of these agents is approved for the treatment of T2DM in adults.[8–10] This article provides an overview of efficacy and safety data for the SGLT2 inhibitors and outlines their role in the management of T2DM.

METHODS

Relevant articles were identified through searches of PubMed (publication date range: 1966–November 2014) and International Pharmaceutical Abstracts (publication date range: January 1970–November 2014) by using the key terms *canagliflozin*, *dapagliflozin*, *empagliflozin*, and *sodium-glucose co-transporter 2 inhibitor*. A review of bibliographies of retrieved articles was also performed to identify additional references. All identified trials published in English and that involved efficacy and safety of SGLT2 inhibitors in the treatment of T2DM were reviewed.

RESULTS

Clinical Pharmacology

Under normal circumstances, the adult kidney filters ~180 g of glucose per day.[11] Almost all of the glucose filtered by the kidney is reabsorbed and returned to the systemic circulation via the SGLT proteins SGLT2 and SGLT1. Even though plasma glucose levels are elevated in T2DM, the kidneys continue to reabsorb glucose through the SGLT proteins, thereby contributing to hyperglycemia. SGLT2 is a low-affinity, high-capacity transporter found exclusively in the proximal renal tubule. It is responsible for reabsorption of 90% of glucose filtered by the kidney. SGLT1 is a high-affinity, low-capacity transporter located further along the proximal tubule, and it reabsorbs the remaining glucose.[12] SGLT1 is also expressed in the brush border of the small intestine where it plays a significant role in glucose absorption. The available SGLT2 inhibitors differ in their relative selectivity for SGLT2 versus SGLT1. For instance, empagliflozin is the most selective for SGLT2 (>2500:1), followed by dapagliflozin (>1200:1) and canagliflozin (>250:1).[13] The clinical significance of SGLT2 selectivity is not fully established. Agents with lower selectivity for SGLT2 may transiently inhibit SGLT1-mediated glucose absorption in the small intestine, thereby reducing postprandial glucose.[14]

The SGLT2 inhibitors exert their main pharmacologic action by preferentially inhibiting SGLT2. Inhibition of SGLT2 decreases reabsorption of glucose, leading to an increase in urinary glucose excretion (UGE) and a reduction in plasma glucose levels. The increased UGE seen with SGLT2 inhibitors also results in a loss of 200 to 300 kcal/d, which may contribute to modest weight loss observed with these agents.[12] In addition, modest reductions in systolic blood pressure may occur, likely attributable to the mild osmotic diuresis produced by this class. Because SGLT2 inhibitors depend on sufficient glomerular filtration to be effective, they subsequently work best in patients with normal renal function or mild renal impairment.[15] Dapagliflozin should not be used in patients with an estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73 m^2. Canagliflozin and empagliflozin should not be used if eGFR is <45 mL/min/1.73 m^2.[8–10]