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Educational Forum

Empagliflozin and metformin combination therapy in Type 2 diabetes mellitus

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ABSTRACT

Diabetes mellitus (DM) is a spectrum of metabolic disorder characterized by chronic hyperglycemia either due to an absolute or a relative insulin deficiency. The prevalence of diabetes varies between various countries and ethnic groups and of late, it has reached epidemic proportions in both the developed as well as in the developing countries. There is an intense need for new and effective therapies for Type 2 DM (T2DM) with improved safety and tolerability profiles to reduce the outcome of the acute and chronic complications of this condition. Empagliflozin is a new class of selective sodium glucose cotransporter-2 inhibitor approved for the treatment of T2DM in 2014. It has a novel and a unique mechanism of action in that it inhibits the reabsorption of glucose in the kidneys, promotes excessive glucose excretion through a non-insulin dependent mechanism and induces glycosuria. Metformin is the only biguanide which is currently the widely accepted first-line drug for T2DM. It is effective as monotherapy and as combination therapy and has proven beneficial effects on microvascular and macrovascular complications of DM. Recently, the US Food and Drug Administration has approved the fixed dose combination of empagliflozin with metformin hydrochloride during August 2015. The combination of empagliflozin/metformin hydrochloride can be used as an adjunctive therapy to diet and exercise in patients those who are not adequately controlled with monotherapy of either empagliflozin or metformin. This drug update focuses on the insulin-independent unique mechanism of action of empagliflozin and its beneficial effects alone and in combination with metformin in patients with T2DM.

Keywords: Type 2 diabetes mellitus, Empagliflozin, Sodium glucose co-transporter 2, Metformin, Activated protein kinase, Fixed dose combination, Food and Drug Administration approved

INTRODUCTION

Diabetes mellitus (DM) is a syndrome consisting of metabolic, vascular, and neuropathic components that are interrelated and has been defined principally to be metabolic disorder characterized by chronic hyperglycemia either due to an absolute or a relative insulin deficiency and is associated with alterations in carbohydrate, fat, and protein metabolism. Type 2 DM (T2DM) is a result of insulin resistance, beta cell dysfunction, and other metabolic and hormonal abnormalities. Obesity and insulin resistance occurs as key components of metabolic syndrome in addition to hypertension, dyslipidemia, and microalbuminuria along with fibrinolytic dysfunction, endothelial dysfunction, vascular inflammation, and abnormal uric acid metabolism.

The pharmacotherapy of T2DM includes insulin secretagogues namely the sulfonylureas and meglitinides; the insulin-sparing drug namely metformin; insulin sensitizers namely the thiazolidinediones; the alpha-glucosidase inhibitors namely acarbose, voglibose, miglitol, and dipeptidyl peptidase (DPP)-4 inhibitors such as sitagliptin, saxagliptin, linagliptin, alogliptin, and vildagliptin; glucagon-like polypeptide-1 (GLP-1) receptor agonists namely exenatide, liraglutide, albiglutide, and dulaglutide; sodium glucose co-transporter 2 (SGLT2) inhibitors, and insulin whenever needed. Given the progressive nature of T2DM, glycemic targets are often achieved by escalating doses of monotherapy and then advancing to dual or triple combination therapy as required.[1] The various limitations of the currently available anti hyperglycemic agents include troublesome effects such as gastrointestinal upset, weight gain and hypoglycemia in addition to the requirement for renal and hepatic dose adjustments and their high cost.

The SGLT-2 inhibitors are a new class of anti-diabetic drugs having a unique mechanism of action. Empagliflozin is a reversible, highly potent, selective, and competitive inhibitor

of SGLT2 proteins. The other compounds of the same category already available are dapagliflozin, canagliflozin, and ipragliflozin. Other "gliflozins" under clinical trial, include ertugliflozin and sotagliflozin. In some countries, in addition to canagliflozin, dapagliflozin, ipragliflozin, tofogliflozin, and luseogliflozin have all also been approved.

MECHANISM OF ACTION

SGLTs are membrane proteins which are responsible for reabsorption of almost 90% of the glucose filtered by the kidneys. They are located on the proximal tubules of the nephrons in the kidneys. SGLT-2 inhibitors increase glucose excretion, independent of insulin secretion, by inhibiting the renal reabsorption of glucose, inducing glycosuria.[2]

The pharmacological inhibition of SGLT2 co-transporters reduces hyperglycemia by decreasing renal glucose threshold and thereby increasing urinary glucose excretion.[3,4] The extent of glucose that is excreted in the urine depends both on the severity of hyperglycemia and the glomerular filtration rate (GFR).

These agents help regulate blood glucose levels by blocking the reuptake of filtered glucose in the proximal tubule, leading to significant excretion of glucose through the urine, which is a novel and insulin-independent approach.[5] Empagliflozin has a high degree of selectivity for the SGLT2 over SGLT1 receptors.[6]

Empagliflozin improves glycemic control and reduces both fasting and post-prandial plasma glucose levels. This mechanism of action of empagliflozin is independent of pancreatic beta cell function and insulin secretion and thus carries only a low risk of hypoglycemia. It has been found that surrogate markers of beta cell function including homeostasis model assessment-β were also improved. In addition, a modest but a significant decrease in body weight has also been noted,[7] and studies have also confirmed that the weight reduction was due to decreased body fat rather than due to dehydration, and was explained by loss of glucose via the kidney.[8]

The glucosuria that occurs due to SGLT inhibition is accompanied by mild diuresis which contributes to an additional benefit of a sustained and moderate reduction in blood pressure (BP). A number of studies have shown that lowering BP in patients with concomitant diabetes and hypertension lowers the cardiovascular risk.[9,10]

Empagliflozin produced changes in arterial stiffness, cardiac oxygen demand, its cardiorenal effects, a decrease in albuminuria and uric acid levels, together with the sustained effect on the glycemic control, reduction in body weight, and BP are the contributory factors behind its beneficial effects on cardiovascular function.[11,12]

Based on their mechanism of action, SGLT2 inhibitors do not have direct effects on restoring pancreatic β-cell function or insulin sensitivity, but recent studies suggest that these underlying defects could be improved via reduced glucotoxicity.[13,14]

Administration of empagliflozin results in a dose-dependent increase in urinary glucose excretion which produces a sustained effect on the glycemic control and a dose-related decrease in HbA1c levels. A significant improvement in glycemic control in patients with T2DM has been demonstrated from various studies. The non-insulin dependent mechanism of action of SGLT 2 inhibitors is responsible for their potential to be used in combination with any of the existing classes of glucose-lowering agents, including insulin.

PHARMACOKINETICS

Empagliflozin is rapidly absorbed after oral ingestion. Food does not have any clinically relevant effects on drug absorption. It has a long half-life allowing once-daily administration and undergoes extensive hepatic metabolism mainly via glucuronidation to inactive metabolites.[15] Empagliflozin has a biphasic decline in plasma concentrations during the decay phase, with a terminal elimination half-life ranging from 8 to 13 hrs.[16]

ADVERSE EFFECTS

The most common adverse effects that can occur include nasopharyngitis, urinary tract infections, and genital tract infections. A decrease in uric acid levels and an increase in the LDL-cholesterol and HDL-cholesterol levels have also been noted.

SGLT2 inhibitors used as monotherapy are not associated with an increased risk of hypoglycemia; however, based on their mechanism of action, hypoglycemia risk might be increased in certain combination regimens.

It has been noted from studies that while empagliflozin may be used without dose adjustments in patients with any degree of renal impairment, reductions in plasma glucose levels would be predicted to be less clinically meaningful for those with severe renal impairment.[17] However, empagliflozin increases serum creatinine and decreases estimated GFR. The risk of impaired renal function is increased in elderly patients and in patients with moderate renal impairment. The efficacy of SGLT inhibitors is reduced in patients with chronic kidney disease, and they are contraindicated[18] in patients with an estimated GFR <45 ml/min/1.73 m^2. It has also been shown that there is no need for adjustment of empagliflozin doses in patients with hepatic impairment when used as monotherapy.[19]

METFORMIN

Metformin is a member of the biguanide class and is currently the most commonly used oral drug for treatment

of T2DM and is accepted as a first-line therapy for this condition.[20]

It activates the cellular activated protein (AMP) dependent protein kinases and has an insulin-sparing action. The AMP kinase stimulates glucose uptake and improves the insulin sensitivity. It decreases hepatic glucose production and decreases intestinal absorption of glucose. It decreases the hepatic glucose output by inhibition of hepatic gluconeogenesis, and it also inhibits lipogenesis. Metformin increases the glucose transport in muscle and increases glucose utilization. It reduces free fatty acid oxidation, reduces insulin resistance, and indirectly improves beta cell function. It is beneficial in overweight, obese individuals and those with normal kidney function. It is absorbed from the small intestine and is excreted unchanged in the urine with a half-life of 2 hrs. It is currently the widely accepted first-line drug for T2DM. It is effective as monotherapy and as combination therapy.

Fixed dose combinations of metformin with glyburide, glipizide, repaglinide, pioglitazone, rosiglitazone, and sitagliptin are available. As a result of its safety and efficacy, metformin should be the cornerstone of dual therapy for most patients. Metformin is effective as monotherapy and in combination with other anti-diabetic agents, including sulfonylureas, TZDs, AGIs, DPP-4 inhibitors, GLP-1 agonists, and pramlintide.[21] Recently, the combined use of SGLT 2 inhibitor empagliflozin with metformin hydrochloride has been approved.

The fixed dose combination of empagliflozin/metformin hydrochloride has a complementary mechanism of action to improve glycemic control in patients with T2DM. Empagliflozin treatment causes reductions in HbA1c and Fasting glucose levels, along with beneficial reductions in body weight. It is efficacious as monotherapy and as add-on therapy for patients with T2DM who are not meeting their treatment goals on metformin alone.[22]

Empagliflozin/metformin hydrochloride combination is indicated as an adjunctive therapy to diet and exercise in patients with Type 2 diabetes not adequately controlled with either empagliflozin or metformin monotherapies or in patients already being treated with empagliflozin and metformin.

Metformin remains the first-line drug for patients starting glucose-lowering therapy SGLT2 inhibitors can be considered as an add-on therapy in patients those who have not achieved glycemic targets with their initial therapies. Their novel mechanism of action makes SGLT2 inhibitors suitable for use as combination therapy with any one of the glucose-lowering agents, including insulin. This is supported by data from numerous clinical trials, where SGLT2 inhibitors have been successfully used as monotherapy and as add-on therapy with metformin alone or in combination with SUs, TZDs, DPP-4 inhibitors, and insulin.

Empagliflozin exhibits a favorable pharmacodynamic and a predictable pharmacokinetic profile, without any drug interactions among other drugs commonly prescribed in T2DM as well as in patients with other comorbidities, especially those on antihypertensive medications, anti-coagulants, and oral contraceptives are well-tolerated with a good safety profile.[23]

The fixed dose combination of empagliflozin/metformin hydrochloride (Synjardy) is available in a tablet form for oral administration. The following doses of the combination are available for use: 5 mg empagliflozin with 500 mg metformin hydrochloride, 5 mg empagliflozin with 1000 mg metformin hydrochloride, 12.5 mg empagliflozin with 500 mg metformin hydrochloride, and 12.5 mg empagliflozin with 1000 mg metformin hydrochloride.

ADVERSE EFFECTS OF COMBINATION THERAPY

Empagliflozin use is commonly associated with urinary tract infection and mycotic infections of the female genital tract. Metformin commonly causes gastrointestinal upset, asthenia, and headache.

CONTRAINDICATIONS AND PRECAUTIONS TO FIXED DOSE COMBINATION

The fixed dose combination of empagliflozin/metformin hydrochloride is contraindicated in patients with renal impairment with estimated GFR of <45 mL/min/1.73 m^2, in diabetic ketoacidosis, and in patients with a history of hypersensitivity reaction to empagliflozin or metformin hydrochloride.

Hepatic dysfunction can predispose to the development of lactic acidosis with metformin therapy and hence the fixed dose combination should be avoided in patients with the hepatic disorder. Hypoglycemia can occur when the combination is used along with insulin and insulin secretagogues. The osmotic diuresis can result in intravascular volume depletion and hypotension.

In addition, other side effects such as a decrease in vitamin B12 levels due to interference with calcium-dependent absorption of vitamin B12-intrinsic factor complex by metformin can also occur. Coadministration of radiocontrast agents while on metformin therapy can lead to acute renal failure. Metformin therapy should be withheld for a day or two and reintroduced only after renal functions are confirmed to be normal. An increase in LDL cholesterol due to empagliflozin can also occur.

CONCLUSION

Empagliflozin is an SGLT inhibitor having a novel and unique mechanism of action independent of pancreatic beta cell function and insulin action. It produces a dose-dependent reduction in HbA1 C levels and a sustained improvement in glycemic control. It shows additional beneficial effects of body weight reduction, a decrease in the BP and a lower risk of hypoglycemia in addition to its potential beneficial effects on cardiovascular risk factors. Metformin is a recommended first-line anti-diabetic drug for T2DM. It activates the cellular AMP-dependent protein kinases and has an insulin-sparing action. It does not cause hypoglycemia except in combination with insulin and insulin secretogogues. It decreases the risk of both the microvascular and macrovascular complications of DM and as well, has a role in the prevention of T2DM in middle-aged, obese individuals with impaired glucose tolerance and fasting hyperglycemia. Fixed dose combination of empagliflozin and metformin can have additional beneficial effects in T2DM patients.

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