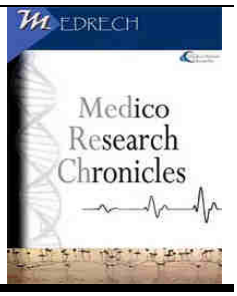
MEDICO RESEARCH CHRONICLES
ISSN NO. 2394-3971
DOI No. 10.26838/MEDRECH.2020.7.1.553
OPEN ACCESS
Contents available at: www.medrech.com



COMBINATION DUAL THERAPY OF EMPAGLIFLOZIN AND LINAGLIPTIN FOR THE MANAGEMENT OF TYPE 2 DIABETES

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ARTICLE INFO **ABSTRACT** **REVIEW ARTICLE**

Article History
Received: January 2020
Accepted: February 2020

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INTRODUCTION

Patients with type 2 diabetes (T2DM) have a significantly higher risk of developing cardiovascular disease (CVD) - namely myocardial infarction, heart failure and stroke [1]. Despite the efforts and advancements, the impact of T2DM on CVD outcomes remains high and continues to escalate. With the escalation in the severity of hyperglycemia, macrovascular complications increases, thus suggesting an almost linear relation between metabolic disturbances and vascular damage[1]. In T2DM patients, each 1% increase in glycosylated hemoglobin (HbA1c) is correlated with as much as a 38% increased risk of a macrovascular event[2]. Thus, stringent control of blood glucose is an essential goal in the management of T2DM. Metformin is the recommended first-line pharmacotherapy for patients with T2DM, however, most patients ultimately need additional therapies to maintain glycemic homeostasis. Therefore, when metformin fails to achieve glycemic control, additional therapy with oral antidiabetic agents is considered to be beneficial[3].

T2DM is a complex and progressive disease. Earlier T2DM was thought to be only a disease of insulin resistance, however current findings indicate the involvement of at least eight pathologic processes that lead to T2DM [4]. These include-

- Abnormal ß-cell insulin secretion,
- Excessive α-cell glucagon production,
- Abnormal incretin effect,
- Insulin resistance at the peripheral tissues,
- Increased hepatic glucose production,
- Increased lipolysis,
- Neurotransmitter dysfunction, and
- Abnormal renal handling of hyperglycemia.

Hypertension is strongly associated with the presence of albuminuria, which is an important predictor of both cardiovascular and renal events in patients with T2DM [4]. Thus, maintenance of normal glucose homeostasis

requires a complex, highly integrated interaction among the liver, muscle, adipocytes, pancreas and neuroendocrine system. Conclusively, a combination therapy (dual or triple) with a different mechanism of anti-diabetic drugs are required for the management of type 2 diabetes[2].

Use of a combination of a sodium-glucose co-transporter-2 (SGLT2) inhibitor with a dipeptidyl peptidase-4 (DPP-4) inhibitor with or without metformin is one such promising approach. A clinical trial with triple therapy wherein, an SGLT2 inhibitor along with a DPP-4 inhibitor was added to metformin therapy resulted in greater improvement in glycemic control[5]. Based on the results of various clinical studies, eventually, in February 2015, a fixed-dose combination of empagliflozin (SGLT2 inhibitor) and linagliptin (DPP-4 inhibitor) was approved by FDA as an adjunct to diet and exercise to improve glycemic control in patients with T2DM who are suitable for the treatment of both empagliflozin and linagliptin.

Pharmacology and clinical efficacy

Ideal glucose homeostasis both in the fasting and postprandial state can be achieved following enhanced glucose-dependent insulin secretion and reduced glucagon production[2]. Thus, a combination therapy wherein molecules exert their action at two different mechanistic levels seems to be a rational approach for the effective management of T2DM.

Mechanistically, kidneys also play a central role in glucose homeostasis by reabsorbing all the filtered glucose which is a normal human adaptive mechanism. This mechanism, however, becomes maladaptive in diabetes. Hyperglycemia augments the expression and activity of the SGLT2 in the proximal tubule of the kidney. As a result, glucose reabsorption may increase by as much as 20% in individuals with poorly controlled diabetes. SGLT2 is a low-affinity, high-capacity glucose transport protein that reabsorbs 90% of filtered glucose, while the high-affinity, low-capacity SGLT1 transporter reabsorbs the remaining 10%. SGLT2 represents a novel target for the treatment of diabetes[4]. Empagliflozin, an SGLT2 inhibitor, reduces glucose reabsorption from the glomerular filtrate to increase urinary glucose excretion (UGE) and reduces hyperglycemia in patients T2DM. Additionally, empagliflozin has also been found to be beneficial in weight loss and a moderate reduction in systolic blood pressure (SBP)[2]. Also, there is no increase in hypoglycemia risk using empagliflozin therapy as its mechanism of action is independent of insulin[3].

Incretins, secreted from the intestinal L- and K-cells after meal intake, regulate glucose homeostasis via elevated insulin synthesis and release from pancreatic ß cells in the presence of normal and elevated blood glucose levels. Linagliptin is an inhibitor of DPP-4, an enzyme that degrades the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). Thus, Linagliptin prolongs the half-life of the intestinal incretins, GLP-1 and GIP, after inhibiting the DPP-4 enzyme. Additionally, GLP-1 lowers glucagon secretion from pancreatic α cells to reduce hepatic glucose output.

The pharmacologic actions of empagliflozin reducing systolic blood pressure is related to weight loss, osmotic diuresis, reduced arterial stiffness and direct vascular effects, while linagliptin glanced off blood pressure. Thus, given the complementary mechanisms of action of SGLT2 inhibitors and DPP-4 inhibitors, a combination of empagliflozin and linagliptin offer therapeutic treatment benefits viz., beneficial effects on the kidney, body weight and systolic blood pressure compared with monotherapy.

Pharmacokinetically, Empagliflozin is rapidly absorbed after oral administration, reaching peak plasma concentrations at 1.5 hours post-dose. A single oral dose of linagliptin is also rapidly absorbed, with time to peak plasma concentration occurring 0.7–3 hours post-dose. After the administration of

multiple oral doses of empagliflozin and linagliptin, steady-state was reached by day 5 and day7, respectively. The mean volume of distribution is 73.8 L for empagliflozin and 1110 L for linagliptin at steady state following oral administration in healthy subjects. The plasma protein binding of empagliflozin is 86.2%, while linagliptin is concentration-dependent; decreasing from about 99% at1 nmol/L to 75% to 89% at ≥ 30 nmol/L. Plasma protein binding is not altered in patients with renal or hepatic impairment. Empagliflozin is a substrate for the P–glycoprotein transporter. Thus, renal and hepatic impairment probably increases plasma concentrations of empagliflozin, but no dose adjustment is recommended. Most of the linagliptin is excreted unchanged after oral administration, indicative of metabolism via a minor elimination pathway while, no major metabolites of empagliflozin are detected in human plasma. Based on the population pharmacokinetic analysis, the elimination half-life of empagliflozin is estimated to be 12.4 h while, the elimination half-life of linagliptin ranged from 70 to 80 h below 50 mg, and from 128–184 h above 50 mg [2]. Also, pharmacokinetic data have demonstrated that there is no difference in the systemic exposure of empagliflozin or linagliptin when administered alone or in combination.

A meta-analysis of the efficacy and safety of the SGLT2 and DPP-4 inhibitors (viz., empagliflozin and linagliptin) combination over monotherapy was carried out. Eight clinical trials comparing SGLT2/DPP4 inhibitor vs DPP4 inhibitor, and five clinical trials comparing SGLT2/DPP4 inhibitor and SGLT2 inhibitor, with three clinical trials involving both comparisons, were included in the metanalysis [6]. The meta-analysis revealed that the SGLT2/DPP4 inhibitor resulted in a greater mean HbA1c reduction [weighted mean difference (WMD]): -0.62%] than did DPP4 inhibitor alone, which was a much less marked reduction (WMD: -0.35%) than with SGLT2 inhibitor alone. Also, the risk of hypoglycaemic events was lower and similar between treatment groups. The meta-analysis concluded that combination therapy with SGLT2 and DPP4 inhibitor is both efficacious and safe; in particular, a marked additional glucose-lowering effect was evident when SGLT2 inhibitor is combined with or added to DPP4 inhibitor, and not vice versa.

Further, a trial to evaluate the therapeutic efficacy of Empagliflozin in patients with high cardiovascular risk was carried out. Data from the Empagliflozin Cardiovascular Outcome Event Trial in T2DM patients Removing Excess Glucose (EMPA-REG OUTCOME) trial demonstrated that in patients with T2DM and a high risk of cardiovascular disease that were randomized to receive empagliflozin, a SGLT2 inhibitor, on top of standard of care exhibited reduced risk of a primary outcome event (viz., cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) relative to those randomized to receive placebo[7].

In another phase III, randomized, double-blind, parallel-group study conducted in 197 centers in 22 countries. The trial was carried out to evaluate the glucose-lowering effect of empagliflozin combined with linagliptin in subjects with T2DM. It was found that at the end of week 24, empagliflozin 25 mg/linagliptin 5 mg and empagliflozin 10 mg/linagliptin 5 mg reduced HbA1c from baseline by −1.08% (0.06) (−11.8 mmol/mol [0.7]) and −1.24%(0.06) (−13.6 mmol/mol [0.7]) compared with the individual components, respectively[7]. A similar study with a 52-week randomized, double-blind study conducted from 2011 to 2013 in 197 centers in 22 countries combining empagliflozin and linagliptin (empagliflozin 25 mg/linagliptin5 mg and empagliflozin 10 mg/linagliptin 5 mg) as second-line therapy in subjects with T2DM inadequately controlled by metformin and reported a significant reduction in HbA1c compared with the individual components alone as add-on to metformin[3]. Additionally, these two clinical trials also demonstrated that

empagliflozin/ linagliptin combination contributed to the significant reduction in weight from baseline at the endpoints compared with linagliptin alone, however, the reduction was not significantly different compared with the empagliflozin alone[3,7].

The safety and tolerability data from published clinical studies have also shown that the co-administration of empagliflozin and linagliptin is generally well-tolerated in patients with T2DM, and exhibit safety profiles similar to that of empagliflozin or linagliptin monotherapy. Occurrence rates of hypoglycemia based on the reported data in the empagliflozin 25 mg/linagliptin 5 mg, empagliflozin10 mg/linagliptin 5 mg, empagliflozin 25 mg, empagliflozin10 mg, and linagliptin 5 mg group were 3.6, 2.2, 3.5, 14, and2.3%, respectively. Overall, a combination of empagliflozin/ linagliptin is well tolerated without significant safety issues, however, this combination must be avoided for patients with severe renal impairment, end-stage renal disease or dialysis[2].

CONCLUSION

Maintenance of glucose homeostasis is a prime requisite for the effective therapeutic management of T2DM along with the avoidance of cardiovascular complications. Ideally, glucose homeostasis is needed both in the fasting and postprandial state. T2DM is a multifactorial disease. Thus, this calls for the use of a combination of drugs that can work at different pathological pathways. Empagliflozin and Linagliptin are two such complementary drugs that work in combination to maintain glucose homeostasis. The combination is well tolerated and provides additional beneficial effects on the kidney, body weight, and systolic blood pressure. Accordingly, a combination of Empagliflozin and Linagliptin is a potential drug combination for the effective management of T2DM.

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