VOLUME-9, ISSUE-3, MARCH-2020 • PRINT ISSN No. 2277 - 8160 • DOI : 10.36106/gjra

Original Research Paper

Medicine

COMBINATION OF EMPAGLIFLOZIN AND LINAGLIPTIN: NOVEL AGENTS FOR MANAGING DIABETIC KIDNEY

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KEYWORDS :

The number of patients with type 2 diabetes is rapidly increasing, and type 2 diabetes is one of the most common chronic diseases. Diabetic kidney disease (DKD) is among the most important complications of diabetes and often leads to the need for renal replacement therapy, including dialysis and renal replacement[1]. Thus, patients with diabetes represent a significant global health burden. The increasing incidence and prevalence of DKD places significant health burdens on patients and costs on our already stressed healthcare system[2]. The Diabetes Control and Complications Trial (DCCT), performed in patients with type 1 diabetes, and the United Kingdom Prospective Diabetes Study (UKPDS), in patients with type 2 diabetes, revealed that intensive glycemic control might inhibit the progression of DKD. Thus, hyperglycemia could be a major factor in the progression of DKD. However, DKD develops despite good glycemic control. Thus, novel therapeutic agents beyond those for glycemic control in patients with DKD are needed[1]. There are about 200 million people in the world with DKD in different stages, and hypertension, arteriosclerosis and diabetes mellitus are responsible for over 50% of end-stage renal disease. About 40% of patients with (diagnosed or not) diabetes mellitus has an advanced stage of kidney disease, often because of serious deficiencies in the management of the disease itself. In patients with diabetes mellitus, kidney disease occurs and often develops insidiously; the main renal dysfunctions are due to the thickening of the glomerular basement membranes, the formation of microaneurysms and the development of mesangial nodules[3]. The onset of a clinically documented diabetic nephropathy is generally preceded by the appearance of proteinuria greater than 500 mg/day[4]. Conventional therapies used in patients with type 2 diabetes mellitus include medications such as metformin, sulphonylureas, thiazolidinediones, meglitinides, and insulin. Except for pioglitazone, which is a thiazolidinedione, all other drugs require dose adjustments and an immediate suspension in patients with a reduction in the glomerular filtration rate (eGFR). In these cases, in fact, there is the risk of development of lactic acidosis (metformin) or hypoglycaemic episodes (sulfonylureas, meglitinides, and insulin)[3].

Some reports suggest that hyperglycemia may play a significant role in the development of DKD; thus, appropriate glycemic control seems to protect against DKD. Several large clinical trials such as DCCT and UKPDS have shown that intensive glycemic control in patients with type 1 or 2 diabetes could delay the development of DKD. In contrast, recent studies have indicated that intensive glycemic control reduces albuminuria and proteinuria but cannot improve renal outcomes. Furthermore, hypoglycemia exacerbates both macro- and microvascular complications, including DKD. Thus, glycemic control is insufficient to prevent DKD[1].

In recent years, there have been several new categories of medications approved for the treatment of diabetes, including new insulins, glucagon-like peptide-1 receptor agonists (GLP-1 Ras), dipeptidyl peptidase-4 inhibitors (DPP-4i), an amylin analog, and sodium-glucose cotransporter-2 inhibitors (SGLT-2i). Two classes of oral medications, DPP-4i and SGLT-2i, are potentially considered as options for add-on therapy to metformin for the management of diabetic kidney. DPP-4i acts via inhibiting the DPP-4 enzyme thus prolonging glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide activity.

Sodium-glucose linked cotransporters (SGLT) is expressed in the proximal tubule and are of two isoforms: SGLT1 and SGLT2. In particular, SGLT2 is a high-capacity, low-affinity glucose transporter that is expressed in the S1 and S2 segments of the proximal tubule. SGLT2 is an efficient glucose transporter of the ATP-dependent system that reabsorbs glucose.3 Interestingly, SGLT2 expression in the proximal tubule is increased in patients with type 2 diabetes, resulting in increases in glucose uptake exacerbating hyperglycemia.4 SGLT2 inhibition can block glucose and sodium reabsorption at the proximal tubule. Therefore, the administration of SGLT2 inhibitors can excrete 80–100 g/day glucose in the urine, translating to 240–400 kcal/day. They have been proven to decrease glycated hemoglobin (HbA1c) by 0.7–1.0% without severe hypoglycemia and to reduce body weight by 3–4 kg. Empagliflozin is a potent and selective SGLT2 inhibitor. The Empagliflozin and Progression of Kidney Disease in type 2 diabetes (EMPA-REG Renal OUTCOME) trial and the CANagliflozin cardiovascular Assessment Study program clearly showed the protective effects of SGLT2 inhibitors on renal outcomes in patients with type 2 diabetes, including decreases in albuminuria and progression of nephropathy, doubling of serum creatinine levels, and initiation of renal replacement therapy[1]. The potential mechanism of the beneficial effects of SGLT2 inhibitors may be through decre asing hyperfiltration. By reducing proximal reabsorption of sodium, distal sodium delivery is increased, activating tubular glomerular feedback leading to afferent arteriolar vasoconstriction and a reduction in hyperfiltration. This is a class effect and is reversible after stopping the drug[2]. Renal function should be regularly monitored in patients taking SGLT2 inhibitors.

Inhibitors of DPP-4 reduce blood glucose in patients with type 2 diabetes by preventing degradation of incretin peptides such as GLP-1, stimulating insulin release and inhibiting glucagon

secretion. Briefly, glucagon-like peptide 1 (GLP-1) produced by the L cells in the gut stimulates the secretion of insulin from the pancreatic beta cells in response to a carbohydrate-rich meal, slows gastric emptying inducing satiety, and reduces the endogenous production of glucagon during fasting states, therefore improving postprandial as well as fasting glycemia. The half-life of GLP-1 is extremely short as it is cleaved by the dipeptidyl peptidase 4 (DPP-4). The activity of DPP-4 is increased in obese individuals and those with diabetes, therefore reducing the availability of GLP-1. Treatment with DPP-4 inhibitors improves glycemic control by restoring the physiologic levels of GLP-1[5]. As DPP-4 inhibition leads to a glucose-dependent release of insulin, it is associated with a low risk of hypoglycemia. Linagliptin is a potent and selective DPP-4 inhibitor[6]. Pooled data from 13 phases 2 or 3 trials of the DPP-4, linagliptin in type 2 diabetics showed intervention reduced the risk of kidney disease events by 16% compared to placebo.

Empagliflozin and Linagliptin have complementary mecha nisms of action to maintain glucose homeostasis in patients with type 2 diabetes. Empagliflozin lowers glucose through the urine by blocking glucose reabsorption in the kidney. The previous study showed that SGLT2i treatment would increase endogenous glucose production. Similarly, in addition to lowering FPG and post-challenge plasma glucose (PPG), empagliflozin would also induce a compensatory increase in endogenous glucose production. Glucagon increase would switch back after 4weeks of treatment. Linagliptin, a DPP-4i, probably has the potential of inhibiting the increase in endogenous glucose production and then improve the glucose-lowering activity of empagliflozin. In addition, this combination has been proved beneficial to improve ß cell functions and insulin sensitivity. The American Diabetes Association recommends a glycemic target of glycosylated hemoglobin (HbA1c) < 7%. The clinical trial combined empagliflozin with linagliptin showed that the number of patients reaching HbA1c< 7% exceeded 50%. In addition to both empagliflozin and linagliptin being highly effective in achieving glucose homeostasis, there are other reasons for considering the combination. Cherney et al. found that empagliflozin could recede renal hyperfiltration, which represents intra-glomerular pressure[7]. Empagliflozin consistently contributed to the weight loss during combining with linagliptin. The pharmacologic actions of empagliflozin reducing SBP contain weight loss, osmotic diuresis, reduced arterial stiffness, and direct vascular effects, while linagliptin glanced off blood pressure. In consequence, combining empagliflozin with linagliptin has a significant advantage in exerting hypoglycemic actions and beneficial effects on the kidney, body weight, and SBP[8].

The potential mechanism of the beneficial effects of SGLT2i is believed to be through decreasing hyperfiltration. If true, then these SGLT2i drugs may also be effective in nondiabetic kidney disease, a hypothesis that is being tested in the Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in patients with CKD (DAPA CKD) in which half the patients are diabetic and half are nondiabetic. The primary outcome is a composite of ≥50% sustained decline in eGFR, ESRD, or CV or kidney death.

CONCLUSION

Slowing progression of kidney disease is a critical goal for diabetic kidney patients. Thus, the management of renal function in diabetic patients is critical. Various big trials have established that intensive glycemic control might inhibit the progression of DKD. Thus, hyperglycemia could be a major factor in the progression of DKD. However, DKD develops despite good glycemic control. Thus, novel therapeutic agents beyond those for glycemic control in patients with DKD are the need of the hour. A combination of empagliflozin and linagliptin is one such new therapeutic approach for the management of DKD. Empagliflozin is a potent and selective SGLT2i while, linagliptin is a potent and selective DPP-4i. Given the complementary mechanisms of action of Empagliflozin and Linagliptin, the combination is expected to slow the progression of DKD. Few trials have shown their potential as a renoprotective combination in diabetic patients. However, larger clinical trials need to be undertaken to establish their efficacy in slowing the progression of DKD.

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