Original Research Paper

Volume -10 | Issue - 3 | March - 2020 | PRINT ISSN No. 2249 - 555X | DOI : 10.36106/ijar

Medicine

COMBINATION THERAPY OF EMPAGLIFLOZIN AND LINAGLIPTIN AS SECOND-LINE THERAPY IN TYPE 2 DIABETES

Amit Modgil	537, Suman Hospital, Model Town, Ludhiana-141002
Amit Kumar Singh*	Kalyanpur, Kanpur,208017 *Corresponding Author
Amitav Mohanty	N-4/ 213, Irc Village Bhubaneswar - 751015
Antony Benedict	Kalpana Medical Centre, Mettupalayam Road, Jayanthi Nagar , Koundampalayam, Coimbatore-641030
Arijit Samanta	Tamluk , Purba Medinipur , Pin- 721636,near Tamluk Hospital More

KEYWORDS :

Many pharmacotherapies are now available for glycaemic control in type 2 diabetes (T2D); however, the management of T2D remains complex and challenging, in part due to the limiting side effects of current therapies as well as the variable pathogenesis and progressive natural history of T2D. Thus, the quest to develop therapeutic agents with novel mechanisms of action that might fulfill the unmet needs of the currently available therapies continues[1].

Metformin is the recommended first-line pharmacotherapy for patients with type 2 diabetes, but most patients ultimately require additional therapies to maintain glycemic control[2]. The progressive deterioration of ß-cell function in T2D often requires combination therapy to address hyperglycemia. While several novel therapies for T2D are indeed on the horizon, dipeptidyl peptidase-4 inhibitors (DPP4is) and sodium-glucose cotransporter type 2 inhibitors (SGLT2is) are the most recently introduced novel classes of antihyperglycaemic drugs that have shown significant potential for the management of T2D[1]. DPP4is improve glycaemic control by increasing insulin secretion from pancreatic ß-cells and decreasing glucagon secretion from pancreatic α-cells, thereby reducing endogenous glucose production (EGP). 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). Incretins, respectively secreted from the intestinal L- and K-cells after meal intake, regulate glucose homeostasis through increasing insulin synthesis and release from pancreatic ß cells in the presence of normal and elevated blood glucose levels. In addition, GLP-1 lowers glucagon secretion from pancreatic α cells to reduce hepatic glucose output. Linagliptin prolongs the half-life of the intestinal incretins, GLP-1 and GIP, after inhibiting the DPP-4 enzyme. Ideal glucose homeostasis both in the fasting and postprandial state can be achieved following enhanced glucose-dependent insulin secretion and lessened glucagon production[3].

SGLT2is reduce plasma glucose concentrations by inhibiting renal glucose reabsorption and promoting urinary glucose excretion, which is also accompanied by weight loss of approximately 2–3 kg due to the resultant negative energy balance[1]. Placebo-controlled trials of DPP4is have reported that this class of drug as monotherapy improves HbA1c by an average 0.6–0.7% (6.6–7.6 mmol/mol), and has a low risk of hypoglycemia with weight neutrality[4-6]. Meta-analyses of placebo-controlled trials have demonstrated that an SGLT2i as monotherapy improves glucose control with a 0.5–1.0% (5.4– 10.9 mmol/mol) decrease in HbA1c[7,8], and a low risk of hypoglycemia unless co-administered with insulin or insulin secretagogues[9,10].

The kidneys also play a vital role in maintaining glucose homeostasis. Plasma glucose physiologically is freely filtered in the kidney glomeruli and reabsorbed into the circulation. The sodium-glucose co-transporter 2, located in the proximal tubule, is responsible for the glucose reabsorption from the glomerular filtrate in the tubular lumen, which is independent of insulin. Empagliflozin, an SGLT2 inhibitor, reduces glucose reabsorption from the glomerular filtrate to increase urinary glucose excretion (UGE) and reduces hyperglycemia in patients with type 2 diabetes. In addition to the anti-diabetic activity, empagliflozin is also found to be beneficial to weight loss and a moderate reduction in systolic blood pressure (SBP). Meanwhile, there is no increase in hypoglycemia risk using empagliflozin[3].

Given the complementary mechanisms of action of SGLT2 inhibitors and DPP-4 inhibitors, a combination of empagliflozin and linagliptin as an add-on to metformin (triple therapy) may offer particular treatment benefits. Combination therapy using various hypoglycemic drugs with complementary modes of action is recommended in the 2013 AACE Comprehensive Diabetes Management Algorithm and the 2015 Position Statement of the ADA/EASD[11,12]. In addition, this combination has been proven to be beneficial in improving ß cell function and insulin sensitivity.

Data from the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patientse Removing Excess Glucose (EMPA-REG OUTCOME) trial demonstrated that in patients with T2D and with a high risk of cardiovascular (CV) disease, that were randomized to receive empagliflozin, a sodium-glucose cotransporter 2 (SGLT2) inhibitor, on top of standard of care had reduced risk of a primary outcome event (cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) relative to those randomized to receive placebo[13]. In EMPA-REG OUTCOME, 7,020 T2DM patients with high CV risk were randomized to receive 10 mg or 25 mg of empagliflozin or placebo once daily. After a median observation time of 3.1 years, empagliflozin (pooled 10 mg and 25 mg doses) significantly reduced the primary composite outcome of CV death, nonfatal MI, or nonfatal stroke (HR 0.86; 0.74-0.99; p=0.04 for superiority. empagliflozin did not show a direct effect on the rates of MI or stroke, death from CV causes, hospitalization for heart failure (HF), and death from any cause were reduced by 38%, 35%, and 32%, respectively. A subgroup analysis of the EMPAREG OUTCOME data confirmed that empagliflozin reduces HF hospitalization and CV death, with a consistent benefit in patients with and without baseline HF. The reduced CV effect has been attributed to hemodynamic changes due to the tubulo-glomerular feedback mechanism of empagliflozin. Although, further studies are needed to understand the mechanism and plausible reason for the improvement of CV outcomes with empagliflozin treatment. Still, the benefits of this drug on CV outcomes is indisputable, at least as far as HF and CV mortality are concerned[14].

Hypoglycemia is associated with increased morbidity and mortality, reduced quality of life, and poor glycemic control in patients with T2D. Thus the risk of hypoglycemia is an important consideration for the choice of add-on therapy for patients with T2D who do not achieve adequate glycemic control with metformin. Both empagliflozin and linagliptin are associated with a low risk of hypoglycemia when given as add-on to metformin.

DeFronzo et al., evaluate the efficacy and safety of combinations of

empagliflozin/linagliptin as second-line therapy in subjects with T2D inadequately controlled on metformin[2]. Subjects were randomized to a combination of empagliflozin 25 mg/linagliptin 5mg (n = 137), empagliflozin 10 mg/linagliptin 5mg (n = 136), empagliflozin 25 mg (n = 141), empagliflozin 10 mg (n = 140), or linagliptin 5 mg (n = 132) as add-on to metformin for 52 weeks. The primary end point was the change from baseline in HbA1c at week 24. At week 24, it was found that reduction in HbA1c (mean baseline 7.90–8.02% [62.8–64.1 mmol/mol]) with empagliflozin/linagliptin were superior to those with empagliflozin or linagliptin alone as add-on to metformin; adjusted mean (SE) changes from baseline were 21.19% (0.06) (213.1 mmol/mol [0.7]) with empagliflozin 25 mg/linagliptin 5 mg, 21.08% (0.06) (211.8 mmol/mol [0.7]) with empagliflozin 10 mg/linagliptin 5 mg, 20.62% (0.06) (26.8 mmol/mol [0.7]) with empagliflozin 25 mg, 20.66% (0.06) (27.2 mmol/mol [0.7]) with empagliflozin 10 mg, and 20.70% (0.06) (27.6 mmol/mol [0.7]) with linagliptin 5 mg ($P < 0.001$ for all comparisons). In these groups, respectively, 61.8, 57.8, 32.6, 28.0, and 36.1% of subjects with baseline HbA1c ≥7% (‡53 mmol/mol) had HbA1c <7% (<53 mmol/mol) at week 24. Efficacy was found to persist and maintained till week 52. The proportion of subjects with adverse events (AEs) over 52 weeks was similar across treatment arms (68.6–73.0%), with no hypoglycemic AEs requiring assistance. The safety profiles of empagliflozin/linagliptin were similar to the known safety profiles of the individual components. It was concluded that combination of empagliflozin/linagliptin as second-line therapy for 52 weeks significantly reduced HbA1c compared with the individual components and was well tolerated.

These findings are significant in light of the fact that some of the recent meta-analyses have raised some doubt on the dogma that metformin should be the drug of choice in T2DM especially when some patients do not tolerate metformin and in others metformin use is contraindicated or becomes contraindicated in the course of disease, mainly for reduced renal function. In addition, monotherapy with metformin fails over the years in many patients. It has been reported that as many as 60% of T2D patients, on a cross-sectional basis, need 2-3 oral agents or injectable medications (mostly insulin) to control blood glucose years after diagnosis. Also, since prevention of CV disease is a major goal in diabetes care, the selection of antidiabetic drugs should be based upon the information on CV disease safety or, if any, on CV disease benefits along with glycemic control[15]. In various trials, SGLT-2is viz., empagliflozin exhibited appreciable results on glucose levels and body weight and also on blood pressure. Two large RCTs exploring the CVD safety of SGLT-2 inhibitors are ongoing (DECLARE and CANVAS). Some of the outcomes of these trials were recently presented and it shows extremely favorable effects of empagliflozin vs. placebo on hard endpoints such as all-cause and CV disease mortality as well as hospitalization for heart failure observed in patients with prior CV disease participating in the EMPAREG. Results of such mega-trial might substantially change the scenario of treatment of T2D when the disease is associated with established CV disease (i.e., those in secondary prevention) [15]. The CAROLINA trial has been designed to examine the effect of linagliptin on cardiovascular outcomes with an active comparator (glimepiride) rather than placebo and its outcome will further throw light on the efficacy of linagliptin.

CONCLUSION

Patients who initially achieve glycemic goals with one oral antidiabetes drug frequently require additional agents over time in order to maintain glycemic control due to the progressive nature of T2D. The combination of empagliflozin and linagliptin added on to metformin offers a sustained reduction in HbA1c, FPG, weight, and blood pressure. Also, reductions in weight and SBP with empagliflozin alone are maintained even when empagliflozin is used in combination with linagliptin. Combined therapy with SGLT2i/DPP4i is effective and safe and has the potential to be considered as a second-line treat ment for T2D.

REFERENCES

1. Cho YK, Kang YM, Lee SE, et al. Efficacy and safety of combination therapy with SGLT2 and DPP4 inhibitors in the treatment of type 2 diabetes: A systematic review and meta-analysis. Diabetes Metab. 2018;44(5):393-401. doi:10.1016/j.diabet.2018.01.011
2. DeFronzo RA, Lewin A, Patel S, et al. Combination of empagliflozin and linagliptin as second-line therapy in subjects with type 2 diabetes inadequately controlled on metformin. Diabetes Care. 2015;38(3):384-393. doi:10.2337/dc14-2364
3. Tan X, Hu J. Traitement combiné par empaglifozine et linagliptine chez les patients atteints de diabète de type 2. Ann Endocrinol (Paris). 2016;77(5):557-562. doi:10.1016/j.ando.2015.11.003
4. Aschner P, Kipnes MS, Lunceford JK, Sanchez M, Mickel C W-H, DE et al. Effect of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy on glycemic control in patients with type 2 diabetes. Diabetes Care. 2006;29:2632–7.
5. Del Prato S, Barnett AH, Huisman H, Neubacher D, Woerle HJ DK. Effect of linagliptin monotherapy on glycaemic control and markers of beta-cell function in patients with inadequately controlled type 2 diabetes: a randomized controlled trial. Diabetes Obes Metab. 2011;13:258–67.
6. Rosenstock J, Aguilar-Salinas C, Klein E, Nepal S, List J, Chen R et al. Effect of saxagliptin monotherapy in treatment-naive patients with type 2 diabetes. Curr Med Res Opin. 2009;25:2401–11.
7. Liakos A, Karagiannis T, Athanasiadou E, Sarigianni M, Mainou M P, K et al. Efficacy and safety of empagliflozin for type 2 diabetes:a systematic review and meta-analysis. Diabetes Obes Metab. 2014;16:984–93.
8. J. D. SGLT2 inhibitor/DPP-4 inhibitor combination therapy – complementary mechanisms of action for management of type 2 diabetes mellitus. Postgr Med. 2017;129:409–20.
9. M. A-G. Where does combination therapy with an SGLT2 inhibitor plus a DPP-4 inhibitor fit in the management of type 2 diabetes? Diabetes Care. 2015;38:373–5.
10. Ferrannini G, Hach T, Crowe S, Sanghvi A, Hall KD FE. Energy balance after Sodium-Glucose Cotransporter 2 Inhibition. Diabetes Care. 2015;38:1730–5.
11. Garber AJ, Abrahamson MJ, Barzilay JI et al. American Associa-tion of Clinical Endocrinologists' comprehensive diabetes managementalgorithm 2013 consensus statement–executive summary. Endocr Pr. 2013;19:536–57.
12. Inzucchi SE, Bergenstal RM, Buse JB et al. Management of hypergly-caemia in type 2 diabetes (2015): a patient-centered approach. Update toa position statement of the American Diabetes Association (ADA) and theEuropean Association for the Study of Diabetes (EASD). Diabetes Care. 2015;38:140–9.
13. Zinman B, Wanner C, Lachin JM, et al.Zinman B, Wanner C, Lachin JM et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med. 2015;373:2117e2128.
14. Paneni F, Lüscher TF. Cardiovascular Protection in the Treatment of Type 2 Diabetes: A Review of Clinical Trial Results Across Drug Classes. Am J Cardiol. 2017;120(1):S17-S27. doi:10.1016/j.amjcard.2017.05.015
15. Bonora E, Cigolini M. DPP-4 inhibitors and cardiovascular disease in type 2 diabetes mellitus. Expectations, observations and perspectives. Nutr Metab Cardiovasc Dis. 2016;26(4):273-284. doi:10.1016/j.numecd.2016.03.002