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Empa + Lina Symphony Of Protection With Many Chords

Introduction

Type 2 diabetes mellitus (T2DM) is a chronic progressive disease with multiple pathophysiological defects. The sequential addition of therapies is recommended to address increasing hyperglycemia during the disease course (1). However, clinical inertia is common in the management of T2DM even after diagnosis leading to prolonged periods of hyperglycemia (2). Using drug treatments in combination may be preferred to adding agents sequentially addressing multiple metabolic abnormalities (3).

Combination Approach Of Empagliflozin/Linagliptin

The combination of empagliflozin/linagliptin provides a new first-in-class treatment option for treating T2DM as an adjunct to diet and exercise or as add-on therapy to other glucose-lowering agents (4). Empagliflozin/linagliptin combination was the first approved combination of sodium-glucose co-transporter 2 (SGLT2) inhibitor with a dipeptidyl peptidase-4 (DPP-4) inhibitor in the United States in 2015. It was also approved in Europe in 2016 and in India in 2017.

DPP-4i – SGLT2i combined therapies are more efficacious than either monotherapy to control blood glucose, without worsening of the safety profile. DPP-4i as oral incretin-based therapy is increasingly used in the management of T2DM as an alternative or add-on therapy to other glucose-lowering agents. They **offer the advantage of reducing hyperglycemia while minimizing hypoglycemia**. Furthermore, they d**o not induce weight gain and have proven their cardiovascular safety** in two large prospective cardiovascular outcome studies CARMELINA (Cardiovascular safety & clinical outcome with Linagliptin) (5) and

CAROLINA (Cardiovascular Outcome study of Linagliptin versus glimepiride in patients with type 2 diabetes) studies (6).

Mechanism of Combination Therapy

SGLT2i inhibit glucose reabsorption at the proximal tubule and thereby promote glucosuria, an effect independent of insulin. The pharmacological action of SGLT2i, being independent of pancreatic beta-cell function can be considered as a suitable option to be used anywhere along the continuum of disease, even with advanced T2DM where significant deterioration of beta-cell function is expected (7). **SGLT2i reduces glucotoxicity, which indirectly results in an improvement of beta-cell function and peripheral insulin sensitivity.** However, treatment with SGLT2i increased plasma glucagon concentrations, which was accompanied by a substantial increase in endogenous (hepatic) glucose production. The latter has been estimated to offset approximately half of the glucose excreted in the urine as a result of SGLT2i (8).

Thus, the **addition of a DPP-4 inhibitor, which inhibits glucagon and stimulates insulin secretion has the potential to block an increase in endogenous glucose production. Therefore, combination therapy with these two agents appears appealing and expected to be synergistic in reducing glycated hemoglobin (HbA1c)**, though not yet proven. **The demonstration of a remarkable reduction in cardiovascular and all-cause mortality with empagliflozin in T2DM patients with a history of cardiovascular disease in the EMPA-REG OUTCOME trial has also been noted (9). This unique combination expedites glucose control (HbA1c reductions 1.1% to 1.2%) with possible earlier treatment intensification. Interestingly, some studies also found a reduced rate of genito-urinary infections associated with the combination therapy, compared to SGLT-2I alone.**

Conclusion

In conclusion, it offers good tolerability, low risk of hypoglycemia, potential weight loss (approximately 2 kg), and minimal pill burden improving compliance of patients with T2D (10,11). Moreover, this combination has the promise of cardiovascular benefit, with positive efficacy data of SGLT2 inhibitor and consistent cardiovascular safety data for the DPP-4 class.

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Influencing Effect Of Telmisartan On Glycemic Control

With hypertension and diabetes being frequently overlapping comorbidities, their management involves a multifaceted approach.[1,2] Telmisartan has a unique ability to control blood pressure as well as to influence glycemic parameters.[3] The present article highlights the effect of telmisartan on glycemic control in hypertension and diabetes.

Hypertension and diabetes are the most commonly occurring comorbidities that subsequently worsen the clinical outcomes.[1,2] A drug that inhibits the renin-angiotensin system (RAS) and acts as a peroxisome proliferator-activated receptor-γ (PPARγ) agonist could be beneficial in the management of these comorbid conditions. The inhibition RAS lowers the blood pressure, whereas PPARγ agonism increases the insulin sensitivity.[3]

Telmisartan: A Drug that Targets Two Receptors

Telmisartan belongs to the class of angiotensin II receptor blockers (ARBs) which lowers the blood pressure by blocking angiotensin Type 1 (AT1)-receptor. It has structural similarity with pioglitazone, a drug of the thiazolidines class which bind to PPARγ to activate insulin-responsive genes that regulate carbohydrate and lipid metabolism. Evidence suggests that teneligliptin also has partial PPARγ agonistic properties.[3,4] However, the PPARγ binding potency of telmisartan is 25–30% of that of pioglitazone; thus, it is referred to as a selective PPARγ modulator (SPPARM).[4] Thus, telmisartan, an AT1-receptor antagonist and PPARγ agonist, represents the prototype of a new approach for management of comorbid hypertension and diabetes.[3,4]

Telmisartan and Its Effect on Glycemic Control

The hypotensive efficacy of telmisartan has already been established.[5] Moreover, several studies suggest that telmisartan have beneficial effects on insulin resistance and lipid profiles. A report revealed that unlike other ARBs, telmisartan induces adipogenesis and increase the expression of PPARγ target genes.[4] Following are some of the clinical trials that assessed the efficacy of telmisartan in influencing glycemic control.

Effect on glycemic control: A retrospective study was conducted to evaluate the correlation between telmisartan and glycemic control in 263 patients with type 2 diabetes mellitus and hypertension. They were given telmisartan 20 mg/day (n=54, mean age 61.9 ± 1.1 years), 40 mg/day (n=31, mean age 69.0 ± 1.2 years) or 80 mg/day (n=19, mean age 66.8 ± 2.7 years) for 6 months. The results showed that at 3 months, telmisartan 40 and 80 mg/day caused a significant decrease in glycated hemoglobin (Hb1Ac, 7.40 ± 0.11% and 7.52 ± 0.21% respectively). Similarly, the reduction was significant following 6 months of treatment (7.35 ± 0.09% and 7.42 ± 0.15% respectively) (Figure 1).[4]

Figure 1. Effects of telmisartan on glycemic control.[4] (a) Mean – standard error (SE) glycosylated hemoglobin (HbA1c) at baseline and at 3 and 6 months after starting treatment with Telmisartan 20, 40 or 80mg/day. † $p < 0.05$, †† $p < 0.01$, ††† $p < 0.001$ when compared with baseline.

When patients were classified based on telmisartan dose, 20 mg/day group showed no significant correlation between baseline HbA1c and change in HbA1c levels over time, whereas ≥40mg/day group showed a negative correlation between baseline HbA1c and change in HbA1c at 6 months. Regression analysis revealed that baseline HbA1c and telmisartan dose were the predictive factors. The study showed that telmisartan influences glycemic control in a dose-dependent manner with doses of 40 mg/day and above may be required to improve glycemic control. The results also suggest that higher the baseline HbA1c greater the improvements in glycemic control with telmisartan.[4]

Effect on insulin resistance: Furthermore, a placebo-controlled, randomized, double-blind, cross-over study showed that in hypertensive patients with insulin resistance (n=14, mean age 62.3 ± 15.5 years) and type 2 diabetes (n=27, mean age between 55.9 ± 14 to 57.1 ± 9.3 years), 5 months of telmisartan 40 mg/day treatment resulted in improved insulin sensitivity as suggested by homeostasis model for insulin resistance (HOMA-IR, 4.44 ± 1.90 before vs. 2.23 ± 0.87 after, p = 0.0009).[6] Similarly, a study by Nagel et al. revealed that 12 weeks of telmisartan 40 mg/day treatment in 20 patients with insulin resistance, resulted in enhancing insulin sensitivity as suggested by attrition in the glucose area under the curve (AUC), HOMA-IR. Moreover, improvement in and beta-cell function was also observed as evident by increased in insulinogenic index (Figure 2).[7]

Figure 2. Changes induced by telmisartan compared to placebo. [RRsyst, Percent reduction in systolic blood pressure; RRdiast, diastolic blood pressure][7]

- **Metanalysis confirms the efficacy of telmisartan in glycemic control:**

- *Effect on fasting plasma glucose (FPS)* – Eight trials comprising 763 patients showed that telmisartan (40 mg and 80 mg) decreased FPG better compared with other ARBs such as periastron, losartan, irbesartan, candesartan, olmesartan and valsartan (mean pooled difference, -8.63 mg/dL, 95% confidence interval [CI] -12.29 mg/dL to -4.98 mg/dL; p < 0.00001).[8]
- *Effect on fasting plasma insulin* – In a subgroup analysis of seven trials, telmisartan 80 mg significantly reduced fasting plasma insulin compared with other ARBS (mean difference, -6.06 mg/dL; 95% CI -9.27 to -2.84 mg/dL; p = 0.0002).[8]
- *Effect on insulin resistance* – Seven trials assessing insulin resistance using HOMA-IR reported that telmisartan and other ARBs had a comparable effect on insulin resistance.[8]
  Effect on adiponectin – Six trials reported that telmisartan significantly elevate adiponectin levels compared with the control group (pooled mean difference, 0.93 mcg/dL; 95% CI 0.28 mcg/dL to 1.59 mcg/dL; p = 0.005).[8]

The available evidence suggests that in hypertensive patients with insulin resistance or diabetes, telmisartan treatment helps in improving insulin sensitivity as demonstrated by the decrease in FPG and an increase in adiponectin levels.[8]

Conclusion

Telmisartan, with its ability to act on two receptors simultaneously can be potentially beneficial in managing two commonly occurring comorbid conditions viz. hypertension and diabetes. Available data suggest that telmisartan provide benefits in terms of improving insulin resistance, FPS, adiponectin level thereby conferring glycemic benefits to hypertensive patients with diabetes.

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