KSN 2018
Seoul, Korea · May 17 - 20

Abstract Type : Oral
Presentation No. : OR 07 TL-09

Effect of Dual Inhibition of Dipeptidyl Peptidase IV (DPP4) and Sodium/glucose Cotransporter (SGLT2) on Tacrolimus-Induced Diabetic Rats

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Objectives: Sodium/glucose co-transporter-2 inhibitor (SGLT2i) and depeptidyl peptidase IV inhibitor (DPP4i) are promising antidiabetic drug but their combined use in tacrolimus (TAC)-induced diabetes mellitus (DM) is still undetermined. We evaluated the effect of dual inhibition of dipeptidyl deptidase IV (DPP4) and sodium/glucose cotransporter (SGLT2) on TAC-induced diabetes mellitus (DM) and renal injury in an experimental rat model.

Methods: DM was induced by injection of injection of TAC (1.5mg/kg, subcutaneously) for 3 weeks, then DPP4i gemigliptin (20mg/kg/day, oral gavage) and/or SGLT2i empagliflozin (10mg/kg/day, oral gavage) were given for 4 more weeks. The effect of gemigliptin and/or empagliflozin was evaluated by assessing intraperitoneal glucose tolerance test (IPGTT) and by measuring markers of oxidative stress, apoptosis. Also, Morphologic change of kidney was observed.

Results: IPGTT showed that dual inhibition of DPP4 and SGLT2 showed synergistic effect on glucose lowering compared to DPP4i alone or SGLT2i alone group. In Kidney, combination treatment group of gemigliptin and empagliflozin alleviated TAC-induced renal dysfunction and decreased albumin excretion and histopathogic injury compared with TAC group or gemigliptin or empagliflozin alone group. Increased oxidative stress and apoptotic cell death by TAC was remarkably decreased with gemigliptin or empagliflozin treatment in serum and renal tissues, and this improvement was significantly prominent in combination group compared to gemigliptin or empagliflozin alone group. TAC induced a two-fold increase in SGLT-2 expression, while combination of gemigliptin and empagliflozin decreased SGLT-2 expression and further increased urinary glucose excretion compared to the TAC group.

Conclusions: In conclusion, dual inhibition of DPP4 and SGLT2 is effective in controlling TAC-induced hyperglycemia and has protective effect on TAC-induced renal injury, this finding provides basis clinical use of dual inhibition of DPP4 and SGLT2 in renal transplant patients with TAC-induced DM.