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AMPK activator O304
A novel potential treatment for diabetic kidney disease

Diabetic kidney disease

Globally ~40% of type 2 diabetes (T2D) patients develop diabetic kidney disease (DKD), and diabetes is the leading cause of end stage renal disease, requiring dialysis or a kidney transplant. Standard of care consists of antihypertensive medication (ACEi/ARB inhibitors), and regulation of the blood sugar level as part of regular diabetes care, but with very limited efficacy. Thus, in addition to risks, personal suffering, and reduced quality of life for millions of people, DKD is associated with billions in costs to society.

No new drugs - SGLT2 inhibitors?

Despite decades of research on various mechanisms including fibrosis and inflammation there have not been any new drugs approved in the last 15 years for the treatment of chronic kidney disease.

Glomerular hyperfiltration is common in type 2 diabetic patients and believed to cause a later decline in filtration rate (eGFR) and in kidney function. Reduced renal filtration/hyperfiltration is currently the only mechanism that shows efficacy in DKD. ACEi/ARB inhibitors act directly on the vascular system to reduce hyperfiltration. SGLT2 inhibitors are recently introduced anti-hyperglycaemic agents that show improved renal outcome in T2D patients with established cardiovascular disease. SGLT2 inhibitors act indirectly via the tubular system on the renal vascular system to cause an initial decline in eGFR that then stabilizes. In contrast, eGFR steadily declines in patients who develop DKD. SGLT2 inhibitors are currently, however, contra-indicated in T2D patients with impaired renal function.

AMPK activator O304 as a novel potential treatment for DKD

Multiple interventional studies in animal models have suggested potential beneficial effects of AMPK activation in DKD. Post hoc analyses of phase I and phase IIA clinical trials of O304, an AMPK activator in development, show that O304 lowers blood pressure and potently reduces eGFR by a rapid, stable and reversible hemodynamic effect both in obese non-diabetic subjects and in T2D patients, and that O304 is at least as potent as SGLT2 inhibitors. Moreover, O304 also reduces eGFR in T2D patients treated with ACEi/ARB inhibitors i.e. standard of care, indicating different mechanisms of action of O304 compared to both ACEi/ARB and SGLT2 inhibitors.

Hyperglycemia, hyperinsulinemia and insulin resistance are also implicated in the development of DKD, and all are reduced by O304 both in diet induced obese mice and in T2D patients. Thus, AMPK activator O304 may exhibit both hemodynamic and metabolic effects that are beneficial for preventing the development of DKD in T2D patients. O304 may also prevent chronic kidney disease in obese non-diabetic individuals.

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O304 and SGLT2 inhibitors in combination

SGLT2 inhibitors are currently contra-indicated in T2D patients with impaired renal function due to lack of anti-glycemic efficacy in this group of patients. However, O304 and SGLT2 inhibitors in combination potently and synergistically reduce hyperglycemia, hyperinsulinemia and insulin resistance in diet induced obese mice. Due to the apparent divergent vascular and tubular mechanisms of action of these two classes of compounds one may also expect a beneficial combinatorial renal hemodynamic effect. Thus, O304 in combination with a SGLT2 inhibitor may both improve glucose homeostasis and prevent DKD in T2D patients. In particular, in the recently identified subgroup 3 of T2D patients that are obese (BMI ~35), insulin resistant, hyperinsulinemic and have a 5 fold higher risk of developing DKD, and that currently lack efficient treatment[1].

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1. Ahlqvist et. al., Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables. Lancet Diabetes Endocrinol 6:361-369, 2018.