Title

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APABETALONE, A BROMODOMAIN AND EXTRATERMINAL PROTEIN INHIBITOR, DECREASES KEY FACTORS IN VASCULAR CALCIFICATION IN VITRO AND IN CLINICAL TRIALS

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INTRODUCTION AND AIMS: Apabetalone, an orally active bromodomain and extraterminal (BET) protein inhibitor, reduced incidence of major adverse cardiac events (MACE) in patients with CVD and improved eGFR in a subpopulation with chronic kidney disease (CKD) in phase 2 trials. In CKD patients, vascular calcification (VC) increases CVD risk & is a predictor of all-cause mortality. The process of VC involves differentiation of vascular smooth muscle cells (VSMCs) into osteoblast-like cells resulting in altered gene expression, loss of contractility & extracellular mineralization. Here we report clinical effects of apabetalone on circulating levels of factors involved in VC, including alkaline phosphatase (ALP), an enzyme regulating pyrophosphate levels & contributing to calcium deposition. Circulating ALP is derived primarily from liver, & elevated ALP is associated with mortality in CKD or patients on dialysis. In vitro, cell systems demonstrate effects of apabetalone on expression of VC markers, differentiation of coronary artery VSMCs & pathological process of extracellular calcium deposition.
METHODS: Effects of apabetalone on expression of osteogenic markers were investigated in primary human hepatocytes (PHH), human macrophages (U937), and primary human VSMCs. Extracellular calcium deposition induced by osteogenic culture conditions was measured in VSMCs. Proteomic assessment of plasma from a phase 1 trial in CKD patients receiving a single 100 mg oral dose of apabetalone was conducted using Ingenuity® Pathway Analysis. Proteins associated with VC were also assessed in plasma of CVD patients receiving apabetalone in 3 month (ASSERT) and 6 month (SUSTAIN & ASSURE) phase 2 trials.
RESULTS: Factors involved in the process of VC are derived from multiple cell types. In PHH cells from multiple donors, ALP was downregulated 60-80% by apabetalone. Apabetalone also reduced expression of osteopontin, another established marker of VC, in PHH, VSMCs & U937 macrophages. Differentiation of primary VSMCs with osteogenic conditions induced expression of ALP, osteoprotegerin, RUNX2 & WNT5A, which was suppressed by apabetalone. Further, apabetalone dose dependently countered calcium deposition in VSMCs. Clinical trials support translational mechanisms investigated in vitro. Proteomic analysis of plasma from stage 4 CKD patients (n=8) demonstrated significant activation of pathways driving calcification including "BMP-2 signaling" and "RANK signaling in osteoclasts" versus age, gender & BMI matched individuals (n=8). Both pathways were downregulated by apabetalone 12 hours after a single dose. Apabetalone also significantly reduced circulating levels of proteins associated with VC in phase 2 trials in CVD patients, including ALP, osteopontin & osteoprotegerin.
CONCLUSIONS: Apabetalone mediates reduction of factors & pathways associated with VC. Simultaneous effects on multiple contributing elements from a variety of cell types suggest apabetalone may decrease pathologic calcification in CKD & contribute to a reduction in MACE in patients with high CVD risk. The potential of apabetalone to reduce CVD in CKD patients is currently being explored in a subpopulation of the phase 3 BETonMACE cardiovascular outcomes trial in patients with established CVD and diabetes mellitus.