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Publication Date
2017

P6483 | BEDSIDE

Apabetalone (RVX-208) impacts key biomarkers and pathways associated with cardiovascular disease in patients with severe renal impairment

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Introduction: Apabetalone is a first-in-class orally active bromodomain and extraterminal (BET) inhibitor associated with a reduction in major adverse cardiac events (MACE) in patients with cardiovascular disease (CVD) from phase 2 clinical trials. Apabetalone has previously been shown to downregulate markers of atherosclerosis and vascular inflammation, which may explain its effects on MACE. Chronic kidney disease (CKD) is associated with a progressive loss of renal function and a high risk of CVD.
Purpose: To determine the effect of apabetalone on levels of circulating proteins and pathways that contribute to cardiovascular complications in CKD, in a phase 1, open-label, parallel group study of patients with impaired kidney function.
Methods: Eight subjects with stage 4 CKD not on dialysis (mean eGFR=20 ml/min/1.73m^2) and eight age-, gender-, and BMI-matched subjects (mean eGFR=78.5 ml/min/1.73m^2) received a single 100 mg oral dose of apabetalone. Plasma samples were collected at multiple time points over a period of 48 hours for pharmacokinetic (PK) analysis and at 12 hours post dose for proteomic analysis using the SOMAscan® 1.3K platform. Proteomics data were analysed with Ingenuity® Pathway Analysis (IPA) software to identify pathways dysregulated in CKD patients compared to matched controls, and the effect of apabetalone treatment on those pathways.
Results: Apabetalone PK parameters were similar in controls and CKD patients. At baseline, plasma proteomics showed enrichment of markers that correlate with progression of CKD, as compared to matched controls, including cystatin C and b2 microglobulin (3-fold and 5-fold enrichment, respectively, $p<0.001$). Accordingly, pathway analysis of CKD plasma proteome at baseline showed an upregulation of pathways that underlie CVD in CKD patients such as the inflamma-tory response, atherosclerosis, thrombosis and calcification, when compared to controls. These pathways were robustly and significantly downregulated in CKD patients by apabetalone 12h post dose. In the CKD group, apabetalone treat-ment also reduced the abundance of circulating CVD markers involved in vas-cular inflammation, atherosclerosis, fibrosis, vascular calcification, complement activation and hemostasis including CRP, IL-6, TNFα, IL-1, ICAM-1, VCAM-1, L-selectin, E-selectin, MMP-3, MMP-10, fibronectin, osteopontin, C3 and C5 active fragments, plasminogen activator inhibitor-1, D-dimer and P-selectin ($p<0.05$).
Conclusions: In stage 4 CKD patients, a single oral dose of apabetalone rapidly reduces circulating markers and molecular pathways linked to progression of renal disease and accompanying CVD complications. The potential impact of chronic treatment with apabetalone on biomarkers, renal function and CVD outcomes in patients with impaired kidney function is currently being studied in a subpopulation of the phase 3 BETonMACE CVD outcomes trial.