RVX-208, a selective bromodomain extra-terminal (BET) protein inhibitor, acts on several pathways to benefit cardiovascular risk.

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Abstract

The epigenetic modifying compound RVX-208 selectively inhibits the second ligand binding domain in BET proteins to increase ApoA-I/HDL production. In recent trials of CVD patients given standard of care and RVX-208 (200mg/d) there was a 55% relative risk reduction of MACE vs. placebo. This reduction is greater than expected from modest increases in ApoA-I/HDL, thus suggesting benefits of RVX-208 beyond lipid effects. Whether added benefits exist was explored by microarray survey of differential gene expression in primary human hepatocytes (PHH) and whole blood (WB). In PHH, RVX-208 downregulated genes within the complement, fibrin clotting, cholesterol biosynthesis, fatty acid biosynthesis, diabetes and acute phase response (APR) pathways. These data guided more focused analyses on the known HDL proteome encoded by 89 genes of which 30 were affected by RVX-208 and many of these were members of the APR or complement pathways. In support of the microarray data, we used RT-PCR and found RVX-208 lowered mRNA encoding complement 3, 4a/b and 5 by ≥50% in HepG2 cells and RVX-208. Consistent with the mRNA data, secretion of these complement proteins were less from the treated cells. Next the cells were exposed to cytokines in order to mimic an inflammatory state thus inducing complement expression. Treatment with RVX-208 blocked this affect by ≥50%. Furthermore, in Huh-7 cells, RVX-208 repressed both fibrin clotting factors II (prothrombin) and X (thromboplastin antecedent) consistent with the PHH microarray data thus suggesting an anti-thrombotic effect for RVX-208. To further extend findings in vitro from hepatoma cells, plasma from patients in our clinical trials who received RVX-208 were assayed and found to have decreased levels of both APR and complement proteins. Lastly, microarray studies of WB from healthy donors treated ex-vivo with RVX-208 uncovered differential regulation of anti- and proatherogenic gene sets that were activated and suppressed, respectively by RVX-208. In summary, RVX-208, a selective BET inhibitor, affects several pathways involved in CVD including: vascular inflammation, complement, thrombosis, reverse cholesterol transport, and atherogenesis that cumulatively may reduce MACE in high risk CVD patients.

Results

1. RVX-208 selectively binds BD2 of BET proteins.

2. RVX-208 (200 mg/day) added to standard of care lowers MACE in SUSTAIN and ASSURE human trials.

3. RVX-208 increases HDL-c and ApoA-I.

4. RVX-208 beneficially affects expression of pro- and anti-atherogenic genes in human whole blood.

5A. RVX-208 suppresses pathways in primary human hepatocytes with known roles in MACE.

5B. RVX-208 suppresses expression of acute phase response genes associated with HDL.

5C. RVX-208 (30 uM for 72 hrs) reduces mRNA in complement and coagulation pathways.

5D. RVX-208 reduces basal and inflammatory secretion of complement from PHH.

Summary

RVX-208, an orally active small molecule, selectively inhibits BD2 in BET proteins leading to modest rises in ApoA-I and HDL.

RVX-208 induced lipid changes cannot account for the marked MACE reductions observed in SUSTAIN and ASSURE.

RVX-208 ex-vivo treatment of WB and HPP downregulate genes and pathways with known roles in CVD risk reducing inflammatory mediators i.e. complement system and acute phase response.

RVX-208 also downregulates production of several complement proteins in vitro and circulating components of the complement system and APR in patients given RVX-208.

Conclusions

RVX-208 appears to have beneficial effects on CVD risk that go beyond raising ApoA-I/HDL that affect pathways including vascular inflammation, complement, thrombosis, reverse cholesterol transport, and atherogenesis.

These activities may provide biologic plausibility for the MACE reduction in SUSTAIN and ASSURE..

Note: Potential changes in complement and fibrin clotting pathways had no impact on rates of infection or bleeding in study patients.