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Steroidal and non-steroidal FXR agonists elicit clinically-relevant lipoprotein profiles in mice with chimeric humanized livers

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Background and Aims: Farnesoid X receptor (FXR) agonists are categorized into two major classes, steroidal or non-steroidal, that differ in their pharmacokinetic and possibly therapeutic properties. Clinical and preclinical data comparing non-steroidal compounds with the first-in-class steroidal compound obeticholic acid (OCA) are lacking. Further complicating these issues, preclinical rodent models do not adequately reproduce the clinical response to FXR activation, particularly in cholesterol metabolism and the elevated circulating low-density lipoprotein cholesterol (LDL-c) associated with OCA or chenodeoxycholic acid administration in humans. It was previously shown that mice with chimeric humanized liver reproduce the human effects of OCA on circulating cholesterol. To compare the actions of steroidal and non-steroidal FXR agonists on cholesterol metabolism, chimeric mice were treated with OCA or two non-steroidal FXR agonists, INT-2228 and INT-2231, in this study.

Method: The effects of OCA (10 mg/kg/day) were evaluated in PXB chimeric mice (>80% human hepatocytes; PXB mice, PhoenixBio) as well as SCID mice (PXB background) as non-chimeric controls. In a second cohort, chimeric mice were administered vehicle (1% CMC), 10mg/kg/day of OCA, 0.3 mg/kg/day of INT-2228, or 30mg/kg BID of INT-2231 for 14 days. Genome-wide gene expression levels in the liver were assessed by RNA-sequencing and key genes were validated by quantitative PCR. Western blot analysis was performed for metabolic proteins associated with hepatic cholesterol metabolism. Serum lipoprotein fractions were analyzed by HPLC.

Results: Gene expression profiling in chimeric mice treated with OCA, INT-2228, or INT-2231 showed similar effects on hepatic FXR target genes, including downregulation of CYP7A1 and upregulation of NR0B2, SLC51B, and ABCB11. Furthermore, pathway analysis revealed significant downregulation of hepatic cholesterol genes (e.g. LDLR, HMGCR, HMGCS1, and MVK) across all agonist-treated groups. Consistent with the transcriptional response, protein levels of cleaved (activated) sterol regulatory element-binding protein 2 and LDLR were reduced in chimeric mice, but not in control mice. Importantly, both classes of compounds elicited similar increases (66-89%) in circulating LDL-c levels ($p<0.001$ vs vehicle).

Conclusion: Similar to the effects of OCA, non-steroidal FXR agonists directly activate hepatic FXR and increase circulating levels of LDL-c. We conclude that changes in cholesterol metabolism and elevated LDL-c are a class effect of FXR activation.