IL-6, TNF-α, chemokine (C-X-C motif) ligand 1 (CXCL1/KC) and CRP (inflammatory genes). Gemcabene did not affect VLDL-C, LDL-C, Apo-B, triglycerides (TG) and C-Reactive Protein (CRP). We now describe correlations of

Abstract # XVIII P4.005 ISA Toronto, 2018

EFFECT OF GEMCABENE ON TGs, LDL-C AND CRP IN HUMANS: REDUCTION OF ASCVD RISK

Patients treated with optimal statin therapy and even PCSK9 inhibitors exhibit considerable residual risk for ASCVD events. 1,2 Residual ASCVD risk may occur in part, because these regimens lower only slightly the plasma levels of cholesterol (C) and triglycerides (TG) (Fig. 1) and not other atherogenic lipoprotein species (3,4).

The athrogenic syndrome and type 2 diabetes (T2DM) increase plasma levels of C-TRLs, owing largely to a defect in hepatic clearance. It has also been reported that T2DM steatosis/pseudohypertriglyceridemia (5,6) and that SULF2 inhibits hepatic disposal of C-TRLs in human dyslipidemia (7).

Gemcabene reduces VLDL-C, LDL-C, Apo-B, TG and CRP in rodents and humans. 8,9 Also, gemcabene-treated STAM (a model of type 1 diabetes) showed reduction in plasma TG levels, and downregulation of the SULF2 and SULF2 inhibits hepatic disposal of C-TRLs in human T2DM dyslipoproteinemia.

We show herein that the reduction in plasma CRP levels by gemcabene intervention in STAM mouse was significantly correlated with the downregulation of the expression of IL-6, TNF-α, UCP2, UCP3, IL-1β, CRP, and while lipid trafficking and intracellular metabolism of C-TRLs were not significantly altered by gemcabene, TG levels were significantly downregulated with gemcabene intervention.

RESULTS

EFFECT OF GEMCABENE ON TGs, LDL-C AND CRP IN HUMANS: REDUCTION OF ASCVD RISK

METHODS AND PLASMA CHANGES IN TGs AND CRP

CONCLUSIONS

1. In the STAM mouse model of NASH, gemcabene reduced plasma levels of triglycerides and CRP.
2. Gemcabene reduced the mRNA expression of multiple genes that modulate plasma triglyceride levels. With respect to lipid trafficking, gemcabene down-regulated the hepatic mRNA expression levels of Apo-B, S1L, ANGPT1 and ANGPT4, and up-regulated the hepatic S1L and ANGPT1, intervention showed that such effect was significantly correlated with reduced plasma TG levels, suggesting a coordinated response for TG lowering.
3. Gemcabene regulated the hepatic mRNA expression levels of multiple genes that are associated with inflammation: IL-6, TNF-α, and CRP and each of these were highly correlated with plasma CRP. These results suggest that gemcabene’s pleiotropic mechanisms may have beneficial effects on reduced atherosclerotic risk and NASH.