CAT-2003, an Analog of CAT-2054, a Novel Oral Sterol Regulatory Element Binding Protein Inhibitor, Inhibits Inflammation and Fibrosis in a Murine Model of Nonalcoholic Steatohepatitis (NASH)
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Abstract

Introduction: CAT-2003 and CAT-2054 are orally administered small molecule inhibitors of Sterol Response Element-Binding Protein (SREBP), a master regulator of cholesterol and triglyceride metabolism that impacts liver fat and cholesterol levels. Consistent with this mechanism CAT-2003 and CAT-2054 treatment reduced LDL cholesterol levels in clinical trials. Elevated expression of SREBP isoforms has been described in patients with NASH and NASH. CAT-2054 is currently in a Phase 2a trial for hypercholesterolemia. Here, we use CAT-2003 as an analog molecule of CAT-2054 to study effects in a murine model of NASH.

Objective: To determine the effect of oral administration of CAT-2003 on the progression of inflammation, fibrosis and NASH and the subsequent development of pre-neoplastic lesions in a murine model.

Methods: A two hit model was used to induce a NASH-like disease in male C57BL/6 mice. Streptozotocin was used to induce liver and pancreatic damage in 4 day old mice followed by a second insult of a high fat, high cholesterol diet at week 5 to induce steatohepatitis and fibrosis. CAT-2003 was administered to the diet (0.75% w/w) 2 weeks later for 9 weeks.

Results: CAT-2003 treatment significantly reduced hepatic INSIG1 expression, indicating inhibition of SREBP activity. CAT-2003 significantly reduced steatosis and inflammation and produced a complete abrogation of the ballooning degeneration and progression of fibrosis relative to levels observed in baseline control mice at the start of the treatment. The absolute NAFLD/NASH activity score was significantly reduced from 4.75 in control to 2.83 in treated animals. Similarly, CAT-2003 reduced the fibrosis score from 1.83 in the disease control to 1.17 which was lower than the pretreatment baseline score of 1.38. Livers from CAT-2003 treated animals showed markedly decreased expression of the pro-inflammatory and pro-fibrogenic chemokines CCL2 and CCL3, ACTA2, a marker of hepatic stellate cell activation; and ID1, an indicator of reduced TGFβ signaling. In addition, CAT-2003 also significantly reduced the number of pro-neoplastic foci from a mean of 6.8 to 2.0/cm², demonstrating that treatment with CAT-2003 may help slow progression to hepatocellular carcinoma.

Conclusions: Inhibition of SREBP by oral administration of CAT-2003, an analog of CAT-2054, significantly reduced the progression of multiple morphologic components of NASH including: steatosis, inflammation, hepatocyte injury and fibrosis. CAT-2054, which is in a Phase 2a trial for hypercholesterolemia, may therefore have additional utility in NASH.