The FASN inhibitor, TVB3664, Ameliorates NASH in a Murine Model

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1. INTRODUCTION
Hepatic lipogenesis catalyzed by fatty acid synthase (FASN), is a driver of inflammation and steatosis in NASH. We have tested the activity of a specific FASN inhibitor, TVB3664, in an established murine model of NASH characterized by advanced fibrosis and hepatocellular carcinoma (Tsuchida et al., 2018. J Hepatol, 69: 385-395), based in part on its antifibrotic effect in the human hepatic stellate LX-2 cell line (AASLD 2017 #1994).

2. AIMS
This study was to evaluate the impact of a small molecule of FASN inhibitor (TVB3664) synthesized by 3V Biosciences in a diet and CCl₄ induced mice NASH model that reproducibly induces significant fibrosis and hepatocellular carcinoma (HCC) which characteristically close to human NASH.

3. METHODS
• Six-week-old male C57BL/6J mice were fed a high-fat-cholesterol western diet (WD) and glucose-fructose sugar water (SW) combined with 0.2% gum body weight CCl₄ injection via IP (once/week) for 24 weeks (Tsuchida et al., 2018. J Hepatol, 69: 385-395).
• From week 13 to week 24, animals were additionally administered oral daily doses of either vehicle (30% PEG400 in water) or three different doses of TVB3664 (3 mg/kg, 5 mg/kg or 10 mg/kg in vehicle).
• After 24 weeks (12 weeks of treatment period) mice were sacrificed and necro-inflammatory activity, NAS activity, expression of profibrotic genes and protein were assessed.

4. RESULTS

4.1 Necro-inflammatory activity is improved on TVB3664 treatment

TVB3664 reduces profibrotic gene expression

Figure 5: Relative mRNA expression of profibrotic gene/GAPDH in mice liver tissue was measured by RT-qPCR and fold change was calculated over vehicle control

TVB3664 reduces fibrogenic protein expression

Western blot of liver protein

Figure 6: Relative expression of Collagen1α1 and αSMA protein were reduced in NASH mice liver on TVB3664 treatment

TVB3664 reduces tumor development

Figure 7: Severe fibrosis and HCC develop in NASH mice at week 24. The mice treated with TVB3664 have reduced tumor development.

CONCLUSIONS
- Biochemical analysis of liver injury (AST and ALT) and histopathological data including collagen deposition, NAS and fibrosis stage indicate that TVB3664 reduces NASH activity and associated fibrosis.
- TVB3664 reduces the expression levels of all profibrotic genes as well as protein (Collagen1α1 and αSMA) in liver tissues.
- Reduction of tumor numbers by TVB3664 indicates the potential therapeutic activity of TVB3664.
- These results indicate that the Fatty Acid Synthase inhibitor (FASN) TVB3664 may be a potential candidate for further investigation as an antifibrotic drug in NASH.

Supporting information: 3-V Biosciences

Disclosures: Scott Friedman is a consultant to 3-V Biosciences

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