FATTY ACID SYNTHASE INHIBITOR TVB-3664 REVERSES MULTIPLE COMPONENTS OF DIET-INDUCED NONALCOHOLIC STEATOHEPATITIS IN MICE TREATED WITH OR WITHOUT CO-ADMINISTERED PIRFENIDONE AND REDUCES COLLAGEN ACCUMULATION IN BLEOMYCIN-INDUCED MURINE SKIN FIBROSIS

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INTRODUCTION

Hepatic de novo lipogenesis is elevated in humans with nonalcoholic fatty liver disease and plays a significant role in the development of steatosis and inflammation promoting development of nonalcoholic steatohepatitis (NASH). A key enzyme in the de novo lipogenesis pathway is fatty acid synthase (FASN). In high-fat/fructose/cholesterol diet (HFFCD)-induced murine models of NASH, concurrent administration of TVB-3664, a FASN inhibitor compound, treats steatosis, inflammation and fibrosis.

AIM

Our study objective was to determine the impact of TVB-3664 in models with pre-established liver or skin fibrosis.

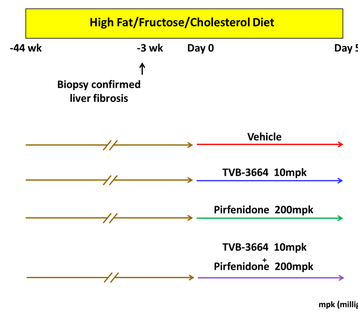
MATERIAL & METHODS

C57BL/6J mice fed a HFFCD for 44 weeks (wks) exhibited obesity, steatohepatitis and fibrosis based on liver biopsy (1). For an additional 8 wks, animals continued a HFFCD and received oral once per day treatments of either TVB-3664, the anti-fibrotic pirfenidone, both TVB-3664 and pirfenidone, or vehicle control. At study end, analyses included histological assessment (NAFLD Activity Score (NAS) and Fibrosis Stage), gene expression (liver), total triglyceride and cholesterol content (liver and plasma), levels of alanine transaminase (ALT) and aspartate transaminase (AST) in plasma and serum cytokine levels. In a separate experiment, bleomycin-induced skin fibrosis was established in C57/BL6 mice by daily subcutaneous injection of bleomycin for 4 wks. Oral once per day treatment with TVB-3664 was concurrent with bleomycin injection or was begun after 2 wks of bleomycin injection. At study end, collagen content at the site of bleomycin injection was biochemically determined.

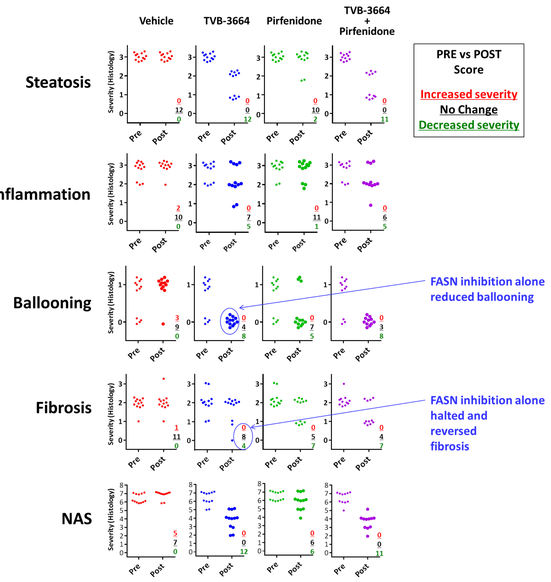
RESULTS

FASN inhibition with TVB-3664 treats NASH in mice with biopsy-confirmed fibrosis

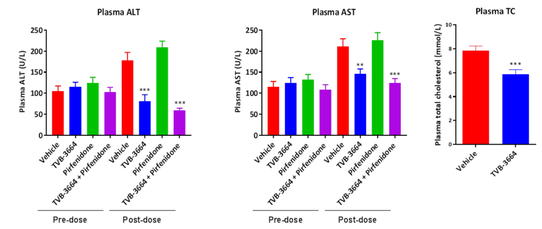
Treatment groups

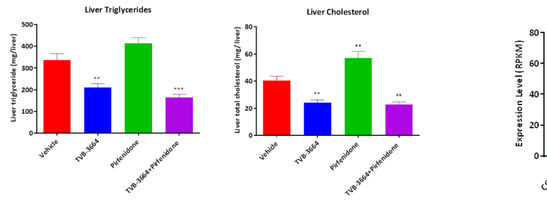


Reduced steatosis, inflammation, ballooning, fibrosis

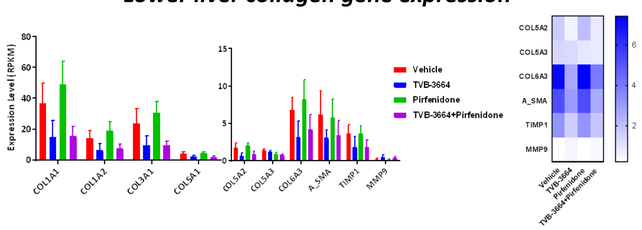


Improved liver function, triglycerides, cholesterol



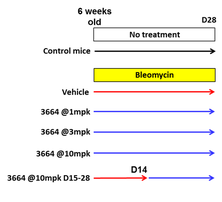


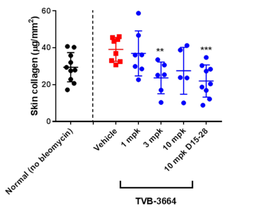
Lower liver collagen gene expression



Data expressed as mean ± SEM
**p<0.01, ***p<0.001 vs. Vehicle; One-Way ANOVA with Dunnett's multiple comparison test

FASN inhibition with TVB-3664 reduces skin collagen in bleomycin-induced skin fibrosis model

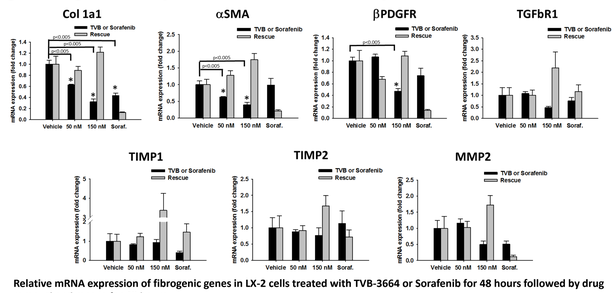




Data expressed as mean ± SD
**p<0.01, ***p<0.001 vs. Vehicle; One-Way ANOVA with Dunnett's multiple comparison test

FASN inhibition reduces fibrogenic gene expression in LX-2 hepatic stellate cells

Fibrogenic Gene	Percent Reduction in Gene Expression After 48 hr Treatment: TVB-3664 (50 nM)	TVB-3664 (150 nM)
Col1a1	37.3	67.9
αSMA	37.2	60.4
βPDGF-R	0	52.7
TGFβ-R1	0	53.5
TIMP1	18.8	7.6
TIMP2	11.9	23.5
MMP2	0	49.9



Relative mRNA expression of fibrogenic genes in LX-2 cells treated with TVB-3664 or Sorafenib for 48 hours followed by drug removal and rescue for 48 hours

CONCLUSION

In a diet-induced biopsy-confirmed mouse model of NASH, FASN inhibition reduced hepatocyte ballooning, hepatic inflammation and steatosis, lowered plasma ALT and AST levels, diminished liver triglyceride and cholesterol and established a signature consistent with resolution of fibrosis including reduced expression of collagens, alpha-SMA and TIMP1 and increased expression of MMP9. Co-administration of pirfenidone further reduced liver fibrosis while maintaining the beneficial effects specific to FASN inhibition.

Reduction of fibrogenic gene expression as a result of FASN inhibition was recapitulated in vitro in LX-2 hepatic stellate cells.

In a bleomycin-induced skin fibrosis model, FASN inhibition reduced skin collagen content whether treatment was concurrent with bleomycin injection or was begun after 2 weeks of bleomycin injection.

These results provide evidence in a diet-induced and biopsy-confirmed mouse model of NASH that FASN inhibition either alone or in combination with a potent anti-fibrotic agent can reverse steatohepatitis and may provide benefit in other diseases in which fibrosis is a component of their pathology.

REFERENCES

1. Kristiansen, M.N.B., Veidal, S.S., Rigbolt, K.T.G., et al. (2016) Obese diet-induced mouse models of nonalcoholic steatohepatitis-tracking disease by liver biopsy. World J Hepatol 8(16): 673-684.

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