Progressive reductions in hepatic DNL with increasing doses of TVB-2640, a first-in-class pharmacologic inhibitor of FASN

Majid M. Syed-Abdul[1], Elizabeth J. Parks[1], Kimberly Bingham[1], Nhan Le[1], Ghassan M. Hammoud[3], Ayman H. Gaballah[4], George Kemble[5], Douglas Buckley[5], William McCulloch[5], Camila M. Manrique[2*]

[1]Department of Nutrition and Exercise Physiology, Divisions of [2]Endocrinology and [3]Gastroenterology and Hepatology, and [4]Department of Radiology, University of Missouri School of Medicine, Columbia, MO; [5]3-V Biosciences, Inc. Menlo Park, CA, *Corresponding author

ABSTRACT

Consumption of dietary sugars induces hepatic de novo lipogenesis (DNL), which left unchecked, promotes liver inflammation, ultimately leading to the development of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH). Treatment with TVB-2640, a pharmacological inhibitor of FASN, has been shown to reduce biomarkers of DNL in rodent models of NAFLD, as well as in studies in cancer patients. The purpose of the present study was to test the effect of TVB-2640 to reduce DNL in obese men with metabolic syndrome characteristics that put them at risk for NAFLD. Twelve subjects (42.1±6.6 y, BMI 37.4±4.1 kg/m2, insulin 26±11 U/L, glucose 103±8 mg/dL, and TG 196±95 mg/dL) with normal AST (29±14 u/L) and ALT (45±21 u/L) underwent 10 days of treatment with TVB-2640 at doses ranging from 50-150 mg/d. Food intake was matched to their typical intake and controlled throughout the study. At baseline and following the last dose, hepatic DNL was measured in the fasting state and after a fructose/glucose bolus using isotopic labeling with $^{13}C_1$-acetate infusion, followed by measurement of labeled palmitate in VLDL via GC/MS. Substrate oxidation was measured by indirect calorimetry. Across the doses, fasting DNL was reduced from 0% to 90% (P=0.002). With regard to PK, increasing plasma levels of TVB-2640 were associated with progressive reductions in fructose-stimulated fractional DNL (R²=0.749, P<0.001) and absolute DNL AUC (R²=0.553, P=0.006). Both ALT and AST were significantly reduced. Substrate oxidation was unchanged. Safety monitoring revealed that the drug was well tolerated. Mild reversible hair loss occurred in two subjects, but otherwise no changes were observed in fasting concentrations of glucose, insulin, NEFA, ketones and renal function. The results from this investigation support a significant therapeutic potential of TVB-2640 in patients with NAFLD.

BACKGROUND

Consumption of dietary sugars induces an increase in hepatic de novo lipogenesis (DNL), which left unchecked, promotes liver inflammation, ultimately leading to the development of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH). Pharmacologic inhibition of fatty acid synthase (FASN), a key enzyme in the DNL pathway, with a TVB-2640 analog prevents steatosis, inflammation, and fibrosis in high-fat, high-sugar diet-fed murine models. In cancer patients, relatively high doses of the first-in-class FASN inhibitor, TVB-2640, reduces markers of DNL systemically. The purpose of the present study was to test the effect of TVB-2640 to reduce hepatic DNL in obese men with metabolic characteristics that put them at risk for NAFLD.

METHODS

Shown in **Figure 1** is the study design. Male subjects with the characteristics of metabolic syndrome were consented and screened for this study (final sample size, n=12). The study was approved by MU IRB (#2006432) and registered at ClinicalTrials.gov (NCT02948569). Prior to starting treatment with TVB-2640, the subject's food intake was analyzed and a 3-day isocaloric diet was provided. A similar diet was continued during the drug treatment (50, 100, or 150 mg daily) for 10 days to maintain body weight. During day 1 and day 10 (pre- and post-drug treatment), the subject completed a 24-hour, in-patient study to measure, 1) DNL via continuous isotopic labeling using $^{13}C_1$-acetate infusion, a fructose/glucose oral tolerance test, followed by measurement of labeled palmitate in VLDL via GC/MS, 2) substrate oxidation measured via indirect calorimetry, 3) body composition via DEXA scan, and 4) liver fat by MRI scan and fibrosis score via FibroScan™. During the 10-day treatment, serial safety visits were conducted three times to identify potential side effects. A final safety visit was conducted 6d after drug treatment was finished. Statistical analysis was performed using Statview®. Data in graphs represent mean ± SEM.

Figure 1: Study design

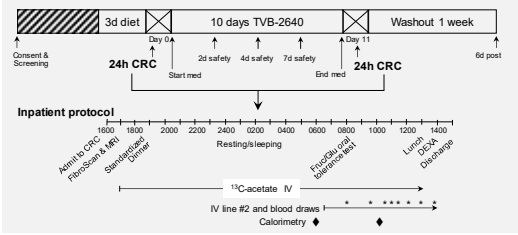


Table 1. Subject characteristics

Subject characteristics	50 mg		100 mg		150 mg		ANOVA*
	Mean	SD	Mean	SD	Mean	SD	*P*-value
Age (years)	40.5	5.8	44.3	8.8	42.5	6.4	0.715
Weight (kg)	124.0	14.8	116.0	20.6	118.2	18.5	0.768
BMI (kg/m2)	37.4	3.5	37.6	5.7	37.3	5.0	0.994
HbA1c (%)	5.6	0.3	5.8	0.5	5.8	0.2	0.702
Fat mass (%)	38.7	3.7	38.1	6.3	39.1	4.2	0.968
Systolic BP (mmHg)	139	14	130	11	123	12	0.268
Diastolic BP (mmHg)	88	12	87	3	81	5	0.614

* *P*-value for difference between groups

RESULTS

Figure 2. Plasma PK of TVB-2640

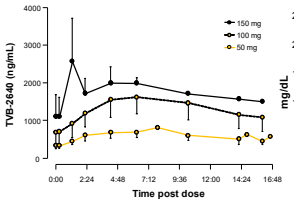


Figure 3. Plasma lipids pre- and post-drug

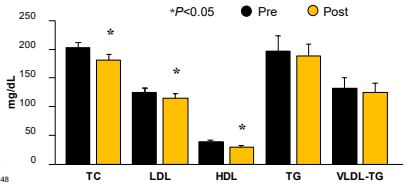


Figure 4. Fractional DNL in VLDL-TG pre- and post-drug

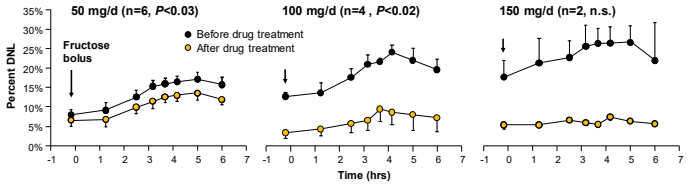


Figure 5. Absolute DNL in VLDL-TG pre- and post-drug

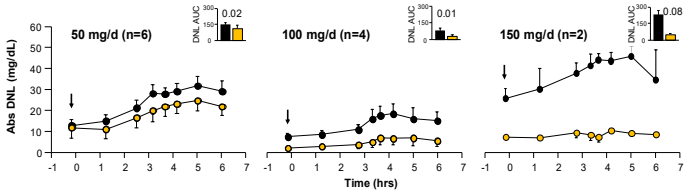


Figure 6. NEFA concentrations pre- and post-drug

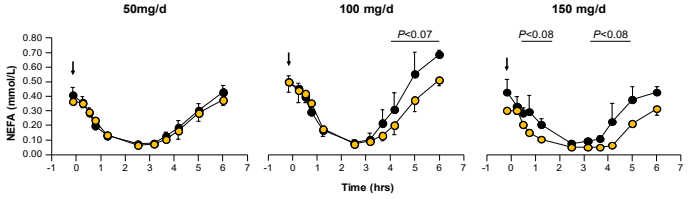


Figure 7. Body weight and liver fat

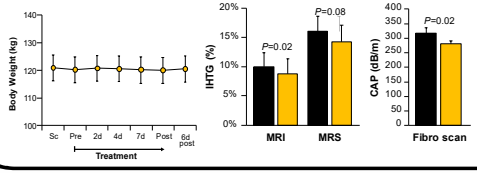


Figure 8. Plasma AST and ALT

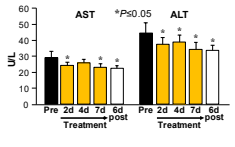
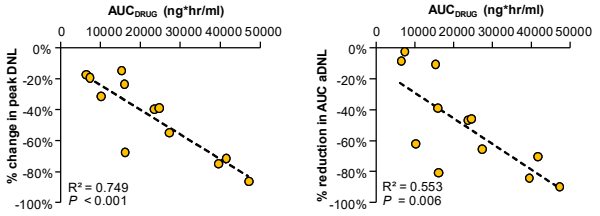


Figure 9. Relationships between drug, DNL, and liver fat



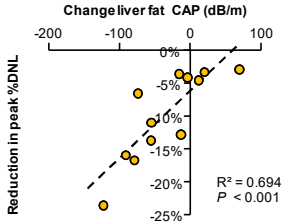


Table 2. Adverse drug reactions

Adverse Drug Reactions	50 mg (n=6)	100 mg (n=4)	150 mg (n=2)
Constipation	1	0	0
Diarrhea	0	1	0
Dry throat	0	0	1
Dry skin	1	0	0
Fatigue	0	0	0
Hair loss	0	1	1
Headache	0	1	0
Loss of cravings	1	0	0
Peeling skin on fingertips	0	1	0

RESULTS

The half-life ($t_{1/2}$) of the drug was determined to be between 10-12 hours (**fig. 2**). Ten days of treatment with TVB-2640 significantly reduced TC, LDL, and HDL cholesterol in all subjects (**fig. 3**). Across the doses, fasting DNL was reduced from 0% to 90% (**fig. 4**, *P*=0.002) and absolute DNL was also reduced significantly (**fig. 5**). Plasma NEFA concentrations tended to be decreased with higher doses (**fig. 6**). No changes were observed in substrate oxidation and body weight, although liver fat was reduced significantly (**fig. 7**). Both plasma AST and ALT were reduced significantly during pharmacological treatment (**fig. 8**). With regard to PK, increasing plasma levels of TVB-2640 were associated with progressive reductions in fructose-stimulated fractional DNL and absolute DNL AUC (**fig. 9**). Further, a decrease in liver fat measured via FibroScan™ was significantly associated with a reduction in peak percent DNL (**fig. 9**). Safety monitoring revealed that the drug was well tolerated. Mild reversible hair loss occurred in the two subjects with the highest level of drug in their plasma, (**table 2**). No changes were observed in fasting concentrations of glucose, insulin, ketones, and renal function (data not shown).

CONCLUSIONS

The increasing doses of TVB-2640 significantly reduced DNL. Levels of cholesterol in lipoproteins were also reduced. Strong relationships were found between decreased DNL and liver fat. Additional studies will be needed to understand the mechanism of TVB-2640 on plasma NEFA. The results from this investigation support a significant therapeutic potential of TVB-2640 in patients with NAFLD with a reassuring safety profile.

ACKNOWLEDGEMENTS

Funding: 3-V Biosciences Inc., CA.

For questions, please contact: Elizabeth Parks ParksEJ@Missouri.edu, George Kemble George.Kemble@3VBIO.com or Dennis Hom Dennis.Hom@3VBIO.com

3-V BIOSCIENCES

University of Missouri