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

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ABSTRACT

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 resulted in significant reductions in hepatic DNL. The purpose of this investigation was to test the effect of TVB-2640 to reduce hepatic DNL in obese mice 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 syndromes 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 completed a 24-hour, in-patient study to measure, (1) DNL (TC, Total Cholesterol; LDL, Low-density Lipoprotein; HDL, High-density Lipoprotein; TG, Triglycerides), (2) NEFA (nmol/L), (3) AST and ALT (U/L), (4) liver fat by MRI scan and FibroScan score via ultrasound. Across the doses, fasting concentrations of glucose, insulin, NEFA, ketones and renal function (creatinine clearance) remained stable (fig. 5). A decrease in liver fat was observed in the two subjects with the highest level of drug in their plasma. (fig. 9). Safety monitoring revealed that the drug was well tolerated. Mild reversible hair loss occurred in two subjects with the highest level of drug in their plasma (table 2).

RESULTS

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

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

Table 1. Subject characteristics

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment</th>
<th>Weight (kg)</th>
<th>BMI (kg/m²)</th>
<th>HbA1c (%)</th>
<th>Fat mass (%)</th>
<th>TC (mg/dL)</th>
<th>TG (mg/dL)</th>
<th>HDL (mg/dL)</th>
<th>LDL (mg/dL)</th>
<th>Glucose (mg/dL)</th>
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<tbody>
<tr>
<td>Pre</td>
<td>50 mg/d</td>
<td>87.2</td>
<td>37.3</td>
<td>5.6</td>
<td>39.7</td>
<td>116.0</td>
<td>150</td>
<td>54</td>
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<td>103</td>
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<tr>
<td>Post</td>
<td>100 mg/d</td>
<td>88.5</td>
<td>37.9</td>
<td>5.6</td>
<td>38.7</td>
<td>118.2</td>
<td>150</td>
<td>54</td>
<td>80</td>
<td>103</td>
</tr>
<tr>
<td>Washout</td>
<td>150 mg/d</td>
<td>88.2</td>
<td>37.9</td>
<td>5.6</td>
<td>39.1</td>
<td>118.2</td>
<td>150</td>
<td>54</td>
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<td>103</td>
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</tbody>
</table>

*Statistically significant between groups

Table 2. Adverse drug reactions

<table>
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<th>Reaction</th>
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<tr>
<td>Headache</td>
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<tr>
<td>Fatigue</td>
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<tr>
<td>Hair loss</td>
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<td>0</td>
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<td>Constipation</td>
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<td>0</td>
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<tr>
<td>Diarrhea</td>
<td>0</td>
<td>0</td>
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</tr>
</tbody>
</table>

*Significant differences between groups

Figure 1. Study design

- 24h-CRC
- 2d
- 4d
- 7d
- 10d
- Washout

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