Introduction

- Sargosylide (SEMA) is a long-acting glucagon-like peptide-1 (GLP-1) receptor agonist currently being evaluated in clinical trials for nonalcoholic steatohepatitis (NASH).
- Cilostazol (CILO) is a formulated farxigla (FXR) agonist in clinical development for NASH. Several preclinical studies have demonstrated reductions in liver fat in patients with NASH and FXR-3 fibrosis. The additional benefit of combining CILOR and FXR (or monotherapy) is currently being evaluated in patients with FXR-3 fibrosis due to NASH (NCT03449446; results pending).

- FIRR is a liver-targeted acyl-CoA oxidase 1 (ACO1)/2 inhibitor that dose-dependently reduces liver fat (by magnetic resonance imaging–proton density fat fraction), and improves markers of liver injury in patients with NASH and FXR-3 fibrosis in preclinical models. ACC inhibition via tool FIR analog GS-834356 enhanced by addition of other agents.

Objective

- To explore the effects of 12 wk of treatment with SEMA and/or CILO and/or ACCi on metabolic parameters and liver pathology in the amylin liver (AMLN) transfad induced obese mouse model of NASH (DIO-NASH).

Methods

- AMLN DIO-NASH Study Design

- Male C57Bl/6J mice (JANVIER LABS, Le Genest-Saint-Ise, France) were fed either a standard chow diet (Aibrinom 1324, Brogamon A/S, Lyngby, Denmark) or AMLN (DIO) diet (DI01001, Research Diet Inc., New Brunswick, NJ) from age −5 wk.

- After 29 wk on AMLN diet, mice were subjected to liver biopsy, and randomized to test groups based on baseline liver steatosis (scores 2–4) and fibrosis.

- All mice were chased up with either vehicles (0.5% sodium carboxymethylcellulose, 1% ethanol, 0.5% MCT oil) or test agent and with either vehicle (0.001% polycarbonate 2.0, 0.5% sodium phosphate, 0.7% MCT oil, cholesterol) or test agent, both at 5 mL/kg, for 12 wk.

- Body weight was measured daily, collected via tail blood during or weekly for measurement of plasma alanine aminotransferase (ALT), aspartate aminotransferase (AST), triglycerides (TG), and total cholesterol (TC; cobas c 5801 module, Roche Diagnostics, Indianapolis, IN).

- Mice were euthanized at the end of the study via subcutaneous anesthetic following 4-h fast. Liver tissue was collected, weighed, and subjected to TG and TC measurement or histological analyses.

Results

- Body weight was significantly reduced (17%) by SEMA treatment.
- Further body weight loss was observed (21%) in SEMA + CILO group, but not with addition of ACCi or in triple-combination group.
- Liver Weight and Triglyceride Content at Week 12

<table>
<thead>
<tr>
<th>Group</th>
<th>Liver Weight (mg)</th>
<th>Liver TG (mg/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chow</td>
<td>873.6</td>
<td>118.2</td>
</tr>
<tr>
<td>Vehicle</td>
<td>932.1</td>
<td>125.3</td>
</tr>
<tr>
<td>SEMA</td>
<td>732.4</td>
<td>90.7</td>
</tr>
<tr>
<td>CILO</td>
<td>768.9</td>
<td>102.8</td>
</tr>
<tr>
<td>SEMA + CILO</td>
<td>675.2</td>
<td>75.6</td>
</tr>
</tbody>
</table>

- AMLN DIO-NASH demonstrated increased liver weight and TG content.
- Liver weight and TG were significantly reduced by SEMA.

Conclusions

- SEMA effectively reduced hepatic lipids and NAS, and the addition of an FXR agonist and ACCi further improved NAS in AMLN DIO-NASH.
- The effects of pharmacology on histologic markers of NASH, particularly in combination groups, approached the maximal effective therapeutics utility of the model.
- These data support the development of combination approaches for NASH.

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