Combination Therapy in Cirrhotic NASH

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Disclosures

- Research Grants/Contracts: Galectin, Intercept, Genfit, Janssen*, Shire, Conatus, Zydus
- Consulting: Astra Zeneca/MedImmune
- * includes IP
Combination Therapy: NASH Cirrhosis

• Defining cirrhosis
• Targeting disease activity and fibrosis
• Safety in more advanced liver disease
• Monitoring combinations over [a long] time
• Endpoints – combining practical and meaningful
Cirrhotic NAFLD: spectrum within a spectrum

Garcia-Tsao G, et al. Now there are many (stages) where before there was one: in search of a pathophysiological classification of cirrhosis. Hepatology 2010; 51: 1445–9
SU Kim, et al. The Laennec staging system for histological sub-classification of cirrhosis is useful for stratification of prognosis in patients with liver cirrhosis. J Hepatol 2012

courtesy P. Bedossa
## Compensated cirrhosis

<table>
<thead>
<tr>
<th>Minimal portal hypertension (MPH)</th>
<th>Clinically significant portal hypertension (CSPH)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5mmHg &lt; HVPG &lt; 10mmHg</td>
<td>HVPG ≥ 10 mmHg</td>
</tr>
<tr>
<td>Very low risk of decompensation</td>
<td>4 times higher risk of decompensation</td>
</tr>
<tr>
<td>Less liver fibrosis</td>
<td>More fibrosis</td>
</tr>
<tr>
<td>Increased intrahepatic resistance</td>
<td>Increased splanchnic blood flow</td>
</tr>
<tr>
<td>Treatment of underlying mechanism = may prevent CSPH</td>
<td>Treatment may decrease <em>time</em> to decompensation but risk still exists</td>
</tr>
</tbody>
</table>
Combos in NASH Cirrhosis

REVERSIBILITY
<table>
<thead>
<tr>
<th>Metabolic substrate</th>
<th>Anti-NASH</th>
<th>Antifibrotic</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACCi</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DGATi</td>
<td>Vitamin E</td>
<td></td>
</tr>
<tr>
<td>LOXL2i</td>
<td>LOXL2i</td>
<td></td>
</tr>
<tr>
<td>Gal-3i</td>
<td>Gal-3i</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pan caspase inhibitors</td>
<td></td>
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</tbody>
</table>
Rationale for Simtuzumab

- Lysyl oxidase-like 2 is a secreted, copper dependent amino oxidase
- LOXL2 contributes to fibrogenesis by cross-linking collagen and elastin
- In murine models, LOXL2 stabilizes fibrotic matrix
  - Inhibition shown to decrease liver fibrosis
- Simtuzumab = monoclonal antibody directed at LOXL2

Marsha C. Lampi and Cynthia A. Reinhart-King Sci Transl Med 2018;10:eaao0475
Liver Related Clinical Events in Cirrhosis

Median follow up 30.1 mos (range, 0.1-45.1)
Events: ascites, encephalopathy, varices (new), EVH, CPT ≥2 point increase and/or MELD ≥15, death

Rationale for GR-MD-02 (Galectin)

- Gal-3 is a lectin protein, binds galactose residues on glycoproteins
  - Increased in NASH, liver fibrosis, cirrhosis
  - Preclinical knockout models: resistant to development of NASH, fibrosis

- GR-MD-02 = complex carbohydrate drug
  - Inhibits gal-3
  - Improves histopathology of NASH and reverses fibrosis in animal models
  - Phase 1 studies demonstrated safety, tolerability in NASH with advanced fibrosis
### HVPG Primary Endpoint (Pre-Specified Analyses)

#### Total Patient Population
- **PLB**
  - n=54
  - +8%
  - Mean ± SEM
- **GR2**
  - n=53
  - -2%
  - Mean ± SEM
- **GR8**
  - n=54
  - -2%
  - Mean ± SEM

#### Mild Portal Hypertension
- **PLB**
  - n=21
  - 26%
  - Mean ± SEM
- **GR2**
  - n=16
  - -3%
  - Mean ± SEM
- **GR8**
  - n=16
  - -2%
  - Mean ± SEM

*ITT with LOCF (last observation carried forward); ANOVA with LSD (least squared difference)*
Emricasan: Rationale

- Caspase-mediated apoptosis has been observed with chronic liver disease (viral, metabolic)
- Accumulation of apoptotic cells and subcellular fragments like microvesicles contain biologically active particles
- Caspase cleaves cytokeratin-18 (CK-18)
  - Cleaved CK18 (cCK18) is a biomarker associated with inflammation in different etiologies of chronic liver disease (HCV, NAFLD, NASH)
- Inhibition of caspase activity may decrease apoptosis and associated microparticles

Ibrahim et al. *Gut*, Jan 2018
• NASH cirrhosis and baseline HVPG ≥12 mmHg
• Randomized vs placebo (5, 25, 50mg)
• N=263
• Primary endpoint HVPG at 24w
• Result: Failed to meet primary endpoint

<table>
<thead>
<tr>
<th>Mean change from baseline at Wk 24</th>
<th>Emricasan 5 mg N=65</th>
<th>Emricasan 25 mg N=65</th>
<th>Emricasan 50 mg N=66</th>
<th>Placebo N=67</th>
</tr>
</thead>
<tbody>
<tr>
<td>HVPG (Overall)</td>
<td>-0.6; p=0.96</td>
<td>-0.8; p=0.79</td>
<td>-1.0; p=0.65</td>
<td>-0.4</td>
</tr>
<tr>
<td>HVPG (compensated, HVPG ≥16 mmHg)</td>
<td>-1.6; p=0.01</td>
<td>-1.7; p&lt;0.01</td>
<td>-1.5; p=0.02</td>
<td>+0.5</td>
</tr>
</tbody>
</table>

Garcia-Tsao EASL/ILC LB 2019
Safety in Cirrhosis

Metabolism altered with more advanced fibrosis and decompensation

<table>
<thead>
<tr>
<th>Study population</th>
<th>CYP 450 enzyme</th>
<th>Child-Pugh scores</th>
<th>Change in activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 explanted cirrhotic livers$^{28}$</td>
<td>CYP1A2</td>
<td>B/C</td>
<td>Reduced activity at Child-Pugh class C</td>
</tr>
<tr>
<td>Controls and liver failure patients$^{53}$</td>
<td>CYP1A2</td>
<td>A/B/C</td>
<td>Reduced activity at Child-Pugh class C</td>
</tr>
<tr>
<td>50 explanted cirrhotic livers$^{28}$</td>
<td>CYP2C9</td>
<td>B/C</td>
<td>Reduced activity at Child-Pugh class C</td>
</tr>
<tr>
<td>Controls and liver failure patients$^{53}$</td>
<td>CYP2C19</td>
<td>A/B/C</td>
<td>Reduced activity at Child-Pugh class A, B, and C</td>
</tr>
<tr>
<td>Controls and liver failure patients$^{53}$</td>
<td>CYP2D6</td>
<td>A/B/C</td>
<td>Reduced activity at Child-Pugh class B and C</td>
</tr>
<tr>
<td>In vitro liver tissue$^{50}$</td>
<td>CYP3A</td>
<td>Noncholestatic cirrhosis</td>
<td>Reduced activity at Child-Pugh class B and C</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cholestatic cirrhosis</td>
<td>No difference at any Child-Pugh class</td>
</tr>
</tbody>
</table>

CYP2D6 also expressed in adipose (Human Protein Atlas)

Doligalski et al. *Gastroenterology and Hepatology* 2012.
Safety – Combos with Caution

• ACCi - increased circulating TG + FXR agonist $\rightarrow$ increased LDL = increased atherogenesis
• Vitamin E + immunomodulators = carcinogenesis (long term follow-up)
• Malignancy concerns with advanced fibrosis
• Potentiation of off-target effects with potent antifibrotic combos
Endpoints in Cirrhosis (Compensated)

<table>
<thead>
<tr>
<th>Proof of Concept</th>
<th>Meaningful Benefit</th>
</tr>
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<tbody>
<tr>
<td>• Improvement in disease activity (NAS)</td>
<td>• Reversal of fibrosis</td>
</tr>
<tr>
<td>• No worsening of fibrosis</td>
<td>• &gt;1 stage improvement in fibrosis</td>
</tr>
<tr>
<td>• No worsening of HVPG</td>
<td>• Time to progression to CSPH</td>
</tr>
<tr>
<td></td>
<td>• Time to liver related clinical events</td>
</tr>
</tbody>
</table>
Proof of Concept

Meaningful benefit

Regulatory Sweet Spot

Adapted from Paul Miller, NavPress 2009.