Can we test liver function to predict the natural course and assess treatment effects in Hepatitis C?

Gregory T. Everson, MD
Professor of Medicine
Director of Hepatology
University of Colorado Denver
In Patients with Chronic Hepatitis C:

Can we measure Hepatic Reserve?
Can we identify the At-Risk Patient?
Can we track progression or recovery from DILI?

Gregory T. Everson, MD
Professor of Medicine
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University of Colorado Denver
Disclosures

• Intellectual property filings with University of Colorado Denver – 6 patents have been issued from 12/2013 to 7/2015; others pending.

• Founder, Manager and Equity Member of HepQuant LLC

The HepQuant (dual cholate) tests discussed in this presentation are NOT FDA APPROVED. They are currently for investigational use only.
Can we measure Hepatic Reserve?
Methods

Fibrosis Stage on liver biopsy as the Invasive “Gold Standard”

Measuring Function and Physiology
  Hepatic Reserve

Dual Cholate SHUNT

Estimating Fibrosis

Liver Stiffness

Metabolism
  Breath Tests

SPECT scan

Biomarkers
Dual Cholate*

* HepQuant® SHUNT test
Elements of Functional Impairment Measured by the Dual Cholate SHUNT Test

Healthy Liver

- Hepatic Vein
- Hepatic Artery
- Portal Vein
- Systemic Blood Compounds
- Portal Blood Compounds

Diseased Liver

- Hepatic Vein
- Hepatic Artery
- Portal Vein
- Systemic Blood Compounds
- Portal Blood Compounds

Factors:
- Viruses
- EtOH
- Auto-Immune
- Biliary
- Fat, other

Dual Cholate SHUNT test

Test Administration

Laboratory Analysis

Isotope Ratiometry-Mass Spectrometry

- Oral (D4-cholate, 40 mg) and IV (13C-cholate, 20 mg)
- Timed blood draws at t = 5, 20, 45, 60 and 90 minutes
- Serum shipped to analytical lab
- A Disease Severity Index (DSI) is measured from HFRs and SHUNT
Single Point STAT test

- Oral dose only – D4 cholate 40 mg
- One blood draw at 60 minutes
- Serum separated and shipped to HQ lab
- Result is STAT (estimate of Portal HFR and DSI)
Decline of Hepatic Functional Reserve

$y = -5.9065x + 99.431$

$R^2 = 0.9842$

<table>
<thead>
<tr>
<th>Stage of Disease</th>
<th>% Hepatic Reserve</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy Persons</td>
<td>100</td>
</tr>
<tr>
<td>F0-F1</td>
<td>94</td>
</tr>
<tr>
<td>F2</td>
<td>88</td>
</tr>
<tr>
<td>F3</td>
<td>82</td>
</tr>
<tr>
<td>F3-F4</td>
<td>76</td>
</tr>
<tr>
<td>F4</td>
<td>70</td>
</tr>
<tr>
<td>F5</td>
<td>64</td>
</tr>
<tr>
<td>F5-F6</td>
<td>58</td>
</tr>
<tr>
<td>Post-LT mix of CTP A B C</td>
<td>52</td>
</tr>
<tr>
<td>Decompensated CTP B C</td>
<td>46</td>
</tr>
<tr>
<td>Decompensated Waiting List Pts</td>
<td>40</td>
</tr>
<tr>
<td>Theoretical Limit</td>
<td>0</td>
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</table>
SHUNT and STAT
Measure Hepatic Reserve.
Can we identify the At-Risk Patient?
With Number of Subjects at Risk and 95% Confidence Limits

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>n=52</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTP +2</td>
<td>18</td>
</tr>
<tr>
<td>Var Bleed</td>
<td>4</td>
</tr>
<tr>
<td>Ascites</td>
<td>8</td>
</tr>
<tr>
<td>Enceph</td>
<td>3</td>
</tr>
<tr>
<td>Asc+Enc</td>
<td>3</td>
</tr>
<tr>
<td>Death</td>
<td>16</td>
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STAT Predicts Risk for Clinical Outcome

With Number of Subjects at Risk and 95% Confidence Limits

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<tr>
<td>Death</td>
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</tr>
</tbody>
</table>
STAT and SHUNT (DSI) Independently Predict Clinical Outcome

**Ishak Fibrosis Stage**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio</th>
<th>Lower 95% CI</th>
<th>Upper 95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrosis ISHAK 5,6 vs 2,3,4</td>
<td>4.00</td>
<td>2.15</td>
<td>7.44</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**STAT**

<table>
<thead>
<tr>
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<th>Upper 95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>STAT tertile 0.73-1.19</td>
<td>2.59</td>
<td>0.70</td>
<td>9.56</td>
<td>0.154</td>
</tr>
<tr>
<td>STAT tertile &gt;1.19</td>
<td>9.82</td>
<td>2.82</td>
<td>34.22</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fibrosis ISHAK 5,6 vs 2,3,4</td>
<td>1.58</td>
<td>0.79</td>
<td>3.17</td>
<td>0.199</td>
</tr>
<tr>
<td>Platelets per unit</td>
<td>0.99</td>
<td>0.99</td>
<td>1.00</td>
<td>0.059</td>
</tr>
<tr>
<td>Age per year</td>
<td>0.98</td>
<td>0.94</td>
<td>1.02</td>
<td>0.263</td>
</tr>
<tr>
<td>Gender Male vs Female</td>
<td>1.10</td>
<td>0.58</td>
<td>2.08</td>
<td>0.771</td>
</tr>
<tr>
<td>Race Black vs Non-Hispanic, White</td>
<td>0.69</td>
<td>0.26</td>
<td>1.81</td>
<td>0.451</td>
</tr>
<tr>
<td>Race Hispanic/other vs Non-Hispanic, White</td>
<td>1.01</td>
<td>0.49</td>
<td>2.05</td>
<td>0.987</td>
</tr>
</tbody>
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**SHUNT (DSI)**

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<th>Upper 95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DSI tertile 15.395-19.898</td>
<td>2.40</td>
<td>0.64</td>
<td>9.04</td>
<td>0.196</td>
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<tr>
<td>DSI tertile &gt;19.898</td>
<td>14.01</td>
<td>3.84</td>
<td>51.08</td>
<td>&lt;0.001</td>
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<tr>
<td>Fibrosis ISHAK 5,6 vs 2,3,4</td>
<td>1.15</td>
<td>0.52</td>
<td>2.54</td>
<td>0.730</td>
</tr>
<tr>
<td>Platelets per unit</td>
<td>0.99</td>
<td>0.99</td>
<td>1.00</td>
<td>0.117</td>
</tr>
<tr>
<td>Age per year</td>
<td>0.98</td>
<td>0.94</td>
<td>1.02</td>
<td>0.300</td>
</tr>
<tr>
<td>Gender Male vs Female</td>
<td>1.23</td>
<td>0.64</td>
<td>2.38</td>
<td>0.538</td>
</tr>
<tr>
<td>Race Black vs Non-Hispanic, White</td>
<td>0.48</td>
<td>0.18</td>
<td>1.26</td>
<td>0.136</td>
</tr>
<tr>
<td>Race Hispanic/other vs Non-Hispanic, White</td>
<td>0.97</td>
<td>0.47</td>
<td>2.00</td>
<td>0.940</td>
</tr>
</tbody>
</table>
SHUNT and STAT identify the At-Risk Patient.
Can we track progression or recovery from DILI?
Measuring Change in DSI

Δ DSI v3.3

F0 - F3  LTx Cirrh  Decomp  HALT C  SVR  HALT C  HALT C  NR  PSC

p <0.002  p <0.02  p = NS  p <0.001  p = NS

------SOLAR 1 On-Rx Wk 4  ------  --------------  HALT C  --------------
Functional deterioration related to SBP occurring on Day 7 of treatment

DSI or MELD Score

Ongoing Ascites, Variceal Rx, Encephalopathy

SBP

SVR
Missed last test at Wk 48 due to GIB. Has varices, edema, encephalopathy.
Function Map for Chronic Liver Disease
PSC Patient during and after AIH Flare

**SHUNT (%)**: 100 80 60 40 20

- Healthy
- Mild Disease
- Moderate Disease
- Severe Disease

**Systemic HFR (mL/min/kg)**

- Baseline 1: 2/25/2011
- Baseline 2: 3/7/2011
- AIH Flare: 4/6/2012
- Recovery: 9/10/2012

**Portal HFR (mL/min/kg)**

**Recovery**
SHUNT and STAT can track progression or recovery from DILI.
- Quantify underlying hepatic reserve
- Identify the At-Risk Group
- Track progression or recovery from DILI
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