1. Defining and Monitoring Liver Disease in Chronic Hepatitis C: A Comparison of the Disease Severity Index (DSI) from the HepQuant SHUNT Test with Ishak Fibrosis Stage (IFS) from Liver Biopsy

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2. Background
A non- or minimally-invasive test of liver function to assess liver disease severity, progression, and treatment effects is desirable.

Objective
This study is a "head-to-head" comparison of the Disease Severity Index (DSI) from the HepQuant SHUNT liver function test with Ishak Fibrosis Stage (IFS) from liver biopsy in measuring baseline disease severity and monitoring disease progression in patients with chronic active hepatitis C (CHC) who were enrolled in the HALT-C Trial.

3. Subjects
There were 137 subjects who were followed long-term in the randomized phase of the HALT-C Trial, co-enrolled in the Quantitative Liver Function Ancillary study of HALT-C, and met the criteria for this study. The subject criteria were: active HCV infection with advanced fibrosis or compensated cirrhosis, completion of both liver biopsy and the HepQuant SHUNT test at both baseline (Base) and month 24 (M24), histology showing Ishak Fibrosis Stages F2 to F5, and follow-up for clinical outcome for up to 8.4 years. Subjects with F6 were excluded since they could not progress histologically. Clinical outcome was defined as increase in Child-Pugh score by 2 or more points, variceal hemorrhage, ascites, encephalopathy, SBP, or liver-related death.

4. Methods
The HALT-C protocol of clinical assessments, lab tests, procedures and centralized systems for data management have been reported (N Engl J Med 2008;359:2429-41; Hepatology 2011; 54:396-405).

Ishak Fibrosis Stage (IFS) was determined by a central committee of expert pathologists. DSI is the main output from the HepQuant SHUNT test, a dual cholate clearance test involving co-administration of 20 mg 13C-cholate intravenously and 40 mg d4-cholate orally with peripheral venous blood sampling at 5, 20, 45, 60, and 90 min. DSI ranges from 0 (healthy) to 50 (severe dysfunction). Difference between subjects with outcomes (N=19) vs. those without outcomes (N=118) at Base was evaluated by non-paired t-test. The change from Base to M24 in each subject (∆DSI and ∆IFS) was evaluated by paired t-test. Difference between subjects w outcomes vs. those w/o outcomes was evaluated by non-paired test for ∆DSI and ∆IFS.

5. Results: Baseline (Base)
Age – 50.3 ± 6.5 years (mean ± SD)
Sex (M:F) – 104:33
BMI – 28.9 ± 4.3

IFS – Higher IFS in subjects w outcomes vs. those w/o outcomes (p=0.0149 by non-paired t-test)

DSI – Higher DSI in subjects w outcomes vs. those w/o outcomes (p=0.0001 by non-paired t-test)*

*The association with outcomes was much more significant for Base DSI than Base IFS.

6. Results: Changes (∆) from Base to M24

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<thead>
<tr>
<th></th>
<th>All Subjects (N=137)</th>
<th>Subjects w Outcomes (N=19)</th>
<th>Subjects w/o Outcomes (N=118)</th>
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<tbody>
<tr>
<td>DSI Mean ± SD</td>
<td>17.95 ± 4.20</td>
<td>19.03 ± 5.73</td>
<td>21.80 ± 4.42</td>
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<td>DSI Mean ± SD</td>
<td>19.03 ± 5.73</td>
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<td>DSI Mean ± SD</td>
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<td>70.12 ± 12.21</td>
<td>80.24 ± 13.15</td>
<td>70.12 ± 12.21</td>
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Paired t-test p value
0.0069 0.0031 0.13

Change in Each Subject
IFS – Did not change significantly at M24 in any group.

DSI – Increased most significantly at M24 in subjects w outcomes (p=0.0031). Those w/o outcomes had a small increase in DSI that was not significant.

Difference Between Subjects w Outcomes vs. Those w/o Outcomes
IFS – The ∆IFS of subjects w outcomes was not significantly greater than the ∆IFS of subjects w/o outcomes (p=0.26 by non-paired t-test).

DSI – The ∆DSI of subjects w outcomes was significantly greater than the ∆DSI of subjects w/o outcomes (p=0.0026 by non-paired t-test).

7. Conclusions
➢ Baseline DSI and increase in DSI are associated with risk for clinical outcome.

➢ DSI could be a sensitive and minimally-invasive alternative to fibrosis staging by biopsy for assessing baseline disease severity and for monitoring chronological changes in chronic liver disease.

Financial disclosures: Gregory T. Everson and Steve M. Helmke are employees of HepQuant, LLC.