Is the benefit to treat patients with cirrhosis proven?

SAVINO BRUNO, MD
Professor of Medicine
Humanitas University Medicine
Rozzano (Milan), Italy
Multi-state Models to Improve Prognostic Scores

- Schematic representation of 5-year transitioning rates across stages and to death.
- Arrows represent transitions and the numbers represent transition rates.
- Analysis for the risk of death showed that this multistate model provides incremental prognostic value to the MELD, together with age and HCC.

Cumulative incidence of hepatic decompensation and hepatic mortality according to absence (stage 1) or presence (stage 2) of varices in 2 cohorts of HCV patients with compensated cirrhosis.

**Gomez EV, et al. J Hepatol 2013**


n = 352 patients

n = 402 patients
Liver – related mortality/O LT since first episode of decompensation.  
A three-years prospective study

<table>
<thead>
<tr>
<th>At risk</th>
<th>P-Y</th>
<th>Type of event</th>
<th>Event</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>188</td>
<td>352</td>
<td>Death/O LT</td>
<td>74</td>
<td>0.21</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HCC</td>
<td>24</td>
<td>0.07</td>
</tr>
</tbody>
</table>

HCV-related compensated cirrhosis: a condition with a wide heterogeneity of clinical, biochemical and histological features at different prognosis

F2 Metavir, F2 to 3 Ishak, LSM ≥ 6 Kpa < 9.5 Kpa (possible overlap with either less or more severe stage), APRI <0.5 (possible overlap)

**ADVANCED FIBROSIS stage**
(F3 Metavir, F3 to 4 Ishak, LSM ≥ 9.5 Kpa < 12.5 Kpa (possible overlap with either less or more severe stage), APRI >0.5 <1.5 (possible overlap)

**WELL COMPENSATED cirrhosis**
(F4 Metavir, F5 to 6 Ishak or LSM≥ 12.5 or 14,3 KPa#, usually no clinically significant portal hypertension**: HVPG ranging between 6, and 10 mmHg, no esophageal varices, **Child A5, MELD < 10**

**MARGINALLY COMPENSATED cirrhosis**
LSM: ≥ 20 KPa#, with moderate to severe portal hypertension§: HVPG ≥12 mmHg, ±esophageal varices, PLT ≤ 100000/mm3, albumin value < 35gr/dl, **Child A6, MELD ≥ 10**

**DECOMPENSATED**
Child B7 to C12. MELD >15, waiting for OLT

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#Castera L. Gastroenterology 2012
*Garcia Tsao G. et al, Hepatology 2010
§Qamar A. et al, Hepatology 2008

Boccaccio V., Bruno S. Liver International 2014
Baveno VI Consensus
New Concept: Compensated Advanced Chronic Liver Disease (cACLD)

The introduction of non invasive methods to diagnose fibrosis has allowed the early identification of patients with chronic liver disease at risk of developing clinically significant portal hypertension.

Does a biological plausibility exist in considering SVR a reliable surrogate marker of disease outcome?
Rates of cirrhosis regression in HCV patients who achieved SVR to IFN-based therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients with cirrhosis (n)</th>
<th>Months from SVR</th>
<th>Staging system</th>
<th>Regression rates (n/%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reichard et al. 1999</td>
<td>3</td>
<td>24-96</td>
<td>Scheuer</td>
<td>3 (100%)</td>
</tr>
<tr>
<td>Arif et al. 2003</td>
<td>6</td>
<td>6-72</td>
<td>Ishak</td>
<td>5 (83%)</td>
</tr>
<tr>
<td>George et al. 2009</td>
<td>8</td>
<td>56</td>
<td>Ishak</td>
<td>6 (75%)</td>
</tr>
<tr>
<td>Poynard et al. 2002</td>
<td>37</td>
<td>&lt;24</td>
<td>Metavir</td>
<td>25 (68%)</td>
</tr>
<tr>
<td>D’Ambrosio et al. 2012</td>
<td>38</td>
<td>48-104</td>
<td>Metavir</td>
<td>23 (61%)</td>
</tr>
<tr>
<td>Everson et al. 2008</td>
<td>40</td>
<td>6</td>
<td>Metavir</td>
<td>20 (50%)</td>
</tr>
<tr>
<td>Shiratori et al. 2000</td>
<td>24</td>
<td>12-120</td>
<td>Metavir</td>
<td>11 (46%)</td>
</tr>
<tr>
<td>Mallet et al. 2008</td>
<td>39</td>
<td>11</td>
<td>Metavir</td>
<td>17 (44%)</td>
</tr>
<tr>
<td>Pol et al. 2004</td>
<td>17</td>
<td>NA</td>
<td>Metavir</td>
<td>4 (24%)</td>
</tr>
<tr>
<td>Maylin et al. 2008</td>
<td>14</td>
<td>6</td>
<td>Metavir</td>
<td>9 (64%)</td>
</tr>
</tbody>
</table>

Effect of Treatment on HVPG According to Virologic Response

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Sustained viral response</th>
<th>Nonresponse&lt;sup&gt;a&lt;/sup&gt;</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HVPG, mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pretreatment</td>
<td>9.0 ± 4.0</td>
<td>8.0 ± 3.1</td>
<td>NS</td>
</tr>
<tr>
<td>Posttreatment</td>
<td>6.9 ± 3.4</td>
<td>8.6 ± 3.7</td>
<td>NS</td>
</tr>
<tr>
<td>Change in HVPG, mm Hg</td>
<td>−2.1 ± 4.6</td>
<td>0.6 ± 2.8</td>
<td>.05</td>
</tr>
<tr>
<td>≧20% decrease in HVPG&lt;sup&gt;b&lt;/sup&gt;</td>
<td>5/7 (71%)</td>
<td>4/20 (20%)</td>
<td>.01</td>
</tr>
</tbody>
</table>

<sup>a</sup>Includes primary nonresponders and relapsers.

<sup>b</sup>Includes only subjects with baseline HVPG of greater than 5 mm Hg.
Impact of SVR on the development of esophageal varices

SVR prevents de-novo development of esophageal varices in compensated HCV cirrhosis

218 Pts

Untreated
n= 69

Treated
n= 149

Varices (n)  Varices (%)

Untreated
21
30,4

Treated

Median follow-up:

Untreated
11,4 years

Treated
7,5 years

p = ns

p = 0,0001 vs "Untreated" and "Non-SVR"

Varices (n)

No SVR
115
34

SVR
89
30

65
27

35
17

7
7

0
0

 Patients at risk

*since antiviral treatment initiation

Cumulative incidence of liver-related complications (A) and liver-related mortality (B) in patients with HCV-related histologically proven cirrhosis stratified according to response to IFN (P=0.001 by log-rank test).

Cumulative incidence of HCC in 883 patients with HCV-related histologically proven cirrhosis stratified according to response to IFN (P=0.001 by log-rank test)

Survival Outcomes in Patients with Advanced Hepatic Fibrosis Due to HCV

Van der Meer AJ, et al. JAMA 2012
Survival after P/R treatment in 440 patients with HCV cirrhosis, C-P A5-6 (mean follow-up time 7.7 yrs)

No esophageal varices (Stage1) before P/R
- Survival probability (%)
- Log rank p = 0.001

Esophageal varices (Stage2) before P/R
- Survival probability (%)
- Log rank p = 0.003

Di Marco V, et al. submitted
A Patients with SVR

- Observed deaths: 28
- Expected deaths: 28.1
- SMR: 1.00 (0.72-1.35)

B Untreated patients

- Observed deaths: 241
- Expected deaths: 80.0
- SMR: 3.01 (2.64-3.42)

C Patients without SVR

- Observed deaths: 309
- Expected deaths: 80.3
- SMR: 3.85 (3.43-4.30)

D Decompensated patients

- Observed deaths: 91
- Expected deaths: 13.6
- SMR: 6.70 (5.39-8.22)
Multivariate analysis of predictors of outcome in patients with SVR

<table>
<thead>
<tr>
<th></th>
<th>Overall mortality (28 deaths)</th>
<th>Liver related deaths (18 events*)</th>
<th>Hepatic decompensation (11 events)</th>
<th>Hepatocellular carcinoma (20 Cases)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>55-59 vs. &lt;55 years</td>
<td>2.63 (0.67-10.3)</td>
<td>0.22</td>
<td></td>
<td>2.52 (0.49-12.9)</td>
</tr>
<tr>
<td>60-64 vs. &lt;55 years</td>
<td>5.54 (1.57-19.5)</td>
<td>0.008</td>
<td></td>
<td>3.64 (0.72-18.3)</td>
</tr>
<tr>
<td>≥65 vs. &lt;55 years</td>
<td>3.80 (0.88-13.4)</td>
<td>0.07</td>
<td></td>
<td>4.85 (0.92-25.7)</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>men vs. women</td>
<td></td>
<td>6.80 (1.51-30.6)</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td><strong>Alfa-fetoprotein</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥10 ng/mL vs. &lt;10 ng/mL</td>
<td></td>
<td></td>
<td></td>
<td>7.19 (2.06-25.1)</td>
</tr>
<tr>
<td><strong>Albumin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤3.5 g/dL vs. &gt;3.5 g/dL</td>
<td>4.32 (1.12-16.7)</td>
<td>0.03</td>
<td>10.7 (2.35-48.8)</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>Platelets</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;80,000/mL vs. ≥80,000/mL</td>
<td>2.94 (1.24-9.92)</td>
<td>0.01</td>
<td>4.47 (1.59-12.6)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

Hazard Ratio (HR) and 95% confidence intervals (CI) obtained from stepwise Cox proportional hazards regression models. All factors that did not satisfy the criteria (Pr Chi-square <0.10) to stay in the model in were removed in a step down phase.

* Including 4 OLTs
## IFN–BASED Tx in Decompensated Cirrhosis

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Rx</th>
<th>EOT</th>
<th>SVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iacobellis</td>
<td>66</td>
<td>Peg/RBV</td>
<td>49%</td>
<td>20%</td>
</tr>
<tr>
<td>Forns</td>
<td>51</td>
<td>Peg/RBV</td>
<td>29%</td>
<td>20%</td>
</tr>
<tr>
<td>Tekin</td>
<td>20</td>
<td>Peg/RBV</td>
<td>45%</td>
<td>30%</td>
</tr>
<tr>
<td>Annichiarico</td>
<td>15</td>
<td>Peg/RBV</td>
<td>47%</td>
<td>20%</td>
</tr>
<tr>
<td>Everson</td>
<td>124</td>
<td>IFN/RBV</td>
<td>46%</td>
<td>24%</td>
</tr>
<tr>
<td>Forns</td>
<td>30</td>
<td>IFN/RBV</td>
<td>30%</td>
<td>20%</td>
</tr>
<tr>
<td>Thomas</td>
<td>20</td>
<td>IFN</td>
<td>60%</td>
<td>20%</td>
</tr>
<tr>
<td>Amarapukar</td>
<td>18</td>
<td>IFN/RBV</td>
<td>61%</td>
<td>38%</td>
</tr>
<tr>
<td>Crippin</td>
<td>15</td>
<td>IFN/RBV</td>
<td>33%</td>
<td>0%</td>
</tr>
<tr>
<td><strong>TOTALS</strong></td>
<td>359</td>
<td></td>
<td>44%</td>
<td>24%</td>
</tr>
</tbody>
</table>

**HCV-RNA Neg**

Cumulative survival after IFN–BASED treatment in patients with decompensated cirrhosis

Deaths and AEs in the first 6 months of follow-up according to treatment or not

Safety and tolerability

Sofosbuvir and Ribavirin in patients with cirrhosis and portal hypertension ± decompensation

On Treatment Virologic Response

*1 patient was a non-responder at Week 8.

Afdhal N, et al. EASL 2014 OC #68
Sofosbuvir and Ribavirin in patients with cirrhosis and portal hypertension ± decompensation

Laboratory Results: Mean Changes from Baseline to Week 24

- **Platelets (103/µL)**
  - CPT A: -9, p=0.003
  - CPT B: -1, p=NS

- **Albumin (g/dL)**
  - CPT A: 0.5, p=0.001
  - CPT B: 0.4, p=0.001

♦ Changes in PT/INR were not observed in either CPT A or B patients with treatment or observation

Afdhal N, et al. EASL 2014 OC #68
Mean Change in MELD Score from Baseline through Week 24

CPT A Patients (n=20)

CPT B Patients (n=29*)

*1 patient had only a baseline MELD score before withdrawing consent and is not depicted.

Afdhal N, et al EASL 2014 OC #68
Sofosbuvir and Ribavirin in patients with cirrhosis and portal hypertension ± decompensation

Effect of SOF+RBV on Hepatic Venous Pressure Gradient (HVPG)

- There were clinically meaningful improvements in portal hypertension in addition to improvements in liver biochemistry, CTP and MELD scores
- The effect of SVR12 and viral suppression on HVPG is being monitored at 1 year post-treatment

A reduction in HVPG ≥20% or below the 12-mm Hg threshold markedly reduces the risk of variceal bleeding, and varices may decrease in size

Afdhal N, et al. EASL 2014 OC #68
Combined Efficacy from the SOLAR-1 and SOLAR-2
LDV+SOF+RBV for 12/24 weeks

Improvement n=60%
Worsening n=23%

Change in MELD

Gane E, et al. AASLD 2015

Total n=250 patients had no assessment at follow-up week 12
SUMMARY AND KEY CONCEPT

HCV-related cirrhosis:
a condition with a wide heterogeneity of clinical,
biochemical and histological features at different risk of
developing complications and with still hidden
characteristics which make unpredictable the benefit of
treatment irrespective to the achievement of SVR

THE NO-RETURN POINT
TAKE HOME MESSAGE 1
Clinical benefits in HCV Compensated Advanced Chronic Liver Disease (cACLD) (Well Compensated Cirrhotic Patients) Achieving a Sustained Virological Response (SVR)

Compared to NON SVR /Untreated patients does a SVR led to

Regression of cirrhosis at histology
Prevention of esophageal varices development
Prevention of clinical decompensation
Reduction of hepatocellular carcinoma incidence (HCC)
Reduction of liver-related mortality
Life expectancy similar to general population

Reduction of all-cause mortality

Yes
Yes
Yes
Yes
Yes
Doubtfoul, TBD
TAKE HOME MESSAGE 2
Clinical benefits in HCV marginally compensated or decompensated Cirrhotic Patients Achieving a Sustained Virological Response (SVR)

Does a SVR led to

- Regression of cirrhosis: No data
- Reversal of clinical decompensation: Partial, may be transient
- Reduction of hepatocellular carcinoma (HCC) incidence: No data, TBD
- De-listing of liver transplant: Few data
- Reduction of liver-related mortality: Likely
- Reduction of all-cause mortality: No data, TBD
Thank you

The opinions expressed here represent the opinion of the author. All products mentioned in the presentation should be applied according to the Product Labels.
Baveno VI Consensus Statements
Criteria to Suspect cACLD

- Liver stiffness by transient elastography is **sufficient** to suspect cACLD in asymptomatic subjects with known causes of CLD (1b;A)

- Transient elastography often has false positive results; hence 2 measurements on different days are recommended in fasting conditions (5;D)

- **TE values <10 kPa in the absence of other known clinical signs rule-out cACLD; values between 10 and 15 kPa are suggestive of cACLD but need further test for confirmation; values >15 kPa are highly suggestive of cACLD** (1b;A)
Sofosbuvir and Ribavirin Prevent Recurrence of HCV Infection After Liver Transplantation

No recurrence/recurrence by days HCV-RNA continuously target not detected (TND) before liver transplantation

The Evolutionary Stages of Hepatitis C Infection

Female sex, young age at infection

Normal liver → Acute infection → Chronic infection (50-80%) → Chronic hepatitis → Cirrhosis (20%) → HCC (1-4%/yr) → Decompensation (3%/yr)

≤ 20 years

Alcohol, steatosis and/or IR, coinfections, old age, male sex

Rates of Cirrhosis Regression According to the METAVIR Scoring System

Stage of cirrhosis

- Compensated
  - No CSPH
  - CSPH

Goal of treatment

- Prevent increase in portal pressure
- Prevent decompensation

Type of treatment

- Etiological therapies
- Antifibrotic therapies
- Lifestyle measures

Decompensated

- Treat complications and prevent recurrences

Time

Courtesy of Dr. Rafael Bañares
# Infections occurring during Peg IFN+RBV treatment

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Pts n.</th>
<th>Type of Pts</th>
<th>Infections</th>
<th>Factors associated</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>255</td>
<td>F3-F4 Metavir 17%</td>
<td>12% (24 / 100 pts / yr)</td>
<td>Neutropenia only in respiratory infection</td>
</tr>
<tr>
<td>2</td>
<td>319</td>
<td>F3-F4 Metavir 34%</td>
<td>23% (41/100 pts / yr)</td>
<td>Age &gt; 60 (not neutropenia)</td>
</tr>
<tr>
<td>3</td>
<td>119</td>
<td>Cirrhosis 15%</td>
<td>18%</td>
<td>None with neutropenia</td>
</tr>
<tr>
<td>4</td>
<td>30</td>
<td>OLT listed (50% CTP A)</td>
<td>13%</td>
<td>n.a.</td>
</tr>
<tr>
<td>5</td>
<td>66</td>
<td>Decompensated cirrhosis</td>
<td>28% (0.45 / 1000) pts / mo. (OR = 2.95 (0.93-9.3))</td>
<td>CTP C; neutrophils &lt; 900</td>
</tr>
</tbody>
</table>

SOLAR-1: LDV+SOF+RBV in G1/G4 HCV patients with decompensated cirrhosis

Change in MELD Score from Baseline to Follow-up Week 4 in CPT B and C Patients

The Impact of Cirrhosis Regression on Clinical Events

Follow-up post-SVR 11 months: cirrhosis regression in 17/39 (44%) No Events among Reversers

Survival Outcomes in Patients with Advanced Hepatic Fibrosis Due to HCV
Baveno VI Consensus Statements
Stage of cirrhosis and goal of treatment

• Management of patients with cirrhosis should focus on preventing the advent of all complications whilst in the compensated phase (1b;A).

• Due to different prognosis, patients with compensated cirrhosis should be divided in those with and without clinically significant portal hypertension (CSPH) (1b;A). The goal of treatment in the first is to prevent CSPH while in the second is to prevent decompensation.

Chronic liver disease with no signs of liver cirrhosis

Chen (n = 702)

- 14% LSM > 13-13.6 Kpa
- 100%

Augustin (n = 173)

- 8% LSM > 13-13.6 Kpa
- 100%

Kim (n = 2876)

- 10% LSM > 13-13.6 Kpa
- 100%

PATIENTS WITH OCCULT ADVANCED Chronic liver disease

Modified from Augustin S et al. Baveno VI Proceedings,
Compensated Advanced Chronic Liver Disease

For these patients, the alternative term “compensated advanced chronic liver disease (cACLD)” has been proposed to better reflect that the spectrum of severe fibrosis and cirrhosis is a continuum in asymptomatic patients, and that distinguishing between the two is often not possible on clinical grounds.

These patients deserve:

- Closer follow-up
- HCC screening
- Consider evaluation for varices and CSPH

Outcome of 352 patients with compensated cirrhosis due to HCV infection

<table>
<thead>
<tr>
<th>Antiviral therapy</th>
<th>Patients N (%)</th>
<th>Hepatic decompensation N (% per year)</th>
<th>Hepatocellular carcinoma N (% per year)</th>
<th>Hepatic Mortality† N (% per year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated</td>
<td>159 (45%)</td>
<td>62 (3.3%)</td>
<td>54 (2.8)</td>
<td>61 (2.9)</td>
</tr>
<tr>
<td>Non-SVR</td>
<td>165 (47%)</td>
<td>70 (3.6%)</td>
<td>57 (2.9)</td>
<td>72 (3.3)</td>
</tr>
<tr>
<td>SVR</td>
<td>28 (8%)</td>
<td>2 (0.4%)</td>
<td>7 (1.7)</td>
<td>5 (1.1)</td>
</tr>
<tr>
<td>P-value (Untreated vs. non SVR)</td>
<td>0.58</td>
<td>0.83</td>
<td>0.46</td>
<td></td>
</tr>
<tr>
<td>P-value (Non SVR vs. SVR)</td>
<td>0.00005</td>
<td>0.17</td>
<td>0.01</td>
<td></td>
</tr>
</tbody>
</table>

SVR: Sustained Virological Response; † includes Orthotopic Liver Transplantation (OLT).

*Updated from Bruno S, et al. Am J Gastroenterol 2009*
Sofosbuvir and Ribavirin in patients with cirrhosis and portal hypertension ± decompensation

Laboratory Results: Mean Changes from Baseline to Week 24

- **Bilirubin (mg/dL)**
  - CPT A: 0.5, Observation 24 weeks: 0.2
  - CPT B: -0.2, Observation 24 weeks: -0.1

- **ALT (U/L)**
  - CPT A: -72, Observation 24 weeks: 0
  - CPT B: -75

Afdhal N, et al. EASL 2014 OC #68