Which hepatitis C patients with advanced liver disease should be treated NOW with first generation DAA?

SAVINO BRUNO, MD

Director

Internal Medicine and Hepatology Unit
AO Fatebenefratelli e Oftalmico, Milano
HCV-related advanced liver disease: a condition with a wide heterogeneity of clinical features

**COMPENSATED (very early stage)**

Histology (F3 Metavir, F4 Ishak) or Liver Stiffness (LS): ≥ 9.5<12.5 KPa#

Recent, often incidentally, diagnosis of full cirrhosis at histology (F4 Metavir, F5/6 Ishak) or LS: ≥ 12.5 KPa#. No clinically significant portal hypertension*: HVPG ≥ 6 mmHg < 10 mmHg, no varices, **Child A**

**COMPENSATED (advanced stage)**

Moderate to severe portal hypertension§Older diagnosis obtained either by histology or clinically based, PLT ≤ 100000 /mm$^3$, lower albumin value, HVPG ≥ 10/12 mmHg, ± esophageal varices, **Child A**

**DECOMPENSATED**

**Child B** or more, MELD >15 and/or waiting for OLT for ESLD

*Boccaccio V and Bruno S. Liver International 2014, in press

*Castera L. Gastroenterology 2012
*Garcia Tsao G. et al, Hepatology 2010
§Qamar A. et al, Hepatology 2008
“Although favorable evidence is growing, there isn’t enough long-term research to know for certain if treatment decreases the risks from complications from chronic hepatitis C infection, such as liver cirrhosis, liver cancer, the need for liver transplantation, or death. In addition, combination therapy is very expensive and can cause a wide range of side effects, some serious”

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Rates of Cirrhosis Regression According to the METAVIR Scoring System

Post hoc analysis of the MIST study

Cirrhosis Regression in 23 (61%) Patients

The Impact of SVR on the “de novo” Development of Esophageal Varices: Pre-primary Profilaxis

Cumulative incidence of esophageal varices in 149 IFN ± RBV-treated patients with compensated HCV-induced (stage 1) cirrhosis according to response to therapy

Survival Outcomes in Patients With CHC and Advanced Hepatic Fibrosis With and Without SVR

Van der Meer AJ, et al. JAMA 2012
HCV-related advanced liver disease: a condition with a wide heterogeneity of clinical features

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

Boccaccio V and Bruno S. Liver International 2014, in press
Impact of severe Fibrosis on SVR

Naive genotype 1 patients (ADVANCE)

SVR according to fibrosis score and historical response in REALIZE study

Relapsers

Partial responders

Null responders

SVR %

Post hoc analysis of SPRINT-2 and RESPOND-2 studies in patients with advanced fibrosis/cirrhosis

<table>
<thead>
<tr>
<th></th>
<th>All Patients</th>
<th>Advanced Liver Disease (F3/4)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SPRINT-2 n=1097</td>
<td>RESPOND-2 n=403</td>
</tr>
<tr>
<td>Male, %</td>
<td>60</td>
<td>67</td>
</tr>
<tr>
<td>Black, %</td>
<td>14</td>
<td>12</td>
</tr>
<tr>
<td>Region, % - North America</td>
<td>73</td>
<td>71</td>
</tr>
<tr>
<td>- Europe</td>
<td>24</td>
<td>29</td>
</tr>
<tr>
<td>- Latin America</td>
<td>3</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Age, mean years ± SD</td>
<td>49 ± 9</td>
<td>53 ± 8</td>
</tr>
<tr>
<td>BMI, mean ± SD</td>
<td>28 ± 5</td>
<td>28 ± 5</td>
</tr>
<tr>
<td>HCV subtype**, % - 1a</td>
<td>64</td>
<td>59</td>
</tr>
<tr>
<td>- 1b</td>
<td>33</td>
<td>40</td>
</tr>
<tr>
<td>Viral load &gt;800,000 IU/mL, %</td>
<td>85</td>
<td>88</td>
</tr>
<tr>
<td>Prior, % - Non-responder</td>
<td>NA</td>
<td>36</td>
</tr>
<tr>
<td>- Relapser</td>
<td>NA</td>
<td>64</td>
</tr>
<tr>
<td>- F3 N°(%)</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>- F4</td>
<td>5</td>
<td>12</td>
</tr>
<tr>
<td>IL28***, % - CC</td>
<td>30</td>
<td>24</td>
</tr>
<tr>
<td>- non CC</td>
<td>70</td>
<td>76</td>
</tr>
</tbody>
</table>

*p<0.05 F3/4 vs F0/1/2; **NS5B sequencing by Virco
***Based on n=655 in SPRINT-2 and n=258 in RESPOND-2
SPRINT-2 and RESPOND-2: Overall SVR by F4

COMBINED STUDIES (SPRINT-2 and RESPOND-2):
SVR by Week 4 Lead-in Response in F4

COMBINED STUDIES (SPRINT-2 and RESPOND-2)
SVR by Early (TW8 HCV-RNA neg) and Late (TW8 HCV-RNA pos) Responders in F4

Meta-Analysis of Cirrhotic Patients in Boceprevir Trials

- **Sources of data**
  - SPRINT-2
  - RESPOND-2
  - PEGASYS study
  - EPO study
  - Interim data from PROVIDE

- **Total of 212** F4 patients (180 on BOC/PR, 32 on PR)
  - Dx by central reading of liver biopsies

- **Aims**
  - to consolidate results from SPRINT2/RESPOND2 in a larger population of patients
  - to provide predictors of SVR by multiple logistic regression analysis
  - to evaluate risk of severe AE’s, as suggested by real-life study (Cupic)
  - to develop newer reliable futility which will enable sparing cost and risk of therapy
  - to assess whether short treatment duration (i.e. 36 weeks) might be used in a subset of patients
Overall SVR by BOC/PR in F4 Patient Subgroups

Vierling JM, et al. EASL 2013
Overall SVR by F3 and F4

Vierling JM, et al. EASL 2013
SVR according to treatment week 4 virologic response in F3 and F4

47/70 (67%) ≥1 log HCV-RNA decline at TW4
10/35 (29%) <1 log HCV-RNA decline at TW4

85/128 (66%) ≥1 log HCV-RNA decline at TW4
10/48 (21%) <1 log HCV-RNA decline at TW4

Vierling JM, et al. EASL 2013
Response to BOC/PR in F4 Patients: SVR by TW8 HCV-RNA detectability

Vierling JM, et al. EASL 2013
SVR according to treatment week 8 virologic response* in F3 and F4

*Treatment-naïve and previous treatment failures combined

Vierling JM, et al. EASL 2013
The importance of TW 8 HCV-RNA decline in patients with cirrhosis (F4 Metavir) during BOC-therapy

43% HCV-RNA undetectable at wk 8 → SVR 89%

57% HCV-RNA detectable at wk 8

≥ 3 log decline

82% SVR 35 %

< 3 log decline

18% SVR 0

0/17

* Vierling JM, et al., EASL 2013
The importance of TW 8 HCV-RNA decline in patients with advanced fibrosis/cirrhosis during BOC-therapy.

HCV-RNA detectable at wk 8

\[
\begin{align*}
&\leq 1000 \text{ U.I.} & > 1000 \text{ U.I.} \\
&88\% & 12\% \\
&\text{SVR 63\%} & \text{SVR 0} \\
&150/238 & 0/31
\end{align*}
\]

Data on file

\[ P<0.0001 \]
SVR according to treatment duration in patients with undetectable HCV RNA at TW 8*

SVR (%, 95% CI)

<table>
<thead>
<tr>
<th>Duration</th>
<th>F3 Patients</th>
<th>F4 Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;28 weeks</td>
<td>4/6</td>
<td>3/7</td>
</tr>
<tr>
<td>28-36 weeks</td>
<td>15/18</td>
<td>16/18</td>
</tr>
<tr>
<td>36-40 weeks</td>
<td>6/6</td>
<td>8/9</td>
</tr>
<tr>
<td>&gt;40 weeks</td>
<td>17/18</td>
<td>38/39</td>
</tr>
</tbody>
</table>

*Treatment-naïve and previous treatment failures combined

Vierling JM, et al. EASL 2013
Multivariate Logistic Regression Analysis
Predictors of SVR in F3/F4 Patients Receiving BOC/PR

- TW8: undetectable vs. detectable HCV-RNA
  - Odds Ratio: 10.57 (5.23 – 21.36); P<0.0001
- TW4: ≥1 log decline vs. <1 log decline
  - Odds Ratio: 2.64 (1.33 – 5.21); P=0.0053
- Male vs. female
  - Odds Ratio: 2.23 (1.18 – 4.24); P=0.0141
- Baseline viral load ≤800,000 IU/mL vs. >800,000 IU/mL
  - Odds Ratio: 2.55 (1.05 – 6.20); P=0.0383
- G1b vs. G1a
  - Odds Ratio: 1.76 (0.90 – 3.44); P=0.0971
- Non-black vs. black
  - Odds Ratio: 1.08 (0.43 – 2.72); P=0.8636

Vierling JM, et al. EASL 2013
### Three Cirrhotic Patients With Potential Hepatic Decompensation or Sepsis

<table>
<thead>
<tr>
<th>Patient ID (Study)</th>
<th>Baseline Data</th>
<th>Event</th>
<th>Treatment regimen (weeks of treatment)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>016301 (PROVIDE)</td>
<td>Male, 64 y; F4. hx of ascites Platelets 108K Albumin 3.7 g/L</td>
<td>Decompensated cirrhosis with ascites and encephalopathy (confusion)</td>
<td>BOC/P/R (TW 6)</td>
<td>Discontinued treatment; events resolved</td>
</tr>
<tr>
<td>012072 (RESPOND-2)</td>
<td>Female, 51 y; F4 Platelets 170K Albumin 3.5 g/L</td>
<td>Bleeding esophageal varices and portal hypertension</td>
<td>P/R (TW2)</td>
<td>Discontinued treatment; events resolved</td>
</tr>
<tr>
<td>000603 (PEG2a study)</td>
<td>Male, 48 y; F4 Diabetic, IVDU Platelets 135K Albumin 3.8 g/L</td>
<td>Multi-organ failure with total bilirubin peak 17.4 mg/dL (Staph. pneumonia, resulting in multi-organ failure)</td>
<td>BOC/P/R (TW12)</td>
<td>Died of multi-organ failure</td>
</tr>
</tbody>
</table>

Vierling JM, et al. EASL 2013
Proposed Treatment Algorithm for Patients with advanced fibrosis/cirrhosis Treated with BOC/PR (naïve and previous treatment failures)

**All Patients**
- Lead-in PR 4 weeks

**TW4**
- Add BOC

**TW8**
- <3 log<br>≥ 1000 IU/ml
  - STOP

**TW8**
- Undetectable<br><1000 IU/ml
  - Continue to Wk 12

**TW12**
- Detectable
  - STOP

**TW12**
- Undetectable
  - Continue to Wk 48*

* Consider stopping based on low chance of SVR in F3 and F4 patients with detectable HCV-RNA and <3 log10 decline in HCV-RNA from baseline (SVR=0/22; 0%; 95% CI [0, 13]).
† Consider stopping treatment of treatment-naïve patients after TW28 if undetectable HCV RNA from TW8 through TW24
HCV-related advanced liver disease: a condition with a wide heterogeneity of clinical features

COMPENSATED (advanced stage)
Moderate to severe portal hypertension§Older diagnosis obtained either by histology or clinically based, PLT ≤ 100000 /mm³, lower albumin value, HVPG ≥ 10/12 mmHg, ± esophageal varices, ± previous episode of decompensation, Child A

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

Boccaccio V, Bruno S. Liver International 2014, in press
CUPIC SVR12 rates and safety (ANRS CO20-CUPIC) - EASL 2013

<table>
<thead>
<tr>
<th>Undetectable HCV RNA (ITT)</th>
<th>BOC n = 190</th>
<th>TVR n = 295</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 12</td>
<td>118(62)</td>
<td>239(81)</td>
</tr>
<tr>
<td>Week 24</td>
<td>128(67)</td>
<td>200(68)</td>
</tr>
<tr>
<td>Week 48 (EOT)</td>
<td>108(57)</td>
<td>165(56)</td>
</tr>
<tr>
<td>SVR$_{12}$ (Total)</td>
<td>79(41)</td>
<td>118(40)</td>
</tr>
</tbody>
</table>

| SVR$_{12}$ in relapsers    | 43/85(51)   | 61/116(53)  |
| SVR$_{12}$ in partial responders | 32/80(40)  | 43/135(32)  |
| SVR$_{12}$ in null responders | 1/9(11)    | 8/28(29)    |

| SAE                        | 51.0%       | 54.2%       |
| Death                      | 1.6%        | 2.4%        |
| Infections                 | 4.2%        | 9.1%        |
| Hepatic decompensation     | 4.7%        | 5.1%        |
| Anemia <8g/dl or blood tx  | 10%/13.7%   | 12.9%/18%   |

Fontaine H, et al. EASL 2013
Multivariate analysis: baseline predictors of severe complications*

<table>
<thead>
<tr>
<th>Predictors</th>
<th>OR</th>
<th>95%CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prothrombin Time (per unit decrease)</td>
<td>1.03</td>
<td>1.01-1.06</td>
<td>0.038</td>
</tr>
<tr>
<td>Age (per year increase)</td>
<td>1.05</td>
<td>1.01-1.11</td>
<td>0.025</td>
</tr>
<tr>
<td>Platelet count ≤100,000/ mm³</td>
<td>3.19</td>
<td>1.32-7.73</td>
<td>0.0098</td>
</tr>
<tr>
<td>Albumin level &lt;35 g/L</td>
<td>4.95</td>
<td>2.04-12.01</td>
<td>0.0004</td>
</tr>
</tbody>
</table>

* Death, severe infection and hepatic decompensation, n=32

## CUPIC: Risk of Occurrence of Death or Severe Complications

<table>
<thead>
<tr>
<th>Factors</th>
<th>Platelets count $&gt;100,000/\text{mm}^3$</th>
<th>Platelets count $\leq 100,000/\text{mm}^3$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin $\geq 35$ g/L</td>
<td>3.4 % (10/298)</td>
<td>4.3 % (3/69)</td>
</tr>
<tr>
<td>Albumin $&lt; 35$ g/L</td>
<td>7.1 % (2/28)</td>
<td>44.1 % (15/34)</td>
</tr>
</tbody>
</table>

Boceprevir: virological response (ITT)

Patients with undetectable HCV RNA (%)

<table>
<thead>
<tr>
<th>Week</th>
<th>4%</th>
<th>51%</th>
<th>62%</th>
<th>65%</th>
<th>67%</th>
<th>57%</th>
<th>41%</th>
</tr>
</thead>
<tbody>
<tr>
<td>W4</td>
<td>31</td>
<td>190</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>W8</td>
<td>97</td>
<td>190</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>W12</td>
<td>118</td>
<td>190</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>W16</td>
<td>124</td>
<td>190</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>W24</td>
<td>128</td>
<td>190</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>W48</td>
<td>108</td>
<td>190</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>W60</td>
<td>79</td>
<td>190</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: The data shows the percentage of patients with undetectable HCV RNA at different time points (W4, W8, W12, W16, W24, W48, W60) during the treatment with Boceprevir.
Telaprevir: virological response (ITT)

Patients with undetectable HCV RNA (%)

<table>
<thead>
<tr>
<th>Time (W)</th>
<th>Week 4</th>
<th>Week 8</th>
<th>Week 12</th>
<th>Week 16</th>
<th>Week 24</th>
<th>Week 48</th>
<th>Week 60</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>49%</td>
<td>79%</td>
<td>81%</td>
<td>77%</td>
<td>68%</td>
<td>56%</td>
<td>40%</td>
</tr>
</tbody>
</table>
Triple therapy for HCV infection in patients with compensated liver cirrhosis: lessons learned from the first real-world experience

- n=48 cirrhotic pts, 31% naïve, platelets 144/nl
- 50% anemia <10g/dl, 27<8.5g/dl, dose reduction in 50%
- TVR 33 (69%), BOC 15 (31%)

<table>
<thead>
<tr>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelets &lt;110/nl and Child-Pugh Score &gt;5 n=7</td>
<td>Platelets &lt;110/nl or Child-Pugh Score &gt;5 n=16</td>
<td>Platelets ≥110/nl and Child-Pugh Score 5 n=20#</td>
</tr>
<tr>
<td>Treatment Failure</td>
<td>100% (n=7/7)</td>
<td>69% (n=11/16)</td>
</tr>
<tr>
<td>SAE</td>
<td>57% (n=4/7)</td>
<td>63% (n=10/16)</td>
</tr>
<tr>
<td>Either SAE or Treatment Failure</td>
<td>100%</td>
<td>94%</td>
</tr>
</tbody>
</table>

- Almost every patient (96%; n=22/23) with a Child-Pugh Score >5 and/or baseline platelets <110/nl (Group A/B) experienced either a treatment failure and or at least one SAE until EOT

HCV-related advanced liver disease: a condition with a wide heterogeneity of clinical features

**DECOMPENSATED**

- **Child B** or more, MELD >15 and/or
- waiting for OLT due to ESLD

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

*Boccaccio V and Bruno S. Liver International 2014, in press*
Registrational Real world

Stage of cirrhosis

Efficacy

Tolerability
Treat vs Deferring Therapy in patients with “very early” stage compensated advanced liver disease

**Treat**
- Successful treatment will stop progression of the disease
- Overall SVR rates acceptable
- Safety profile manageable
- Many patients already “warehoused” awaiting DAAs
- Emerging futility rules which enables to early identify the likelihood of response will further enhance the assessment of Risk-Cost/Benefit

**Defer**
- Short-term prognosis favourable
Treating vs Deferring Therapy in compensated Cirrhotic patients with moderate to severe portal hypertension

**Treat**

- Short-term prognosis unfavourable
- Overall SVR rates acceptable in a subset of patients
- Will the “around-the-corner” 2nd generation treatment be sustainable by Health Care Systems?
- Baseline characteristics of single individual and emerging early futility rules which enables to predict the risk of life-threatening adverse events and the likelihood of SVR will further enhance the assessment of Risk-Cost/Benefit

**Defer**

- Safety profile concerns
- Risk vs benefit questionable in a subset of patients
- Potential for better treatment, with higher response rates fewer adverse events, shorter duration soon available by compassionate use
Treating vs Deferring Therapy in decompensated or waited for OLT Cirrhotic patients

Treat

- Short-term prognosis extremely poor

Defer

- SVR rates unknown, risk vs benefit questionable
- Better treatment options, with higher response rates, fewer adverse events, shorter duration soon available by compassionate use
Treatment Milestones:
The importance of futility rules

- Futility rules for HCV treatments define thresholds for virologic response without which SVR is very unlikely to occur
- Stopping treatment for futility limits adverse events, cost, and the risk of resistance
- Ensure pts understand futility rules before starting therapy
- “The earlier is the futility the higher is the benefit”
Thank you for your attention!

The opinions expressed here represent the opinion of the author. All products mentioned in the presentation should be applied according to the Product Labels.
LAST BUT NOT LEAST

Because F3 and F4 (mainly treatment-naïve) patients treated with BOC with undetectable viral load at treatment week 8 achieved similar SVR rates with durations of treatment between 28 and 40 weeks compared to ≥40 weeks, therapy of these subjects might be stopped after week 28 if the regimen is poorly tolerated.
SVR rates (%) in F3-4 PATIENTS POORLY RESPONSIVENESS TO IFN according to GENOTYPE and baseline HVL (>2,000,000 U.I.)

COMBINED SPRINT 2 AND RESPOND 2 STUDIES

Bruno S, et al, J Hepatol 2013
Mean Hb value during treatment in F4

Grade 0 = ≥11.0 g/dL; Grade 1 = 9.5 to <11.0 g/dL; Grade 2 = 8.0 to <9.5 g/dL; Grade 3 = 6.5 to <8.0 g/dL; Grade 4 = <6.5 g/dL

Improved survival in hepatitis C patients developing hepatocellular carcinoma after sustained virologic response to interferon-based therapy

Cohort 1: 307
Cohort 2: 352

659

Untreated: 307

IFN-treated

352

SVR: 71 (20%)

HCC: 11 (15%)

Non-SVR: 281 (80%)

HCC: 94 (33%)

Decompensated at diagnosis 16

HCC on Study 78 (28%)

Bruno S, Colombo M et al, EASL 2012
Incidence of Liver-Related Decompensation in patients developing HCC According to prior IFN Virological Response

![Graph showing cumulative incidence of liver-related decompensation over time since HCC diagnosis]
Mortality in patients developing HCC According to prior IFN Virological Response

<table>
<thead>
<tr>
<th>Time since HCC diagnosis</th>
<th>Patients at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SVR</td>
</tr>
<tr>
<td></td>
<td>Non SVR</td>
</tr>
<tr>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>5+</td>
<td></td>
</tr>
</tbody>
</table>

Log-Rank P=0.0440
SVR poorly responsiveness (TW4, <1log decline) F4 patients according to viral load and genotype

Vierling JM, et al. EASL 2013