How to optimize current therapy of HCV genotype 1 infection with Boceprevir

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Disclosures

- Board member for: Schering-Plough, Merck, Janssen, Gilead, Boehringer Ingelheim, BMS, Novartis, Roche, Abbott, GSK, Vertex
- Speaker for: Roche, Schering-Plough, Merck, Janssen, Gilead, BMS, Abbvie
Meta-analysis of five Phase 3 clinical trials with Boceprevir

Vierling JM, et al. EASL 2013
Response to BOC/PR in F4 Patient Subgroups

Vierling JM, et al. EASL 2013
Optimize treatment

Select candidates
HCV epidemiology in 2011: Estimation of number of patients ever infected

## HCV Screening Rates: 2011 Estimation

<table>
<thead>
<tr>
<th></th>
<th>Belgium</th>
<th>France</th>
<th>Germany</th>
<th>Italy</th>
<th>Spain</th>
<th>UK</th>
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<tbody>
<tr>
<td><strong>HCV Screening, %</strong></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td><strong>Estimated in 2011, %</strong></td>
<td>50</td>
<td>64</td>
<td>48</td>
<td>46</td>
<td>35</td>
<td>34</td>
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<tr>
<td><strong>HCV Genotype</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>G1, %</td>
<td>60</td>
<td>56</td>
<td>60</td>
<td>62</td>
<td>65</td>
<td>44</td>
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<tr>
<td>G2/3, %</td>
<td>27</td>
<td>32</td>
<td>37</td>
<td>34</td>
<td>23</td>
<td>53</td>
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<tr>
<td>Other genotypes, %</td>
<td>13</td>
<td>12</td>
<td>3</td>
<td>4</td>
<td>12</td>
<td>3</td>
</tr>
</tbody>
</table>

Results: reduction in cumulative incidence of genotype 1 HCV-related cirrhosis, 2012–2021

Greater reduction in HCV-related cirrhosis with PI-based triple therapy than with dual therapy

Reinforcing screening and treatment access: incidence of genotype 1 HCV-related cirrhosis, 2012–2021

Dramatic reduction in HCV-related cirrhosis with PI-based triple therapy + reinforced screening and treatment access

*Assumes 75% of HCV-infected patients will be screened by 2015 and one G1-infected patient in 2 will be treated in 2015 with PI-based triple therapy
Reinforcing screening and treatment access: cumulative incidence of genotype 1 HCV-related deaths, 2012–2021

Dramatic reduction in HCV-related deaths with PI-based triple therapy + reinforced screening and treatment access

*Assumes 75% of HCV-infected patients will be screened by 2015 and one G1-infected patient in 2 will be treated in 2015 with PI-based triple therapy

Optimize treatment

Select ideal candidates
According to risk/benefit ratio

Select candidates
Select ideal candidates according to benefit risk ratio

- The good candidates:

<table>
<thead>
<tr>
<th>Naive</th>
<th>Treatment–experienced</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>effect</strong></td>
<td><strong>OR (95% CI)</strong></td>
</tr>
<tr>
<td>HCV RNA level ≤400,000 vs &gt;400,000</td>
<td>11.6 (1.5-87.8)</td>
</tr>
<tr>
<td>IL28B CC vs TT</td>
<td>2.6 (1.3-5.1)</td>
</tr>
<tr>
<td>IL28B CC vs CT</td>
<td>2.1 (1.2-3.7)</td>
</tr>
<tr>
<td>Cirrhosis no vs yes</td>
<td>4.3 (1.6-11.9)</td>
</tr>
<tr>
<td>Genotype 1b vs 1a</td>
<td>2.0 (1.2-3.4)</td>
</tr>
<tr>
<td>Non Black vs Black</td>
<td>2.0 (1.1-3.7)</td>
</tr>
<tr>
<td><strong>Baseline HCV RNA Level</strong></td>
<td><strong>SVR (%)</strong></td>
</tr>
<tr>
<td>≤ 1,000,000 IU/ml</td>
<td>78% - 83%</td>
</tr>
<tr>
<td>&gt; 1,000,000 IU/ml</td>
<td>57% - 68%</td>
</tr>
</tbody>
</table>


Select ideal candidates according to benefit risk ratio

- The patient who do not be treated:

<table>
<thead>
<tr>
<th>Risk factors for SAE</th>
<th>Platelets count</th>
<th>Platelets count</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&gt; 100,000/mm³</td>
<td>≤ 100,000/mm³</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Albumin 35 g/L</th>
<th>SVR &gt;&gt; SAE (306)</th>
<th>SVR &gt; SAE (74)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin &lt;35 g/L</td>
<td>SAE: 16.1 %</td>
<td>SAE: 51.4 %</td>
</tr>
</tbody>
</table>

SVR >> SAE
SVR > SAE
SAE >> SVR

Missing data in 69 patients

Fontaine H et al. AFEF 2013
HCV-TARGET: Risk Factors for Poor Outcomes in PI-Treated Pts

- Risk factors for decompensation among cirrhotic patients during PI therapy identified[1]

<table>
<thead>
<tr>
<th>Baseline Characteristic</th>
<th>Odds Ratio Minimally Adjusted Estimates</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CrCl (mL/min)</td>
<td>0.99</td>
<td>.03</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>0.30</td>
<td>&lt; .01</td>
</tr>
<tr>
<td>HCV RNA (log IU/mL)</td>
<td>0.76</td>
<td>&lt; .01</td>
</tr>
<tr>
<td>Bilirubin (log mg/dL)</td>
<td>2.93</td>
<td>.02</td>
</tr>
</tbody>
</table>

- Pts with history of decompensation at highest risk for SAEs with PIs[2]


Select ideal candidates according to benefit risk ratio

- The patient who do not be treated: Null responder cirrhotic

![Bar chart showing SVR percentages for Relapsers, Partial responders, and Null responders.]

BOCEPREVIR

- Relapsers: 54% (55/102) with P = 0.032
- Partial responders: 38% (36/94) with P = 0.014
- Null responders: 0% (0/10)

Fontaine H, France, AFEF 2013,
Optimize treatment

Select candidates

Select ideal candidates
According to risk/benefit ratio

Optimize stopping rules
Optimize stopping rules

Naive patients

<table>
<thead>
<tr>
<th>Threshold HCV RNA Level</th>
<th>Patients Stopped by Week 8 Rule (n)</th>
<th>Additional Patients Stopped by Week 24 Rule (n)</th>
<th>Total Patients Stopped (n)</th>
<th>SVR Missed With Week 8 Rule (n)</th>
<th>Patients Stopped by Week 12 Rule (n)</th>
<th>Additional Patients Stopped by Week 24 Rule (n)</th>
<th>Total Patients Stopped (n)</th>
<th>SVR Missed With Week 12 Rule (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥9.3 IU/mL (LLD)</td>
<td>260</td>
<td>11</td>
<td>271</td>
<td>98</td>
<td>144</td>
<td>20</td>
<td>164</td>
<td>21</td>
</tr>
<tr>
<td>≥25 IU/mL (LLQ)</td>
<td>155</td>
<td>25</td>
<td>180</td>
<td>31</td>
<td>83</td>
<td>41</td>
<td>124</td>
<td>5</td>
</tr>
<tr>
<td>&gt;50 IU/mL</td>
<td>147</td>
<td>26</td>
<td>173</td>
<td>26</td>
<td>78</td>
<td>43</td>
<td>121</td>
<td>4</td>
</tr>
<tr>
<td>≥100 IU/mL</td>
<td>120</td>
<td>32</td>
<td>152</td>
<td>16</td>
<td>65</td>
<td>49</td>
<td>114</td>
<td>0</td>
</tr>
<tr>
<td>≥1000 IU/mL</td>
<td>61</td>
<td>57</td>
<td>118</td>
<td>4</td>
<td>43</td>
<td>61</td>
<td>104</td>
<td>0</td>
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<tr>
<td>&lt;2-log decline from the baseline</td>
<td>13</td>
<td>74</td>
<td>87</td>
<td>0</td>
<td>24</td>
<td>71</td>
<td>95</td>
<td>0</td>
</tr>
<tr>
<td>&lt;3-log decline from the baseline</td>
<td>34</td>
<td>66</td>
<td>100</td>
<td>1</td>
<td>34</td>
<td>66</td>
<td>100</td>
<td>0</td>
</tr>
</tbody>
</table>

# Optimize stopping rules

<table>
<thead>
<tr>
<th>Treatment-naive</th>
<th>FDA</th>
<th>Partial responders</th>
<th>EMA</th>
<th>Null responders</th>
<th>cirrhotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEG IFN RBV</td>
<td>PEG-IFN RBV</td>
<td>PEG-IFN / RBV/ Boceprevir</td>
<td>PEG-IFN RBV</td>
<td>PEG-IFN / RBV/ Boceprevir</td>
<td>PEG-IFN / RBV/ Boceprevir</td>
</tr>
<tr>
<td></td>
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</tr>
</tbody>
</table>

**Stopping rules**

- **HCV RNA >100 IU/ml**
- **HCV RNA detectable**
Optimize stopping rules

- Boceprevir: New TW8 stopping rules in patients with advanced fibrosis or cirrhosis

SVR 24 according to TW8 response and fibrosis

Early viral kinetics allows to stop or continue treatment.

Vierling JM et al. EASL 2013, Abs. 1430
Optimize stopping rules

- Boceprevir: New TW8 stopping rules in patients with cirrhosis

Fontaine H, France, AFEF 2013,
Optimize stopping rules

<table>
<thead>
<tr>
<th>Treatment-naive</th>
<th>FDA</th>
<th>Partial responders relapsers</th>
<th>EMA</th>
<th>Null responders cirrhotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEG-IFN / RBV</td>
<td>PEG-IFN / RBV / Boceprevir</td>
<td>PEG-IFN / RBV / Boceprevir</td>
<td>PEG-IFN / RBV / Boceprevir</td>
<td>PEG-IFN / RBV / Boceprevir</td>
</tr>
</tbody>
</table>

**Stopping rules**
- **Label**: HCV RNA detectable
- **<3 log decline F3/4**: HCV RNA >100 IU/ml

**Weeks**
- 0
- 4
- 8
- 12
- 24
- 28
- 36
- 48
Optimize treatment

Select candidates

Select ideal candidates
  According to risk/benefit ratio

Optimize stopping rules

Optimize therapy management
**Side effects**

**Telaprevir**
- Rash (55%) vs 33%
  - Severe 5%
- Anemia x2 (32% vs 15%)
- Anorectal symptoms (26% vs 6%)

**Boceprevir**
- Anemia x2 (~50% vs 25%)
- Dysgeusia (37-45% vs 11-18%)
- Neutropenia < 750/mm³ 20-24% vs 9-14%


Clinical Trials vs Real World

**Clinical trials** (including cirrhotics)

- **Treatment-naïve**
  - Telaprevir: n=727, Boceprevir: n=734, PegIFN/RBV: n=530
  - Telaprevir: 9%, Boceprevir: 12%, PegIFN/RBV: 7%

- **Treatment-experienced**
  - Telaprevir: n=132, Boceprevir: n=530, PegIFN/RBV: n=530
  - Telaprevir: 12%, Boceprevir: 12%, PegIFN/RBV: 5%

**Real world** (cirrhotics only)

- **Treatment-experienced**
  - Telaprevir: n=299, Boceprevir: n=212
  - Telaprevir: 54%, Boceprevir: 44%
Anemia management according to age

**BOCEPREVIR**

- <65 years
- ≥65 years

- Grade 3/4 Anemia:
  - <65 years: 11/168, 7
  - ≥65 years: 16/168, 18

- Transfusions:
  - <65 years: 16/168, 10
  - ≥65 years: 89/168, 20

- EPO:
  - <65 years: 8/44, 30
  - ≥65 years: 30/44, 68

- **p=0.032**
- **p=0.088**
- **p<=0.063**

Hézode C, et al. AASLD 2013
SVR according to time of first RBV dose reduction during first 4 weeks of treatment and HCV RNA status

- Small sample sizes among previously treated patients limit interpretation of data in REALIZE, however similar trends were observed.
Boceprevir: similar SVR when RBV dose modification and EPO are used to manage anemia

Treatment-naïve G1 patients (n=687) received BOC-based therapy. Overall, 500 patients developed anemia (Hb ≤10 g/dL or were expected to reach that nadir before next visit) and were randomized to have anemia managed with either EPO (40 000 units/week SC), or RBV dose reduction (by 200–400 mg/day). Transfusion in patients with Hb ≤8.5 g/dL was allowed to prevent study discontinuation.

Genotype 1 cirrhosis and boceprevir: RBV dose reduction or EPO use?

SVR according to RBV DR or EPO use

SVR according to the need of single or double strategy

RBV DR: RBV dose reduction

Lawitz E, Etats-Unis, AASLD 2012, Abs. 50 actualisé
Conclusions

• Triple therapies with PIs are a major advance in the history of HCV treatment.
• Optimal patients selection is crucial to achieve high SVR rate with reasonable safety profile
• Optimizing BOC treatment includes:
  – Optimizing treatment design according to baseline characteristics
  – Following optimal stopping rules
  – Preventing DDIs
  – Preventing and managing AEs
HCV Therapy: Past, Present and Future

- Ribavirin
- Interferon
- Pegylated interferons

1990

- Proof of concept for DAA (PI)

2000

- Suppression of HCV with DAA combination (PI + NI)

2005

- Telaprevir and boceprevir

2010

- Frequent curability of diverse populations without IFN

2011

- Potential approval of other DAAs with IFN (eg, faldaprevir)

2012

- Approval of simeprevir and sofosbuvir with IFN
- First approved IFN-free therapy: SOF + RBV for GT2/3

2013

- IFN-free DAA combinations (GT1)

2014

-

2015-

IFN-free DAA combinations (GT1)
IFN-Free Therapy for Tx-Naive GT1 HCV: Regimens Effective in Both Subtypes

AVIATOR\(^1\):
ABT-450/RTV + ABT-333 + ABT-267 + RBV

LONESTAR\(^2\):
SOF/LDV FDC 8 wks
SOF/LDV + RBV 8 wks
SOF/LDV FDC 12 wks

AI443-014\(^3\):
Daclatasvir + Asunaprevir + BMS-791325 for 12 wks

C-WORTHY 12-wk regimens\(^4\):
MK-5172 + MK-8742 20 mg + RBV
MK-5172 + MK-8742 50 mg + RBV
MK-5172 + MK-8742 50 mg

## Efficacy of Simeprevir and/or Sofosbuvir in Previous NullResponders

### Phase IIb Trial of Simeprevir + PegIFN/RBV\(^1\)

<table>
<thead>
<tr>
<th>Genotype</th>
<th>F0-2 Fibrosis</th>
<th>F3/4 Fibrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SVR24 (%)</td>
<td>SVR12 (%)</td>
</tr>
<tr>
<td>1a</td>
<td>0</td>
<td>23</td>
</tr>
<tr>
<td>1b</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>24</td>
<td>33</td>
<td>53</td>
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<td>25</td>
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</tr>
<tr>
<td>26</td>
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</table>

### COSMOS\(^2\)

<table>
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<tr>
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<th>F3/4 Fibrosis</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>SVR24 (%)</td>
<td>SVR12 (%)</td>
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<tr>
<td>1a</td>
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<td>13/14</td>
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