Protease Inhibitors for Hepatitis C
Introduction-2012

- Hepatitis C is common and curable
- More than 6 million Americans infected
- SOC therapies
  - Genotype 1 – PEG/RBV/Protease Inhibitor
  - Genotypes 2,3,4,5,6 – PEG/RBV
- SOC Common Side Effects
- HCV RNA testing in the protease era
Treatment of Genotype 1: (75% of patients in USA)

• SOC:
  – PEG/RBV/telaprevir (approved 5/11)
  – PEG/RBV/boceprevir (approved 5/11)

• Many new drugs in clinical trials
  – 2\textsuperscript{nd} generation PI’s
  – Polymerase inhibitors
  – Non-nucleotide analogues
Telaprevir: Improved SVR for All Genotype 1 Patients

**ADVANCE¹ and REALIZE² studies**

<table>
<thead>
<tr>
<th>Category</th>
<th>SVR*</th>
<th>Telaprevir + pegIFN alfa/RBV</th>
<th>PegIFN alfa/RBV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment-naive¹</td>
<td>75</td>
<td>44</td>
<td>31</td>
</tr>
<tr>
<td>Relapse</td>
<td>86</td>
<td>24</td>
<td>15</td>
</tr>
<tr>
<td>Partial responder²</td>
<td>57</td>
<td>15</td>
<td>5</td>
</tr>
<tr>
<td>Null responder²</td>
<td>31</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

*SVR = sustained virological response after 24 weeks off treatment based on Telaprevir 12 week treatment duration.

1. Jacobson IM, et al. AASLD 2010; abstract 211,
Higher SVR Rates With TVR in Patients With HCV Genotype 1b vs 1a

- **Tx Naive**
  - Genotype 1a: 71%
  - Genotype 1b: 79%

- **Relapsers**
  - Genotype 1a: 84%
  - Genotype 1b: 88%

- **Partial Responders**
  - Genotype 1a: 47%
  - Genotype 1b: 68%

- **Null Responders**
  - Genotype 1a: 27%
  - Genotype 1b: 37%

*Pooled TVR arms.

Boceprevir: SVR for All Genotype 1 Patients

Poordad, et al. Combined cohorts from SPRINT-2; Bacon B et al. RESPOND-2; NEJM 2011.

Based on optimal treatment regimen from phase 3 studies
Higher SVR Rates With BOC in Patients With HCV Genotype 1b vs 1a

Adverse Events Reported More Frequently With TVR and BOC vs PegIFN/RBV

**Telaprevir**[1]

<table>
<thead>
<tr>
<th>Adverse Event, %</th>
<th>TVR-Containing Arms (n = 727)</th>
<th>PegIFN/RBV Arm (n = 361)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pruritus</td>
<td>45-50</td>
<td>36</td>
</tr>
<tr>
<td>Nausea</td>
<td>40-43</td>
<td>31</td>
</tr>
<tr>
<td>Rash</td>
<td>35-37</td>
<td>24</td>
</tr>
<tr>
<td><strong>Anemia</strong></td>
<td><strong>37-39</strong></td>
<td><strong>19</strong></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>28-32</td>
<td>22</td>
</tr>
</tbody>
</table>

**Boceprevir**[2]

<table>
<thead>
<tr>
<th>Adverse Event, %</th>
<th>BOC-Containing Arms (n = 734)</th>
<th>PegIFN/RBV Arm (n = 363)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anemia</strong></td>
<td><strong>49</strong></td>
<td>29</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>37-43</td>
<td>18</td>
</tr>
</tbody>
</table>

Clinical Pharmacology and Drug Interactions

- Boceprevir
  - Strong inhibitor of CYP3A4/5
  - Partly metabolized by CYP3A4/5

- Telaprevir
  - Substrate of CYP3A
  - Inhibitor of CYP3A

## Drugs That Are Contraindicated With PIs

<table>
<thead>
<tr>
<th>Boceprevir and Telaprevir</th>
<th>Clinical Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>St. John’s Wort</td>
<td>May lead to loss of virologic response</td>
</tr>
<tr>
<td>Rifampin</td>
<td>May lead to loss of virologic response</td>
</tr>
<tr>
<td>Alfuzosin (BPH)</td>
<td>Increased alfuzosin concentrations can result in hypotension</td>
</tr>
<tr>
<td>Dihydroergotamine, ergonovine, ergotamine, methylergonovine</td>
<td>Potential for acute ergot toxicity (peripheral vasospasm or ischemia)</td>
</tr>
<tr>
<td>Cisapride</td>
<td>Potential for cardiac arrhythmias</td>
</tr>
<tr>
<td>Lovastatin, simvastatin (Atorvastatin with TVR also)</td>
<td>Potential for myopathy including rhabdomyolysis</td>
</tr>
<tr>
<td>Pimozide</td>
<td>Potential for cardiac arrhythmias</td>
</tr>
<tr>
<td>REVATIO® (sildenafil) or ADCIRCA® (tadalafil) for treatment of PAH</td>
<td>Potential for PDE5 inhibitor-associated AEs</td>
</tr>
<tr>
<td>Triazolam; midazolam (oral)</td>
<td>Prolonged or increased sedation or respiratory depression</td>
</tr>
<tr>
<td>Boceprevir</td>
<td><strong>Clinical Comment</strong></td>
</tr>
<tr>
<td>Carbamazepine, phenobarbital, phenytoin</td>
<td>May lead to loss of virologic response to BOC</td>
</tr>
<tr>
<td>Droperidol (oral contraceptive)</td>
<td>Potential for hyperkalemia</td>
</tr>
</tbody>
</table>

UNDERSTANDING HCV-RNA TESTING IN THE PROTEASE ERA
Clinical Statements on HCV Viral Load

• Viral load not predictive of disease progression
• Viral load predictive of maternal-fetal transmission
• Viral load critical for assessing response to therapy and determining duration of treatment
• Prolonged therapy with detectable virus may lead to resistance
Key Challenges Regarding Use of HCV RNA Assays in Protease Inhibitor Era

• Package inserts for BOC and TVR specify different time points for monitoring HCV RNA
• Available HCV RNA assays in practice have different quantifiable ranges
• Different HCV RNA thresholds used for RGT determination with BOC and TVR
• Different HCV RNA thresholds used for defining treatment futility with BOC and TVR
HCV RNA Assays: LLOD Is Distinct From LLOQ

• LLOQ
  – Lowest HCV RNA concentration within linear range of assay
    • ie, smallest amount of HCV RNA that can be not only detected but also accurately quantified

• LLOD
  – Lowest amount of HCV RNA concentration that can be detected with 95% probability to determine presence or absence
HCV RNA Levels and Relationship to LLOD and LLOQ

HOW DO WE USE THE PROTEASE INHIBITORS?
Response-Guided Therapy Paradigm With BOC + PegIFN/RBV in Tx-Naive Patients

- Indicated for all noncirrhotic treatment-naive patients

**HCV RNA**

**Undetectable** < 100 IU/mL  
**Undetectable**

**Early response** stop at Wk 28; f/u 24 wks

<table>
<thead>
<tr>
<th>PegIFN + RBV</th>
<th>BOC + PegIFN + RBV</th>
<th>PegIFN + RBV</th>
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<tbody>
<tr>
<td>0</td>
<td>4</td>
<td>8</td>
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**HCV RNA**

**Detectable** < 100 IU/mL  
**Undetectable**

**Slow response** extend triple therapy to Wk 36; PR to Wk 48; f/u 24 wks

Response-Guided Therapy Paradigm With BOC + PegIFN/RBV in Tx-Exp Patients

- Indicated for noncirrhotic previous relapsers or partial responders

HCV RNA

- Undetectable
- < 100 IU/mL
- Undetectable

Early response stop at Wk 36; f/u 24 wks

PegIFN + RBV  BOC + PegIFN + RBV  PegIFN + RBV

0 4 8 12 24 28 36 48

HCV RNA

- Detectable
- < 100 IU/mL
- Undetectable

Slow response PR to Wk 48; f/u 24 wks

PegIFN + RBV  BOC + PegIFN + RBV  PegIFN + RBV

0 4 8 12 24 28 36 48

Response-Guided Therapy Paradigm With BOC + PegIFN/RBV in Naïve and Tx-Exp Patients with Cirrhosis

Response-Guided Therapy Paradigm With TVR + PegIFN/RBV in Tx-Naïve Patients

- Indicated for all noncirrhotic treatment-naive patients

HCV RNA

![Diagram showing treatment regimen with TVR + PegIFN/RBV for noncirrhotic patients.](image)

Response-Guided Therapy Paradigm With TVR + PegIFN/RBV in Tx-Exp Relapse Patients

- Same as naives; indicated for noncirrhotic previous relapsers\cite{1}\*

\begin{itemize}
  \item TVR + PegIFN + RBV
  \item PegIFN + RBV
  \item HCV RNA
    \begin{itemize}
      \item Undetectable
    \end{itemize}
  \item eRVR stop at Wk 24, f/u 24 wks

  \item TVR + PegIFN + RBV
  \item PegIFN + RBV
  \item HCV RNA
    \begin{itemize}
      \item Detectable (≤ 1000 IU/mL)
      \item Undetectable/detectable (≤ 1000 IU/mL)
      \item Undetectable
    \end{itemize}
  \item No eRVR extend pegIFN + RBV to Week 48; f/u 24 wks
\end{itemize}

\*AASLD guidelines say RGT “may be considered” for prior partial responders\cite{2} but package insert recommends 48 weeks of therapy\cite{1}

Response-Guided Therapy Paradigm With TVR + PegIFN/RBV in Tx-Exp Partial or Null Responder Patients

- Noncirrhotics

HCV RNA

Undetectable

Detectable (≤ 1000 IU/mL)

Undetectable/detectable (≤ 1000 IU/mL)

Undetectable

No eRVR extend pegIFN + RBV to Week 48; f/u 24 wks

TVR + PegIFN + RBV

PegIFN + RBV

TVR + PegIFN + RBV

PegIFN + RBV

0 4 12 24 48

Response-Guided Therapy Paradigm With TVR + PegIFN/RBV in Cirrhotics Naïve and Tx-Exp

## Review of Protease Inhibitor Stopping or “Futility” Rules

### Telaprevir*

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>Criteria for Stopping</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 4 or 12</td>
<td>HCV-RNA &gt; 1000 IU/mL</td>
<td>Discontinue TVR/PEG-IFN/RBV</td>
</tr>
<tr>
<td>Week 24</td>
<td>HCV-RNA detectable</td>
<td>Discontinue PEG-IFN/RBV</td>
</tr>
</tbody>
</table>

### Boceprevir**

<table>
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<tr>
<th>Timepoint</th>
<th>Criteria for Stopping</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 12</td>
<td>HCV-RNA ≥ 100 IU/mL</td>
<td>Discontinue BOC/PEG-IFN/RBV</td>
</tr>
<tr>
<td>Week 24</td>
<td>Confirmed, detectable HCV-RNA</td>
<td>Discontinue BOC/PEG-IFN/RBV</td>
</tr>
</tbody>
</table>

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WHAT LIES AHEAD IN THE FUTURE OF HEPATITIS C THERAPY?
## Timelines for HCV Therapy

<table>
<thead>
<tr>
<th></th>
<th>Current SOC: GEN 2,3,4</th>
<th>Triple Combo: Current SOC</th>
<th>Triple Combo: Enhanced Efficacy</th>
<th>Quad Combo: Enhanced Efficacy</th>
<th>Interferon Free Regimen?</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEG-IFN</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RBV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>?</td>
</tr>
<tr>
<td>DAA protease inhibitor</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>DAA polymerase inhibitor</td>
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</tbody>
</table>
Increasing Complexity of HCV Management

- STAT-C Agents
- Novel combinations
- Resistance mutations
- Response Guided Therapy
- E-prescribing
- Electronic health records
- NPs, PAs
- Genetic predictors
- New interferons
- Cost, Toxicities & Compliance
- Genetic predictors
- New interferons
Conclusions-2012

- Hepatitis C is common and curable
- Therapies cure the majority of treated patients
- All genotype 1 cirrhotic patients are treated for 48 weeks
- Frequent HCV-RNA testing critical while on treatment
  - Futility rules
- Future drug development looks bright