Hepatitis C Virus Treatments: Present and Future

Charles D. Howell, M.D., A.G.A.F
Professor of Medicine
University of Maryland School of Medicine
Baltimore, MD
Charles Howell Disclosures

- Boehringer Ingelheim, Inc.- Research Grant
- Bristol Myer Squibb, Inc.-Research Grant
- Genentech, Inc.-Advisory Board
- Janssen, Inc.-Advisory Board
- Vertex, Inc. -Advisory Board
Hepatitis C Virus (HCV) in US

- ~3-4 million infected with HCV (NHANES 1999-2002)
- Most common blood-borne viral infection
- Leading cause for cirrhosis & primary hepatocellular carcinoma (HCC)
- Indication for ~50% of liver transplants in USA
- $2.0 billion in healthcare cost in 2003
- > 15,000 deaths in 2007; exceed HIV deaths

Greater HCV Burden in African Americans (AA)

- HCV prevalence in AA twice that in CA (3.2% vs. 1.5%)
- Est. ~920,000 AA infected with HCV (NHANES 1999-2002)
- Precise number unknown; ~1.1 to 2 million AA infected
- AA: 12-13% of US pop. & 23% of HCV cases
- 9% of AA 40-49 years old infected compared to 3.8% of CA

Trends in HCC Incidence in US

NCI SEER Data

Per 100,000 Population

0 2 4 6 8 10 12 14


Total
African American
Asian/Pacific Isl
Hispanic
American Indian/Alaska Native
White American

Annual Hepatitis C Mortality Rates: Race/Ethnicity

Projected Prevalence of Chronic HCV, Cirrhosis, and Complications

Projected Number of Patients With Decompensated Cirrhosis and Hepatocellular Carcinoma

HCV Cure: Sustained Virologic Response (SVR)

- Defined: Undetectable serum HCV RNA at end of treatment & for ≥ 6 mos. after treatment
  - Absence of detectable HCV RNA >10 years suggest cure of HCV
  - Progressive and continuous liver histological improvement
  - Decrease incidence of decompensated cirrhosis, HCC, liver transplantation, and liver related death
  - SVR compared to no-SVR

Pradat et al. J. Viral Hepat. 2006; 13:409-414
Morgan et al. Hepatology 2010; 52:832-844
### Progress in Therapy of Hepatitis C: SVR

<table>
<thead>
<tr>
<th>Year</th>
<th>IFN 6 m</th>
<th>IFN 12 m</th>
<th>IFN/RBV</th>
<th>PegIFN</th>
<th>PegIFN/RBV</th>
<th>HCV-PI/PegIFN/RBV GT1</th>
</tr>
</thead>
<tbody>
<tr>
<td>1991</td>
<td>6%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1994-96</td>
<td></td>
<td>16%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1998</td>
<td></td>
<td></td>
<td>42%</td>
<td></td>
<td>39%</td>
<td></td>
</tr>
<tr>
<td>2001</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>54%</td>
<td>73%</td>
</tr>
<tr>
<td>2011</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **IFN**: Interferon
- **PegIFN**: pegylated IFN
- **RBV**: Ribavirin
- **PI**: HCV protease inhibitor

**Sustained Virologic Response**

HCV Genotypes in US

- Genotype 1: 73
- Genotype 2: 12
- Genotype 3: 2
- All Others: 13

Boceprevir\textsuperscript{a} and Telaprevir\textsuperscript{b}: HCV NS34a Protease Inhibitors (2011-)

- Approved by FDA
- Use in combination with Peginterferon and Ribavirin (RBV)
- Chronic HCV genotype 1 (not GT 2, 3, 4, 5, 6)
- Adults
- Compensated liver function
  - Cirrhosis: Child-Pugh score 5-6; Class A
- Treatment-Naïve
- Previous IFN Treated (Treatment-Experienced)
- Not approved for
  - Organ transplant recipients
  - Patients with end-stage liver disease
  - Patients with HIV and/or HBV co-infection
  - Pediatric patients

\textsuperscript{a}Boceprevir 800 mg po TID with food; \textsuperscript{b}Telaprevir 750 mg TID with food
HCV Genome & Gene Products: Potential Targets for Direct Acting Antiviral Agents (Present & Future)

Protease Inhibitors: boceprevir; telaprevir

Phase 3 Boceprevir SPRINT-2: Genotype1 Treatment Naïve Patients

PegIFN α-2b/Ribavirin 48 Weeks (PR 48) N = 363

- PR
- Placebo + PR

Boceprevir Response-Guided Therapy (RGT) N = 368

- PR
- Boceprevir + PR
- Early Responder†
- Placebo + PR
- Late Responder*

Boceprevir/PR 48 Weeks (BOC/PR48) N = 366

- PR
- Boceprevir + PR
- TW 28
- TW 48
- FW 24

Futility Rule TW 24

BOC: boceprevir 800 mg q8h; PR: PegIFN α-2b 1.5 µg/kg/wk + weight-based RBV 600-1400 mg/day
†HCV RNA TW 8-24 undetectable
*HCV RNA TW 8 detectable; TW 24 undetectable

Boceprevir: Treatment Naïve Patients
SVR and Relapse

BOC: boceprevir 800 mg q8h; PR: PegIFN α-2b 1.5 µg/kg/wk + weight-based RBV 600-1400 mg/day; RGT: boceprevir response-guided therapy

**Boceprevir: SVR in Early and Late Responders**

Early Responder: HCV RNA TW 8-24 undetectable (43-44%)

Late Responder: HCV RNA TW 8 detectable; TW 24 undetectable

**BOC**: boceprevir 800 mg q8h; **PR**: PegIFN α-2b 1.5 µg/kg/wk + weight-based RBV 600-1400 mg/day

**RGT**: boceprevir response-guided therapy

[Graph showing the percent of patients in Early and Late Responders]

Boceprevir: Treatment Naïve Patients
SVR and Race

Non-Black/African-American
BOC: boceprevir 800 mg q8h; PR: PegIFN α-2b 1.5 µg/kg/wk + weight-based RBV 600-1400 mg/day
RGT: boceprevir response-guided therapy

Black/African American

<table>
<thead>
<tr>
<th>Group</th>
<th>Non-Black/African-American</th>
<th>Black/African-American</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR48</td>
<td>40%</td>
<td>23%</td>
</tr>
<tr>
<td>RGT</td>
<td>67%</td>
<td>42%</td>
</tr>
<tr>
<td>BOC/PR48</td>
<td>68%</td>
<td>53%</td>
</tr>
</tbody>
</table>

P-values:
- P < 0.0001
- P < 0.0001
- P < 0.004
- P < 0.044

Boceprevir: SVR by Race and METAVIR Fibrosis Score


BOC: boceprevir 800 mg q8h; PR: PegIFN α-2b 1.5 µg/kg/wk + weight-based RBV 600-1400 mg/day
RGT: boceprevir response-guided therapy

Percent of Patients

<table>
<thead>
<tr>
<th>METAVIR Fibrosis Score</th>
<th>Non-Black/African-American</th>
<th>Black/African-American</th>
</tr>
</thead>
<tbody>
<tr>
<td>F0/1/2/3</td>
<td>72</td>
<td>73</td>
</tr>
<tr>
<td>F4</td>
<td>42</td>
<td>41</td>
</tr>
<tr>
<td>F0/1/2/3</td>
<td>50</td>
<td>54</td>
</tr>
<tr>
<td>F4</td>
<td>0</td>
<td>50</td>
</tr>
</tbody>
</table>

RGT: boceprevir response-guided therapy
Boceprevir: Treatment Naïve Patients IL28B Genotype and SVR

PR48: PegIFN α-2b + ribavirin 48 weeks
RGT: boceprevir/response-guided therapy
BOC-PR48: boceprevir/PR48 weeks

BOC: boceprevir 800 mg q8h; PR: PegIFN α-2b 1.5 µg/kg/wk + weight-based RBV 600-1400 mg/day

Phase 3 Telaprevir ADVANCE: Genotype1 Treatment Naïve Patients

PegIFN α-2a /Ribavirin 48 Weeks (Pbo/PR) N = 361

Placebo/PR  | PR

Follow-up  | SVR

Telaprevir + PR 8 Weeks; Response Guided Therapy (TVR8/PR) N = 364

TVR 8/PR  | Pbo/PR  | PR

Follow-up  | eRVR +  | SVR  | Follow-up

Follow-up  | eRVR -  | PR to Wk 48

Follow-up  | SVR

Telaprevir + PR 12 Weeks; Response Guided Therapy (TVR12/PR) N = 363

TVR 12/PR  | PR

Follow-up  | eRVR +  | SVR  | Follow-up

Follow-up  | eRVR -  | PR to Wk 48

Follow-up  | SVR

TVR: Telaprevir 750 mg q8h; PR: PegIFN α -2a 180 µg/wk; weight-based RBV 1000-1200 mg/day
eRVR: extended rapid virological response; undetectable HCV RNA at weeks 4 and 12

FDA Antiviral Drugs Advisory Committee.
Telaprevir: Treatment Naïve Patients
SVR and eRVR

TVR: Telaprevir 750 mg q8h; PR: PegIFN α-2a 180 µg/wk + weight-based RBV 1000-1200 mg/day; Pbo: placebo
eRVR: extended rapid virological response; undetectable HCV RNA at weeks 4 and 12

**Telaprevir: Treatment Naïve Patients**

**SVR Rates by eRVR Status**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>eRVR+</th>
<th>eRVR-</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-Week</td>
<td>92/195/212</td>
<td>87/179/207</td>
</tr>
<tr>
<td>48-Week</td>
<td>60/90/151</td>
<td>52/82/157</td>
</tr>
</tbody>
</table>

- **eRVR**: extended rapid virological response; undetectable HCV RNA at weeks 4 and 12
- **TVR**: Telaprevir 750 mg q8h; **PR**: PegIFN α-2a 180 µg/wk + weight-based RBV 1000-1200 mg/day; **Pbo**: placebo
Telaprevir: Treatment Naïve Patients
SVR Rates by Race or Ethnicity

**Caucasian**
- TVR12/PR: 79/325 (258/325)
- TVR8/PR: 73/315 (229/315)
- Pbo/PR: 48/318 (153/318)

**Black/African American**
- TVR12/PR: 62/26 (16/26)
- TVR8/PR: 60/40 (24/40)
- Pbo/PR: 29/28 (8/28)

**Hispanic/Latino**
- TVR12/PR: 77/44 (27/35)
- TVR8/PR: 68/40 (30/44)
- Pbo/PR: 39/28 (15/38)

**TVR:** Telaprevir 750 mg q8h; **PR:** PegIFN α-2a 180 µg/wk + weight-based RBV 1000-1200 mg/day; **Pbo:** placebo

Telaprevir: Treatment Naïve Patients
SVR Rates by Fibrosis Stage

TVR: Telaprevir 750 mg q8h; PR: PegIFN α -2a 180 µg/wk + weight-based RBV 1000-1200 mg/day; Pbo: placebo

FDA Antiviral Drugs Advisory Committee.
Telaprevir: Treatment Naïve Patients
IL28B Genotype and SVR

<table>
<thead>
<tr>
<th></th>
<th>C/C</th>
<th>C/T</th>
<th>T/T</th>
</tr>
</thead>
<tbody>
<tr>
<td>TVR12/PR</td>
<td>90</td>
<td>71</td>
<td>73</td>
</tr>
<tr>
<td>TVR8/PR</td>
<td>84</td>
<td>57</td>
<td>59</td>
</tr>
<tr>
<td>PR48</td>
<td>64</td>
<td>25</td>
<td>23</td>
</tr>
</tbody>
</table>

TVR: Telaprevir 750 mg q8h; PR: PegIFN-α -2a 180 µg/wk + weight-based RBV 1000-1200 mg/day

FDA Antiviral Drugs Advisory Committee.
SVR Rates With BOC or TVR in GT1 Treatment-Experienced Patients

### Boceprevir Safety

#### Most Common Treatment-Related Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>PR (N = 547 patients)</th>
<th>BOC/PR (N = 1548 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>57%</td>
<td>57%</td>
</tr>
<tr>
<td>Anemia</td>
<td>29%</td>
<td>49%</td>
</tr>
<tr>
<td>Nausea</td>
<td>40%</td>
<td>45%</td>
</tr>
<tr>
<td>Headache</td>
<td>43%</td>
<td>44%</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>15%</td>
<td>37%</td>
</tr>
<tr>
<td>Chills</td>
<td>29%</td>
<td>33%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>31%</td>
<td>32%</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>31%</td>
<td>31%</td>
</tr>
<tr>
<td>Alopecia</td>
<td>25%</td>
<td>26%</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>23%</td>
<td>25%</td>
</tr>
<tr>
<td>Myalgia</td>
<td>24%</td>
<td>23%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>18%</td>
<td>23%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>18%</td>
<td>23%</td>
</tr>
<tr>
<td>Influenza-like illness</td>
<td>25%</td>
<td>22%</td>
</tr>
</tbody>
</table>

PR: PegIFN α-2b + ribavirin; BOC: boceprevir

## Telaprevir Safety

### Adverse Events ≥ 5% Higher Frequency in Telaprevir Subjects

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Pbo/PR (N = 493)</th>
<th>TVR/PR (N = 1797)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash*</td>
<td>34%</td>
<td>56%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>50%</td>
<td>56%</td>
</tr>
<tr>
<td>Pruritus</td>
<td>28%</td>
<td>47%</td>
</tr>
<tr>
<td>Nausea</td>
<td>28%</td>
<td>39%</td>
</tr>
<tr>
<td>Anemia*</td>
<td>17%</td>
<td>36%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>17%</td>
<td>26%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>8%</td>
<td>13%</td>
</tr>
<tr>
<td>Hemorrhoids</td>
<td>3%</td>
<td>12%</td>
</tr>
<tr>
<td>Anorectal discomfort</td>
<td>3%</td>
<td>11%</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>3%</td>
<td>10%</td>
</tr>
<tr>
<td>Anal pruritis</td>
<td>1%</td>
<td>6%</td>
</tr>
</tbody>
</table>

*Rash and anemia based on special search category (SSC) grouped terms

# Drug-Drug Interactions a Clinical Challenge*

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Contraindicated With BOC(^1)</th>
<th>Contraindicated With TVR(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha 1-adrenoreceptor antagonist</td>
<td>Alfuzosin</td>
<td>Alfuzosin</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>Carbamazepine, phenobarbital, phenytoin</td>
<td>N/A</td>
</tr>
<tr>
<td>Antimycobacterials</td>
<td>Rifampin</td>
<td>Rifampin</td>
</tr>
<tr>
<td>Ergot derivatives</td>
<td>Dihydroergotamine, ergonovine, ergotamine, methylergonovine</td>
<td>Dihydroergotamine, ergonovine, ergotamine, methylergonovine</td>
</tr>
<tr>
<td>GI motility agents</td>
<td>Cisapride</td>
<td>Cisapride</td>
</tr>
<tr>
<td>Herbal products</td>
<td><em>Hypericum perforatum</em> (St John’s wort)</td>
<td><em>Hypericum perforatum</em></td>
</tr>
<tr>
<td>HMG CoA reductase inhibitors</td>
<td>Lovastatin, simvastatin</td>
<td>Atorvastatin, lovastatin, simvastatin</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>Drospirenone</td>
<td>N/A</td>
</tr>
<tr>
<td>Neuroleptic</td>
<td>Pimozide</td>
<td>Pimozide</td>
</tr>
<tr>
<td>PDE5 inhibitor</td>
<td>Sildenafil or tadalafil for tx of pulmonary arterial hypertension</td>
<td>Sildenafil or tadalafil for pulmonary arterial hypertension</td>
</tr>
<tr>
<td>Sedatives/hypnotics</td>
<td>Triazolam; orally administered midazolam</td>
<td>Orally administered midazolam, triazolam</td>
</tr>
</tbody>
</table>

*Studies of drug-drug interactions incomplete.

## Treatment-Emergent Substitutions During PI-Based Therapy

- Pooled analyses of subjects who had on-treatment failure or relapse during clinical trials with boceprevir or telaprevir
  - Patterns of treatment-emergent substitutions varied by subtype 1a vs 1b
  - Resistance most common among previous null responders and patients with subtype 1a

<table>
<thead>
<tr>
<th>HCV Genotype 1 Subtype</th>
<th>Treatment-Emergent Substitutions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Telaprevir(^{[1]})</td>
</tr>
<tr>
<td>1a</td>
<td>V36M</td>
</tr>
<tr>
<td></td>
<td>R155K</td>
</tr>
<tr>
<td></td>
<td>Combination of V36M and R155K</td>
</tr>
<tr>
<td>1b</td>
<td>V36A</td>
</tr>
<tr>
<td></td>
<td>T54A/S</td>
</tr>
<tr>
<td></td>
<td>A156S/T</td>
</tr>
<tr>
<td></td>
<td>I/V170A</td>
</tr>
</tbody>
</table>

Limitations of HCV BOC/TVR

- Complex Regimens
  - TID Protease Inhibitor with snack (fatty meal)
  - BID Ribavirin (RBV)
- Contraindicated in those with poor tolerance to pegIFN and or RBV
- Many drug interactions
- Drug-related side effects increased
- Low barrier for viral resistance/cross-resistance
- Less effective in African Americans, null and partial responders to PegIFN/Rbv
- Not yet established in certain special populations
  - Organ transplant recipients
  - Patients with end-stage liver disease
  - Patients with HIV and/or HBV coinfection
  - Pediatric patients
## Select DAAs in Development (Future)

<table>
<thead>
<tr>
<th>Category</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Protease Inhibitors</strong></td>
<td>ABT-450</td>
<td>CTS-1027</td>
<td>BMS-650032</td>
</tr>
<tr>
<td></td>
<td>ACH-1625</td>
<td>Danoprevir</td>
<td>BI 201335</td>
</tr>
<tr>
<td></td>
<td>GS 9451</td>
<td>GS 9256</td>
<td>TMC435</td>
</tr>
<tr>
<td></td>
<td>MK-5172</td>
<td>IDX320</td>
<td></td>
</tr>
<tr>
<td></td>
<td>VX-985</td>
<td>Vaniprevir</td>
<td></td>
</tr>
<tr>
<td><strong>Nonnucleoside polymerase inhibitors</strong></td>
<td>BI 207127</td>
<td>ABT-333</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IDX375</td>
<td>ABT-072</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>ANA598</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>BMS-791325</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Filibuvir</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tegobuvir</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>VX-759</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>VX-222</td>
<td></td>
</tr>
<tr>
<td><strong>Nucleoside polymerase inhibitors</strong></td>
<td>IDX184</td>
<td></td>
<td>PSI-7977</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RG7128</td>
<td></td>
</tr>
<tr>
<td><strong>NS5A inhibitors</strong></td>
<td>A-831</td>
<td>BMS-824393</td>
<td>BMS-790052</td>
</tr>
<tr>
<td></td>
<td>PPI-461</td>
<td>CF102</td>
<td></td>
</tr>
</tbody>
</table>
Evolution of HCV Therapy

2001
- PegIFN/RBV
- Protease inhibitor
- Nucleos(t)ide polymerase inhibitor
- Nonnucleoside polymerase inhibitor
- Host targeting agent

2011
- PegIFN/RBV
- Protease inhibitor
- Nucleos(t)ide polymerase inhibitor
- Nonnucleoside polymerase inhibitor
- NS5A inhibitor
Evolution of HCV Therapy

2001 2011 Beyond

- PegIFN/RBV
- Protease inhibitor
- Nucleos(t)ide polymerase inhibitor
- Nonnucleoside polymerase inhibitor
- NS5A inhibitor
- Host targeting agent
Future

- DAAs dosed daily
- DAAs with higher barriers to resistance
- Quadruple therapy (2 DAA, PegIFN/Rbv) for null and partial responders
- Interferon-free (oral DAAs ± Rbv)
- Shorter treatment duration
- Greater efficacy for less responsive