Protease Inhibitors for Chronic Hepatitis C Infection:
The New Kids on the Block,
But do they have “The Right Stuff” for all patients?

Lindsey M. Childs, PharmD, MPH
PGY2 Infectious Diseases Pharmacy Resident
South Texas Veterans Health Care System

September 30, 2011

Learning Objectives:
- Describe the epidemiology and the clinical progression of hepatitis C infection
- Identify the current treatment recommendations for chronic hepatitis C infection
- Evaluate the clinical evidence of protease inhibitors for hepatitis C and their place in therapy
- Explain which patients would be good candidates for protease inhibitor therapy
Hepatitis C Infection (HCV)

I. Epidemiology
   A. Prevalence\textsuperscript{1,2,3,4}
      i. Estimated that \sim3\% of world’s population (\sim170 million) is infected
      ii. Highest prevalence in Africa and Asia
      iii. About 17,000 Americans contract Hepatitis C annually
      iv. About 3 million Americans with chronic Hepatitis C (\sim1.3\% prevalence)
      v. Veterans population higher prevalence of chronic HCV (\sim4\%)
      vi. Estimated 8,000-10,000 deaths in United States annually
   B. Risk Groups\textsuperscript{1,2,3,4}
      i. Injection drug users (IDUs)
         1. Primary mode of transmission in the United States (>60\% new cases)
         2. One-third of young IDUs (age 18-30 years) infected
         3. Older, former IDUs much higher prevalence (80-90\%)
      ii. Intranasal drug users
      iii. Tattoos and body piercings
      iv. Blood transfusion or organ transplant recipients before 1992
      v. Healthcare workers who are exposed to needlesticks with HCV-positive blood
      vi. Child born to a HCV-positive mother
      vii. Sexual contact with an HCV-positive individual

Figure 1: Map of HCV Infection Prevalence

II. Etiology, Presentation, and Diagnosis
   A. Virus\textsuperscript{5,6}
      i. Small, enveloped, positive-sense, single-stranded RNA virus, family flaviviridae
      ii. More prone to mutations than DNA viruses (i.e. Hepatitis B)
B. Acute Infection\textsuperscript{7,8}
   i. 20% of all acute hepatitis cases are caused by HCV
   ii. Incubation period 6-10 weeks
   iii. Mostly asymptomatic, but symptoms can include abdominal pain, nausea, vomiting, fever, fatigue, jaundice
   iv. \textasciitilde80\% fail to clear acute infection and will progress to chronic infection

C. Chronic Infection\textsuperscript{7,8}
   i. Leading cause of chronic liver disease, liver transplantation, and death stemming from liver disease
   ii. Mostly asymptomatic until liver failure becomes clinically apparent
   iii. Persistently elevated or fluctuating liver function tests (LFTs) in \textasciitilde70\% chronic HCV patients
   iv. 10-20\% chronic HCV patients progress to cirrhosis
      1. Progression typically takes 20-30 years
   v. 25\% of HCV cirrhotics progress to liver failure and death
      1. Progression typically takes about 10 years
   vi. Hepatocellular carcinoma (HCC) 1-5\% annually in chronic HCV patients
   vii. HCV patients account for 40-50\% of liver transplants\textsuperscript{8}

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{image.png}
\caption{Natural Progression of Hepatitis C infection\textsuperscript{9}}
\end{figure}

D. Diagnosis\textsuperscript{7,8}
   i. Patients with high risk behaviors should be screened for HCV antibody (anti-HCV) and for HCV RNA
   ii. Liver biopsies may be undertaken to assess degree of liver injury and fibrosis and to help guide treatment initiation decisions
      1. Fibrosis stage 0, 1, 2- low risk of liver complications or liver-related death over following 10-20 years
      2. Bridging fibrosis (stage 3)- high risk of progression to cirrhosis
         a. Indication for HCV treatment per AASLD 2009 Guidelines
      3. Cirrhosis is stage 4 fibrosis
   iii. Child-Pugh Score\textsuperscript{8}
      1. Differentiates compensated (Class A) vs. decompensated (Class B and C) liver disease
         a. Compensated disease is indication for HCV treatment
2. Calculated by adding up point values for each variable
   a. Class A: Score 5-6
   b. Class B: Score 7-9
   c. Class C: Score 10-15

<table>
<thead>
<tr>
<th>Variable</th>
<th>1 point</th>
<th>2 points</th>
<th>3 points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum bilirubin (mg/dL)</td>
<td>&lt; 2</td>
<td>2-3</td>
<td>&gt; 3</td>
</tr>
<tr>
<td>Serum albumin (mg/dL)</td>
<td>&gt; 3.5</td>
<td>2.8-3.5</td>
<td>&lt; 2.8</td>
</tr>
<tr>
<td>INR</td>
<td>&lt; 1.7</td>
<td>1.7-2.3</td>
<td>&gt; 2.3</td>
</tr>
<tr>
<td>Ascites</td>
<td>None</td>
<td>Easily controlled</td>
<td>Poorly controlled</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>None</td>
<td>Minimal</td>
<td>Advanced Coma</td>
</tr>
</tbody>
</table>

iv. Extrahepatic HCV
1. Mixed cryoglobulinemia
2. Non-Hodgkin’s lymphoma
3. Indication for HCV treatment per AASLD 2009 Guidelines

v. HCV genotyping should be done in patients receiving a HCV diagnosis and before starting treatment

E. HCV Genotypes
i. Genotype 1b most prevalent worldwide
ii. Genotype 1a seen in North America and Western Europe, mostly with injection drug users
iii. ~75% of HCV patients in U.S. have Genotype 1
iv. Genotypes 2-6 seen in Africa, Middle East, Asia, and Europe

Current Treatment for Chronic Hepatitis C

III. Treatment Goals
A. Prevent complications, clinical progression, and death

IV. Treatment Response Measurement
A. Prevention of complications difficult to measure
B. Surrogate endpoints (virological response) used instead
C. Virological Response Definitions (full list in Appendix)
   i. Sustained Virological Response (SVR)
      1. Undetectable HCV RNA 24 weeks after end of treatment
      2. Regarded as virological cure
   ii. Rapid Virological Response (RVR)
      1. Undetectable HCV RNA at 4 weeks of therapy
      2. Predicts high likelihood of SVR
   iii. Virological Relapse
      1. Reappearance of HCV RNA after therapy was discontinued and virus undetectable at end of treatment
iv. Null Responder
   1. Failure to decrease HCV RNA by $\geq 2$ logs after 24 weeks of therapy

v. Non-responder
   1. Failure to clear HCV RNA after 24 weeks of therapy

vi. Partial Responder
   1. 2 log decrease in HCV RNA but still detectable at 24 weeks of therapy

V. Treatment History

Figure 3: SVR Rates with Recommended HCV Treatments\(^8\)
VI. What patient factors predict a favorable treatment outcome with peginterferon + ribavirin?\textsuperscript{12,13}

![Figure 4: Patient Factors Affecting Treatment Outcome](image-url)

Figure 4: Patient Factors Affecting Treatment Outcome

- Genotype: 1, 2, 3
- None, minimal
- Fibrosis: Bridging
- Baseline Viral Load: < 800,000, ≥ 800,000
- Race: White, Black
- Adherence: Yes, ≥ 80%, No, < 80%
- RVR: Yes, No
- IL-28B Genotype: CC, TC, TT
VII. Preferred Regimen from AASLD 2009 Guidelines: Peginterferon α + Ribavirin

A. Treatment Duration
   i. Genotype 1: 48 weeks
   ii. Genotypes 2 & 3: 24 weeks

**Figure 5: SVR Impact by Genotype, Treatment Duration, and Ribavirin Dose**

- 24 weeks- Low Dose Ribavirin + Peginterferon α-2a
- 24 weeks- Weight Based Ribavirin + Peginterferon α-2a
- 48 weeks- Low Dose Ribavirin + Peginterferon α-2a
- 48 weeks- Weight Based Ribavirin + Peginterferon α-2a

B. Ribavirin
   i. Dosing: Weight based superior to standard 800mg dose in achieving SVR
      1. With Peginterferon α-2a
         a. Weight ≤ 75kg: 1000 mg
         b. Weight > 75kg: 1200 mg
      2. With Peginterferon α-2b
         a. Weight < 65kg: 800 mg
         b. Weight 65-85kg: 1000 mg
         c. Weight 85-105kg: 1200 mg
         d. Weight > 105kg: 1400 mg
   ii. Adverse Drug Events (ADEs)
      1. Hematological abnormalities (~20-33%): anemia, thrombocytopenia, neutropenia
      2. Teratogenicity
   iii. Dose reductions due to ADEs: by 200mg daily increments
      1. At least 20% of patients will require dose reductions due to hematological ADEs

C. Peginterferon α 2a & 2b
   i. Dosing
      1. Peginterferon α-2a 180 mcg/week
      2. Peginterferon α-2b 1.5 mcg/kg/week
ii. No difference in treatment efficacy of two drugs

iii. ADEs:
   1. Flu-like symptoms (> 50%): muscle aches, fatigue, malaise,
   2. Psychiatric symptoms (20-30%): depression, anxiety, irritability, sleep disturbance, difficulty concentrating,
   3. Others: hair loss, rash, photosensitivity, itching, injection site reactions

iv. Dose adjustments due to ADEs
   1. Peginterferon α-2a 150 mcg/week
   2. Peginterferon α-2b 1 mcg/kg/week

VII. Who gets HCV treatment per the 2009 AASLD guidelines?

A. Patients in whom to start treatment
   i. Age > 18 years
   ii. HCV RNA detectable
   iii. Biopsy showing chronic hepatitis and significant fibrosis
   iv. Compensated liver disease
   v. Acceptable lab values (Hgb >13 for men, >12 for women, ANC 1500, SCr <1.5)
   vi. Willing to be treated and adhere to treatment requirements
   vii. No contraindications

B. Patients where treatment is contraindicated
   i. Major uncontrolled depression
   ii. Solid organ transplant, other than liver
   iii. Autoimmune hepatitis or disease
   iv. Untreated thyroid disease
   v. Pregnant or unwilling to use contraception
   vi. Severe comorbidity (HTN, heart failure, significant CAD, diabetes, COPD)
   vii. Age < 2 years
   viii. Hypersensitivity to treatment drugs

C. Patients in whom treatment should be individualized
   i. Non-responder, relapse with interferon + ribavirin
   ii. Non-responder, relapse with peginterferon monotherapy
   iii. Substance abusers willing to participate in a support program
   iv. Biopsy showing no or mild fibrosis
   v. Acute hepatitis C
   vi. HIV coinfection
   vii. Age 2-18 years
   viii. Chronic renal disease
   ix. Decompensated cirrhosis
   x. Liver transplant recipient

D. Retreatment in patients who fail therapy is not recommended

E. Who was evaluated in peginterferon + ribavirin clinical studies
   i. Patients included: Treatment naïve adults with serum HCV RNA > 2000 copies/mL, elevated ALT within 6 months, liver biopsy consistent with chronic HCV in last year
ii. **Patients excluded:** Neutropenia, thrombocytopenia, anemia, serum creatinine ≥ 1.5x ULN, decompensated liver disease, HIV co-infection, uncontrolled or severe psychiatric condition, substance abuse within 1 year, malignancy, severe cardiovascular disease, auto-immune disease, seizures, pregnancy, unable or unwilling to use contraception
   1. Other exclusion criteria of individual studies: Hepatitis A or B co-infection and previous organ transplantation

VIII. Cost-effectiveness of current therapy
A. Peginterferon + Ribavirin weekly cost $900 (2011 US$)\(^\text{19}\)
   i. Genotype 1 treatment (48 weeks): $43,200 (2011 US $)\(^\text{19}\)
B. 1\(^{st}\) year liver transplant cost: $523,400\(^\text{20}\) (2008 US$)
   i. Subsequent years: ~$20,000
C. Long-term effectiveness and cost-effectiveness analyses\(^\text{21}\)
   i. Peginterferon + Ribavirin vs. no treatment
      1. Life-Years Gained (LYGs): 3.6-4.7
      2. Quality Adjusted Life Years (QALYs): 2.8-5.2
   ii. Peginterferon + Ribavirin vs. Interferon + Ribavirin
      1. Incremental Cost-Effectiveness Ratio (ICER): Cost saving-
         ~$122,000/QALY
         a. Most studies $7000-$14000/QALY
      2. Peginterferon + Ribavirin considered by each study to be cost-effective
         and most cost-effective regimen available

---

**Direct-Acting Antivirals (DAAs): The Protease Inhibitors**

IX. **Mechanism of Action\(^\text{12,22}\)**
A. Inhibit NS3/4A serine protease ability to cleave HCV polyprotein and interferon β promoter stimulator 1
B. Restores hepatocyte innate immune signaling cascades

![Diagram](image)

Figure 6: Structure of HCV Virus\(^\text{b}\)
X. Clinical Trials

A. Patient baseline characteristics for all studies

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>49</td>
<td>50</td>
<td>51</td>
<td>53</td>
</tr>
<tr>
<td>Male (%)</td>
<td>60</td>
<td>60</td>
<td>70</td>
<td>65</td>
</tr>
<tr>
<td>White (%)</td>
<td>90</td>
<td>80</td>
<td>90</td>
<td>85</td>
</tr>
<tr>
<td>BMI (kg/m^2)</td>
<td>26</td>
<td>Not given (Weight 80kg)</td>
<td>27</td>
<td>28.5</td>
</tr>
<tr>
<td>Genotype 1a (%)</td>
<td>60</td>
<td>60</td>
<td>45</td>
<td>60</td>
</tr>
<tr>
<td>HCV RNA &gt; 800,000 IU/ml (%)</td>
<td>77</td>
<td>85</td>
<td>87</td>
<td>88</td>
</tr>
<tr>
<td>Fibrosis score 0, 1, 2 (%)</td>
<td>80</td>
<td>90</td>
<td>50</td>
<td>75</td>
</tr>
<tr>
<td>Cirrhosis (%)</td>
<td>6</td>
<td>Not given</td>
<td>25</td>
<td>12</td>
</tr>
<tr>
<td>Steatosis (%)</td>
<td>Not given</td>
<td>65</td>
<td>Not given</td>
<td>65</td>
</tr>
<tr>
<td>Non or partial responder (%)</td>
<td>N/A</td>
<td>N/A</td>
<td>47</td>
<td>35</td>
</tr>
<tr>
<td>Prior relapse (%)</td>
<td>N/A</td>
<td>N/A</td>
<td>53</td>
<td>65</td>
</tr>
</tbody>
</table>

B. Important considerations in PI trials

i. Lead-in phase or not
ii. Duration of PI treatment
iii. SVR rates for relapsers vs. partial responders vs. non-responders
iv. ESA use allowed for anemia treatment
XI. Treatment Naïve Studies

Table 3: Jacobson I et al. Telaprevir for previously untreated chronic Hepatitis C virus infection. NEJM 2011;364:2405-2416. (ADVANCE)^

<table>
<thead>
<tr>
<th>Purpose</th>
<th>To determine the efficacy and safety of the addition of telaprevir to peg-interferon and ribavirin in treatment naive patients with HCV Genotype 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>Randomized, double-blind, placebo-controlled, parallel-group, multicenter study</td>
</tr>
</tbody>
</table>
| Intervention | • T12PR: Telaprevir + Peginterferon α-2a + Ribavirin x 12 weeks  
• T8PR: Telaprevir + Peginterferon α-2a + Ribavirin x 8 weeks then Placebo + Peginterferon α-2a + Ribavirin x 4 weeks  
• PR: Placebo + Peginterferon α-2a + Ribavirin x 12 weeks  
• Response-Guided Therapy  
  o T12PR, T8PR patients with undetectable HCV RNA at weeks 4 & 12 (extended Rapid Virological Response- eRVR): 12 weeks of PEG + RBV (24 total treatment weeks)  
  o T12PR, T8PR patients without eRVR: 36 weeks of PEG + RBV (48 total treatment weeks)  
  o All PR patients: 36 weeks of PEG + RBV (48 total treatment weeks)  
  • Plus 24 week follow-up |
| Methods | • Randomized in 1:1:1 ratio, stratified by high or low baseline HCV RNA and genotype subtype  
• Stopping Rules  
  o Telaprevir patients HCV RNA > 1000 IU/mL at week 4: stop telaprevir but continue PR  
  o All patients HCV RNA < 2 log decrease from baseline at week 12: stop all treatment  
  o HCV RNA detectable between weeks 24 & 40: stop all treatment |
| Outcomes | Primary Endpoint: SVR rate  
Secondary Endpoints: Undetectable HCV RNA at week 72, RVR, eRVR, Relapse |
| Statistics | • Primary and Secondary Outcomes: Logistic regression adjusting for baseline characteristics  
• Descriptive statistics reported for those patients who relapse  
• Adjustment for multiple comparisons using Hochberg procedure  
• For 92% power to detect a 14% increase in SVR in telaprevir patients with α=0.05, 350 patients in each arm needed (1050 total) |
| Results | 1088 patients included in analysis, baseline characteristics similar  
Primary outcome: SVR T12PR 69%, T8PR 75%, PR 44% p<0.001  
Secondary outcomes: Undetectable at week 72 T12PR 67%, T8PR 73%, PR 44% p<0.001  
RVR T12PR 66%, T8PR 68%, PR 9% p<0.001  
eRVR T12PR 57%, T8PR 58%, PR 8% p<0.001  
Relapse T12PR & T8PR 9%, PR 28%  
Subgroup analyses: All subgroups had higher SVR rates with a telaprevir-containing regimen except for baseline HCV RNA ≤ 800,000 and cirrhosis (no difference)  
Adverse effects: Nausea (43% telaprevir, 31% PR), diarrhea (28% telaprevir, 22% PR), pruritus (50% telaprevir, 36% PR), rash (37% telaprevir, 24% PR), anemia (37% telaprevir, 19% PR), hemorrhoids (12% telaprevir, 4% PR), ano-rectal discomfort (13% telaprevir, 4% PR) |
| Authors’ Conclusions | The addition of telaprevir to PEG and RBV significantly increased the SVR in treatment naïve HCV genotype 1 patients. |
| Critique | • No analysis of null or partial responders to triple therapy  
• Small minority enrollment  
• No ESA use for anemia treatment allowed  
• No measure of treatment adherence |
### Table 4: Poordad F, et al. Boceprevir for untreated chronic HCV genotype 1 infection. NEJM 2011;364: 1195-1206. (SPRINT-2)\(^4\)

<table>
<thead>
<tr>
<th>Purpose</th>
<th>Compare efficacy of two treatment regimens of boceprevir in combination with peginterferon and ribavirin to therapy with only ribavirin in untreated HCV patients.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>Phase 3 multi-center, double-blind, randomized, placebo-controlled study</td>
</tr>
<tr>
<td>Patient Population</td>
<td>Included both black and non-black cohorts</td>
</tr>
</tbody>
</table>
| Intervention | All groups: Peginterferon alfa-2b 1.5mcg/kg weekly + Ribavirin 600-1400mg daily divided BID for 4 week lead in followed by:  
  - Group 1: placebo + PEG + RBV for 44 weeks  
  - Group 2: boceprevir + PEG + RBV for 24 weeks  
    - HCV RNA undetectable at week 8: 44 week follow-up  
    - HCV RNA detectable at week 8: placebo + PEG + RBV for 20 weeks  
  - Group 3: boceprevir + PEG + RBV for 44 weeks |
| Methods |  
  - Randomized in 1:1:1 ratio, stratification based on genotype 1a vs. 1b and high vs. low baseline viral load  
  - Stopping rule at week 24: detectable HCV RNA in all groups led to discontinuation of treatment and advancement to follow-up |
| Outcomes | **Primary**: SVR at week 24 in non-black cohort  
**Secondary**: ETR, Relapse, RVR |
| Statistics |  
  - Primary outcome: Two-sided Cochran-Mantel-Haenszel chi-square test adjusted for baseline characteristics  
  - Secondary outcomes: 95% Confidence Interval of the difference of proportions  
  - Step Down Approach to control for Type I error in multiple comparisons  
  - Multivariate logistic regression to identify predictors of SVR  
  - For 90% power to detect a 13% increase in SVR in group 3 compared with group 1 with an alpha 0.05, 310 subjects per group needed to be enrolled |
| Results | 940 patients enrolled, baseline characteristics similar  
  **Primary outcome**: SVR Group 1 38%, Group 2 63%, Group 3 66% (p<0.001)  
  **Secondary outcome**: SVR if RVR Group 1 97%, Group 2 89%, Group 3 90%  
  ETR Group 1 53%, Group 2 71%, Group 3 76%  
  Relapse Group 1 22%, Group 2 9%, Group 3 9%  
  Significant predictors of SVR: Boceprevir-containing regimen, non-black cohort, baseline HCV RNA < 400,000, age < 40, no cirrhosis, statin Use  
  Adverse events: Dysgeusia (40% boceprevir, 18% PR), anemia (49% boceprevir, 29% PR) |
| Authors’ Conclusions | The addition of boceprevir significantly increased the rate of SVR among previously untreated HCV patients. |
| Critique |  
  - Limited subgroup analysis for those who achieved SVR  
  - No assessment of treatment adherence |
XII. Important Protease Inhibitor Therapy Considerations

A. Pharmacokinetics

<table>
<thead>
<tr>
<th></th>
<th>Telaprevir(^{27})</th>
<th>Boceprevir(^{28})</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Food Effect on Absorption</strong></td>
<td>Increased by 237% (standard fat meal)</td>
<td>Increased by 65%</td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td>Hydrolysis, oxidation, reduction (CYP and non-CYP)</td>
<td>Major: Alpha-ketoreductase Minor: CYP3A4/5</td>
</tr>
</tbody>
</table>
| **Drug Interactions** | • CYP 3A4/5 Inhibitor- Increases levels of drugs metabolized by CYP 3A4/5  
 • PGP Inhibitor- Increases levels of drugs excreted through PGP  
 • Telaprevir levels may be decreased when given with CYP 3A4/5 inducers | • CYP 3A4/5 Inhibitor- Increases levels of drugs metabolized by CYP 3A4/5  
 • PGP Inhibitor- Increases levels of drugs excreted through PGP  
 • Boceprevir levels may be decreased when given with CYP 3A4/5 inducers |

B. High pill burden\(^{27,28}\)
   i. Telaprevir 750mg TID= 2 tabs PO TID with meal (at least 20gm fat each meal)
   ii. Boceprevir 800mg TID= 4 caps PO TID with meal

C. Adherence may dictate response
   i. At least 80% adherence correlates with SVR with peginterferon + ribavirin\(^{29,30}\)
   ii. No reporting of patient adherence to therapy in PI trials
   iii. Boceprevir-resistant mutants found during lead-in phase of both SPRINT-2 and RESPOND-2\(^{31}\)
      a. Overall, ~15% of patients without RVR found to be infected with boceprevir-resistant strains
   iv. Rapid development of resistance and cross-resistance possible\(^{32}\)

D. Dose Adjustments\(^{27,28}\)
   i. Not studied in moderate to severe hepatic impairment
   ii. Not studied in CrCl < 50 mL/min
   iii. Doses should never be reduced for organ dysfunction or ADEs; only option is to discontinue PI therapy

E. MUST be used in combination with both peginterferon and ribavirin
   i. Lower SVR rate found when PI added to only peginterferon in phase 2 trial\(^{33}\)
   ii. If ribavirin is stopped, protease inhibitor must also be stopped due to increased rate of resistance with PI monotherapy
### XIII. Treatment Experienced Studies

<table>
<thead>
<tr>
<th>Purpose</th>
<th>To determine the efficacy and safety of the addition of telaprevir to peg-interferon and ribavirin in patients with HCV genotype 1 who did not achieve SVR with prior treatment.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>Randomized, double-blind, placebo-controlled phase 3 trial.</td>
</tr>
</tbody>
</table>
| Intervention | All groups: 4 week screening period then:  
  - T12PR48: Telaprevir 750mg q8h + PEG + RBV for 12 weeks then Placebo + PEG + RBV for 4 weeks then PEG + RBV for 32 weeks  
  - Lead-in T12PR48: Placebo + PEG + RBV for 4 weeks then Telaprevir 750mg q8h + PEG + RBV for 12 weeks then PEG + RBV for 32 weeks  
  - PR48: Placebo + PEG + RBV for 16 weeks then PEG + RBV for 32 weeks  
  Plus 24 week follow-up |
| Methods |  
  - Randomized in 2:2:1 ratio, stratified by high or low baseline HCV RNA and prior treatment response  
  - Stopping rule: <2 log decrease in HCV RNA at week 12 (T12PR48 & PR48) or week 16 (Lead-in T12PR48) or HCV RNA >100 IU/mL at weeks 4, 6, or 8 (T12PR48) or weeks 8, 10, 12 (Lead-in T12PR48) |
| Outcomes | Primary: SVR  
Secondary: Effect of lead-in with PEG and RBV on SVR, rate of undetectable HCV RNA at weeks 4 and 8, rate of relapse, RNA change from baseline |
| Statistics |  
  - Primary and secondary outcomes: Logistic regression controlling for baseline characteristics  
  - Hochberg procedure for multiple comparisons adjustment  
  - For 90% power to detect 26% increase in SVR in telaprevir patients with alpha 0.05, 650 patients needed |
| Results | 663 patients randomized, Baseline characteristics similar  
Primary outcome: Relapsers SVR 83% T12PR48, 88% Lead-in T12PR48, 24% PR48 (p<0.001); Non-responders SVR 41% telaprevir groups, 9% PR48 (p<0.001)  
Secondary outcomes: No difference in SVR for telaprevir groups  
relapse lower in telaprevir groups (Relapsers: 7% telaprevir groups, 65% PR48, Non-responders: 25% telaprevir groups, 60% PR48)  
Adverse events: Nausea (35% telaprevir, 23% PR48), diarrhea (25% telaprevir, 14% PR48), pruritus (52% telaprevir, 27% PR48), rash (37% telaprevir, 19% PR48), anemia (30% telaprevir, 15% PR48), hemorrhoids (15% telaprevir, 7% PR48) |
| Authors’ Conclusions | Telaprevir + PEG + RBV significantly increased the SVR rate for patients with chronic HCV genotype 1 in comparison to PEG + RBV alone for previously treated patients. |
| Critique |  
  - No subgroup analyses besides classification of response to previous therapy  
  - Very low minority enrollment  
  - No use of ESAs allowed for treatment of anemia  
  - No measure of treatment adherence |
Table 6: Bacon BR, et al.  Boceprevir for previously treated chronic HCV genotype 1 infection. NEJM 2011;364:1207-1217. ([RESPOND-2])

<table>
<thead>
<tr>
<th>Purpose</th>
<th>Compare the safety and efficacy of two treatment regimens of boceprevir in combination with peginterferon and ribavirin to therapy with only peginterferon and ribavirin in previously treated HCV patients.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>Prospective, randomized, double-blind, controlled, multicenter study over 72 weeks</td>
</tr>
</tbody>
</table>
| Intervention | All Groups: Peginterferon alfa-2b 1.5mcg/kg weekly + Ribavirin 600-1400mg daily divided for 4 week lead in followed by:  
• Group 1: Placebo + peginterferon + ribavirin for up to 44 weeks  
• Group 2: Boceprevir 800mg TID + peginterferon + ribavirin for 32 weeks  
• Group 3: Boceprevir 800mg TID + peginterferon + ribavirin for 44 weeks |
| Methods |  
• Patients randomized to one of three groups in 1:2:2 fashion, stratified based on previous therapy response and HCV sub-genotype  
• Stopping rule at week 12: detectable HCV RNA level in all groups led to discontinuation of all therapies and advancement to follow-up |
| Outcomes | Primary: Sustained virologic response (undetectable HCV RNA level at week 24, SVR)  
Secondary: Patients with early response and sustained virologic response, Patients with relapse |
| Statistics |  
• Primary outcome: two-sided Cochran-Mantel-Haenszel chi-square test adjusted for baseline characteristics  
• Statistical Power of 90%, predicted SVR improvement of 21%, alpha = 0.05  
• Step-down approach used to control for Type I error in multiple comparisons  
• Multivariable logistic-regression used to identify independent predictors of SVR |
| Results |  
403 patients enrolled, Baseline characteristics equal except higher VL in group 2 vs. group 1  
Primary outcome: SVR Rates Group 1 21%, Group 2 59%, Group 3 66% (p<0.001)  
Secondary outcome: SVR in undetectable HCV RNA at week 8 Group 1 100%, Group 2 86%, Group 3 88%  
Relapse Group 1 32%, Group 2 15%, Group 3 12%  
Subgroup analyses: Higher SVR in boceprevir-containing regimen in all subgroups except weight <75kg, platelets < 150,000 or 150,000-200,000, Metavir fibrosis score 3 or 4, statin use in comparison of Group 2 and Group 1  
Adverse events: Anemia (45% boceprevir, 20% PR), dysgeusia more frequent in boceprevir groups than PR alone |
| Authors’ Conclusions | Adding boceprevir to peginterferon-ribavirin increased the SVR rate in previously treated patients with chronic HCV genotype 1 infection |
| Critique |  
• Excluded null responders to previous treatment  
• No assessment of adherence  
• Small minority enrollment |

XIV. Patients who participated in PI studies23,24,25,26  
a. Included  
i. All studies: Adults; genotype 1; no neutropenia, thrombocytopenia, anemia; agree to use contraception; no HCC
b. Excluded
   i. All studies: Decompensated liver disease, other causes of significant liver
disease, HIV or HBV co-infection, active cancer, psychiatric condition, seizures,
prior organ transplant, pregnancy, active substance abuse, contraindication to
peginterferon or ribavirin, eye complications from diabetes or hypertension,
previous study participant, systemic steroid use, chronic pulmonary disease,
pancreatitis, Genotypes 2-6

XV. The Downside to PI Therapy: Significant treatment costs\textsuperscript{19}
a. Peginterferon + Ribavirin alone
   i. 48 weeks: $43,200
b. Telaprevir (+ Peginterferon + Ribavirin)
   i. 24 weeks: $77,600
   ii. 48 weeks: $99,200
c. Boceprevir (+ Peginterferon + Ribavirin)
   i. 28 weeks: $56,000
   ii. 36 weeks: $73,500
   iii. 48 weeks: $84,250

XVI. The Future of Chronic HCV Treatment\textsuperscript{12}
a. Mathematical model projects if response to antivirals for chronic HCV increases to 80%
and 50% of chronic HCV patients are treated, complications will decrease in 10 years\textsuperscript{12,34}
   i. Cirrhosis decreases by 15%
   ii. HCC decreases by 30%
   iii. Deaths due to liver disease decrease by 34%
b. Over 50 drugs and drug combinations in the development pipeline
c. Possibility of interferon-free therapy in next few decades?

\textbf{Summary}

| XVII. | Chronic Hepatitis C infection is a significant cause of morbidity and mortality worldwide |
| XVIII. | Current treatment recommendations include peginterferon and ribavirin |
| a. Rates of SVR are less than 50% for patients with Genotype 1 |
| XIX. | Direct-acting antivirals, including protease inhibitors, provide effective treatment options |
| for chronic Hepatitis C patients |
| a. Rates of SVR are up to 75% in treatment naive patients and up to 88% in previously |
| treated patients |
| b. Cost of protease inhibitor therapy could be prohibitive |

\textbf{Conclusion}

XX. Presenter’s Conclusions
   a. Patients with documented success with PI + peginterferon + ribavirin therapy over |
   peginterferon + ribavirin only
i. Genotype 1
ii. Age > 18 years
iii. All stages of fibrosis
iv. Treatment naive
v. Prior relapse if treatment experienced
vi. All detectable viral loads
vii. All races, including African-Americans
b. Patients whom I would not treat with PIs until more data is available
i. Age < 18 years
   1. Pediatric patients excluded from clinical trials
ii. HIV or HBV co-infection
   1. Co-infected patients excluded from clinical trials
   2. Concerned for significant drug interactions
iii. Solid organ transplant recipients
   1. Transplant recipients excluded from clinical trials
   2. Significant drug interactions with PIs and immunosuppressive drugs
iv. Anemia and/or neutropenia
   1. Neutropenic and anemic patients excluded from clinical trials
   2. Hematological side effects seen in patients receiving PIs in all studies
v. Decompensated liver disease
   1. Patients with decompensated liver disease excluded from clinical trials
vi. Chronic renal disease
   1. Patients with CrCl < 50ml/min excluded from clinical trials
vii. Failed PI + peginterferon + ribavirin therapy
   1. No studies looking at those who failed triple therapy
   2. Concern for development of resistance to PIs
viii. Anticipated low adherence rate
   1. Adherence rates not reported in clinical trials
   2. Unclear impact of non-adherence to treatment on SVR
c. Patients who benefit sufficiently with peginterferon + ribavirin and PI treatment may not be necessary
i. IL-28B Genotype CC
   1. 80% success rate with peginterferon + ribavirin
ii. Achieve RVR in lead-in phase with only peginterferon + ribavirin
   1. Can be detected with boceprevir treatment
   2. 97% of patients achieving RVR during lead-in achieved SVR with only peginterferon + ribavirin
d. Patients who may benefit from PIs but other groups given priority
i. No or minimal fibrosis
   1. Low likelihood of disease progression to cirrhosis
   2. Possibility of future treatment options before complications set in
ii. Non-responders and null responders
   1. Null responders not enrolled in RESPOND-2
   2. Non-responders 29% SVR rate in REALIZE
References

## Appendix: Virological Response Definitions and Implications for Treatment Success

<table>
<thead>
<tr>
<th>Virological Response</th>
<th>Definition</th>
<th>Implication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sustained Virological Response (SVR)</td>
<td>Absence of HCV RNA 24 weeks after end of treatment</td>
<td>Predictor of long-term response “Virological cure”</td>
</tr>
<tr>
<td>Rapid Virological Response (RVR)</td>
<td>Undetectable HCV RNA after 4 weeks of treatment</td>
<td>Predicts high likelihood of SVR</td>
</tr>
<tr>
<td>Extended Rapid Virological Response (eRVR)</td>
<td>Undetectable HCV RNA after both 4 weeks and 12 weeks of treatment</td>
<td>Predicts high likelihood of SVR in telaprevir trials</td>
</tr>
<tr>
<td>End of Treatment Response (ETR)</td>
<td>Undetectable HCV RNA at end of 24 or 48 weeks of therapy</td>
<td>Not predictive of SVR, but required in order to attain SVR</td>
</tr>
<tr>
<td>Early Virological Response (EVR)</td>
<td>≥ 2 log reduction or undetectable HCV RNA at week 12 of therapy</td>
<td>Predicts SVR</td>
</tr>
<tr>
<td>Virological Breakthrough</td>
<td>Reappearance of HCV RNA while on therapy</td>
<td></td>
</tr>
<tr>
<td>Virological Relapse</td>
<td>Reappearance of HCV RNA after therapy was discontinued and an ETR was documented</td>
<td></td>
</tr>
<tr>
<td>Null Responder</td>
<td>Failure to decrease HCV RNA by ≥ 2 logs after 24 weeks of therapy</td>
<td></td>
</tr>
<tr>
<td>Non-responder</td>
<td>Failure to clear HCV RNA after 24 weeks of therapy</td>
<td></td>
</tr>
<tr>
<td>Partial Responder</td>
<td>2 log decrease in HCV RNA but still detectable at 24 weeks of therapy</td>
<td></td>
</tr>
</tbody>
</table>