Hepatitis C 2012

Paul Y. Kwo, MD, FACG
Professor of Medicine
Medical Director, Liver Transplantation
Gastroenterology/Hepatology Division
Indiana University School of Medicine
975 W. Walnut, IB 327
Indianapolis, IN 46202-5121
phone 317-274-3090
fax 317-274-3106
pkwo@iupui.edu

2 Protease Inhibitors Approved for Genotype 1 HCV Infection

<table>
<thead>
<tr>
<th>Protease Inhibitor</th>
<th>Additional Regimen Components</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boceprevir 800 mg TID</td>
<td>PegIFN alfa + weight-based RBV</td>
<td>• Naive to previous therapy</td>
</tr>
<tr>
<td>(q7-9hrs) [1,2]</td>
<td></td>
<td>• Previous treatment failure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Compensated cirrhosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• RGT</td>
</tr>
<tr>
<td>Telaprevir 750 mg TID</td>
<td>PegIFN alfa + weight-based RBV</td>
<td>• Naive to previous therapy</td>
</tr>
<tr>
<td>(q7-9hrs) [2,3]</td>
<td></td>
<td>• Previous treatment failure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Compensated cirrhosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• RGT</td>
</tr>
</tbody>
</table>

For patients with genotype 2/3 infection, HCV therapy with pegIFN/RBV remains the standard of care

Factors Predictive of Response to IFN/RBV based therapy

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype 2/3</td>
<td>Lack of steatosis/insulin resistance</td>
<td>Race/ethnicity</td>
</tr>
<tr>
<td>No advanced fibrosis</td>
<td>Adherence</td>
<td>low viral load</td>
</tr>
<tr>
<td>Low viral load</td>
<td>Rapid viral response (RVR)</td>
<td>absence of cirrhosis</td>
</tr>
<tr>
<td>Younger age</td>
<td>Ribavirin dosage</td>
<td>statin use</td>
</tr>
<tr>
<td>&lt;40 years</td>
<td>Race/ethnicity</td>
<td>IL-28B</td>
</tr>
<tr>
<td>Female</td>
<td>IL-28B</td>
<td>Genotype 1a/1b</td>
</tr>
<tr>
<td>Weight</td>
<td>Anemia</td>
<td>On treatment viral response</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lead-in</td>
</tr>
<tr>
<td></td>
<td></td>
<td>eRVR</td>
</tr>
</tbody>
</table>


2.9-4 Million Individuals With Chronic HCV Infection
US: Proportion of Patients With Chronic HCV Projected to Develop Cirrhosis or Complications

HCV cirrhosis  Hepatic decompensation

% of Patients With HCV

Year

2000 2010 2020 2030 2040

Telaprevir/Boceprevir in Combination with PEG-IFN/RBV in Genotype 1 HCV Treatment

- Factors to consider when offering therapy in 2012
  - HCV genotype 1a/1b (1b better response)
  - Quantitative viral level (low viral load does well)
  - IL-28 genotype (treatment naïve, high percentage CC in Asia)
  - Previous viral kinetics if non-responder
    - IL-28 not as helpful with accurate viral kinetics
  - Fibrosis assessment (more advanced fibrosis higher priority)
  - Concomitant medicines/Drug-Drug interaction query
  - Management plan for side effects
    - Rash, anemia, GI side effects: Will they tolerate side effects

Telaprevir + PegIFN/RBV in G1 Tx-Naïve Patients

Important Futility Milestones: Weeks 4, 12, 24

- Treatment duration: Patients with extended RVR (eRVR, undetectable* HCV-RNA at Week 4 and Week 12): receive 24 weeks of therapy
  - Patients without eRVR continue on PegIFN and RBV for a total of 48 weeks

Futility

- Week 4 HCV RNA > 1000 IU/mL
- Week 12 HCV RNA > 1000 IU/mL
- Week 24 HCV RNA detectable

*assay should have a lower limit of HCV-RNA quantification ≤ 25 IU/mL for RGT
What can we tell our patients?
Significantly Higher SVR rates in Telaprevir-Treated Patients Compared to Peg IFN/Ribavirin Alone

![Graph showing SVR rates](image)


ADVANCE Study:
Influence of Race on SVR with PegIFN/RBV ±Telaprevir

![Graph showing influence of race on SVR](image)

Jacobson NEJM 2011
ADVANCE Study: Role of Age on SVR with PegIFN/RBV ± Telaprevir


ADVANCE Study: Role of Viral Level on SVR with PegIFN/RBV ± Telaprevir

Role of HCV Genotype

- Evidence that 1a more difficult to treat than 1b with PR
  - Genotype 1a associated with lower SVR than genotypes 1b, 4a, and 4d when treated with PR for 48 weeks in 537 patients
  - Genotype 1a associated with lower SVR in 115 patients receiving PR for 48 weeks than 1b
- Initial HCV subgenomic replicons derived from genotype 1b virus

Science, 2000

ADVANCE Study: Influence HCV Genotype on SVR with PegIFN/RBV ±Telaprevir

<table>
<thead>
<tr>
<th>Genotype</th>
<th>PR+TVR</th>
<th>PR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1b</td>
<td>79</td>
<td>48</td>
</tr>
<tr>
<td>1a</td>
<td>71</td>
<td>41</td>
</tr>
</tbody>
</table>

ADVANCE Study: Influence of Hepatic Fibrosis on SVR with PegIFN/RBV ± Telaprevir


ADVANCE Study: Role of *IL28B* on SVR with PegIFN/RBV ± Telaprevir

42% (454 of 1088) of patients available for *IL28B* analysis; all patients were white

TVR increased SVR rates across *IL28B* genotypes, but CC still did better

Boceprevir for genotype 1 naïve HCV
Milestones: Weeks 8, 12, 24

- PR + EOC (24 weeks) Ncn-cirrhotic
- PR + BOC (44 weeks) poorly responsive pts

Week 4
Week 28
Week 48
Week 72

TW 8-24 HCV-RNA Undetectable*
Follow-up

Week 36

PR+BOC (32 weeks) PR Follow-up

TW 8 HCV-RNA Detectable/ TW 24 undetectable

Week 12 Futility Week 24 Futility HCV > 100 IU/ml Detectable HCV RNA

*assay should have a lower limit of HCV-RNA quantification ≤ 25 IU/mL, and limit of HCV-RNA detection of approximately 10-15 IU/mL

Lead-in Strategy: A Strategy to determine who to treat

- Four weeks of Peg interferon and ribavirin lead-in prior to boceprevir/telaprevir
  - Lower HCV burden
  - May identify rapid responders who may not need DAA
  - Allows assessment of interferon responsiveness
    - may provide useful information regarding likelihood of SVR with addition of DAA
    - clinicians can determine who can tolerate Peg IFN/RBV
SPRINT 2: SVR* and Relapse Rates

*SVR was defined as undetectable HCV RNA at the end of the follow-up period. The 12-week post-treatment HCV RNA level was used if the 24-week post-treatment level was missing (as specified in the protocol). A sensitivity analysis was performed counting only patients with undetectable HCV RNA documented at 24 weeks post-treatment and the SVR rates for Arms 1, 2 and 3 in Cohort 1 were 39%, 66% and 68%, respectively and in Cohort 2 were 21%, 42% and 51%, respectively.

SPRINT 2: Influence of Race on SVR with PegIFN/RBV ± Boceprevir

SPRINT 2: Influence of Age on SVR with PegIFN/RBV ± Boceprevir

- PR+BOC: 69% ≤ 40, 65% > 40
- PR+BOC RGT: 73% ≤ 40, 64% > 40
- PR: 52% ≤ 40, 34% > 40


SPRINT 2: Influence of Viral Level on SVR with PegIFN/RBV ± Boceprevir

- PR+BOC: 85% < 800,000, 63% ≥ 800,000
- PR+BOC RGT: 76% < 800,000, 61% ≥ 800,000
- PR: 64% < 800,000, 33% ≥ 800,000

SPRINT 2: Influence of HCV Genotype on SVR with PegIFN/RBV ± Boceprevir


SPRINT 2: Influence of Fibrosis on SVR with PegIFN/RBV ± Boceprevir

SPRINT 2: Influence of Cirrhosis SVR with PegIFN/RBV ± Boceprevir

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No Cirrhosis</th>
<th>Cirrhosis</th>
<th>No Cirrhosis</th>
<th>Cirrhosis</th>
<th>No Cirrhosis</th>
<th>Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR+BOC</td>
<td>67 (42/24)</td>
<td>42</td>
<td>66 (31/16)</td>
<td>37</td>
<td>46 (6/13)</td>
<td>66</td>
</tr>
</tbody>
</table>


SPRINT-2: SVR by IL28B Polymorphism

62% of individuals (653/1048) had consented to IL28 pharmacogenomic studies

*~90% eligible for short duration therapy
IL28B is no longer an important predictor of SVR when Lead-in Response is considered

<table>
<thead>
<tr>
<th>SPRINT-2 (effect)</th>
<th>Odds Ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BOC/PR48 vs PR48</td>
<td>7.0 (4.1, 12.0)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>BOC/RGT vs PR48</td>
<td>6.0 (3.5, 10.2)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Baseline HCV-RNA: ≤400,000 vs. &gt;400,000 IU/mL</td>
<td>5.8 (1.9, 17.5)</td>
<td>0.002</td>
</tr>
<tr>
<td>Log decline in HCV-RNA at TW 4 (continuous variable)</td>
<td>2.6 (2.1, 3.0)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Genotype: 1b/others vs 1a</td>
<td>2.3 (1.5, 3.6)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>BMI: 25-30 kg/m² vs. &gt;30 kg/m²</td>
<td>2.3 (1.4, 3.9)</td>
<td>0.002</td>
</tr>
<tr>
<td>BMI: ≤25 kg/m² vs. &gt;30 kg/m²</td>
<td>1.9 (1.1, 3.3)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Only covariates remaining significant at α=0.05 after adjustment for the other variables were retained in the model as shown in the table.
Telaprevir for all non-responders
4 week PR lead-in neither improves nor reduces SVR rates

RGT therapy with relapsers receiving 24 weeks of therapy who undergo eRVR
All others (nulls, partial responders, cirrhotics) 48 weeks

Futility (no LI)
Week 4 HCV RNA > 1000 IU/ml
Week 12 HCV RNA > 1000 IU/ml
Week 24 HCV RNA detectable

REALIZE: SVR in Prior Relapsers, Prior Partial Responders and Prior Null Responders

prior relapsers prior partial responders prior null responders

SVR (%)

T12/ PR48 83 63 29 2
LI T12/ PR48 88* 54* 33* 5
Pbo/ PR48 24 15 5 0

T12/ PR48 121/145
LI T12/ PR48 124/141
Pbo/ PR48 16/88

p<0.001 vs Pbo/PR48
REALIZE: SVR by Baseline Fibrosis Stage and Prior Response

Prior relapers
- Pooled T12/PR48
- Pbo/PR48

Prior partial responders
- Pooled T12/PR48
- Pbo/PR48

Prior null responders
- Pooled T12/PR48
- Pbo/PR48

SVR Rates by IL28B Genotype and Prior Response

Prior relapers
- Pooled T12/PR48 (n=209)
- Pbo/PR48 (n=52)

Prior partial responders
- Pooled T12/PR48 (n=79)
- Pbo/PR48 (n=20)

Prior null responders
- Pooled T12/PR48 (n=134)
- Pbo/PR48 (n=33)
Resistant Profiles in non-SVR Patients

<table>
<thead>
<tr>
<th>Variant</th>
<th>% of sequenced patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Subtype 1a</td>
</tr>
<tr>
<td>WT</td>
<td>16%</td>
</tr>
<tr>
<td>V36M</td>
<td>10%</td>
</tr>
<tr>
<td>R155K</td>
<td>20%</td>
</tr>
<tr>
<td>V36M+R155K</td>
<td>46%</td>
</tr>
<tr>
<td>V36A</td>
<td>3%</td>
</tr>
<tr>
<td>T54A</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>A156S/T</td>
<td>3%</td>
</tr>
</tbody>
</table>

Loss of Resistance by NS3 Position

<table>
<thead>
<tr>
<th></th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time After Treatment Failure (months)</td>
<td></td>
</tr>
<tr>
<td>R155K</td>
<td>Median mos. to loss (95% CI)</td>
</tr>
<tr>
<td>V36M</td>
<td>9 (8,11)</td>
</tr>
<tr>
<td>T54A</td>
<td>10 (9,11)</td>
</tr>
<tr>
<td>V36A</td>
<td>4 (3,4)</td>
</tr>
<tr>
<td>A156S/T</td>
<td>4 (3,6)</td>
</tr>
</tbody>
</table>

Hash marks indicate censored observations.
Boceprevir for genotype 1 non-responders HCV
Key time points 8, 12, 24

- Week 4
- Week 36
- Week 48
- Week 72

BOC RGT for Non-cirrhotics

PR lead-in

PR ⊕ Boceprevir (32 weeks)

Week 12

Week 24

PR ⊕ BOC (44) weeks for cirrhotic patients/ poorly responsive pts

Follow-up

*assay should have a lower limit of HCV-RNA quantification ≤ 25 IU/mL, and limit of HCV-RNA detection of approximately 10-15 IU/mL

SVR by Historical Response
Non-responders and Relapsers*

<table>
<thead>
<tr>
<th></th>
<th>Arm 1: 48 P/R N = 80</th>
<th>Arm 2: BOC RGT N = 162</th>
<th>Arm 3: BOC/PR48 N = 161</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-responder – n/n (%)</td>
<td>2/29 (6.9)</td>
<td>23/57 (40.4)</td>
<td>30/58 (51.7)</td>
</tr>
<tr>
<td>Relaper – n/n (%)</td>
<td>15/51 (29.4)</td>
<td>72/105 (68.6)</td>
<td>77/103 (74.8)</td>
</tr>
</tbody>
</table>

*Non-responders had a decrease in plasma HCV-RNA of at least 2-log_{10} by week 12 of prior therapy but with detectable HCV-RNA throughout the course of therapy. Relapser had undetectable HCV-RNA at end of prior therapy without subsequent attainment of a sustained virologic response.
SVR by Advanced Fibrosis/Cirrhosis in Patients Receiving BOC + PegIFN/RBV

- **Recommendation:** All cirrhotic patients receiving BOC + PR should receive 48 weeks of therapy\(^{[1,2]}\)

Subgroup Analysis of RESPOND-2\(^{[4]}\)


RESPOND-2: SVR by IL28B Polymorphism

*~80% eligible for short duration therapy*
SVR by Week 4 PR Lead-In Response

Poorly Responsive to IFN
<1 log_{10} viral load decline at treatment week 4

Responsive to IFN
≥1 log_{10} viral load decline at treatment week 4

SVR in Poor IFN Responders Based on TW8 Response (Log Decline in VL Compared to BL VL) (BOC Arms Combined)
Sustained Virologic Response (SVR) in Prior PegInterferon/Ribavirin (PR) Treatment Failures After Retreatment with Boceprevir (BOC) + PR: PROVIDE Study Interim Results


1University Henri Poincare of Nancy, Vandoeuvre-lès-Nancy, France; 2South Florida Center of Gastroenterology, Wellington, FL; 3Northwestern Feinberg School of Medicine, Chicago, IL; 4Henry Ford Hospital, Detroit, MI; 5Alamo Medical Research, San Antonio, TX; 6University of British Columbia and Vancouver General Hospital, Vancouver, BC, Canada; 7Liver Specialists of Texas, Houston, TX; 8Virginia Commonwealth University School of Medicine, Richmond, VA; 9Mt. Vernon Endoscopy Center, Alexandria, VA; 10Weill Cornell Medical College, New York, NY; 11Université Denis Diderot-Paris, Paris; 12Hôpital Beaujon, Clichy, France; 13Duke University School of Medicine, Durham, NC; 14Cedars-Sinai Medical Center, Los Angeles, CA; 15Merck Sharp & Dohme Corp, Whitehouse Station, NJ; 16Baylor College of Medicine, Houston, TX

International Liver Congress 2012, Abstract 204
47th Annual Meeting of the European Association for the Study of the Liver
Barcelona, Spain
April 20, 2012

SVR Rates if lead-in dropouts included: nulls 38% (19/50), partials 68% (53/78), relapsers 50% (5/10), overall 57% (81/142).

† denominator for relapse rate = patients with undetectable HCV RNA at EOT and not missing end of follow-up data.
Futility Rules for BOC or TVR + PegIFN/RBV in Tx-Exp Patients

- Recommendation: All therapy should be discontinued in patients with the following

<table>
<thead>
<tr>
<th>Time Point</th>
<th>Criteria</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wk 12</td>
<td>HCV RNA ≥ 100 IU/mL</td>
<td>Discontinue all therapy</td>
</tr>
<tr>
<td>Wk 24</td>
<td>HCV RNA detectable</td>
<td>Discontinue all therapy</td>
</tr>
</tbody>
</table>

- Recommendation: < 1 log reduction with lead in, DC if less than 3 log reduction at week 8 with boceprevir

---

TELAPREVIR[1-3]

<table>
<thead>
<tr>
<th>Time Point</th>
<th>Criteria</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wk 4 or 12</td>
<td>HCV RNA &gt; 1000 IU/mL</td>
<td>Discontinue all therapy</td>
</tr>
<tr>
<td>Wk 24</td>
<td>HCV RNA detectable</td>
<td>Discontinue pegIFN/RBV</td>
</tr>
</tbody>
</table>

Assay should have a lower limit of HCV RNA quantification of ≤ 25 IU/mL and a limit of HCV RNA detection of approximately 10-15 IU/mL.


---

Conclusions Telaprevir/Boceprevir + PR for non-responders

- Excellent SVR rates for relapsers with RGT
  - 24 weeks with Telaprevir, 36 weeks with Boceprevir

- Good SVR rates for partial responders
  - RGT with Boceprevir
  - Cirrhotics receive 48 weeks with both drugs
  - < 1 log reduction with PR lead in, 44 weeks of Boc/PR

- Null responder SVR rates 32-40%
  - Lower in advanced fibrosis (who need treatment now)
  - Greatest risk of resistance
  - Adhere to futility rules
  - PR responsiveness may be helpful to minimize risk of resistance
Who to treat?

- Both telaprevir and boceprevir added to PR improve SVR rates
- All patients are candidates for therapy now
- Disease severity drives those we treat now
  - Stage 3-4 Fibrosis
  - Earlier stages of fibrosis can wait for more effective better tolerated therapies if desired
  - Look for factors that allow successful treatment
  - IL-28 CC predicts 6 month duration of treatment
  - PR responsiveness, no harm in giving 4 weeks of PR
  - Non-black race, genotype 1b, low viral level
  - For non-responders, did they tolerate therapy with PR?
  - Careful monitoring, especially in those with advanced fibrosis

Treatment of Chronic Hepatitis C

<table>
<thead>
<tr>
<th>Year</th>
<th>Standard interferon (12-18 mos)</th>
<th>PegIFN/ribavirin (6-12 mos)</th>
<th>PegIFN monotherapy (6-12 mos)</th>
<th>PI + PegIFN/RBV (6-12 mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1991</td>
<td>8-12</td>
<td>38-43</td>
<td>50-60</td>
<td>70-75</td>
</tr>
<tr>
<td>1995</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1998</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2011</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>