Triple Therapy for Genotype 1 Treatment Experienced Patients

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Triple Therapy for Treatment-Experienced Patients

- Fast growing segment of patients
- Goal remains permanent viral eradication
- Limited, generally unsatisfactory response with currently available medications
  - “Those who cannot remember the past are doomed to repeat it” George Santayana 1905
- Triple therapy will offer an excellent therapeutic option for many patients
  - Telaprevir
  - Boceprevir
Definitions of Non-Sustained Response

- Differentiate Relapser from Partial responder from Null responder
  - Implications for subsequent treatment success, even for triple therapy combinations
  - Phase II and phase III studies of both protease inhibitors used different definitions and inclusion/exclusion criteria
    - General concepts apply, however
Telaprevir in Treatment Experienced Patients

**PROVE3: Study Design**

**T12PR24**
- TVR + Peg-IFN + RBV
- Placebo + Peg-IFN + RBV
- SVR
- 1-Year Durability

**T24PR48**
- TVR + Peg-IFN + RBV
- Peg-IFN + RBV
- SVR
- 1-Year Durability

**T24P24 (no RBV)**
- TVR + Peg-IFN
- SVR
- 1-Year Durability

**PR48 (control)**
- Placebo + Peg-IFN + RBV
- Peg-IFN + RBV
- SVR

(P) Peg-IFN = pegylated interferon alfa-2a 180 μg/wk. subcutaneous injection;
(R) RBV = ribavirin 1,000 mg/day (body weight <75 kg) or 1,200 mg/day (body weight ≥75 kg);
(T) TVR = telaprevir 750 mg q8h (initial loading dose 1125 mg)

Telaprevir in Treatment Experienced Patients

PROVE3: Methods – Definition of Prior Peg-IFN + RBV Treatment Response

<table>
<thead>
<tr>
<th>Category</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonresponders</td>
<td>Patients who never achieved undetectable HCV RNA after a course of Peginterferon and ribavirin of at least 12 weeks during or at the end of treatment period</td>
</tr>
<tr>
<td>Relapsers</td>
<td>Patients who achieved undetectable HCV RNA during treatment for at least 42 weeks but detectable HCV RNA levels observed during the follow-up period and did not achieve SVR</td>
</tr>
<tr>
<td>Breakthroughs</td>
<td>Patients who had undetectable HCV RNA during the treatment period, but detectable levels of HCV RNA before the end of treatment period</td>
</tr>
</tbody>
</table>

Eligibility and categorization of prior response was determined from medical records and prior HCV values

Telaprevir in Treatment Experienced Patients

PROVE3: Stopping Rules

- Breakthrough from Week 4 through Week 24 of treatment
  - Increase in HCV RNA of $>1 \log_{10}$ as compared with nadir; or
  - HCV RNA level of $>100$ IU/mL after undetectability

- Nonresponse at Week 4
  - Control arm: $<1 \log_{10}$ HCV RNA decrease from baseline to Week 4
  - Telaprevir arms: HCV RNA levels $\geq 30$ IU/mL

- Nonresponse at Week 12
  - All arms: $\leq 2 \log_{10}$ reduction from baseline in HCV RNA by Week 12

- Week 24
  - Control (PR48) and T24PR48 arms: detectable HCV RNA by Week 24

Telaprevir in Treatment Experienced Patients

PROVE3: SVR Rates by Prior Response and Treatment Group

Telaprevir in Treatment Experienced Patients

PROVE3: Cumulative Viral Breakthrough Rate From Baseline Through Week 24 by Treatment Group

VBT associated with mutations at positions 36,54,155,156

Telaprevir + Peg-IFN α-2a/RBV in Prior Nonresponders: REALIZE

Prior NR, G1, CHC N=662

Randomization 2:2:1 (two telaprevir arms and control PR48 arm, respectively)

NR = nonresponders (prior relapsers, 53%; prior partial responders, 19%; prior null responders, 28%)

* Includes a 4-week lead-in arm with Peg-IFN α-2a + RBV

REALIZE: Definition of Prior Nonresponse

- Null responders: $< 2 \log_{10}$ decline in HCV RNA at 12 weeks of prior Peg-IFN/RBV therapy

- Partial responders: $\geq 2 \log_{10}$ decline in HCV RNA at week 12 of prior Peg-IFN/RBV therapy but not undetectable by week 24 of prior therapy

- Relapsers: undetectable HCV RNA at the completion of at least 42 weeks of prior Peg-IFN/RBV therapy but who relapsed after treatment ended (during follow-up)

Telaprevir for Treatment Experienced Patients - SVR in REALIZE

Realize Press Release, September 7, 2010. Available at:

T = telaprevir
PR = Peg-IFN α-2a + ribavirin

<table>
<thead>
<tr>
<th>Category</th>
<th>T/PR (83%)</th>
<th>T-Delayed/PR (59%)</th>
<th>PR (24%)</th>
<th>T/PR (54%)</th>
<th>T-Delayed/PR (15%)</th>
<th>PR (15%)</th>
<th>T/PR (29%)</th>
<th>T-Delayed/PR (33%)</th>
<th>PR (5%)</th>
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</thead>
<tbody>
<tr>
<td>Relapser</td>
<td>(n=354)</td>
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<tr>
<td>Partial</td>
<td>(n=124)</td>
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<td>Null</td>
<td>(n=184)</td>
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</table>
Boceprevir: RESPOND-2 Study Design

Control
48 P/R
N = 80

PR lead-in
Week 4
PR + Placebo
Week 36
Follow-up

Week 12 futility

BOC RGT
N = 162

PR lead-in
PR + Boceprevir
TW 8 HCV-RNA Undetectable
Follow-up
TW 8 HCV-RNA Detectable/
TW 12 Undetectable
PR + placebo
Follow-up

BOC/PR48
N = 161

PR lead-in
PR + Boceprevir 800mg tid
Follow-up

Patients with detectable HCV-RNA at week 12 were considered treatment failures.

Peginterferon (P) 1.5 μg/kg, plus Ribavirin (R) 600-1400 mg/day in a divided daily dose

Bacon et al. Hepatology 2010; 52 (S1) [abstract 216]
Boceprevir RESPOND-2
Definition of prior nonresponse

- Nonresponder: $\geq 2 \log_{10}$ decline in HCV RNA by week 12 of prior Peg-IFN/RBV therapy but with detectable HCV RNA throughout the course of therapy
  - Prior null-responders excluded

- Relapsers: undetectable HCV RNA at the end of prior Peg-IFN therapy without subsequent attainment of an SVR

Bacon BR, et al. Hepatology 2010; 52 (S1) [abstract 216]
Boceprevir RESPOND-2
SVR and Relapse Rates (ITT)

100 80 60 40 20 0

% of Patients

PR 48 BOC RGT BOC/PR48

21 59 66
32 15 12

SVR

Relapse Rate

p < 0.0001

p < 0.0001

SVR rates in BOC RGT and BOC/PR48 arm not statistically different (OR, 1.4; 95% CI [0.9, 2.2])

12-week HCV RNA level used if 24-week post-treatment level was missing. A sensitivity analysis where missing data was considered as non-responder, SVR rates for Arms 1, 2 and 3 were 21% (17/80), 58% (94/162) and 66% (106/161), respectively.
RESPOND-2: SVR rates in prior nonresponders and relapsers to Peg-IFN/RBV

- Nonresponder
  - BOC RGT: 40%
  - BOC + PR: 52%
  - PR: 7%
  - Numbers: 23/57

- Relapser
  - BOC RGT: 69%
  - BOC + PR: 75%
  - PR: 29%
  - Numbers: 72/105

Data from Bacon BR, et al. Hepatology 2010; 52 (S1) [abstract 216]
Boceprevir SPRINT-2
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

Bacon et al. Hepatology 2010; 52 (S1) [abstract 216]
SVR by Week 8 HCV RNA Response

Intention to Treat Population

- Undetectable HCV RNA at Week 8
- Detectable HCV RNA at Week 8

- 46% of patients in BOC RGT arm were eligible for shorter therapy (36 weeks)
- ~6 times as many patients on BOC regimens (46-52%) achieved undetectable HCV RNA at week 8 compared to control (9%)

Bacon et al. Hepatology 2010; 52 (S1) [abstract 216]
IL28B Genotypes in Naïve and Treatment-Experienced Patients

Impact of IL28B among non-responders is less than in treatment naïve patients suggesting that additional factors play a role

Asselah et al, AASLD 2010
Triple Therapy in Genotype 1 Treatment-Experienced Patients

- Telaprevir and Boceprevir will benefit many treatment-experienced patients
  - Subtle differences in study design, inclusion criteria, stopping criteria, RGT, make it impossible to compare across studies

- Common messages:
  - Ribavirin remains a critical component ("triple")
  - Prior IFN response is predictive of outcome
    - Relapser > Partial Responder > Null responder
    - Virological breakthrough higher in non-responders
  - Early stopping rules are important to minimize resistance
Unanswered Questions

- What are the long-term clinical consequences of viral breakthrough and resistant mutations?
- Should null-responder patients be treated with triple therapy?
- Should some patients wait for quad therapy or combinations of other classes of drug?
- What factors will be most predictive so we can make informed decisions with our patients?