New HCV Protease Inhibitors: Implications for Naive Patients

1st Latin American Meeting on Treatment of Viral Hepatitis
Sao Paulo, Brazil – September 21-22, 2012

Stefan Zeuzem
Goethe University Hospital
Frankfurt a.M., Germany
1st Generation Protease-Inhibitors

- Telaprevir and Boceprevir are both linear ketoamid HCV-NS3/4A protease inhibitors
- Clinical trials: SOC + PI vs. SOC (PEG-IFN/RBV)

**Telaprevir (phase 3)**
- **ADVANCE**: tx-naive GT1 pts
- **ILLUMINATE**: response-guided therapy in tx-naive GT1 pts
- **REALIZE**: tx-experienced GT1 patients (relapsers, partial responders, null responders)

**Boceprevir (phase 3)**
- **SPRINT-2**: tx-naive GT1 patients
- **RESPOND-2**: tx-experienced GT1 patients (relapsers and partial responders)
Treatment-naive Patients

The data
## Virologic response rates in treatment naive patients

(no head-to-head data)

<table>
<thead>
<tr>
<th></th>
<th>ADVANCE (TVR)</th>
<th>SPRINT-2 (BOC)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PR + TVR</td>
<td>PR</td>
</tr>
<tr>
<td><strong>RVR (wk 4)</strong></td>
<td>66-68%</td>
<td>9%</td>
</tr>
<tr>
<td><strong>Wk 8 (LI + 4 wk)</strong></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>eEVR(^1)</strong></td>
<td>57-58%</td>
<td>8%</td>
</tr>
<tr>
<td><strong>EoT</strong></td>
<td>81-87%</td>
<td>63%</td>
</tr>
<tr>
<td><strong>Relapse</strong></td>
<td>9%</td>
<td>28%</td>
</tr>
<tr>
<td><strong>SVR (all)</strong></td>
<td>69-75%</td>
<td>44%</td>
</tr>
</tbody>
</table>

RVR, rapid virologic response; LI, lead-in; eRVR, extended RVR; EoT, end of treatment; SVR, sustained virologic response

\(^1\) Different definitions of eEVR in ADVANCE and SPRINT-2

Jacobson et al., NEJM 2011
Reddy et al., APASL 2011
Poordad et al., NEJM 2011
### SVR rates in treatment naive patients (no head-to-head data)

<table>
<thead>
<tr>
<th>SVR</th>
<th>ADVANCE (TVR)</th>
<th>SPRINT-2 (BOC)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PR + TVR</td>
<td>PR</td>
</tr>
<tr>
<td>Lead-in &lt; 1 log</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Lead-in ≥ 1 log</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>eRVR¹ achieved</td>
<td>83-89%</td>
<td>97%</td>
</tr>
<tr>
<td>eRVR¹ not achieved</td>
<td>50-54%</td>
<td>39%</td>
</tr>
<tr>
<td>Caucasian, non-black</td>
<td>70-75%</td>
<td>46%</td>
</tr>
<tr>
<td>African Amer., black</td>
<td>58-62%</td>
<td>25%</td>
</tr>
<tr>
<td>Stage F0-2</td>
<td>73-78%</td>
<td>47%</td>
</tr>
<tr>
<td>Stage F3-4</td>
<td>53-62%</td>
<td>33%</td>
</tr>
<tr>
<td>IL28B CC</td>
<td>84-90%</td>
<td>64%</td>
</tr>
<tr>
<td>IL28B CT/TT</td>
<td>57-73%</td>
<td>23-25%</td>
</tr>
</tbody>
</table>

¹ Different definitions of eEVR in ADVANCE and SPRINT-2

Jacobson et al., AASLD 2010; EASL 2011
Reddy et al., APASL 2011
Poordad et al., NEJM 2011; EASL 2011
## Telaprevir and Boceprevir - Safety

(no head-to-head data)

<table>
<thead>
<tr>
<th></th>
<th>ADVANCE (TVR)</th>
<th>SPRINT-2 (BOC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TVR12/PR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td>10%</td>
<td>7%</td>
</tr>
<tr>
<td>Discontinuation due to AEs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia (&lt;10 / &lt; 8.5 g/dL)</td>
<td>36% / 9%</td>
<td>14% / 2%</td>
</tr>
<tr>
<td>Use of EPO</td>
<td>Not permitted</td>
<td>43%</td>
</tr>
<tr>
<td>Discontinuation due to rash</td>
<td>7%</td>
<td>1%</td>
</tr>
<tr>
<td>BOC RGT</td>
<td>12%</td>
<td>16%</td>
</tr>
<tr>
<td>PR</td>
<td>14% / 2%</td>
<td>45% / 5%</td>
</tr>
<tr>
<td>Use of EPO</td>
<td>43%</td>
<td>24%</td>
</tr>
</tbody>
</table>

Jacobson et al., NEJM 2011
Poordad et al., NEJM 2011
Cirrhosis spectrum

Number of prevalent patients

Efficacy of triple therapy

Side effects

CPT score

A          B          C
Telaprevir & Boceprevir
Approved schedules
Telaprevir in Genotype 1 Patients

- 750 mg (two 375-mg tablets) q8hr with food (not low fat; standard fat meal is >20 g, eg, 1/2-cup nuts or 2-oz cheddar cheese)

### Treatment Naive and Previous Relapsers

<table>
<thead>
<tr>
<th>Time</th>
<th>Treatment</th>
<th>Stopping Rule</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>Detectable HCV RNA</td>
<td>Discontinue PR</td>
</tr>
<tr>
<td>Any</td>
<td>Discontinuation of PR for any reason</td>
<td>Discontinue TVR</td>
</tr>
</tbody>
</table>

### Previous Partial or Null Responders

- Treatment-naive patients with compensated cirrhosis and eRVR may benefit from additional 36 wks of pegIFN + RBV (ie, to Wk 48)

Boceprevir in Genotype 1 Patients

- 800 mg (four 200-mg capsules) q8hr with meal or light snack

**Treatment Naive**

<table>
<thead>
<tr>
<th>Time</th>
<th>Treatment</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>PR</td>
<td>BOC + PR</td>
</tr>
<tr>
<td>4</td>
<td>PR</td>
<td>BOC + PR</td>
</tr>
<tr>
<td>8</td>
<td>PR</td>
<td>BOC + PR</td>
</tr>
<tr>
<td>12</td>
<td>PR</td>
<td>BOC + PR</td>
</tr>
<tr>
<td>24</td>
<td>PR</td>
<td>BOC + PR</td>
</tr>
<tr>
<td>28</td>
<td>PR</td>
<td>BOC + PR</td>
</tr>
<tr>
<td>36</td>
<td>PR</td>
<td>BOC + PR</td>
</tr>
<tr>
<td>44</td>
<td>PR</td>
<td>BOC + PR</td>
</tr>
</tbody>
</table>

**Previous Relapsers or Partial Responders**

<table>
<thead>
<tr>
<th>Time</th>
<th>Treatment</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>PR</td>
<td>BOC + PR</td>
</tr>
<tr>
<td>4</td>
<td>PR</td>
<td>BOC + PR</td>
</tr>
<tr>
<td>8</td>
<td>PR</td>
<td>BOC + PR</td>
</tr>
<tr>
<td>12</td>
<td>PR</td>
<td>BOC + PR</td>
</tr>
<tr>
<td>24</td>
<td>PR</td>
<td>BOC + PR</td>
</tr>
<tr>
<td>28</td>
<td>PR</td>
<td>BOC + PR</td>
</tr>
<tr>
<td>36</td>
<td>PR</td>
<td>BOC + PR</td>
</tr>
<tr>
<td>44</td>
<td>PR</td>
<td>BOC + PR</td>
</tr>
</tbody>
</table>

- All cirrhotic patients should receive lead-in followed by PR + BOC for 44 wks
- If considered for treatment, null responders should receive lead-in then PR + BOC for 44 wks
- EMA label recommends fixed-duration therapy for all tx-expd patients: LI + 32 wks triple + 12 wks PR

**Time Point** | **Criterion** | **Stopping Rule**
--- | --- | ---
Wk 12 | HCV RNA ≥ 100 IU/mL | Discontinue all therapy
Wk 24 | Detectable HCV RNA | Discontinue all therapy
Any | Discontinuation of PR for any reason | Discontinue BOC

Practical Approach to Treatment
Treatment Indication

- Symptoms, extrahepatic manifestations
- Stage and progression of disease (in particular: cirrhosis, portal hypertension ?)
- Chances for SVR
- Motivation of the patient
- Contraindication
Virologic Assessment and Previous Treatment

- Genotype, Subtype (HCV-1a, -1b, ...)
- Viral load
- Previous treatment response (if any)
  - Relapser
  - Partial Responder
  - Null Responder
- Tolerability and side effects of previous treatment
- Adherence and persistence to previous treatment
SVR Rates in LI T12/PR48 Arm by HCV RNA Reduction at Week 4 and Prior Response

Foster et al., EASL 2011
Basic laboratory tests

- Full blood count
  - Anemia?
  - Neutropenia? Thrombocytopenia?
- Liver function
  - Aminotransferases, GGT
  - Synthesis parameters
- Co-Infections (HBV, HIV?)
- Exclusion of concomitant liver disease (autoimmune hepatitis)
- Thyroid function
- IL28B (tx-naive pts: YES; tx-experienced pts: NO)
Counselling the patients about current and future treatment options

- Previously untreated patients
  - HCV1: Triple therapy,
  - Remaining indication for PEG-IFN/RBV dual therapy (?)
  - HCV2-6: no approved DAAs/HTAs; PEG-IFN/RBV

- Treatment-experienced patients
  - HCV1: Triple therapy
  - HCV2-6: no approved DAAs/HTAs; PEG-IFN/RBV

- Future options (when ?)
  - Quadruple treatment
  - IFN-free regimen
Choice between first generation protease inhibitors in HCV-1

**Boceprevir**
- Tx duration 24-44 wks
- Total Tx duration in Relapsers always 48 wks
- Main side effects
  - Anemia
  - Dysgeusia
- Approved with LI phase
- 3 x 4 tablets/day with food
- DDI (perhaps less critical ?)

**Telaprevir**
- Tx duration 12 wks
- Tx duration in Relapsers response-guided (24/48 wks)
- Main side effects
  - Rash (potentially severe)
  - Anemia
- LI phase not required, but possible
- Fatty meal required with intake, 3 x 2 tablets
- DDI
Practical considerations concerning DDI

- Check necessity of concurrent medications
- Pausing of any concurrent medication possible?
- Study package inserts of BOC / TVR
- http://www.hep-druginteractions.org/Interactions.aspx (University of Liverpool)
- Exchange tables are missing and required
General considerations with either protease inhibitor

- Counselling patient and partner
- Begin of therapy (early in the week preferred)
- Optimize turnaround time with virology lab
- Dates for safety assessments and viral load quantifications
  - Interference with holidays
  - Adjustment of social and professional life
- Reminder of dosing intervals (q8h)
- Potentially: RBV also q8h to avoid four time points of drug intake per day
**Adherence**

- **Triple therapy** presents challenges with already busy schedules\[^{143}\]
  - TID dosing
  - Food requirements
- **Data show PegIFN/RBV adherence decreases over time\[^{5}\]**
  - Addition of PIs may exacerbate this trend

---

Some considerations concerning a lead-in phase

- Virologic value of LI phase is questionable
  - SPRINT-1: higher SVR rates with lead-in (but small number of patients)
  - REALIZE: Lead-in phase did not affect breakthrough, relapse and SVR rates
- Lead-in may be clinically useful if physician is willing to take decisions at week 4
  - only PEG/RBV, no PI in excellent initial virologic responders (RVR)
  - stop therapy in patients with poor initial virologic response (< 1 log) to avoid treatment failure and selection of resistant variants
- Improve adherence
Strict adherence to stopping rules

**Boceprevir**
- HCV RNA > 100 IU/mL at week 12 (i.e. after 8 weeks of boceprevir)
- HCV RNA detectable at week 24

**Telaprevir**
- HCV RNA > 1000 IU/mL at week 4 and 12
- HCV RNA detectable at week 24
Management of anemia

- Check frequently hemoglobin levels, however, avoid iatrogenic anemia
- Cave: patients with liver cirrhosis
- Never (!!!) dose reduce the protease inhibitor
- Use stepwise reduction of RBV
- Start RBV dose reduction early
- Consider the use of erythropoetin (Reimbursement ?) and blood transfusions
- Reduced efficacy of EPO in patients with cirrhosis (no studies)
Rash management plan with Telaprevir

• Inform patient on the likelihood of rash
• Explain 9er-rule for estimating body surface area
• Explain potential severities and the respective need of treatment discontinuation at > stage 2
• Inform about potential risk of DRESS and SJS
• Preemptive (?) prescription of e.g. Cetirizine and highly potent steroid creme
• Establish collaboration with dermatologist
Telaprevir-associated rash

- Rash primarily eczematous and resolves (slowly) upon cessation of therapy
- Moderate and severe rash with progression are managed by sequentially discontinuing TVR, followed by RBV and, if indicated, Peg-IFN for continued progression
- Mainly grade 1–2 in severity (3% grade 3 in the pooled TVR treatment arms)
- Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) and Stevens-Johnson Syndrome (SJS) in < 1% of patients
- Biomarker required (GWAS)
## Grading of TVR-associated rash severity

<table>
<thead>
<tr>
<th>Description</th>
<th>Management</th>
</tr>
</thead>
</table>
| **Grade 1 (Mild)**
Localized skin eruption and/or a skin eruption with limited distribution, w/wo associated pruritus | Telaprevir interruption generally not necessary |
| **Grade 2 (Moderate)**
Diffuse skin eruption involving up to approx. 50% of body surface area, w/wo superficial skin peeling, pruritus, or mucous membrane involvement with no ulceration | Telaprevir interruption generally not necessary
For progressive eruption, TVR should be discontinued first
Consider interrupting ribavirin and/or peginterferon if no improvement in eruption within 7 days of stopping telaprevir, or earlier if rash worsens |

Cacoub et al., *J Hepatol* 2012;56:455–463
TVR-associated rash during triple therapy (grade 2)
TVR-associated mucosal rash
TVR-associated rash during triple therapy (grade 3)
Grading of TVR-associated rash severity

**Description**

*Grade 3 (Severe)*

Generalized rash involving either >50% of BSA or rash presenting with any of the following characteristics:
- Vesicles or bullae
- Superficial ulceration of mucous membranes
- Epidermal detachment
- Atypical or typical target lesions
  - Palpable purpura/non-blanching erythema

*Life-threatening or systemic reactions*

Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), erythema multiforme (EM), acute generalized exanthematous pustulosis (AGEP), rash that requires therapy with systemic corticosteroids.

**Management**

Telaprevir must be stopped

Interrupt RBV and/or pegIFN if no improvement in rash within 7 d of stopping TVR, or earlier if rash worsens

Careful monitoring of skin, mucosa, CRP, full blood count (eosinophils)

Steroid treatment

Experienced dermatologist

Permanent discontinuation of all treatment is required

Steroid treatment

Admission

Cacoub et al., *J Hepatol* 2012;56:455–463
TVR-associated rash starting in wk 13 after discontinuation of TVR
Any role for switching the PI during therapy?

- No role for switching from one PI to the other in case of emergence of resistant variants
- Switch from TVR to BOC in case of severe rash safety-wise not explored

<table>
<thead>
<tr>
<th></th>
<th>TVR</th>
<th>BOC</th>
</tr>
</thead>
<tbody>
<tr>
<td>V36A/M</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>T54S/A</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>V55A</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>R155K/T/Q</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>A156S</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>A156T/V</td>
<td>+</td>
<td>in vitro</td>
</tr>
<tr>
<td>D168A/V/T</td>
<td></td>
<td>in vitro</td>
</tr>
<tr>
<td>V170A/T</td>
<td>in vitro</td>
<td>+</td>
</tr>
</tbody>
</table>
Loss of Detectable Resistance in Pts Stopping BOC or TVR + PegIFN/RBV

*Data from phase II studies.

Key messages

- First generation PIs allow for major improvement of SVR rates in GT1-infected patients with hepatitis C
- Treatment schedules are complex and require thorough planning for patient and physician
- Careful consideration of potential DDI
- Optimal management of side effects
- Follow virological (resistance) and clinical (side effects) stopping rules
- Don‘t be afraid of triple therapy, but be carefully prepared !
- Know about future treatment developments and advice your patients accordingly