Overview on Clinical Trials with Protease Inhibitors

Joint Session
6th International Workshop on Clinical Pharmacology of Hepatitis Therapy and 6th International Workshop on Hepatitis C Resistance and New Compounds
Boston, 23. June 2011

Stefan Zeuzem
Goethe-University Hospital
Frankfurt, Germany
Some questions ...

• What is the role of a lead-in phase with PEG-IFN and RBV?
• What is the best predictor of SVR? Previous response to PR, response during LI, or IL28B?
• What is the impact of other viral and host parameters on SVR?
• Are there differences in the resistance profiles between Telaprevir and Boceprevir?
• Are prescribing information reflecting the clinical trials?
• What are the main practical problems with BOC and TVR?
• What are the benefits of second wave/generation PIs?
• Should patients who failed triple therapy be re-exposed to a PI-containing regimen?
What is the role of a lead-in phase with PEG-IFN and RBV?
SPRINT-1: Boceprevir + PegIFN / RBV in Tx-Naive GT1 Patients (Phase 2)

Sustained Virologic Response*

Virologic Breakthrough‡

*SVR12 for 48-wk arms and SVR24 for 28-wk arms.

‡Persistent HCV RNA ≥2 log₁₀ increase from nadir and ≥ 50,000 IU/mL.

Presented at the 6th International Workshop on Clinical Pharmacology of Hepatitis Therapy, 22-23 June 2011, Cambridge, USA.

Kwo P et al., Lancet 2010
REALIZE: Undetectable Viral Load over Time in Prior Relapsers

T12/PR48 prior relapsers (n=145)
LI T12/PR48 prior relapsers (n=141)
Pbo/PR48 prior relapsers (n=68)

Patients with undetectable HCV RNA (% ± SE)

Time (weeks)

Presented at the 6th International Workshop on Clinical Pharmacology of Hepatitis Therapy, 22-23 June 2011, Cambridge, USA

Zeuzem et al., NEJM 2011
REALIZE: Undetectable Viral Load over Time in Prior Partial and Null Responders

Patients with undetectable HCV RNA (% ± SE)

- T12/PR48 prior partial responders (n=49)
- LI T12/PR48 prior partial responders (n=48)
- Pbo/PR48 prior partial responders (n=27)
- T12/PR48 prior null responders (n=72)
- LI T12/PR48 prior null responders (n=75)
- Pbo/PR48 prior null responders (n=37)

Undetectable HCV RNA defined as <25 IU/mL

Zeuzem et al., NEJM 2011

Presented at the 6th International Workshop on Clinical Pharmacology of Hepatitis Therapy, 22-23 June 2011, Cambridge, USA
REALIZE: SVR in Prior Relapsers, Partial Responders and Null Responders

Zeuzem et al., NEJM 2011

* indicates p<0.001 vs Pbo/PR48.
Historical data vs lead-in response for predicting SVR

- 9–16% with $<1 \log_{10}$ decline during lead-in can still become undetectable after 4 weeks of triple therapy, despite poor IFN responsiveness.
- Lead-in should not be used for futility as 33% with $<1 \log_{10}$ decline during lead-in achieve SVR.

Esteban, et al., EASL 2011

Presented at the 6th International Workshop on Clinical Pharmacology of Hepatitis Therapy, 22–23 June 2011, Cambridge, USA
Role of PEG/RBV lead-in phase

• Lead-in concept independant from DAA
• Virologic value of LI phase is questionable
  – SPRINT-1; REALIZE
  – Silen-C1 and -C2
• Lead-in may be clinically useful if physician (and patient) is willing to take decisions at wk 4
  – only PEG/RBV, no PI in excellent initial virologic responders (LVL and RVR)
  – stop therapy in patients with poor initial virologic response (< 1 log) to avoid treatment failure and selection of resistant variants
• Lead-in for assessment of adherence (?)
• Future role of lead-in phase (??)
What is the best predictor of SVR?

Previous response to PR, response during LI, IL28B?
Historic virologic response vs lead-in response in RESPOND-2 and REALIZE

<table>
<thead>
<tr>
<th>Historic</th>
<th>Frequency of lead-in response $&lt;1 \log_{10}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RESPOND-2</td>
</tr>
<tr>
<td>Relapse</td>
<td>18%</td>
</tr>
<tr>
<td>Partial</td>
<td>39%</td>
</tr>
<tr>
<td>Null</td>
<td>No data</td>
</tr>
</tbody>
</table>

Foster et al., EASL 2011; Esteban et al., EASL 2011
SVR Rates in LI T12/PR48 Arm by HCV RNA Reduction at Wk 4 and Prior Response

Presented at the 6th International Workshop on Clinical Pharmacology of Hepatitis Therapy, 22-23 June 2011, Cambridge, USA

Foster et al., EASL 2011, Zeuzem et al. NEJM 2011

SVR rates in LI T12/PR48 Arm by HCV RNA Reduction at Wk 4 and Prior Response

- Prior relapsers
- Prior partial responders
- Prior null responders

<1 log₁₀ HCV RNA reduction at Week 4

<table>
<thead>
<tr>
<th>Proportion of patients</th>
<th>SVR rate</th>
<th>Proportion of patients</th>
<th>SVR rate</th>
<th>Overall SVR rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>59</td>
<td>62</td>
<td>56</td>
<td>59</td>
</tr>
<tr>
<td>40</td>
<td>15</td>
<td>60</td>
<td>41</td>
<td>59</td>
</tr>
<tr>
<td>58</td>
<td>30</td>
<td>90</td>
<td>90</td>
<td>58</td>
</tr>
</tbody>
</table>

≥1 log₁₀ HCV RNA reduction at Week 4

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</thead>
<tbody>
<tr>
<td>90</td>
<td>59</td>
<td>94</td>
<td>54</td>
<td>58</td>
</tr>
<tr>
<td>90</td>
<td>30</td>
<td>90</td>
<td>30</td>
<td>58</td>
</tr>
</tbody>
</table>

Overall SVR rate
SPRINT-2 (BOC): SVR rates by *IL28B* genotype

![Bar chart showing SVR rates by *IL28B* genotype](chart.png)

- **CC**
  - PR48: 78/64
  - BOC RGT: 82/77
  - BOC44/PR48: 80/55

- **CT**
  - PR48: 28/116
  - BOC RGT: 65/103
  - BOC44/PR48: 71/115

- **TT**
  - PR48: 27/37
  - BOC RGT: 55/42
  - BOC44/PR48: 59/44

**Samples were available for 653/1048 (62%) patients enrolled in SPRINT-2**

Poordad, et al., EASL 2011

Presented at the 6th International Workshop on Clinical Pharmacology of Hepatitis Therapy, 22-23 June 2011, Cambridge, USA
ADVANCE (TVR): SVR rates by *IL28B* genotype

Samples were available for 454/1088 (42%) patients (Caucasian) enrolled in ADVANCE

Jacobson, et al., EASL 2011

Presented at the 6th International Workshop on Clinical Pharmacology of Hepatitis Therapy, 22-23 June 2011, Cambridge, USA
IL28B is a strong BL predictor of IFN response at end of lead-in (≥1 log at TW 4)

<table>
<thead>
<tr>
<th>RESPOND-2 (effect)</th>
<th>Odds Ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL28B Genotype: CC vs. Non-CC</td>
<td>4.5 (1.5 – 13.7)</td>
<td>0.007</td>
</tr>
<tr>
<td>Previous Response: Relapser vs Nonresponder</td>
<td>3.2 (1.6 – 6.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BOC/PR48 vs PR48</td>
<td>0.2 (0.05 – 0.7)</td>
<td>0.01</td>
</tr>
<tr>
<td>BOC/RGT vs PR48</td>
<td>0.14 (0.4 – 0.5)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

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</tr>
</thead>
<tbody>
<tr>
<td>IL28B Genotype: CC vs. Non-CC</td>
<td>15.8 (6.3 – 39.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Baseline HCV-RNA: ≤400,000 vs. &gt;400,000</td>
<td>4.3 (1.3 – 14.6)</td>
<td>0.02</td>
</tr>
<tr>
<td>Steatosis 0 vs &gt;0</td>
<td>2.6 (1.6 – 0.7)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Race (non-black vs black)</td>
<td>2.1 (1.2 – 3.7)</td>
<td>0.007</td>
</tr>
<tr>
<td>Gender (female vs male)</td>
<td>1.7 (1.1 – 2.6)</td>
<td>0.03</td>
</tr>
<tr>
<td>BMI: ≤25 kg/m² vs &gt;30 kg/m²</td>
<td>0.4 (0.2 to 0.7)</td>
<td>0.001</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.

Presented at the 6th International Workshop on Clinical Pharmacology of Hepatitis Therapy, 22-23 June 2011, Cambridge, USA
IL28B is no longer an important predictor of SVR when Lead-in Response is considered

<table>
<thead>
<tr>
<th>RESPOND-2 (effect)</th>
<th>Odds Ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BOC/PR48 vs PR48</td>
<td>11.4 (4.6 to 28.0)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>BOC/RGT vs PR48</td>
<td>7.9 (3.3 to 18.9)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Previous Response: Relapser vs Nonresponder</td>
<td>2.2 (1.2 to 4.3)</td>
<td>0.01</td>
</tr>
<tr>
<td>Log decline in HCV-RNA at TW 4 (continuous variable)</td>
<td>1.8 (1.3 to 2.4)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>BMI: ≤25 kg/m² vs &gt;30 kg/m²</td>
<td>3.4 (1.4 to 8.2)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

<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.
Predictors of SVR

- Both
  - the previous response to PR
  - PR response in a lead-in phase
  are clinically relevant and partly independent
- Any predictor is only useful if physician (and patient) is willing to take decisions!
- If decided to start with a lead-in phase, IL28B genotype provides no additional information
- Benefit of triple therapy (very likely) in all IL28B genotypes (SVR, shortening of total tx duration)

Presented at the 6th International Workshop on Clinical Pharmacology of Hepatitis Therapy, 22-23 June 2011, Cambridge, USA
What is the impact of other viral and host parameters on SVR?
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>HCV-1a</td>
<td>71%</td>
<td>41%</td>
</tr>
<tr>
<td>HCV-1b</td>
<td>79%</td>
<td>48%</td>
</tr>
<tr>
<td>HCV RNA &lt; 800,000</td>
<td>78%</td>
<td>70%</td>
</tr>
<tr>
<td>HCV RNA ≥ 800,000</td>
<td>74%</td>
<td>36%</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>

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

Presented at the 6th International Workshop on Clinical Pharmacology of Hepatitis Therapy, 22-23 June 2011, Cambridge, USA
REALIZE: SVR by HCV Subtype and Prior Response

Prior relapsers:
- HCV subtype 1a: 119/142 (84%)
- HCV subtype 1b: 123/140 (88%)

Prior partial responders:
- HCV subtype 1a: 26/55 (47%)
- HCV subtype 1b: 27/40 (68%)

Prior null responders:
- HCV subtype 1a: 24/88 (29%)
- HCV subtype 1b: 22/59 (37%)

Zeuzem et al., NEJM 2011

Presented at the 6th International Workshop on Clinical Pharmacology of Hepatitis Therapy, 22-23 June 2011, Cambridge, USA
REALIZE: SVR by Baseline Fibrosis Stage and Prior Response

Zeuzem et al., NEJM 2011
Important predictors of SVR at baseline

- Genotype: HCV1b > 1a
- Viral load: LVL > HVL
- Previous response: relapse > partial > null
- Ethnicity: Caucasian > AA
- Fibrosis: F0-2 > F3-4 (partial/nulls)
- IL28B genotype: CC > CT/TT
- Age: less than 40 yrs > more than 40 yrs
- BMI: less than 25 kg/m$^2$ > more than 30 kg/m$^2$
Are there differences in the resistance profiles between Telaprevir and Boceprevir?
Telaprevir and Boceprevir - Resistance

Presented at the 6th International Workshop on Clinical Pharmacology of Hepatitis Therapy, 22-23 June 2011, Cambridge, USA

Sarrazin & Zeuzem; *Gastroenterology* 2010; 138:447-62

<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>+</td>
</tr>
<tr>
<td>V170A/T</td>
<td>in vitro</td>
<td>+</td>
</tr>
</tbody>
</table>

HCV-1a: 2 steps required (clinically observed)

HCV-1b: 4 steps required (not yet clinically observed)

V36M + R155K
Probability of Resistant Variant by Subtype

- Significant difference ($p<0.0001$) between subtypes for the time to become WT by population sequencing (median, 95% CI)
  - HCV-1a: 10 months (9,11)
  - HCV-1b: 0.8 months (0,2)

1 Based on Kaplan-Meier estimation using population sequencing; hash marks in plot indicate censored observations

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>1a</th>
<th>1b</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>16%</td>
<td>46%</td>
</tr>
<tr>
<td>3</td>
<td>22%</td>
<td>66%</td>
</tr>
<tr>
<td>6</td>
<td>32%</td>
<td>87%</td>
</tr>
<tr>
<td>12</td>
<td>60%</td>
<td>98%</td>
</tr>
<tr>
<td>16</td>
<td>94%</td>
<td>100%</td>
</tr>
</tbody>
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Presented at the 6th International Workshop on Clinical Pharmacology of Hepatitis Therapy, 22-23 June 2011, Cambridge, USA
Telaprevir and Boceprevir - Resistance

- Similar resistance pattern
- Differences between HCV-1a and -1b
- Studies ongoing to evaluate the time to reversal to *wildtype*
- Role of compensatory mutations
- Relevance of the duration of drug exposure
- Influence of futility rules
Are prescribing information reflecting the clinical trials?
**Boceprevir (Victrelis™):**
US prescribing information for previously untreated patients

<table>
<thead>
<tr>
<th>Assessment (HCV-RNA Results)</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>At Treatment Week 8</strong></td>
<td><strong>At Treatment Week 24</strong></td>
</tr>
<tr>
<td>Undetectable</td>
<td>Undetectable</td>
</tr>
<tr>
<td>Detectable</td>
<td>Undetectable</td>
</tr>
</tbody>
</table>

Pts with compensated cirrhosis and pts. who are poorly interferon responsive should receive 4 wks PR followed by 44 wks PR+BOC

**Treatment Futility:** If the patient has HCV-RNA results greater than or equal to 100 IU/mL at TW12, then discontinue three-medicine regimen. If the patient has confirmed, detectable HCV-RNA at TW24, then discontinue three-medicine regimen.
Boceprevir (Victrelis™): US prescribing information for previous partial responders or relapsers

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Pts with compensated cirrhosis and pts. who are poorly interferon responsive should receive 4 wks PR followed by 44 wks PR+BOC

**Treatment Futility**: If the patient has HCV-RNA results greater than or equal to 100 IU/mL at TW12, then discontinue three-medicine regimen. If the patient has confirmed, detectable HCV-RNA at TW24, then discontinue three-medicine regimen.
Telaprevir (Incivek™): US prescribing information for previously untreated patients and prior relapse patients

<table>
<thead>
<tr>
<th>HCV-RNA</th>
<th>Triple (PR+TVR)</th>
<th>Dual (PR)</th>
<th>Tx duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Undetectable at Weeks 4 and 12</td>
<td>First 12 weeks</td>
<td>Additional 12 weeks</td>
<td>24 weeks</td>
</tr>
<tr>
<td>Detectable (1000 IU/mL or less) at Weeks 4 and/or 12</td>
<td>First 12 weeks</td>
<td>Additional 36 weeks</td>
<td>48 weeks</td>
</tr>
</tbody>
</table>

**Treatment-naive patients with cirrhosis** who have undetectable HCV RNA at weeks 4 and 12 of PR+TVR may benefit from an additional 36 weeks of PR (48 weeks total)

**Treatment Futility**: If the patient has HCV-RNA results greater than 1000 IU/mL at TW 4 or 12, then discontinue PR + TVR. If the patient has detectable HCV-RNA at TW24, then discontinue PR.
**Telaprevir (Incivek™):**
US prescribing information for previous partial and null responder patients

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<thead>
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<th>Triple (PR+TVR)</th>
<th>Dual (PR)</th>
<th>Tx duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>First 12 weeks</td>
<td>Additional 36 weeks</td>
<td>48 weeks</td>
</tr>
</tbody>
</table>

**Treatment Futility:** If the patient has HCV-RNA results greater than 1000 IU/mL at TW 4 or 12, then discontinue PR + TVR. If the patient has detectable HCV-RNA at TW24, then discontinue PR.
Presenting informaitions

- In the US prescribing informations several treatment recommendations do not reflect the clinical trials
- EU prescribing informations are expected to be different
- Further prospective trials are required to better define treatment algorithms, in particular response-guided treatment durations
- Futility rules require prospective validation
What are the main practical problems with BOC and TVR?
Practical issues with first-wave PIs

**Boceprevir**
- Genotype restrictions
- q8h with food
- Duration of PI tx
- Complicated label
- Only with LI approved
- Side effects
- EPO use
- DDI (limited studies)
- Price (US $ 1100/wk)

**Telaprevir**
- Genotype restrictions
- q8h (q12h) with food (20 g fat)
- LI not in the label
- Side effects (DRESS, SJS)
- DDI
- Price (US $ 49,200)
What are the benefits of second wave/generation PIs?
SILEN-C1: BI201335 combined with PR in treatment naive patients with CHC (GT1)

Virologic response rates (%)

- Peginterferon alfa-2a 180 µg qw
- Ribavirin 1000-1200 mg/day
- LI: lead-in with PR for 3 days
- Total N=429 patients
- 24 wks of triple therapy, followed by 24 wks of PR
- * Pts with eRVR re-randomized to 24 vs. 48 wks

Asselah et al., EASL 2011
SILEN-C2: BI201335 combined with PR in prior partial and null responders (GT1)

Sustained virologic response rates (%)

- Peginterferon alfa-2a 180 µg qw
- Ribavirin 1000-1200 mg/day
- LI: lead-in with PR for 3 days
- Total N=288 patients
- 24 wks of triple therapy, followed by 24 wks of PR
- * Pts with eRVR re-randomized to 24 vs. 48 wks
- RGT response lower with 24 vs 48 wks (40 vs. 72%)

Sulkowski et al., EASL 2011

Presented at the 6th International Workshop on Clinical Pharmacology of Hepatitis Therapy, 22-23 June 2011, Cambridge, USA
ASPIRE: Phase 2b Interim Data

**Sustained virologic response rates at wk 4 (%)**

- **Relapser**
  - TMC12PR48: 84/25 (33.6%)
  - TMC24PR48: 93/27 (34.8%)
  - TMC435: 85/26 (32.3%)
  - TMC48PR48: 50/24 (20.8%)
  - PR48: 21/25 (8.4%)

- **Partial Responder**
  - TMC12PR48: 64/14 (45.7%)
  - TMC24PR48: 86/22 (38.6%)
  - TMC435: 82/18 (44.4%)
  - TMC48PR48: 11/21 (52.4%)
  - PR48: 12/24 (50.0%)

- **Null Responder**
  - TMC12PR48: 56/16 (35.0%)
  - TMC24PR48: 60/15 (40.0%)
  - TMC435: 56/16 (35.0%)
  - TMC48PR48: 23/13 (17.7%)
  - PR48: 9/16 (56.2%)

**Peginterferon alfa-2a 180 µg qw**

**Ribavirin 1000-1200 mg/day**

**TMC435 150 mg qd**

Medivir Press Release 20 May 2011

Presented at the 6th International Workshop on Clinical Pharmacology of Hepatitis Therapy, 22-23 June 2011, Cambridge, USA
Benefits of second wave/generation HCV protease inhibitors

- Safety and tolerability
- Dosing interval
- Lower discontinuation rates
  - with effects on SVR rates (?)
- Broader GT activity
- Shorter treatments durations (?)
- Improved resistance profile (?)
- Less DDI (?)
Should patients who failed triple therapy be re-exposed to a PI-containing regimen?
Re-treatment with TMC435 + PR in pts. with prior exposure to TMC435 monotherapy

- Six G1 IFN non-responders treated for 5 d with TMC435 200 mg QD monotherapy (Phase I)
  - 5/6 subsequently received TMC435 200 mg QD + PR for 28 d then PR for 44 weeks (Phase II)
  - All had rapid ↓ on re-treatment in first 6 d
  - Therapy outcomes: 1 d/c day 14 (AE) but had a poor response and had RAVs; 3 SVR, 1 breakthrough at Wk 28
  - Dominant RAV seen in previous therapy returned during re-treatment in those with less vigorous viral decay
  - Deep sequencing: Baseline Phase I = no RAVs; baseline Phase II = RAVs at low levels (<2%) in 3/5

Evidence that re-exposure to DAA (with previous RAV emergence) can result in SVR. Critical to understand threshold % of RAV that results in loss of antiviral efficacy

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Conclusions (1)

• P/R plus PI are (well) tolerated and efficacious in patients with HCV-G1 infection
• Additional side effects are mainly anaemia and dysgeusia (BOC) and rash (TVR)
• Previous response to PR and lead-in phase are both informative to predict outcome with triple therapy
• The role of a lead-in phase is dependent on the willingness to take decisions
• RGT is feasible for the easier to cure patients, further refinement awaited
Conclusions (2)

- IL-28B should not be applied to deny triple therapy
- Approved regimen and their futility / stopping rules are heterogeneous and require simplification
- Persistence of resistant variants and long-term consequences (re-tx) not yet fully elaborated
- Price is prohibitive for patients with chronic hepatitis C in many parts of the world, including “first world” countries
- Controlled trials against the new SOC will have extraordinary drug costs (400 patients ≈ e.g. US $ 19,680,000 only for TVR)