Virological Monitoring of Hepatitis C Therapy

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Presented at the 10th Eu Meeting on HIV & Hepatitis, 28-30 March 2012, Barcelona
Outline

• Serological tools

• Molecular tools

• Response-guided therapy
Outline

• Serological tools
  – Core antigen quantification

• Molecular tools

• Response-guided therapy
Core Antigen: an Indirect Marker of Viral Replication


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Assessment of Virological Responses During Antiviral Treatment

**RVR (G1b)**

**SVR (G1b)**

**Relapser (G1b)**

**Non-respondeur (G1a)**

Clinical Achievements of Core Antigen Quantification

• Satisfactory analytical performances
  – Sensitivity, specificity
  – Broad range of linear quantification

• Alternative to HCV RNA measurements
  – To decide to treat
  – To follow virological responses during antiviral treatment
Outline

• Serological tools
  – Core antigen quantification

• Molecular tools

• Response-guided therapy
Molecular Assays in Virology

- **Qualitative-Quantitative assays**
- Is HCV present and in what amount?
- **Genotyping assays**
  - What is the HCV genotype?
- **Detection of resistance**
  - What type of HCV is present?
Outline

• Serological tools
  – Core antigen quantification

• Molecular tools
  – Available HCV RNA assays

• Response-guided therapy
Dynamic Ranges of Quantification

- Cobas Amplicor HCV Monitor v2.0
- SuperQuant
- LCx HCV RNA Assay
- Versant HCV RNA 3.0 (bDNA)
- Cobas TaqMan HCV v1.0 (Roche)
- HCV Quant ASR (Abbott)
- Cobas TaqMan HCV v2.0 (Roche)*
- Artus HCV QS-RGQ (Qiagen)*

*in development
Technical Achievements of Real-Time PCR

- No carryover contamination
- Improved analytical sensitivity
- Extended range of linear quantification
- Precision and reproducibility
- High throughput through automation
Clinical Achievements of Real-Time PCR

- Replaces qualitative viral genome detection assays

- Accurately quantifies a broad range of viral levels observed in clinical practice:
  - High pretreatment levels
  - Low levels during antiviral treatment

- Efficiently monitors viral kinetics (early assessment of virological responses to therapy)
Outline

• Serological tools
  – Core antigen quantification

• Molecular tools
  – Available HCV RNA assays
  – What real-time PCR should be used?

• Response-guided therapy
HCV RNA Quantification (CAP v1.0, Roche)

<table>
<thead>
<tr>
<th>HCV RNA level in CAP/CTM48 v1.0 (Log_{10} IU/mL)</th>
<th>HCV RNA level in Versant HCV 3.0 Assay bDNA (Log_{10} IU/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype 1 (n=29)</td>
<td>Genotype 1 (n=29)</td>
</tr>
<tr>
<td>Genotype 2 (n=27)</td>
<td>Genotype 2 (n=27)</td>
</tr>
<tr>
<td>Genotype 3 (n=29)</td>
<td>Genotype 3 (n=29)</td>
</tr>
<tr>
<td>Genotype 4 (n=30)</td>
<td>Genotype 4 (n=30)</td>
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<tr>
<td>Genotype 5 (n=9)</td>
<td>Genotype 5 (n=9)</td>
</tr>
<tr>
<td>Genotype 6 (n=2)</td>
<td>Genotype 6 (n=2)</td>
</tr>
</tbody>
</table>

$r = 0.889; \ p < 0.0001$

HCV RNA Quantification (CAP v2.0, Roche)

Vermehren et al., 2011; J Clin Microbiol, 49(9): 3309-3315.

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HCV RNA Quantification (m2000, Abbott)

Summary

• In clinical practice, HCV RNA quantification should be based on an accurate real-time PCR assay
  – with a lower limit of detection of the order of 10 to 15 IU/mL

• HCV RNA measurements should be regularly performed before, during and after viral treatment

• Ideally, HCV RNA assessments should be performed with the same real-time PCR platform
Outline

• Serological tools
  – Core antigen quantification

• Molecular tools
  – Available HCV RNA assays
  – What real-time PCR should be used?
  – HCV type-subtype determination

• Response-guided therapy
The HCV Genotype Drives HCV Treatment Indication

• Genotype 2/3, 4, (5/6)
  – Still PegIFN and ribavirin therapy

• Genotype 1
  – Triple combination of an HCV protease inhibitor with pegIFN and ribavirin
  – Boceprevir (Victrelis) or Telaprevir (Incivek) recently approved by FDA and EMA
HCV Genotype/Subtype Determination

• Molecular methods (genotyping)
  – Direct sequence analysis
  – Reverse hybridization of PCR-products onto genotype-specific probes coated on solid supports: Line Probe Assay (INNO-LiPA HCV, Innogenetics)
  – Real-time PCR with genotype specific probes/primers

• Serological methods (“serotyping”)
  – Competitive ELISA

HCV Genotype/Subtype Determination

• **Molecular methods (genotyping)**
  
  – Direct sequence analysis
  
  – Reverse hybridization of PCR-products onto genotype-specific probes coated on solid supports: Line Probe Assay (INNO-LiPA HCV, Innogenetics)

  – Real-time PCR with genotype specific probes/primers

• **Serological methods (“serotyping”)**

  – Competitive ELISA

Versant® HCV Genotype 2.0 Assay

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# Genotype 1 Subtype Determination

<table>
<thead>
<tr>
<th></th>
<th>Sequence Analysis of the 5’NCR</th>
<th>1st Generation of Line Probe Assay (LiPA 1.0)</th>
<th>2nd Generation of Line Probe Assay (LiPA 2.0)</th>
<th>RealTime HCV Genotype II</th>
</tr>
</thead>
<tbody>
<tr>
<td>GT 1a (n=237)</td>
<td>GT 1a (n=237)</td>
<td>GT 1a (n=237)</td>
<td>GT 1a (n=237)</td>
<td>GT 1a (n=237)</td>
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<tr>
<td>77.6% (n=184)</td>
<td>77.6% (n=184)</td>
<td>77.6% (n=184)</td>
<td>77.6% (n=184)</td>
<td>77.6% (n=184)</td>
</tr>
<tr>
<td>GT 1b (n=263)</td>
<td>GT 1b (n=238)</td>
<td>GT 1b (n=238)</td>
<td>GT 1b (n=238)</td>
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<td>90.5% (n=238)</td>
</tr>
</tbody>
</table>


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Utility of HCV Genotype 1 Subtype Determination

• Modest difference in antiviral efficacy with protease inhibitor-based therapy

• No influence on the therapeutic decision

• Different resistance profiles between subtype 1a and 1b
Outline

• Serological tools
  – Core antigen quantification

• Molecular tools
  – Available HCV RNA assays
  – What real-time PCR should be used?
  – HCV type-subtype determination
  – Resistance testing

• Response-guided therapy
Quasispecies Distribution of HCV Viral Populations

Adapted from Domingo, E. Cell 1978, 13 (4):735-744.
Resistance to Protease Inhibitors


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# Pre-existing HCV Resistant Variants

<table>
<thead>
<tr>
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</thead>
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<td>CT</td>
<td>1a</td>
<td>NR</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<td>-</td>
<td>-</td>
<td>0.1%</td>
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<td>NR</td>
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<td>0.1%</td>
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<td>-</td>
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<td>0.5%</td>
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<td>-</td>
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<tr>
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<td>1b</td>
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<td>29.4%</td>
<td>-</td>
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<td>-</td>
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<td>-</td>
<td>-</td>
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<td>SVR</td>
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<td>-</td>
<td>0.7%</td>
<td>-</td>
<td>-</td>
<td>0.3%</td>
<td>-</td>
<td>-</td>
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<td>1a</td>
<td>SVR</td>
<td>-</td>
<td>-</td>
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<td>-</td>
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<td>-</td>
<td>0.1%</td>
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<td>0.1%</td>
<td>-</td>
<td></td>
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<td>1a</td>
<td>SVR</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.6%</td>
<td>1.8%</td>
<td>-</td>
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<tr>
<td>Pt-10</td>
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<td>SVR</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<td>-</td>
<td>0.6%</td>
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<td>Pt-11</td>
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<td>1a</td>
<td>RR</td>
<td>-</td>
<td>-</td>
<td>100.0%</td>
<td>0.1%</td>
<td>6.0%</td>
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<td>SVR</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.3%</td>
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<td>0.1%</td>
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<td>Pt-13</td>
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<td>SVR</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.2%</td>
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<td>-</td>
<td>0.8%</td>
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<td>Pt-14</td>
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<td>NR</td>
<td>-</td>
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<td>-</td>
<td>-</td>
<td>-</td>
<td>0.1%</td>
<td>0.2%</td>
<td>-</td>
<td>0.1%</td>
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<tr>
<td>Pt-15</td>
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<td>SVR</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.4%</td>
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<td>Pt-16</td>
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<td>1a</td>
<td>SVR</td>
<td>-</td>
<td>-</td>
<td>1.3%</td>
<td>0.5%</td>
<td>7.8%</td>
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<td>Pt-17</td>
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<td>SVR</td>
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<td>47.4%</td>
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<td>0.1%</td>
<td>0.4%</td>
<td>0.1%</td>
<td>0.1%</td>
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<tr>
<td>Pt-18</td>
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<td>1b</td>
<td>SVR</td>
<td>-</td>
<td>20.0%</td>
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<td>-</td>
<td>-</td>
<td>-</td>
<td>0.1%</td>
<td>0.4%</td>
<td>0.1%</td>
<td>0.1%</td>
<td></td>
</tr>
</tbody>
</table>

*Cutoff=0.1% according to statistical test based on Poisson’s law

*SNP rs12979860

Treatment Failure Rates

Telaprevir Trials

![Bar chart showing treatment failure rates for Telaprevir trials: ADVANCE (25%), ILLUMINATE (31%), REALIZE (28%), T12PR48 (46%), LI-T12PR48 (44%).]
Treatment Failure Rates
Boceprevir Trials

<table>
<thead>
<tr>
<th>Proportion of patients (%)</th>
<th>SPRINT-2</th>
<th>RESPOND-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>BOC/PR TGR</td>
<td>33</td>
<td>41</td>
</tr>
<tr>
<td>BOC/PR48</td>
<td>32</td>
<td>34</td>
</tr>
</tbody>
</table>
# Boceprevir Resistance in Treatment Failures

## Resistance by genotype

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Patients with no sequence data</th>
<th>Patients with mutations detected</th>
<th>Patients with no mutations detected</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>97</td>
<td>32</td>
<td>117</td>
</tr>
<tr>
<td>1b</td>
<td>38</td>
<td>15</td>
<td>43</td>
</tr>
</tbody>
</table>

Total n=342*  

## Frequency and distribution of resistance mutations by genotype

(Expressed as a % of mutations detected for each genotype)

<table>
<thead>
<tr>
<th>Variant</th>
<th>Genotype 1a</th>
<th>Genotype 1b</th>
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<tbody>
<tr>
<td>V36A</td>
<td>33</td>
<td>33</td>
</tr>
<tr>
<td>V36M</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>T54A</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>T54C</td>
<td>0</td>
<td>0</td>
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<tr>
<td>T54G</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>T54S</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>V55A</td>
<td>19</td>
<td>19</td>
</tr>
<tr>
<td>V55I</td>
<td>3</td>
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<td>R155K</td>
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<td>5</td>
<td>5</td>
</tr>
<tr>
<td>V170I</td>
<td>7</td>
<td>7</td>
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<tr>
<td>I170F</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>I170T</td>
<td>10</td>
<td>10</td>
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<tr>
<td>V170F</td>
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<td>0</td>
</tr>
<tr>
<td>V170S</td>
<td>3</td>
<td>3</td>
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<tr>
<td>M175L</td>
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</tr>
</tbody>
</table>

Presented at the 10th Eu Meeting on HIV & Hepatitis, 28-30 March 2012, Barcelona.
Probability of Telaprevir-Resistant Variant Detection

Median time to wild-type by population sequencing = 7 months (CI95% : 5-8)
Clinical Relevance of HCV Resistance Testing?

• Before the start of protease inhibitor-based therapy
  – Preexistence of resistance variants in all HCV-infected patients
  – No clinical indication for resistance testing at baseline

• In case of virological breakthrough
  – Resistant viral populations were enriched in all patients who developed resistance
  – No clinical indication for resistance testing
Outline

• Serological tools
  – Core antigen quantification

• Molecular tools
  – Available HCV RNA assays
  – What real-time PCR should be used?
  – HCV type-subtype determination
  – Resistance testing

• Response-guided therapy
Responses to Therapy According to Viral Kinetics

HCV RNA reduction from baseline ($\log_{10}$ IU/mL)

- Diminution $\geq 2$ Log
- Detection cut-off (10-15 IU/mL)

Weeks

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### Definitions of Virological Responses

<table>
<thead>
<tr>
<th>Response</th>
<th>Definition</th>
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</thead>
<tbody>
<tr>
<td>SVR</td>
<td>HCV RNA undetectable 24 weeks after the end of treatment</td>
</tr>
<tr>
<td>RVR</td>
<td>HCV RNA undetectable at week 4</td>
</tr>
<tr>
<td>EVR</td>
<td>HCV RNA undetectable at week 12</td>
</tr>
<tr>
<td>DVR</td>
<td>$&gt;2 \log_{10} \text{IU/mL}$ drop but detectable HCV RNA at week 12</td>
</tr>
<tr>
<td>Null response</td>
<td>Less than $2 \log_{10} \text{IU/mL}$ in HCV RNA from baseline at week 12</td>
</tr>
<tr>
<td>Partial response</td>
<td>$&gt;2 \log_{10} \text{IU/mL}$ decrease in HCV RNA from baseline at week 12 but still detectable at weeks 12 and 24</td>
</tr>
<tr>
<td>Viral breakthrough</td>
<td>HCV RNA detectable at any time during treatment after virological response</td>
</tr>
<tr>
<td>Relapse</td>
<td>HCV RNA detectable after withdrawal treatment in patient who was undetectable at the end of treatment</td>
</tr>
</tbody>
</table>

**New response categories with protease inhibitor-based therapy**

<table>
<thead>
<tr>
<th>Response with BOC</th>
<th>Definition</th>
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</thead>
<tbody>
<tr>
<td>eRVR with BOC</td>
<td>HCV RNA undetectable at weeks 8 and 24</td>
</tr>
<tr>
<td>eRVR with TVR</td>
<td>HCV RNA undetectable at weeks 4 and 12</td>
</tr>
</tbody>
</table>
Monitoring of Treatment Responses

- BOC/PR
- TVR/PR
- PR

Timepoints:
- W4
- W8
- W12
- W24
- W36
- W48
- W72
Outline

• Serological tools
  – Core antigen quantification

• Molecular tools
  – Available HCV RNA assays
  – What real-time PCR should be used?
  – HCV type-subtype determination
  – Resistance testing

• Response-guided therapy
  – In genotype-1 treatment naïve patients
Benefits of Response-Guided Therapy

• Reduce unnecessary exposure to drugs
  – By shortening therapy in patients likely to achieve SVR without requiring the full duration
  – By terminating therapy early in patients unlikely to achieve SVR

• May identify patients who do not need a protease inhibitor
  – Due to high likelihood of SVR with pegIFN plus ribavirin alone
Higher SVR Rates in Patients Achieving an RVR

**ADVANCE**

- **PR48**: 97% Indetectable HCV RNA at W4 and W12, 39% Detectable HCV RNA at W4 or W12
- **T12PR RGT**: 89% Indetectable HCV RNA at W4 and W12, 54% Detectable HCV RNA at W4 or W12
- **T8PR RGT**: 83% Indetectable HCV RNA at W4 and W12, 50% Detectable HCV RNA at W4 or W12

**SPRINT-2**

- **PR48**: 85% Indetectable HCV RNA at W8, 30% Detectable HCV RNA at W8
- **BOC/PR RGT**: 88% Indetectable HCV RNA at W8, 36% Detectable HCV RNA at W8
- **BOC/PR48**: 90% Indetectable HCV RNA at W8, 40% Detectable HCV RNA at W8


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RVR : An Early Guide to Success

- Patients who achieve an RVR have a very high chance of achieving an SVR
- This applies to pegIFN and ribavirin with or without a protease inhibitor

But

- With a protease inhibitor, many more patients achieve an RVR
  - Defined as Wk 4 of triple therapy (i.e, Wk 8 of the treatment course in patients receiving BOC)
Boceprevir Regimens

- **Treatment-naïve patients without cirrhosis**
  - No treatment required if HCV RNA undetectable at W8.
  - Boceprevir (BOC) + PR for those with detectable HCV RNA at W8.

- **Cirrhotic patients, poor-IFN responders (<1 Log at W4) and null responders**
  - Boceprevir (BOC) + PR for those with detectable HCV RNA at W8.
  - PR for those with undetectable HCV RNA at W8.

Boceprevir. European Medicines Agency.

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Futility Rules

• Different for **BOC** and TVR
  – If HCV RNA is $\geq 100$ IU/mL at **Wk 12**, all 3 medications should be discontinued
  – If HCV RNA is **confirmed detectable** at **Wk 24**, all 3 medications should be discontinued
Telaprevir Regimens

- Treatment-naïve patients without cirrhosis:
  - TVR + PR
  - PR
  - HCV RNA undetectable at W4-12
  - Follow-up

- Cirrhotic treatment-naïve patients:
  - TVR + PR
  - PR
  - HCV RNA detectable at W12 and/or W24 but ≤1000 IU/mL
  - Follow-up

Presented at the 10th Eu Meeting on HIV & Hepatitis, 28-30 March 2012, Barcelona

Telaprevir. European Medicines Agency.
Futility Rules

• Different for TVR and BOC
  – If HCV RNA is $> 1000$ IU/mL at Wk 4 or 12, all 3 medications should be discontinued
  – If HCV RNA is confirmed detectable at Wk 24, pegIFN/RBV should be discontinued
Outline

• Serological tools
  – Core antigen quantification

• Molecular tools
  – Available HCV RNA assays
  – What real-time PCR should be used
  – HCV type-subtype determination
  – Resistance testing

• Response-guided therapy
  – In genotype-1 treatment-experienced patients
Higher SVR Rates in Patients Achieving an RVR (i.e., At Week 8)

![Graph showing SVR rates for different treatments and week 8 HCV RNA levels.](chart.png)
Higher SVR Rates in Relapsers
Achieving an RVR (i.e., at Week 4)

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Boceprevir Regimens

Boceprevir. European Medicines Agency.

*FDA recommends RGT in relapsers and partial responders

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Futility Rules

• Differ for **BOC** and TVR
  – If HCV RNA is \( \geq 100 \text{ IU/mL} \) at Wk 12, all 3 medications should be discontinued
  – If HCV RNA is **confirmed detectable** at Wk 24, all 3 medications should be discontinued
Telaprevir Regimens

- **Treatment-naïve patients without cirrhosis and relapsers**
  - TVR + PR
  - PR
  - HCV RNA undetectable at W4-12
  - Follow-up
  - HCV RNA detectable at W12 and/or W24 but ≤1000 IU/mL

- **Partial and null responders and cirrhotic treatment-naïve patients**
  - TVR + PR
  - PR
  - Follow-up

- **Follow-up**

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Futility Rules

• Differ for TVR and BOC
  – If HCV RNA is $> 1000$ IU/mL at Wk 4 or 12, all 3 medications should be discontinued
  – If HCV RNA is confirmed detectable at Wk 24, pegIFN/RBV should be discontinued
Response-Guided Therapy

• Boceprevir
  – RGT recommended for non-cirrhotic treatment-naive patients
  – Different recommendations from FDA vs EMA for previous relapsers or non responders
  – For previous null responders treated with BOC, fixed duration 48-week course of therapy recommended
  – For treatment-naive patients with < 1 Log reduction in HCV RNA after the lead-in phase, consideration should be given to 4-plus-44 wks regimen rather than RGT
  – Cirrhotic patients should receive a fixed duration 48-week course of therapy

• Telaprevir
  – RGT recommended for treatment-naive patients and previous relapsers
  – All previous partial or null responders and cirrhotic patients should receive a fixed-duration 48-week course of therapy