Resistance to HCV protease inhibitors: Game over? – No!

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Hepatitis C virus
Genome variability (genotypes, subtypes, isolates)

Nucleotide variability
Genotypes 31-33%
Subtypes 20-25%
Isolates ~10%

Simmonds et al., Hepatology 2005
Hepatitis C virus
High viral turnover - generation of viral variants

Hepatitis C virus: ~9600 nucleotides
Error rate during replication: ~10^{-4} – 10^{-5} per copied nucleotide
Viral turnover: ~10^{12} virions produced every day

<table>
<thead>
<tr>
<th>Number of nucleotide change</th>
<th>Probability of generation after one round of replication</th>
<th>Number of virions with nucleotide change(s) produced per day</th>
<th>Number of all possible nucleotide mutants</th>
<th>Fraction of all possible mutants created per day</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>91%</td>
<td>9.1 x 10^{11}</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>8.7%</td>
<td>8.7 x 10^{10}</td>
<td>2.9 x 10^{4}</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>0.4%</td>
<td>4.2 x 10^{9}</td>
<td>4.1 x 10^{8}</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>0.001%</td>
<td>1.3 x 10^{8}</td>
<td>4.0 x 10^{12}</td>
<td>3.4 x 10^{-5}</td>
</tr>
</tbody>
</table>

Resistance to Triple-Therapy PEG/R + DAA
PEG-IFN + Riba + PI / NS5A / NonNuc / NUC

Sensitivity to peginterferon/RBV

Sensitive
(IL28B CC/CT, low ISG, low fibrosis, low viral load, RVR …)

Intermediate
(IL28B TT/CT/CC, medium ISG, medium fibrosis, early to slow and partial responders, …)

Resistant
(IL28B TT/CT, high ISG, null-responders, …)

RBV: ribavirin; ISG: interferon-stimulating gene; RVR: rapid virologic response
Sensitivity to PEG-IFN / Ribavirin
Virologic response to PEG/R versus PEG/R + Telaprevir

Null Responder
(<1log wk. 4 / <2log wk. 12)

"resistant"

Partial Non-Responder
(pos. wk. 24)

"intermediate"

Relapser

"sensitive"

Shiffman et al., AASLD 2008
Sensitivity to PEG-IFN / Ribavirin
Triple PEG/R + DAA accord. to previous tx response (GT 1)

Relapser (REL): negative at end-of-treatment but relapse thereafter
Partial Non-Responder (P-NR): ≥2log wk12 but pos HCV RNA wk 24
Null-Responder (NULL): <2log wk 12

Zeuzem et al., NEJM 2011
Bacon et al., NEJM 2011
Vierling et al., AASLD 2011
Zeuzem et al., EASL 2012
Resistance to Triple-Therapy PEG/R + DAA
PEG-IFN + Riba + PI / NS5A / NonNuc / NUC

Sensitivity to peginterferon/RBV

Sensitive
(IL28B CC/CT, low ISG, low fibrosis, low viral load, RVR …)
~30%

Intermediate
(IL28B TT/CT/CC, medium ISG, medium fibrosis, early to slow and partial responders, …)
~60%

Resistant
(IL28B TT/CT, high ISG, null-responders, …)
~10%

Sensitivity to DAA

Wild-type Variants

Resistant Variants

Frequency of resistant variants?

RBV: ribavirin; ISG: interferon-stimulating gene; RVR: rapid virologic response
Preexistence of resistance mutations
Population based sequencing

Baseline variant without resistance on its own but influence on selection of Q30R (1a)

Relative high level of variation between HCV geno- and subtypes
(natural variant for certain geno- subtypes / isolates may confer resistance)

Variants at 4 allosteric binding sites

Kuntzen et al., Hepatology 2008; Gaudieri et al., Hepatology 2009; Bartels et al., JID 2008; Vicenti et al., J Anti Chemo 2012
Lenz et al., AASLD 2011; Sun et al., Hepatology 2012; Friedel et al., AAC 2010
## Combined resistance

Major-type resistant variant plus non-responsiveness to Peg-IFN/RBV

Population-based sequencing of treatment-experienced patients (PEG/Riba) at baseline and subsequent treatment with telaprevir, PEG/Riba triple therapy (Realize study)

<table>
<thead>
<tr>
<th>Number of patients by treatment outcome</th>
<th>V36M</th>
<th>T54S</th>
<th>R155K</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Null</td>
<td>Part</td>
<td>Rel</td>
</tr>
<tr>
<td>Total number of patients</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>SVR</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>On-treatment virologic failure</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Detectable at EOT – no viral break-through</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Undetectable at EOT – discontinued before SVR</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

EOT: end of treatment; null: prior null responder; part: prior partial responder; rel: prior relapser

## Combined resistance Boceprevir

Major-type resistant variant plus non-responsiveness to Peg-IFN/RBV

### Resistant associated variants (RAVs) and IFN-responsiveness

<table>
<thead>
<tr>
<th>Patients</th>
<th>Total†</th>
<th>Patient n</th>
<th>SVR (%)</th>
<th>Patients n</th>
<th>SVR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients without Baseline RAVs</td>
<td>902</td>
<td>648</td>
<td>79%</td>
<td>254</td>
<td>34%</td>
</tr>
<tr>
<td>Patients with Baseline RAVs</td>
<td>64</td>
<td>51</td>
<td>76%</td>
<td>13</td>
<td>23%</td>
</tr>
<tr>
<td>Other Baseline RAVs</td>
<td>21</td>
<td>15</td>
<td>80%</td>
<td>6</td>
<td>50%</td>
</tr>
<tr>
<td><strong>V36M, V55A, T54S/A and R155K</strong></td>
<td>43</td>
<td>36</td>
<td>78%</td>
<td>7</td>
<td>0%</td>
</tr>
</tbody>
</table>

†Total with Week 4 vial load available (treatment week 4 data not available for 12 patients without baseline RAVs and 2 with baseline RAVs).
‡Patients with ≥1 log₁₀ decrease in viral load at treatment week 4.
§Patients with <1 log₁₀ decrease in viral load at treatment week 4.
SVR=sustained virologic response; RAVs=resistance associated amino acid variants.

acc. to Barnard et al., Merck/MSD data on file
Importance of pre-existing resistance (triple therapy)
NS3 protease inhibitor resistant variant Q80K (TMC-435)

NS3 Protease-Inhibitor Simeprevir (TMC435)
HCV Genotype 1, treatment-naive (Pillar Study)

<table>
<thead>
<tr>
<th>Response %</th>
<th>Simeprevir 75mg (n=153)</th>
<th>Simeprevir 150mg (n=156)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virologic breakthrough</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q80K</td>
<td>14.3</td>
<td>16.7</td>
</tr>
<tr>
<td>No Q80K</td>
<td>3.0</td>
<td>4.2</td>
</tr>
<tr>
<td>SVR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q80K</td>
<td>57.1</td>
<td>66.7</td>
</tr>
<tr>
<td>No Q80K</td>
<td>81.8</td>
<td>84.7</td>
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<tr>
<td>Relapse</td>
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<td></td>
</tr>
<tr>
<td>Q80K</td>
<td>29.4</td>
<td>20.0</td>
</tr>
<tr>
<td>No Q80K</td>
<td>13.4</td>
<td>7.5</td>
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</table>

Lenz et al., AASLD 2011
### Selection of resistant variants during DAA therapy
Cross resistance between NS3 protease inhibitors

<table>
<thead>
<tr>
<th>Type</th>
<th>Molecule</th>
<th>V36A/M</th>
<th>T54S/A</th>
<th>V55A</th>
<th>Q80R/K</th>
<th>R155K/T/Q</th>
<th>A156S</th>
<th>A156T/V</th>
<th>D168A/E/G/H/T/Y</th>
<th>V170A/T</th>
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<tbody>
<tr>
<td>Linear</td>
<td>Telaprevir*</td>
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<td></td>
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<tr>
<td></td>
<td>Boceprevir*</td>
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<tr>
<td></td>
<td>Narlaprevir*</td>
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<tr>
<td>Macrocyclic</td>
<td>Danoprevir*</td>
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<td>✔️</td>
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<tr>
<td></td>
<td>Vaniprevir*</td>
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<tr>
<td></td>
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<tr>
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<td>IDX-320**</td>
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<tr>
<td></td>
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<tr>
<td>Macrocyclic</td>
<td>MK-5172**</td>
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<td>✔️</td>
<td>✔️</td>
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<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
</tr>
</tbody>
</table>

* mutations associated with resistance in patients
** mutations associated with resistance in vitro

Sarrazin et al., J Hepatol 2012
Probability of treatment-failure
Triple-therapy telaprevir / boceprevir (break-through or stopping rule)

**Telaprevir**
- naiv: 8%
- REL: 1%
- P-NR: 18%
- NULL: 57%

**Boceprevir**
- naiv: 9%
- REL: 20%
- P-NR: 42%
- NULL: 20%

- ~25% failures in HCV-1a
- ~9% failures in HCV-1b

**Analysis of <1log lead-in**
- ~75% failures in HCV-1a
- ~53% failures in HCV-1b

BT or stopping rule TVR wk 4, 6, 8 >100 /1000 IU/ml entire tx. <2log wk 12/HCV RNA pos. wk 24

Jaconson et al., NEJM 2011; Zeuzem et al., NEJM 2011

**Boceprevir**

BT or stopping rule tx wk 24 or wk 12

Bacon et al., NEJM 2011; Poordad et al., NEJM 2011

* PROVIDE Study, Vierling AASLD 2011
Persistence of resistant variants?
Long term follow-up

NS3 protease inhibitors
- Telaprevir  median follow up ~2 years: 85% pts. wild-type
- Boceprevir median follow-up ~1 year: 90% pts. wild-type

NS5A inhibitors
- Different rates of persistence for up to 1 year according to HCV subtype and variant selected

NS5B non-nucleoside inhibitors
- Insufficient data

NS5B nucleoside analogues
- S282T variant selected in single patients only
- Rapid reversion to wild-type

Sherman et al., AASLD 2011; Barnard et al., AASLD 2011; Gane et al., EASL 2012; Susser et al., J Clin Virol 2011; Wong et al., EASL 2012
Re-Treatment of Telaprevir-exposed patients
viral kinetics, week 8 interim analysis, n=9

Resistance during first TVR exposure but no NS3 protease resistant variants at baseline before re-treatment (deep-sequencing)

One patient had a confirmed viral breakthrough at Week 8 (V36M/V + R155K/R)

CV RNA values below LOQ are imputed with an arbitrary value:
17.5 for <25 IU/mL detectable and 5 for <25 IU/mL undetectable

HCV genotype 1b patient treated twice with NS3 PI (MK7009) + PEG-IFN + Ribavirin

Treatment 1 and 2: MK-7009 300 mg b.i.d. + peg-IFN + RBV

Barnard et al., International HIV and Hepatitis Virus Drug Resistance, Sitges July, 2012
IFN-free therapies
Treatment failures on mono, dual, triple and quad all oral regimens

Viral breakthrough was associated with selection of single, double and triple resistant variants within NS3, NS5A and NS5B genes

Sarrazin et al., Gastroenterology 2007; Lok et al., NEJM 2012; Zeuzem et al., Hepatology 2011; Sulkowski et al., EASL 2012
Summary
Many factors associated with treatment success

Host factors
- Fibrosis stage
- IL28B Genotype
- Race
- ...

Treatment factors
- Mode of action
- Antiviral activity
- Barrier to resistance
- Coverage of geno-subtypes
- ...

Viral factors
- Viral load
- HCV geno- and subtype
- Resistance mutations
- ...

Eradication of HCV