HCV Resistance Associated variants: impact on chronic hepatitis C treatment

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Concern Only Emerged With the Introduction of DAAs\textsuperscript{1-5}

**IFN/RBV-containing regimens**
- IFN: Multiple antiviral targets preclude specific mutations in the HCV genome conferring resistance to it\textsuperscript{2,3}
- RBV: Molecular mechanism of action unknown, major role in the prevention of relapse
- Treatment failure is due to host factors, disease characteristics, and viral factors

**First DAAs**
- Target specific sites on the HCV molecule
- Selection of viral variants alters drug interactions with the target to confer resistance to the DAA\textsuperscript{2}

Drug-Resistant Variants Observed With All DAAs: Common RAVs in Non-SVR Patients in Clinical Trials

### NS3/4 Protease Inhibitors

<table>
<thead>
<tr>
<th>Position</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>V36</td>
<td>Boceprevir</td>
</tr>
<tr>
<td>T54</td>
<td>Telaprevir</td>
</tr>
<tr>
<td>V55</td>
<td>Simeprevir</td>
</tr>
<tr>
<td>Q80</td>
<td>Asunaprevir</td>
</tr>
<tr>
<td>S122</td>
<td>Vanaprevir</td>
</tr>
<tr>
<td>R155</td>
<td>Paritaprevir</td>
</tr>
<tr>
<td>A156</td>
<td>Grazoprevir (MK-5172)</td>
</tr>
</tbody>
</table>

### NS5B Polymerase Inhibitors

<table>
<thead>
<tr>
<th>Position</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>V36</td>
<td>Sofosbuvir (nucleoside)</td>
</tr>
<tr>
<td>M414</td>
<td>MK-382 (nucleoside)</td>
</tr>
<tr>
<td>V55</td>
<td>Beclabuvir (NNI-1, thumb 1)</td>
</tr>
<tr>
<td>L419</td>
<td>Deleobuvir (NNI-1, thumb 1)</td>
</tr>
<tr>
<td>R422</td>
<td>VX222 (NNI-2, thumb 2)</td>
</tr>
<tr>
<td>M423</td>
<td>Setrobuvir (NNI-3, palm 1)</td>
</tr>
<tr>
<td>A421</td>
<td>Dasabuvir (NNI-1, palm 1)</td>
</tr>
</tbody>
</table>

DAA = direct-acting antiviral; RAV = resistance-associated variant; SVR = sustained virologic response.

In Vitro Resistance Profile of Daclatasvir

- Emergent DCV RAVs observed at N-terminus of NS5A
- Fold change in EC50 value is genotype (subtype)-dependent
- Resistance barrier is genotype-specific
  - 2 amino acid substitutions are required to substantially increase resistance in GT-1b

GT-1a and GT-1b activity profiles of 1st generation NS5A inhibitors in advanced clinical development are generally comparable
- Varied activity against GT-1a-NS5A-M28T and GT-1b-NS5A-Y93H

Profiles of NS5A inhibitors differ against GT-2 an GT-3 reference strains
Persistence of NS3/NS5A RAVs

- Replacement of emergent NS5A resistance-associated variants (RAV) is infrequent overtime
  - Complete NS5A replacement observed in 5% (3/59) of virological failures monitored ≥ 24 weeks post-treatment
  - Partial NS5A replacement observed in 27% (16/59) GT1b patients

- NS3 RAVs are less fit than NS5A RAVs and complete replacement with wild-type sequences is more frequent
  - Complete replacement observed in 71% (29/41) GT1b patients
  - Partial replacement observed in 15% (6/41) GT1b patients

- 3-year long-term follow-up study ongoing

Data on file - AI444-046 study interim analysis
Replacement of NS5A RAVs has been observed in patients

- Complete replacement of RAVs was observed by population sequencing in 10 of 73 (14%) GT 1a, 3 of 59 (5%) GT 1b, 1 of 4 (25%) GT 3a, and 0 of 2 GT 4 patients monitored during long-term follow-up

Complete replacement of NS3 RAVs with wild-type sequence is observed more frequently compared with NS5A RAVs

- Complete replacement was observed in 10 of 17 (59%) GT 1a and 29 of 41 (71%) GT 1b patients monitored during long-term follow-up

Replacement of SMV-Resistant Viruses by Wild-Type Viruses

Persistence of NS5A Inhibitor-Resistant Viruses

Prevalence of NS5A Preexisting RAVs in GT-1b

Baseline RAVs in NS5A were generally more common among Asian patients than non-Asians.
Japanese patients had a higher prevalence of L31 and/or Y93 RAVs than patients from other Asian or non-Asian countries.

Data from HALLMAK Nippon (026) and HALLMAK DUAL (028) trials

McPhee et al. 2015 APASL Conference Poster.
Among all GT-1b patients, only baseline L31 or Y93 RAVs were associated with reduced SVR<sub>12</sub> following DCV+ASV. No influence of L28M or R30Q substitutions in the absence of L31 or Y93H.
DUAL SVRs by Baseline RAV Status

Non-Asian countries (N = 485)

SVR₁₂ (%)

<table>
<thead>
<tr>
<th>Category</th>
<th>With RAV</th>
<th>Without RAV</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>39</td>
<td>57</td>
</tr>
<tr>
<td>Treatment-naïve</td>
<td>54</td>
<td>428</td>
</tr>
<tr>
<td>Prior non-responders</td>
<td>29</td>
<td>134</td>
</tr>
<tr>
<td>IFN ineligible/intolerant</td>
<td>39</td>
<td>138</td>
</tr>
</tbody>
</table>

McPhee et al. 2015 APASL Conference Poster.
Baseline NS5A polymorphisms L31 and/or Y93 were present in ~18% of Japanese and ~12% of non-asian patients.

Baseline NS5A polymorphisms at amino acid positions 31 and 93 affect virologic response to DUAL.

Baseline resistance testing to select those without key NS5A polymorphisms increases chance of achieving SVR.

Across all patient groups of prior treatment experience, age and cirrhosis, very high SVR\textsubscript{12} rates were observed in patients without baseline L31 and Y93H polymorphisms.
DACLATASVIR+ASUNAPREVIR: RE-TREATMENT OPTIONS
Re-Treatment of GT-1b Patients who do not Achieve SVR with DCV/ASV

- When GT-1b patients fail DCV/ASV, NS5A-L31M-Y93H and NS3-D168V are most frequently detected together.

- NS5A and NS3 RAPs can persist
  - NS5A resistance variants persist > 1 year post-treatment.
  - Although NS3 resistance variants frequently replaced by 1 year post-treatment, persistence has been observed.

- HCV replicon harboring NS5A-L31M-Y93H and NS3-D168V used to study potential retreatment options.
In-Vitro Analysis: Retreatment Options for Patients not Achieving SVR with DCV/ASV

In-Vitro Analysis: Retreatment Options for Patients not Achieving SVR with DCV/ASV

BMS-791325 = NS5B Thumb 1 inhibitor; alfa = interferon-alfa

No elimination of HCV replicons harboring NS5A-L31M-Y93H and NS3-D168V after treatment with DCV/ASV

DCV-Trio eliminates DCV/ASV-resistant replicons at 30x EC50 when compared with DCV/ASV

Best potential treatment options against DCV/ASV-resistant replicons include:

- DCV/SOF and SOF/LDV
- DCV-Trio + SOF and SOF/IFNα/RBV
- SOF/next-gen NS3 PI and SOF/next-gen NS5A offer future options

Retreatment clinical studies required to confirm in vitro findings