Hepatitis C Resistance Associated Variants (RAVs)

Atif Zaman, MD MPH
Oregon Health & Science University
Professor of Medicine
Division of Gastroenterology and Hepatology
Disclosure

• Nothing to disclose
HCV Resistance Associated Variants

- Identification, how they work
- Classes of RAV’s (NS5a, NS3b, NS5b)
- What RAV’s are clinically significant?
- Interpretation of RAV’s in prior DAA failures
Mechanisms of Resistance

Viral Population

Sensitive (wild-type)

Add Drug

Outgrowth of Resistant Virus

Sensitive

Resistant
Mechanisms of Resistance

- Likelihood that a DAA will select for and allow outgrowth of viral populations carrying RAVs depends on the DAA’s
  - Genetic barrier to resistance (number and type of base pair mutation(s) needed to result in amino acid substitution(s) that confer resistance)
  - Efficacy/barrier to resistance of drug
  - Viral fitness of the resistant variant (replicative capacity)

Mechanisms of Resistance

Viral Population
Sensitive (wild-type) → Add Drug → Resistant

Stop Drug → Resistant → Outgrowth of Sensitive Virus
Sensitive Virus

Persistence of Resistant Virus
Sensitive Virus

Low Viral Fitness of Resistant Population
High Viral Fitness of Resistant Population
HCV Polyprotein:
Nonstructural Proteins are Primary Targets for DAAs
HCV Resistance Testing in Clinical Practice: Current Barriers for Routine Clinical Use

• Few assays established, implications for regimen selection unknown
  – Level of resistance of a certain RAV is not necessarily directly associated with treatment failure
    • Presence of other predictors of virologic treatment response are also important (eg, genotype, presence of cirrhosis, duration of therapy)

• Lack of standardization among the different assays

• Lack of validation on when to use
  – Prior to HCV therapy
  – At the time of virologic relapse
  – Prior to retreatment
NS3/4A Protease Inhibitors: Natural Occurrence and Persistence of RAVs

- NS3 PIs prevent HCV polyprotein cleavage into non-structural proteins (NS3, NS4A, NS4B, NS5A, and NS5B)
- Many NS3 PI RAVs are associated with a replicative impairment
  - Low frequency of natural occurrence and rapid replacement by wild-type virus
- Frequency of a single NS3 RAV in HCV genotype 1: 0.1% to 3.1%*
  - Exception: Q80K (almost exclusively in genotype 1a)
    - North America: up to 48% patients
    - South America: 9%
    - Europe: 19%

<table>
<thead>
<tr>
<th></th>
<th>Genotype 1a</th>
<th>Genotype 1b</th>
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</thead>
<tbody>
<tr>
<td>Simeprevir (months)</td>
<td>8.3</td>
<td>5.5</td>
</tr>
<tr>
<td>Boceprevir (months)</td>
<td>14.0</td>
<td>12.5</td>
</tr>
<tr>
<td>Telaprevir (months)</td>
<td>10.6</td>
<td>0.9</td>
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</table>

Paritaprevir (genotype 1a): NS3 RAVs have been observed in 46% and 9% of patients after 24 and 48 weeks of follow-up, respectively.

*Population-based sequencing.

Sarrazin C. *J Hepatol.* 2016;64:486-504.
NS5A Inhibitors: Natural Occurrence and Persistence of RAVs

- Mechanism of action of NS5A inhibitors is not fully understood
  - NS5A regulation of viral replication, assembly, and HCV particle not fully understood
- Frequency of a single NS5A RAV in HCV genotype 1: 0.3% to 2.8%*
  - 2 exceptions in HCV genotype 1b
    - Y93H (confers medium to high resistance to daclatasvir, ledipasvir, ombitasvir): 3.8%-14.1%
    - L31M (confers low to medium resistance to daclatasvir, ledipasvir): 2.1%-6.3%
  - Limited data in other genotypes
- Long-term persistence of NS5A RAVs after treatment is stopped
  - 1 to 2 years in >85% of patients

*Population-based sequencing.

NS5B Polymerase Inhibitors: Natural Occurrence and Persistence of RAVs

• NS5B is the RNA-dependent RNA polymerase of the membrane-associated HCV replication complex (palm and thumb domains)

• Frequency of a single NS5B RAV in HCV genotype 1: 0.3% to 2.8%*
  – Sofosbuvir (nucleotide inhibitor): 0% to date
  – Dasabuvir (non-nucleoside inhibitor): 0.2%-3.1%
    • 2 exceptions in HCV genotype 1b (both confer low level of resistance to dasabuvir)
      – C316N: 10.9%-35.6%
      – S55G: 7%-25%

• Persistence of NS5B RAVs after treatment is stopped
  – Dasabuvir: some RAVs (M414T, S556G) for >1 year
    • RAVs detectable in 75% and 57% of patients after 24 and 48 weeks, respectively
  – Sofosbuvir: emergent S282T reverts to wild-type within a few weeks

*Population-based sequencing.

Impact of Baseline RAVs on SVR12 Rates With Elbasvir/Grazoprevir

- Genotype 1b
  - No impact on SVR12 rates

- Genotype 1a
  - Significant impact on SVR12 rates in treatment-naïve and PR-experienced patients receiving elbasvir/grazoprevir for 12 weeks
    - Baseline resistance testing is recommended
  - No impact of baseline RAVs with addition of RBV and extending treatment to 16/18 weeks

- Genotype 4 and 6
  - Insufficient data to draw conclusions

Summary

- After treatment-failure with IFN-free, DAA-based regimens
  - NS3 variants resistant to HCV PIs progressively disappear and are replaced by wild-type virus
  - NS5A variants resistant to NS5A inhibitors may persist for years
  - NS5B variants resistant to NS5B nucleotide inhibitors are not an issue
- Detection of baseline RAVs using population sequencing impacts SVR12 rates of Elbasvir/Grazoprevir regimen for genotype 1a patients
- Treatment induced NS5A RAVs can be an issue
# POLARISIS Phase 3 Program

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<thead>
<tr>
<th>DAA-Experienced</th>
<th>DAA-Naïve</th>
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<tbody>
<tr>
<td><strong>POLARIS-1</strong></td>
<td><strong>POLARIS-2</strong></td>
</tr>
<tr>
<td>N = 415</td>
<td>N = 941</td>
</tr>
<tr>
<td>NS5A-experienced ± cirrhosis (46%)</td>
<td>± cirrhosis</td>
</tr>
<tr>
<td><strong>POLARIS-4</strong></td>
<td><strong>POLARIS-3</strong></td>
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<tr>
<td>N = 333</td>
<td>N = 219</td>
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<tr>
<td>Non-NS5A-experienced ± cirrhosis (46%)</td>
<td>Cirrhosis</td>
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<tr>
<th>GT 1 2 3 4 5 6</th>
<th>GT 1 2 3 4 5 6</th>
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<tbody>
<tr>
<td>SOF/VEL/VOX 12 weeks (n=263)</td>
<td>SOF/VEL/VOX 12 weeks (n=182)</td>
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<td>Placebo (n=152)</td>
<td>SOF/VEL 12 weeks (n=151)</td>
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<tr>
<td>SOF/VEL/VOX 8 weeks (n=501)</td>
<td>SOF/VEL 12 weeks (n=440)</td>
</tr>
<tr>
<td>SOF/VEL/VOX 8 weeks (n=110)</td>
<td>SOF/VEL 12 weeks (n=109)</td>
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Study Conclusions

• In a wide variety of DAA-experienced patients across all genotypes SOF/VEL/VOX for 12 weeks resulted in:
  – 96% SVR in NS5A experienced patients
  – 97% in DAA-experienced patients
  – Including patients with multiple unfavorable characteristics including multiple RAVs across NS5A and NS3/4A
  – Baseline RAVs did not impact treatment outcome for SOF/VEL/VOX with SVR rates of 94-100%
  – No treatment-emergent RAVs were observed among patients who relapsed with SOF/VEL/VOX

• SOF/VEL/VOX and SOF/VEL was well tolerated with an AE profile similar to that observed in placebo recipients

• SOF/VEL/VOX for 12 weeks provides a simple, safe, and effective single tablet, once daily, RBV-free treatment for DAA-experienced patients, including NS5A and non-NS5A failures
What do I Conclude From the POLARIS Studies?

- SOF/VEL/VOX for 12 weeks an effective treatment for all DAA-experienced patients

- SOF/VEL for 12 weeks an effective treatment for DAA-naive patients regardless of cirrhosis status
Recent FDA Approved Regimens in 2017: Glecaprevir/Pibrentasvir (SVR>95%)

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<thead>
<tr>
<th>HCV Genotype</th>
<th>TREATMENT NAÏVE</th>
<th>No cirrhosis</th>
<th>Child’s A Cirrhosis</th>
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<tbody>
<tr>
<td>1,2,3,4,5, or 6</td>
<td>TREATMENT EXPERIENCED</td>
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<td></td>
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<tr>
<td></td>
<td>Previous Regimen</td>
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<tr>
<td>1</td>
<td>NS5A inhibitor without NS 3/4 Protease Inhibitor</td>
<td>16 weeks</td>
<td>16 weeks</td>
</tr>
<tr>
<td>1</td>
<td>NS 3/4 Protease Inhibitor without NS5A inhibitor</td>
<td>12 weeks</td>
<td>12 weeks</td>
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<tr>
<td>1,2,4,5, or 6</td>
<td>Sofosbuvir, Interferon, Ribavirin</td>
<td>8 weeks</td>
<td>12 weeks</td>
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<tr>
<td>3</td>
<td>Sofosbuvir, Interferon, Ribavirin</td>
<td>16 weeks</td>
<td>16 weeks</td>
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