Resistance Testing in HCV Infection: Is It Necessary?

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Conflict of Interest Disclosure

• I have received research grants from Gilead and Abbvie

• I have served as an advisor for Abbvie, Bristol-Myers Squibb, Gilead, Janssen and Merck
Resistant variant

Resistance-associated substitution (RAS)

(Pawlotsky JM, Gastroenterology 2016;151:70-86)
I

DAA Classes and Resistance
Available HCV DAA Classes

(Pawlotsky JM, Antivir Ther 2012;17:1109-17)
HCV DAA Barriers to Resistance

Low-barrier-to-resistance drug

- NS5A inhibitors
- NS3 protease inhibitors
- Non-nucleoside RdRp inhibitors

High-barrier-to-resistance drugs

- Nucleotide analogues
Nucleotide Analogue Resistance

(Lontok et al., Hepatology 2015;62:1623-32)
High-level resistance in vitro

Protease Inhibitor Resistance

Genotype and subtype designations: 1a - red, 1b - blue, 4d - orange

(Lontok et al., Hepatology 2015;62:1623-32)
NNI Resistance

High-level resistance *in vitro*

(Lontok et al., Hepatology 2015;62:1623-32)
NS5A Inhibitor Resistance

High-level resistance in vitro

Genotype and subtype designations: 1a - red, 1b - blue, 3a - green, X - amino acid deletion
4 - orange (daclatasvir - genotype 4, ombitasvir - genotype 4d)

(Lontok et al., Hepatology 2015;62:1623-32)
II

Influence of Baseline RASs on Virological Outcomes
SVR According to Baseline NS5A RASs
SOF/LDV, GT1, guidelines-recommended treatment

(Zeuzem et al., AASLD 2015)
Ombitasvir/Paritaprevir/r + Dasabuvir + RBV

GT1a, guidelines-recommended regimens + RBV, 12 wks in non-cirrhotics, 24 wks in cirrhotics

(Sulkowski et al., CROI 2016)
Influence of Baseline NS5A RASs

Grazoprevir-Elbasvir, 12 or 16-18 weeks, prior NR, w/o RBV

Pts with RASs by population sequencing
Pts without RASs

GT1a, Previous nonresponse

GT1b, Previous nonresponse

SVR12 (%)

EBR RASs 97% N=61
NS5A class RASs 96% N=54
EBR RASs 100% N=51
NS5A class RASs 100% N=44
NS5A class RASs 100% N=8

EBR/GZR 12 wks

EBR/GZR + RBV 16/18 wks

EBR RASs 100% N=28
NS5A class RASs 67% N=6
EBR RASs 100% N=22
NS5A class RASs 83% N=12
EBR RASs 100% N=26
NS5A class RASs 100% N=12
NS5A class RASs 100% N=16

(Jacobson et al., AASLD 2015)
Influence of NS5A RASs on SOF/VEL 12 wks

**ASTRAL-1 to 3 - Deep sequencing, 1% cutoff**

<table>
<thead>
<tr>
<th>Study</th>
<th>GT</th>
<th>Cirrhosis</th>
<th>No NS5A RASs</th>
<th>With NS5A RASs</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASTRAL-1</td>
<td>1, 2, 4, 5, 6</td>
<td>16%</td>
<td>100%</td>
<td>99%</td>
</tr>
<tr>
<td>N=257</td>
<td>N=359</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASTRAL-2</td>
<td>2</td>
<td>14%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>N=80</td>
<td>N=53</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASTRAL-3</td>
<td>3</td>
<td>30%</td>
<td>97%</td>
<td>88%</td>
</tr>
<tr>
<td>N=43</td>
<td>N=231</td>
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</tr>
</tbody>
</table>

Influence of NS5A RASs on SOF/VEL 12 wks

ASTRAL-4- GT1, Decompensated (CPT-B) cirrhosis (deep seq 1% cutoff)

(Curry et al., N Engl J Med 2015;373:2618-28)
Summary

• The presence at baseline of HCV RASs that confer high-level resistance to NS5A inhibitors has an effect on the rate of SVR with IFN-free regimens

• Parameters that influence their effect include:
  • The genotype/subtype (1a and 3)
  • The patient’s background (cirrhosis, PegIFN-RBV nonresponse)
  • The treatment regimen received (class of DAA, duration)

• Adding RBV and/or increasing treatment duration prevent the impact of baseline NS5A RASs on SVR
Utility of HCV Resistance Testing at Baseline
Reasons for Not Recommending Systematic HCV Resistance Testing

- No standardized assay externally validated for its performance and easy to routinely use available as a purchasable kit
- No standardized interpretation and reporting of HCV resistance data
- No precise definition of clinically relevant RASs
- No clearcut guidelines from international societies to guide treatment decisions

(Pawlotsky JM, Gastroenterology 2016;151:70-86)
Systematic testing for HCV resistance prior to treatment is NOT recommended. Indeed, this obligation would seriously limit access to care and treatment regimens can be optimized without this information.

Physicians who have easy access to a reliable test assessing HCV resistance to NS5A inhibitors (spanning amino acids 24 to 93) can use these results to guide their decisions.

The test should be based on population sequencing (reporting RASs as “present” or “absent”) or deep sequencing with a cutoff of 15% (only RASs that are present in more than 15% of the sequences generated must be considered).

(EASL Recommendations on Treatment of Hepatitis C 2016)
HCV Resistance Testing Prior to First-Line DAA Therapy

Not available

Optimize therapy to avoid treatment failure

• SOF/LDV, SOF/DCV, SOF/SIM: Add RBV in G1a-4-5-6 TE
• SOF/VEL: Add RBV in G3 TE patients and cirrhotics
• GZR/EBR: use 16 weeks with RBV in GT1a

Available, reliable, interpretable, understandable*

Presence of NS5As RASs conferring high-level resistance (pop seq or >15%)

Add ribavirin and/or increase treatment duration in patients with NS5A RASs

(EASL Recommendations on Treatment of Hepatitis C 2016)
Sequencing Strategies

Major populations

Intermediate populations

Minor populations

Final results:

Population sequencing

Next Generation sequencing

A%  B%  C%  D%  E%
Sequencing Strategies

Population sequencing

Major population

Intermediate populations

Minor populations

Final results:

Next Generation sequencing

A%  B%  C%  D%  E%
Influence of Baseline NS5A RASs
Grazoprevir-Elbasvir, 12 or 16-18 weeks, w/o RBV

No Baseline NS5A RASs

<table>
<thead>
<tr>
<th>NGS Sensitivity Threshold</th>
<th>SVR12 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1% (All RASs)</td>
<td>99% 100%</td>
</tr>
<tr>
<td>20% (All RASs) (Positions 30, 31, 58)</td>
<td>98% 100%</td>
</tr>
<tr>
<td>20% (All RASs)</td>
<td>99% 100%</td>
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With Baseline NS5A RASs

<table>
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<tr>
<th>NGS Sensitivity Threshold</th>
<th>SVR12 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1% (All RASs)</td>
<td>64%</td>
</tr>
<tr>
<td>20% (All RASs) (Positions 30, 31, 58)</td>
<td>38% 25%</td>
</tr>
</tbody>
</table>

NGS Sensitivity Threshold

(Jacobson et al., AASLD 2015)
Summary

• HCV resistance testing is not required to offer optimal first-line therapy or retreatment

• HCV resistance testing, if available and reliable, may help avoid overusing ribavirin in patients who do not need it

• Population sequencing or deep sequencing with a cutoff of 15% have the best predictive values

• Standardized assays are in development and their performances need to be better characterized
IV

Utility of HCV Resistance Testing at Retreatment of DAA Failures
Two Types of DAA Failures

• **Easy to retreat:**
  - Never exposed to an NS5A inhibitor
  - No need for HCV resistance testing

• **Difficult to retreat**
  - Failed an NS5A inhibitor-containing regimen
  - HCV resistance testing may help

*(EASL Recommendations on Treatment of Hepatitis C 2016)*
Replacement of PI-Resistant Viruses by Wild-Type Viruses

(Lenz et al., J Hepatol 2015;62:1008-14)
Persistence of NS5A RASs in Patients who Failed after LDV (no SOF)

(From: Dvory-Sobol et al., EASL 2015)
Persistence of RASs in Patients who Relapsed after 3D

67/2510 patients with genotype 1a and virologic failure after 3D

Prevalence of RAVs (%)

- NS3 RASs (paritaprevir): 46% (N=67), 9% (N=57)
- NS5A RASs (ombitasvir): 97% (N=70), 96% (N=51)
- NS5B RASs (dasabuvir): 75% (N=44), 57% (N=35)

(Krishnan et al., EASL 2015)
HCV Resistance Testing Prior to Retreating NS5A Inhibitor Failures

- Not absolutely necessary, but useful to guide retreatment decision
- Particularly useful in patients with advanced liver disease who need to rapidly cure infection
- Still empirical in the absence of trial data and guidelines

(Pawlotsky JM, Gastroenterology 2016;151:70-86)
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