Retreatment of DAA failures: An issue but for how long?

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What we won’t talk about and why...

- Interferon treatment failures
  - Retreatment options are well defined and efficacious

- DAA + interferon failures
  - Well represented (PI + Peg/RBV failures) in DAA trials
  - DAA regimens efficacious in this setting

- Impact of RASs in non-DAA exposed patients (baseline RASs)
Case 1: GJ

- 57 AA male HIV and HCV GT1a
  - Cirrhosis F5/6 (bx 3/14); no h/o decompensation
  - U/S negative 7/16; EGD w/o varices (2014)
  - Null responder to PEG/ RBV
  - Relapse after 12 weeks SOF + DCV (clinical trial)
    - No RBV
    - HCV RNA UD at week 4; relapse at SVR4 time point (250,000 IU/mL)
- HIV well controlled on DTG/ABC/3TC
- PMH
  - DMII; HTN
  - HBV and HAV immune
Case 1: Labs (OCT 2016)

- Chemistry:
  - Cr. 1.3; AST/ALT 39/25; TB 0.5; ALB 4.1
- CBC:
  - Hg 14.3; plt 107; INR 1.1
- HCV RNA: 3,457,502 IU/mL
- APRI = 0.91; Fib 4 = 4.16
- CD4: 509 (33%)
- HIV RNA: 25 (<20 on 7/19/16)

Additional test? What are his re-treatment options?
Considerations for Pts Who Failed a DAA-Based Regimen

1. Was initial therapy suboptimal (or submaximal)?
   - IFN + DAA vs DAA failure
   - Duration and RBV use

2. Stage of liver disease/host characteristics

3. Indications of other problems
   - Adherence?
   - Significant drug interactions?

4. What does the drug resistance profile look like?
   - What medication classes were used in the failing therapy?
Key HCV Resistance Concepts

1. HCV resistance associated substitutions (RASs) can be present without drug exposure
2. HCV RASs impacts treatment responses in specific situation
3. HCV is resistance is NOT absolute
4. Patient characteristics are just (if not more) important than RASs
5. Future regimens appear to obviate the need for most resistance testing
   • More from Professor Esteban
### Resistance Characteristics of HCV Antiviral Classes

<table>
<thead>
<tr>
<th>Class</th>
<th>Antiviral Potency</th>
<th>Genotype Activity</th>
<th>Resistance Barrier</th>
<th>FDA Approvals</th>
</tr>
</thead>
</table>
| NS3 Protease Inhibitors | +++ to ++++       | 1, 4 (± 2, 3, 6)  | Low to High        | *Simeprevir* (2013)  
                           |                   |                   |                                                 | *Paritaprevir* (2014)  
                           |                   |                   |                                                 | *Grazoprevir* (2016)  
                           |                   |                   |                                                 | *Voxilaprevir* (2017)*  
                           |                   |                   |                                                 | *Glecaprevir* (2017)*  |
| NS5B Nucleotide        | ++++              | 1-6               | Very High          | *Sofosbuvir* (2013)                                 |
| NS5B Nonnucleoside     | ++                | 1                 | Low                | *Dasabuvir* (2014)                                  |
| NS5A Inhibitors        | ++++              | 1, 4, 6 (± 2, 3)  | Low To High        | *Ledipasvir* (2014)  
                           |                   |                   |                                                 | *Daclatasvir* (2015)  
                           |                   |                   |                                                 | *Ombitasvir* (2014)  
                           |                   |                   |                                                 | *Elbasvir* (2016)  
                           |                   |                   |                                                 | *Velpatasvir* (2016)  
                           |                   |                   |                                                 | *Pibrentasvir* (2017)* |

*Anticipated US FDA approvals*
Resistance Testing Approaches

• Ultra-deep (or next-generation sequencing [NGS]) vs population (Sanger) sequencing

• What is broadly available:
  1. HCV NS5A drug resistance assay (LabCorp/Monogram Biosciences)
     • NGS with 10% detection level reported
  2. Hepatitis C viral RNA genotype 1/3 NS3/NS5 drug resistance assays (Quest Diagnostics)
     • RT-PCR with DNA sequencing

• Both assays now available for GT1 and GT3 HCV
  • GT1 assays are subtype specific

Examples: NS5A Resistance Genotyping

**Important Definitions**

- **Resistance Possible**: Resistance-associated variants (RAVs) detected that (a) represent naturally-occurring polymorphisms or treatment-emergent variants associated with reductions in sustained virologic response (SVR) rates; (b) emerge during direct-acting antiviral (DAA) treatment or relapse, or after (c) may confer reductions in susceptibility based on in vitro data. Affected to prescribing information for specific details regarding the impact of these variants on treatment response is defined in patient populations and when administered in combination with other antiviral agents.
- **Non-assessed(R):** None, no RAVs detected. Unassessed variants are defined that have a subtle or uncertain impact on DAA treatment responses.

**Notes**

- All mutations are reported relative to the HCV genogroup 1a specific reference strain H77
- Assessment of drug susceptibility is based on individual mutations and is interpreted using a rules-based algorithm (version 4).
- Naturally-occurring polymorphisms may impact the emergence of resistance, leading to failure of DAA combination therapy.
- Naturally-occurring DAA resistance-associated polymorphisms identified at baseline may impact SVR if the treatment regimen or adherence are suboptimal. The impact of these polymorphisms may vary in treatment-naïve and treatment-experienced patients with varying disease states (e.g. HCV chronic vs cirrhotic).
- Reduced susceptibility to any one component of a DAA-containing regimen may be overcome by the activity of the other components of the regimen and/or longer treatment duration.
- Treatment-emergent RAVs may persist for prolonged periods of time and may impact subsequent treatment regimens.

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**HCV NS5A Drug Resistance Assay Product Label. 2016.**
Baseline versus selected RAVs

**Baseline**
- Single variants
- Variable fold change
- Variable prevalence in viral population
- Any patient

**Selected**
- Multiple variants (w/ “linkage”)
- High fold change
- High prevalence in viral population
- “Difficult to treat” populations

Why NS3 PI resistance is not a big deal

1. Baseline RASs are not a significant clinical issue
   • RASs at key PI positions (R155, A156, D168) are rare (<1%) without drug exposure
   • No evidence for impact of Q80K with *recommended* SOF+SMV regimens

2. After failure selected PI RASs are “lost” rather quickly
   • Do they still have an impact, even if no longer detectable?

3. Non-PI options are available for sequencing of treatment
   • Eliminates the issue of a persistent effect
Rate of selection of NS5A resistance upon virologic failure

- Varies by regimen and duration
  - PI based
    - Vedroprevir + tegobuvir + LDV: >99%
    - GZR/EBR: 85%
    - 3D: 68%
  - Nucleotide based
    - SOF/LDV: 75%
      - 8 weeks: 65%
    - SOF/VEL: 93% (14/15; majority GT3 and with baseline RASs)
  - Nuc-based triple
    - SOF/5816/9857 (≤ 6 weeks): 0% (n=15)
    - SOF + GZR/EBR (≤ 8 weeks): 37% (n=30)

Durability of Treatment-Emergent NS5A RAVs

- Study assessing NS5A RASs in pts failing LDV-containing regimens (non-SOF)

Wyles D, Dvory-Sobol H. et al. #O059 EASL 2015
### Broad Cross-Resistance With “Early Generation” NS5A Inhibitors

<table>
<thead>
<tr>
<th>Fold Change</th>
<th>Genotype 1a</th>
<th>Genotype 1b</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M28T</td>
<td>Q30R</td>
</tr>
<tr>
<td>Ledipasvir</td>
<td>20x</td>
<td>&gt; 100x</td>
</tr>
<tr>
<td>Ombitasvir</td>
<td>&gt; 1000x</td>
<td>&gt; 100x</td>
</tr>
<tr>
<td>Daclatasvir</td>
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</tr>
<tr>
<td>Velpatasvir</td>
<td>&lt; 10x</td>
<td>&lt; 3x</td>
</tr>
<tr>
<td>Pibrentasvir</td>
<td>&lt; 3x</td>
<td>&lt; 3x</td>
</tr>
<tr>
<td>Ruzasvir</td>
<td>&lt; 10x</td>
<td>&lt; 10x</td>
</tr>
</tbody>
</table>

### When do the guidelines recommend RAS testing?

<table>
<thead>
<tr>
<th>Definitely</th>
<th>Probably</th>
<th>Maybe</th>
</tr>
</thead>
<tbody>
<tr>
<td>All GT1a prior to EBR/GZR NS5A (EBR RASs) 8#, Q30, L31, and Y93 10% impacted not include M28V</td>
<td>Who: All GT1 DAA failure What: NS3 and NS5A</td>
<td>Who:</td>
</tr>
</tbody>
</table>
*GT1a treatment experienced*  
*GT3 non-cirrhotic (SOF + DCV)*  
*GT3 TE or cirrhosis (SOF/VEL)*  
What: NS5A (LDV RAVS or GT3 Y93H) |

| Action: 1. Select non-cross resistant therapy (if possible)  
2. Add RBV (regardless)  
3. Extend therapy | Action: 1. GT1a-consider RBV with LDV  
24wks + RBV with F4  
2. GT3- add RBV to SOF+DCV  
3. GT3 TE OR cirrhosis- add RBV to SOF/VEL (if Y93H) |  

hcvguidelines.org
Back to our patient:
HCV Genotypic Resistance Sequencing

Resistance possible: DCV, EBR, LDV, OBV, VEL

Based on his RAS testing how would you proceed?

1. Yikes, defer!
2. I don’t know why I even sent the test: SOF/VEL + RBV for 24 weeks
3. Resistance is everything: SOF + SMV + RBV for 24 weeks
4. Kitchen sink 1: SOF + EBR/GZR + RBV 12 weeks
5. Kitchen sink 2: SOF + OBV/r/PTV + DSV + RBV 24 weeks
Retreatment of DAA failures
NS5A RASs Are Associated With Retreatment Failure

8/12-wk SOF/LDV-based tx failures (n = 41)

Retreatment with SOF/LDV

SVR12 (%)

Combined No RASs RASs

29/41 11/11 18/30

Wks

0 12 24

SVR12

100 80 60

Q30R or M28T L31M Y93H/N

100 80 33

5/5 4/5 2/6

Lawitz E. #0005 EASL 2015.
Impact of Multiple Negative Predictors on Response

- Retrospective analysis of phase 2/3 studies of SOF + RBV ± PegIFN
- > 850 pts, genotypes 1, 2, and 3 HCV

What Roles Do RBV and Duration Play in Overcoming Resistance and Optimizing Retreatment?

- Male: 78%
- 1a: 78%
- HCV RNA: 6.4 (± 0.8)
- Black: 100%
- Non-CC: 100%
- Cirrhosis: 22%
- NS5A RAVs: 78%

HIV coinfected SOF/LDV failures at 12 wks

N = 9

SOF/LDV + RBV

weeks

SVR12 (%)

0 20 40 60 80 100

EOT
SVR12

100 89

Failure
55-yr-old male
GT1a
No cirrhosis
L31M

Cooper C. CID 2016.
What Roles Do RBV and Duration Play in Overcoming Resistance and Optimizing Retreatment?

26% cirrhosis
20% GT2
41% VEL 25mg
74% <12 weeks

Only 18% of GT1 with NS5A RASs

N=69

VEL/SOF 400/100 + RBV

SVR12 (%)

Total 91 33/34 13/14 13/17
G1 59/65 97 91 76
G2 13/14
G3 13/17

4 pts pending SVR12

Retreatment of DAA Failures with SOF + 3-D

- 22 DAA-treated pts
  - 20 GT1a, 2 GT1b HCV pts
    - 6/20 with cirrhosis
  - 14/20 GT1a pts failed OBT/PTV/RTV + DSV
  - No SOF/LDV failures
- BL RASs (n)
  - D168E/V (5)
  - Y93C/F/H (4); Q30E/H/R (12)
- SOF + OBT/PTV/RTV + DSV
  - RBV for all GT1a
  - **GT1a tx: 12 wks for noncirrhotics, 24 wks for cirrhotics**

Poordad F, et al. EASL. Abstract SAT-156.
Retreatment of SOF + EBR/GZR Failures

- 25 pts who failed short course SOF + GZP/EBR (4-8 wks)
  - 22 GT1a, 3 GT1b
    - 20 failed 4 wks
  - 5 (20%) cirrhosis
  - 80% with NS5A RASs
  - 52% NS3 RASs
  - 44% NS3/NS5A RASs
- Received SOF + EBR/GZR + RBV for 12 wks

100% SVR12 (9/9) in pts with dual RASs

Lawitz E, et al. AASLD 2015. Abstract LB
Consider waiting, *even if* cirrhotic

New therapies Q2 2017:
- **G/P**
- **SOF/VEL/VOX**

Genotypic resistance testing

GT1 DAA failures

- **NO**
  - 16/24 week failure?
  - **NO**
    - No NS5A RASs
      - **NS5A RASs**
        - **NS3** (R155, A156, D168) + NS5A RAVs
          - **SOF/VEL + RBV (24)**
            - (esp if no L31M, Y93H)
              - SOF quad/triple
          - **SOF/VEL + RBV (24)**
            - (esp if no L31M, Y93H)
              - SOF quad/triple
        - **SOF + SMV + RBV (24)**
          - (esp if no L31M, Y93H)
          - SOF quad/triple
      - **SOF + RBV (24)**
      - **SOF/VEL + RBV (24)**
        - G/P
      - **SOF/VEL + RBV (24)**
        - (esp if no L31M, Y93H)
        - **SOF quad/triple**
  - **YES**
    - OR
      - **SOF-based triple or quad regimens**
      - Wait for **G/P**
      - **SOF/VEL/VOX**

For 2 drug regimens:
1. Increase duration
2. Add RBV
No Impact of Baseline NS5A or NS3 RAVs on SVR4 (Resistance Analysis Population)

**NS5A**
- **16 Weeks + RBV**: 100% 100%
- **24 Weeks**: 100% 100%

**NS3**
- **16 Weeks + RBV**: 100% 100%
- **24 Weeks**: 100% 100%

**PREVALENCE**
- **No RAVS**: 12/43 28%
- **RAVs**: 31/43 72%
- **No RAVS**: 10/38 26%
- **RAVs**: 28/38 74%

**SVR4**
- Patients without RAVs: 12 12 31 31
- Patients with RAVs: 3 3 35 35

**SVR4**=proportion of patients with HCV RNA <15 IU/mL at 4 weeks after end of treatment.

*RAVs detected by next-generation sequencing with 15% sensitivity; NS5A RAV: any change from wild-type at 4 positions (28, 30, 31, or 93); NS3 RAVs = any change from wild-type at 14 positions (36, 54, 55, 56, 80, 107, 122, 132, 155, 156, 158, 168, 170, or 175).

† Excludes 1 patient from the 16-week group who withdrew after receiving 3 doses of study medication; includes 38 of 49 patients who have reached follow-up week 4.

Wyles D et al. #193
Back to the case...

SOF + SMV + RBV was requested and approved.

• HCV RNA <15 IU/mL (detected) at week 4
• Undetectable at week 8
• Tolerated therapy well, no RBV dose reduction

• Pt late on refills
  • By week 24 still had ~3 weeks of meds left per pt
  • Stopped all therapy at week 28

• Achieved SVR 4 and 12
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