Retreatment in the face of DAA resistance

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Case: TG

62 WM with HCV GT1b and cirrhosis (CPT A5); prior breakthrough on PEG/RBV+TVR. Treatment complicated by severe anemia and neutropenia:

- Week 8: Required transfusion, RBV dose reduction
- Week 12: PEG dose reduction, GCSF
- HCV RNA 127 IU/ml at week 4; viral BT at week 26

► Treatment discontinued
  - Follow-up HCV RNA 2.7 million

Retreated in a study (12 weeks of SOF/LDV).

► Week 4: HCV RNA <25 IU/mL (detected)
► All subsequent HCV RNA UD (week 6 and on)
► SVR4 f/u: HCV RNA +
Case: TG

Re-retreated in another study [SOF/LDV for 24wks]

► HCV RNA UD at week 4

► SVR4 f/u: AST/ALT 45/67....
  – HCV RNA: 253,000 IU/mL

What to do now?

► Updated labs:
  – PLT 61, Hgb 13.8 g/dL
  – AST/ALT: 59/59, TB 0.7, DB 0.3, ALB 4.1, INR 1.1
  – Cr 1.29 (prior 1.08)
  – HCV RNA 1.2 million

► U/S: Nodular liver, no lesions. 12mm PV, 15cm spleen. No ascites. Non-occlusive R PVT.

► EGD: grade 1 esophageal varices
Considerations for Pts Who Failed a DAA-Based Regimen

1. Was initial therapy suboptimal (outside guidelines)?
   - 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 clinical questions prior to deciding on re-treatment?

1. Should additional testing be done?
   – What is the role of resistance testing in retreatment?

2. Can the patient take RBV?

3. Should you wait and retreat once better medications are available?
   – What is the chance liver disease will progress?

[What can I get approved for patient?]
Compare/Contrast: Initial vs. retreatment with DAAs

**Initial Treatment**
- Robust data
- Established treatment guidelines
- Population
  - Diverse
  - Limited negative predictors in a given patient
- Resistance
  - Limited in scope
  - Limited significance
  - Clear management approach

**Retreatment**
- Limited data
- Limited guidance (see above)
  - Improving with next generation regimens
- Population
  - Enriched for negative predictors
  - Multiple in same patient
- Resistance
  - Widespread
  - Significant (for now?)
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

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 as (if not more) important than RASs
5. Future regimens appear to obviate the need for most resistance testing
## 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>
<tbody>
<tr>
<td>NS3 Protease Inhibitors</td>
<td>+++ to ++++</td>
<td>1, 4 (± 2, 3, 6)</td>
<td>Low to High</td>
<td>Simeprevir (2013)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Paritaprevir (2014)</td>
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<td></td>
<td></td>
<td>Grazoprevir (2016)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Voxilaprevir (2017)*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Glecaprevir (2017)*</td>
</tr>
<tr>
<td>NS5B Nucleotide</td>
<td>++++</td>
<td>1-6</td>
<td>Very High</td>
<td>Sofosbuvir (2013)</td>
</tr>
<tr>
<td>NS5B Nonnucleoside</td>
<td>++</td>
<td>1</td>
<td>Low</td>
<td>Dasabuvir (2014)</td>
</tr>
<tr>
<td>NS5A Inhibitors</td>
<td>++++</td>
<td>1, 4, 6 (± 2, 3)</td>
<td>Low To High</td>
<td>Ledipasvir (2014)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Daclatasvir (2015)</td>
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<td></td>
<td>Ombitasvir (2014)</td>
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<td></td>
<td></td>
<td></td>
<td>Elbasvir (2016)</td>
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<tr>
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<td></td>
<td></td>
<td></td>
<td>Velpatasvir (2016)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pibrentasvir (2017)*</td>
</tr>
</tbody>
</table>

*anticipated US FDA approvals
Baseline versus selected RASs

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

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

<table>
<thead>
<tr>
<th>GT1a RASs</th>
<th>BL 1% cut-off</th>
<th>BL 15% cut-off</th>
<th>VF 1% cut-off</th>
<th>VF 15% cut-off</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>23</td>
<td>29</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>1</td>
<td>10</td>
<td>9</td>
<td>14</td>
<td>15</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>3</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>≥3</td>
<td>3</td>
<td>1</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

## Broad Cross-Resistance With “Early Generation” NS5As

<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>
<td>&gt; 100x</td>
<td>&gt; 1000x</td>
</tr>
<tr>
<td>Elbasvir</td>
<td>20x</td>
<td>&gt; 100x</td>
</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>

Durability of Treatment-Emergent NS5A RAVs

LDV + NNI + PI

<table>
<thead>
<tr>
<th>Patients With NS5A RAVs (%)</th>
<th>VF</th>
<th>Baseline</th>
<th>FU-12</th>
<th>FU-24</th>
<th>FU-48</th>
<th>FU-96</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parent Study</td>
<td>62/63</td>
<td>58/58</td>
<td>42/43</td>
<td>45/55</td>
<td>52/55</td>
<td>50/58</td>
</tr>
<tr>
<td>Registry Study</td>
<td>98</td>
<td>100</td>
<td>98</td>
<td>100</td>
<td>95</td>
<td>86</td>
</tr>
</tbody>
</table>

EBR/GZR

NS5A RASs

NS3 RASs

Examples: NS5A Resistance Genotyping

<table>
<thead>
<tr>
<th>Drug</th>
<th>HCV GenoSure®</th>
<th>Assessment</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generic Name</td>
<td>Brand/Regimen</td>
<td>Region</td>
<td>Drug Resistance Associated Variants* Detected</td>
</tr>
<tr>
<td>Daclatasvir</td>
<td>NS5A</td>
<td>M28V</td>
<td>DCV</td>
</tr>
<tr>
<td>Elbasvir</td>
<td>NS5A</td>
<td>M28V</td>
<td>EBR</td>
</tr>
<tr>
<td>Ledipasvir</td>
<td>NS5A</td>
<td>M28V</td>
<td>LDV</td>
</tr>
<tr>
<td>Ombitasvir</td>
<td>NS5A</td>
<td>M28V</td>
<td>OBV</td>
</tr>
</tbody>
</table>

**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, and/or (c) may confer reductions in susceptibility based on in vitro data. Refer to prescribing information for specific details regarding the impact of these variants on treatment response in defined patient populations and when administered in combination with other antiviral agents.

- **None/Udetermined** - None; no RAVs detected. Undetermined variants detected that have a subtle or uncertain impact on DAA-treatment responses.

**Notes:**

- All mutations are reported relative to the HCV genotype subtype-specific reference H77.
- Assessment of drug susceptibility is based on detected 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, is suboptimal. The impact of these polymorphisms may vary in treatment-naïve and treatment-experienced patients and with varying disease states (e.g., non-critically vs critical).
- 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.

**Region**

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Summary of All Variants Observed</th>
</tr>
</thead>
</table>

Comments: NS5A RAVs at position(s) 28, 30, 31 or 63 DETECTED. If considering an NS5A inhibitor-containing regimen, please refer to the prescribing information, or current guidelines, to determine the appropriate treatment regimen and duration.
### When do the guidelines recommend RAS testing?

<table>
<thead>
<tr>
<th>Definitely</th>
<th>Probably</th>
<th>Maybe</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Who:</strong> All GT1a prior to EBR/GZR</td>
<td><strong>Who:</strong> All GT1 DAA failure</td>
<td><strong>Who:</strong> All GT1a treatment experienced</td>
</tr>
<tr>
<td><strong>What:</strong> NS5A (EBR RASs)</td>
<td><strong>What:</strong> NS3 and NS5A</td>
<td><strong>GT1a treatment experienced</strong></td>
</tr>
<tr>
<td>- M28#, Q30, L31, and Y93</td>
<td></td>
<td><strong>GT3 non-cirrhotic (SOF + DCV)</strong></td>
</tr>
<tr>
<td>- 5-10% impacted</td>
<td></td>
<td><strong>GT3 TE or cirrhosis (SOF/VEL)</strong></td>
</tr>
<tr>
<td># does not include M28V</td>
<td></td>
<td><strong>What:</strong> NS5A (LDV RAVS or GT3 Y93H)</td>
</tr>
</tbody>
</table>

### Action:

1. Extend to 16 weeks **AND**
2. Add RBV **OR**
3. Consider other therapy

2. Add RBV (regardless)
3. Extend therapy

Action:

1. GT1a-consider RBV with LDV/SOF
   - 24wks + RBV with F4
2. GT3- add RBV to SOF+DCV
3. GT3 TE OR cirrhosis- add RBV to SOF/VEL (if Y93H)
Back to our patient:
HCV Genotypic Resistance Sequencing

<table>
<thead>
<tr>
<th>Drug</th>
<th>HCV GenoSure® NS3/4A</th>
<th>Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generic Name</td>
<td>Brand Name</td>
<td>Region</td>
</tr>
<tr>
<td>Boceprevir</td>
<td>NS3</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>NS4A</td>
<td>None</td>
</tr>
<tr>
<td>Simeprevir</td>
<td>NS3</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>NS4A</td>
<td>None</td>
</tr>
<tr>
<td>Telaprevir</td>
<td>NS3</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>NS4A</td>
<td>None</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Region</th>
<th>Genotype</th>
<th>Summary of All Mutations Observed</th>
</tr>
</thead>
</table>

Resistance possible: DCV, EBR, LDV, OBV, VEL
Retreatment Clinical Trial Data
NS5A RASs Are Associated With Retreatment Failure

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

Retreatment with SOF/LDV

SVR12 (%)

Combined: 29/41
No RASs: 11/11
RASs: 18/30

Q30R or M28T: 5/5
L31M: 4/5
Y93H/N: 2/6

Lawitz E. #0005 EASL 2015.
What Roles Do RBV and Duration Play in Overcoming Resistance and Optimizing Retreatment? RESCUE/A5348

SOF failures without NS5A exposure

- Non-cirrhotic
  - SOF/LDV + RBV: N=16
  - SOF/LDV: N=17
- Cirrhosis
  - SOF/LDV + RBV: N=25
  - SOF/LDV: N=24

37% (30/82) failed SOF+SMV

6/10 VFs SOF/SMV failures; 7/10 cirrhotic

No impact of baseline NS5A or NS5B RASs

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

HIV coinfected SOF/LDV failures at 12 wks

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

N = 9

SOF/LDV + RBV

0 12 24
weeks

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

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

Genotypic resistance testing

Consider waiting, even if cirrhotic

No NS5A RASs
- LDV/SOF + RBV (24)
- SOF/VEL + RBV (24)

NS5A RASs
- SOF + SMV + RBV (24)
- SOF/VEL + RBV (24) (esp if no L31M, Y93H)
- SOF quad/triple

NS3 (R155, A156, D168) + NS5A RAVs
- SOF/VEL + RBV (24) (esp if no L31M, Y93H)
- SOF quad/triple

GT1 DAA failures

16/24 week failure?
- NO
- YES

SOF-based triple or quad regimens

Or
Wait for G/P SOF/VEL/VOX

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

For 2 drug regimens:
1. Increase duration
2. Add RBV
How long can your patient afford to wait?

Baseline platelet count associated with incidence of decompensation:

<100: 7.9% vs. >200: 1.3%

Dienstag JL. Hepatology 2011.
What happened to TG?

► He was Re-re-retreated in yet another clinical trial

► SOF/VEL/VOX for 12 weeks
  – I was nervous
  – After placebo for 12 weeks
  – That made me more nervous

► HCV RNA undetectable at week 4 and SVR4

► SVR12!
Triple DAA therapy for re-treatment: SOF/VEL/VOX

**POLARIS-1 (n=263)**
- NS5A experienced
- 46% cirrhosis
- SVR12: 96% GT1a; 100% GT1b; 95% GT3

**POLARIS-4 (n=182)**
- NO NS5A exposure
- 46% cirrhosis
- 97% SVR vs 90% SOF/VEL

Glecaprevir/Pibrentasvir in DAA-experienced patients

- GT1 and 4
- DAA experienced
  - PI: 30%
  - NS5A: 37%
  - PI+NS5A: 29%
- 30% cirrhosis

Grazoprevir/Ruzasvir/Uprifosbuvir for DAA failures (NS5A exposed)

PREVALENCE

16 Weeks + RBV

NS5A

RASs
31/43
72%

No RASs
12/43
28%

24 Weeks

RASs
35/38
92%

No RASs
3/38
8%

16 Weeks + RBV

RASs
24/43
56%

No RASs
19/43
44%

24 Weeks

RASs
28/38
74%

No RASs
10/38
26%

SVR12

16 Weeks + RBV

12
31
31

24 Weeks

3
3
35

16 Weeks + RBV

19
24
24

24 Weeks

10
28
28

100% SVR (38/38) with Y93 RASs


RAS detection: NGS with 15% threshold
Take home points:

► Retreatment is challenging and resistance is only one component

► Resistance (NS5A) is prevalent after failure
   – Resistance testing plays a role in re-treatment evaluations (for now)

► HCV treatment regimens continue to evolve at a rapid pace

► Most patients with DAA failure and resistance are probably better served by waiting for new regimens
Acknowledgements

► UCSD AVRC
  – Kathy Nuffer
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QUESTIONS?