More Cases
Is Resistance Futile?

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Disclosure Statement for Arthur Kim

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I will discuss the following off-label use in this presentation:
Treatment of acute HCV infection

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National Institute of Drug Abuse), Patient-Centered Outcomes
Research Institute

Learning objectives

• After attending this presentation, learners will be able to:
  • List treatment options for treatment experienced patients
  • Describe the relevance of resistance associated substitutions
Considerations for treatment failures after DAAs

• Was initial therapy appropriate?
• Was staging accurate? Is it needed again?
• Was adherence adequate?
• Were drug interactions present?
• What medication classes were used?

Case

• 69 y/o African-American gentleman with HIV / HCV co-infection
• HIV suppressed, CD4 568 cells/mm³, TDF/FTC/rilpivirine
• Plt=135K, Cirrhosis by ultrasound, no decompensation, no varices, albumin 3.6
• BMI 33, Cr 1.1, IL-28B T-T, No prior treatment
• 12 weeks of ledipasvir/sofosbuvir, week 4 HCV RNA is target detected but not quantifiable
• Reports good adherence, takes pills with HIV medication upon awakening, missed 2 doses (took 84 pills over 86 days). HIV RNA remains suppressed on treatment
• HCV RNA positive at week 4 post-treatment
• He was eating more tomatoes during the last two months of treatment that caused heartburn, was taking TUMS at night

What type of HCV resistance testing would you perform at this time?

1. NS3
2. NS5A
3. NS5B
4. Both NS3 and NS5A testing
5. None
Case part 2

- NS5A resistance testing:
  - Mutation: Q30R

- NS3/4A resistance (2 years earlier):
  - Mutation: I37V

<table>
<thead>
<tr>
<th>Agent</th>
<th>Result</th>
<th>Agent</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daclatasvir</td>
<td>Resistance Probable</td>
<td>Boceprevir</td>
<td>Sensitive</td>
</tr>
<tr>
<td>Ledipasvir</td>
<td>Resistance Probable</td>
<td>Sofosbuvir</td>
<td>Sensitive</td>
</tr>
<tr>
<td>Ombitasvir</td>
<td>Resistance Probable</td>
<td>Telaprevir</td>
<td>Sensitive</td>
</tr>
<tr>
<td>Elbasvir</td>
<td>Resistance Probable</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Was resistance testing helpful?

- THAT WAS HELPFUL.
- FALSE. THAT DID NOT HELP ME IN ANY WAY.

Key principles of HCV resistance-associated substitutions (RASs)

- Viruses with RASs may exhibit variable "fitness" compared to wildtype
- RAS are present at baseline in the absence of drug exposure, but may or may not be detected
- RASs may impact treatment responses in select situations
- Resistance is NOT futile
- For newly approved regimens detection of RASs is most often NOT necessary
Cirrhosis does not impact SVR rates for 12 weeks of EBR/GZR.

![Graph showing SVR rates for 12 weeks of EBR/GZR with and without cirrhosis.](image)

SVR rates are similar between cirrhotic and non-cirrhotic patients in these trials.

EBR/GZR - RASs at NSSA positions 28, 30, 31, 93 associated with lower SVR for genotype 1a.

<table>
<thead>
<tr>
<th>RAS Position</th>
<th>28</th>
<th>30</th>
<th>31</th>
<th>93</th>
</tr>
</thead>
<tbody>
<tr>
<td>SVR12 Subjects with RAS (%)</td>
<td>28%</td>
<td>30%</td>
<td>31%</td>
<td>93%</td>
</tr>
</tbody>
</table>

Baseline testing for NSSA resistance recommended if using this regimen for GT1a.

Addition of RBV and extension of therapy to 16 weeks recommended with certain RASs.
Resistance Testing Assays

- Traditional approach is population sequencing, newer assays use "ultra-deep sequencing (next-generation sequencing, or NGS)
- Available:
  - HCV NS5A drug resistance assay (LabCorp / Monogram Biosciences)
  - NGS - 10% threshold for reporting
  - HCV NS3 and NS5 HCV RNA genotype + resistance (Quest)
  - RT-PCR with DNA sequencing
  - For GT1 and GT3
  - GT1 assays are subtype specific

Adapted from David Wyles

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>NS5A Inhibitors</th>
<th>NS5B Nucleos(t)ide Polymerase Inhibitors</th>
<th>NS5B Nonnucleoside Polymerase Inhibitors</th>
<th>Reassess Initiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs in Class</td>
<td>Simeprevir</td>
<td>Paritaprevir</td>
<td>Grazoprevir</td>
<td>Voxilaprevir</td>
</tr>
<tr>
<td>Barriers to resistance</td>
<td>Variable (1a lower barrier than 1b)</td>
<td>Extremely High (1a=1b)</td>
<td>Very low (1a lower barrier than 1b)</td>
<td>Variable (1a lower barrier than 1b)</td>
</tr>
<tr>
<td>Comments</td>
<td>2nd and 3rd generation</td>
<td>Single target Active site</td>
<td>Allosteric Many targets</td>
<td>Multiple antiviral Mechanism of Action</td>
</tr>
</tbody>
</table>

Differences in the barrier to resistance by drug class

- RAVs to one drug are generally cross resistant to other drugs within a class (but not always)
- Viral fitness of RAVs effects their persistence after discontinuation of therapy

What do we mean by barrier to resistance? Mutations may produce strains of varying fitness to replicate

A "fit" mutant strain

An "unfit" mutant strain

Viruses with RASs may exhibit variable "fitness" compared to wildtype

• Sofosbuvir RASs are rare at baseline:

  S282T rarely detected
  Disappears quickly

Viruses with RASs may exhibit variable "fitness" compared to wildtype

- NS5A RASs in patients who failed LDV treatment without SOF
- Positions 24, 28, 30, 31, 32, 58, 93 that confer >2.5-fold reduced susceptibility to LDV in vitro were included

Majority of RASs Still Detected After 96 Weeks (>1% of Population)

Almost All Patients Who Failed Had Detectable NS5A RASs at Treatment Failure

Patients with NS5A RASs
Patients without NS5A RASs

16% (12/76)
84% (64/76)

1% (72/73)
99% (72/73)


Treatment-associated RASs

Adapted from David Wyles et al.

Duration of exposure also matters

<6 weeks <=8 weeks

<6 weeks
<8 weeks

ERB 0% SOF

37%
Baseline RAS vs. selected RAS:

**Baseline RAS more likely to be:**
- Single variants
- Variable prevalence within populations
- Present regardless of other characteristics

**Selected RAS more likely to be:**
- Multiple variants
- High prevalence within populations
- More difficult to treat characteristics

### Additional factors matter!

- **Ideally:**
  - IL28B CC
  - Female sex
  - Lower BMI
  - Low fibrosis
  - Low HCV RNA
  - No RAS

- **Our case:**
  - IL28B TT
  - Male sex
  - Higher BMI
  - Cirrhosis
  - HCV RNA
  - No RAS
Develops 2.4 cm mass visualized on ultrasound c/w HCC, elevated AFB
Undergoes radiofrequency ablation
After cure of HCC, what would you treat with?
1. Defer treatment, first refer for liver transplant
2. SOF/VEL/RBV x 24 weeks
3. SOF/OD/RBV x 12 weeks
4. Glecaprevir / pibrentasvir x 16 weeks
5. SOF/VEL/VOX x 12 weeks
6. SOF/VEL/VOX/RBV x 12 weeks

**Broad Cross-resistance With “Early Generation” NSSAs**

<table>
<thead>
<tr>
<th>First-Phase</th>
<th>1a</th>
<th>1b</th>
<th>1c</th>
<th>2a</th>
<th>2b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ledipasvir</td>
<td>2%</td>
<td>10%</td>
<td>2%</td>
<td>10%</td>
<td>1%</td>
</tr>
<tr>
<td>Omibasvir</td>
<td>10%</td>
<td>10%</td>
<td>10%</td>
<td>10%</td>
<td>10%</td>
</tr>
<tr>
<td>Daclatasvir</td>
<td>10%</td>
<td>10%</td>
<td>10%</td>
<td>10%</td>
<td>10%</td>
</tr>
<tr>
<td>Elbasvir</td>
<td>2%</td>
<td>10%</td>
<td>2%</td>
<td>10%</td>
<td>1%</td>
</tr>
<tr>
<td>Velpatasvir</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>ACH-3102</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Pibrentasvir</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

**Glecaprevir / pibrentasvir for re-treatment of NSSA failures - MAGELLAN 1**

- 12 versus 16 weeks, GT1, 4-6
- 34%/26% cirrhosis per group
- Baseline RAS
  - NS5A only: 55%/52%
  - NS3+NS5A: 11%/9%
- Overall SVR 89% vs 91%
- 12wks higher relapse w/ NS5A RAS
- Dual NS3/NS5A - 55% relapse

**SVR12 by DAA Class in Prior Therapy**

- 100 RVR
- 89 RVR
- 79 RVR
- 81 RVR
Glecaprevir / pibrentasvir for re-treatment of NS5A failures - MAGELLAN 1

SVR12 by Key NS3 and NS5A Baseline Substitutions

Poordad et al. EASL 2017

Glecaprevir / pibrentasvir for re-treatment of NS5A failures - MAGELLAN 1

Adverse Events (AE) and Laboratory Abnormalities

Poordad et al. EASL 2017

SOF/VEL/VOX for re-treatment of NS5A failures

Bourliere et al. NEJM 2017

• POLARIS 1
  - GT 3 & 4 (30% GT3)
  - 12 weeks of therapy
  - vs placebo
  - including compensated cirrhosis (48%)
  - 2.2% relapse
  - 4 GT 3 relapse = all 3a and ¾ had BL NS5A RAS
  - 8.1% treatment emergent RAS
  - all VF had cirrhosis (6 R, 1 V)

Bourliere et al. NEJM 2017
Resistance testing is generally not recommended for these regimens.
When should one test for RASs?

<table>
<thead>
<tr>
<th>HCV Regimen</th>
<th>HCV Genotype 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TN</td>
</tr>
<tr>
<td>Elbasvir/grastraprevir®</td>
<td>NA</td>
</tr>
<tr>
<td>Ledipasvir/sofosbuvir®</td>
<td>NA</td>
</tr>
<tr>
<td>Pirtaprevir/tonavir/ombitasvir® plus dosabavir</td>
<td>NA</td>
</tr>
</tbody>
</table>


When should one NOT test for RASs?

<table>
<thead>
<tr>
<th>NOT RECOMMENDED</th>
</tr>
</thead>
<tbody>
<tr>
<td>TN</td>
</tr>
<tr>
<td>TE*</td>
</tr>
</tbody>
</table>

### Prevention and surveillance for hepatocellular carcinoma

- **HCV: F3/F4**
  - Older age, black race, lower platelet count
  - Increased with dual infection HBV, possibly HIV and other liver diseases (e.g., alcohol, fatty liver)
  - SVR reduces risk substantially
  - Coffee consumption protective
- Imaging every 6 months
  - Preferred modalities vary - but 6 months superior to 12 months
- **Alpha-fetoprotein**
  - Has poor specificity and poor sensitivity, perhaps most useful when

### Controversy regarding HCC after DAA therapy

"Unexpected high rate and pattern of tumor recurrence coinciding with HCV clearance" Reg J Hepatol 2016  
versus  
"We did not observe an increased risk of HCC recurrence after DAA treatment" Pol et al. J Hepatol 2016  
Difference between IFN-induced and DAA-induced SVR?  
Some speculated an effect of DAA's

### Controversy regarding HCC after DAA therapy

Meta-analysis of available studies

**Impact of Follow-up and Age on HCC Incidence**

Warrny R, EASL 2017
Controversy regarding HCC after DAA therapy

Meta-analysis of available studies

<table>
<thead>
<tr>
<th>HCC occurrence</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted RR</td>
<td>Adjusted RR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Average follow-up</td>
<td>0.99</td>
<td>0.77</td>
<td>0.85</td>
</tr>
<tr>
<td>Average age</td>
<td>1.11</td>
<td>1.06</td>
<td>0.99</td>
</tr>
<tr>
<td>Treatment</td>
<td>1.17</td>
<td>0.87</td>
<td>0.63</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HCC recurrence</th>
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<td>95% CI</td>
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<tr>
<td>Average follow-up</td>
<td>0.66</td>
<td>0.10</td>
<td>0.76</td>
</tr>
<tr>
<td>Average age</td>
<td>1.11</td>
<td>0.45</td>
<td>0.66</td>
</tr>
<tr>
<td>Treatment</td>
<td>1.16</td>
<td>0.65</td>
<td>0.61</td>
</tr>
</tbody>
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Key principles of HCV resistance-associated substitutions (RASs)

- Viruses with RASs may exhibit variable “fitness” compared to wildtype
  - Higher fitness last longer, lower fitness may be transient
- RAS are present at baseline in the absence of drug exposure, but may or may not be detected
  - Possibility of transmission
- RASs may impact treatment responses in select situations
  - Situation is often worse in presence of other treatment characteristics
- Resistance is NOT futile
  - May be overcome by longer durations, addition of ribavirin, or later-generation agents
- For newly approved regimens detection of RASs is most often NOT necessary

Take home points regarding case

- The most important factor in deciding upon re-treatment regimens is the prior DAA failure
- Resistance-associated substitutions are NOT futile
  - May impact select situations
  - Certain mutations may require longer treatment courses, ribavirin
  - Ribavirin-free regimens are newly available approved for many re-treatment considerations
- Continue surveillance for those with hepatocellular carcinoma
  - Referral to liver transplant center if possible
  - When controlling for age and length of follow-up, no apparent increase of HCC occurrence or recurrence in DAA era