Current Hepatitis C Treatment and Viral Resistance Concerns

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Disclosure

- Under guidelines established by the Accreditation Council for Pharmacy Education, disclosure must be made regarding financial relationships with commercial interests within the last 12 months.

- The authors of this presentation have no relevant financial relationships or affiliations with commercial interests to disclose.
Learning Objectives

At the completion of this activity, pharmacists will be able to:

- Define a treatment algorithm for Hepatitis C from readily available resources.
- Select a genetic variant associated with treatment resistance of Hepatitis C.
- Define a method for addressing treatment resistance in patients with Hepatitis C.

Pre-Assessment Question #1

What is the leading cause of newly diagnosed HCV infections tripling from 2011-2016?

A. Incarceration  
B. Opioid Crisis  
C. More Baby-boomers requesting screening  
D. Non-professional tattoo
Pre-Assessment Question #2

- A 60 y/o 80kg male HCV patient has laboratory screening done prior to therapy. The patient has genotype 1a and cannot remember the regimen that they were on but believe it might have been ribavirin. The physician elects to have NS5a resistance testing done. It shows probable Ledipasvir resistance. Upon further review, a Q30R mutation with >100 fold change is shown. What is the best treatment course for this patient per guidelines?

  A. Harvoni (Ledipasvir/Sofosbuvir) 1 tablet daily for 12 weeks
  B. Wait for a few months, then treat as this type of resistance will fade in that time.
  C. Harvoni (Ledipasvir/Sofosbuvir) 1 tablet daily + Ribavirin 600mg BID for 24 weeks
  D. Eclusa (Velpatasvir/Sofosbuvir) 1 tablet daily for 12 weeks

HCV Review

- Hepatitis C (HCV) is the most common blood-borne pathogen
  - 5 times more common than HIV
  - Total costs exceeding $10 billion dollars from 2010-2019 with over 190,000 related deaths
  - Estimated 2.4 million people are chronically infected in the US ~ 1% of US population
  - Over half of those infected do not know they have HCV
  - Risk factors include: IVDU (biggest risk factor), Other illicit drugs (due to contamination of paraphernalia), healthcare associated transmission (rare), tattoos, transfusions (rare), Birth to HCV positive mother, sexual activity with HCV-infected person (inefficient means)
HCV Overview

- Single-stranded RNA virus of the Flaviviridae family
- Does not have proofreading polymerase
- Enables frequent viral mutations
- Copious replication poses problems for host immune control

HCV Overview

- There are currently 6 genotypes of Hepatitis C
- In the US, genotypes 1-3 are most common
- Genotype 1a and 1b is by far the most common, followed by 2 and 3, respectively
- Genotypes 4-6 continue to pose a therapeutic challenge
- In most instances acute infection leads to chronic infection, since immune system for most instances is insufficient to clear virus
HCV Acute Infection

- Up to 85% of acute HCV infections will lead to chronic infections
- HCV RNA levels are detectable after 1-2 weeks of exposure
- Patients are largely asymptomatic at this time
- ALT can rise up to 10 times ULN during ensuing weeks
- After 7 weeks, 1/3 can experience symptoms include fatigue (most common), anorexia, weakness, jaundice, abdominal pain, or dark urine.

HCV Infection progress

Once exposed to HCV:
- 75-85% will go on to develop chronic infection
- 10-20% will go on to develop cirrhosis over a period of 20-30 years

Among patients with cirrhosis, there is:
- 1-2% annual risk of hepatocellular carcinoma
- 3-6% annual risk of hepatic decompensation, for which the risk of death in the following year is 15-20%
- Progression to cirrhosis occurs after 20+ years of infection
Who should be tested for HCV?

**CDC recommends HCV testing for:**
- Current or former injection drug users, including those who injected only once many years ago
  - A multi-state systematic review of global HCV infection prevalence among PWID published in 2017 provided a point estimate of 53.1% in the United States, with a range of 38.1% to 68.0%
- Everyone born from 1945 through 1965
- Recipients of clotting factor concentrates made before 1987, when less advanced methods for manufacturing those products were used

Who should be tested for HCV?

- Recipients of blood transfusions or solid organ transplants prior to July 1992, before better testing of blood donations became available
- Chronic hemodialysis patients
- People with known exposures to HCV, such as
  - health care workers after needle sticks involving HCV-positive blood
  - recipients of blood or organs from a donor who tested HCV-positive
- People with HIV infection
- Children born to HCV-positive mothers
Current HCV Concerns

- New HCV Infection diagnosis more than tripled from 2011-2016
- Per CDC Expanded testing, treatment, and prevention services are urgently needed, especially in light of the surge in new infections linked to the opioid crisis.
- Opioid crisis puts new generations at risk of hepatitis C infections
- Resistance-associated substitutions

HCV Treatment

- Screen Patients
  - HCV antibody
    - Confirm with PCR
  - Obtain Viral Load
  - Genotype
    - With Compensated Cirrhosis or without cirrhosis
    - Choose the most appropriate therapy for patient
  - Provide therapy for the patient
    - Evaluation for retreatment is recommended as effective alternative treatments become available if treatment failed to achieve Sustained Virologic Response
Viral Resistance

- Hepatitis C, much like HIV, is an RNA virus that replicates copiously (Billions of copies daily)
- Replication of the virus will result in an approximate error rate of 33%
- The result of these errors will either be no discernable change, non-functional (or dead viruses), or viral mutations lead to viral resistance
- Regarding mutated viruses, subtherapeutic antiviral therapy allows for selective pressure that promotes these variants to prosper
- The most common areas of mutation are to NS5A and NS3 sites
  - These are more prevalent in patient who have failed antiviral therapy
- NS5B Resistance associated substitutions (RASs) are rare due to the conserved catalytic site and account for <1% of RASs.

Viral Resistance

- NS5A RASs maintain high replication competence in the absence of continued drug pressure (for years) relative to NS3 and NS5B RASs (which to be overtaken by wild type virus within months).
- It is important to remember that the impact of RASs on treatment outcomes will vary due to a multitude of factors including:
  - Co-Administered Drugs
  - Patient Factors (cirrhosis)
  - Change in potency conferred by each RASs
- It is important to consider that testing alone will not dictate optimal therapy nor will the presence of a RASs eliminate a therapy option in all patients.
Viral Resistance

- Certain viral mutations can lead to treatment failure, but the impact varies by genotype.
- Genotype 1a and 3 have the most clinically significant Resistance associated substitutions (RAS)
  - NS5A inhibitors are the most clinically significant viral variants
  - NS3/4A Protease Inhibitors seem to be less significant
  - At least 15% of the total virus load should carry the RAS in order to effect efficacy
- RAS testing is recommended with Zepatier (Elbasvir/Grazoprevir), Harvoni (Ledipasvir/Sofosbuvir), Epclusa (Sofosbuvir/Velpatasvir), and Daclatasvir plus Sofosbuvir

Viral Resistance in Literature

- For Daclatasvir+Sofosbuvir, in the ALLY-3 study, in patients with genotype 3 and the Y93H mutation: 67% achieved SVR w/o cirrhosis vs 25% with cirrhosis. Note: All patients analyzed showed SVRs of 97% in those without cirrhosis vs 58% with cirrhosis.
- For Elbasvir/Grazoprevir, treatment-naive or prior relapse patients treated for 12 weeks w/o ribavirin with NSSA RASs showed an SVR of 58% versus 98% for those without. Treatment experienced patients with NSSA RASs showed an SVR of 29% versus 97%.
- For Harvoni, when RASs with >100-fold resistance were present SVR12 rates dropped to 64.7% with 12 weeks of therapy versus 100% with 24 weeks of therapy. One small cohort showed adding Ribavirin did not show as much efficacy as extending the interval to 24 weeks. In general, those with baseline RASs did not show SVR12 less than 90%
Viral Resistance

- For Vosevi, RASs have not shown an impact on SVR12 rates
- For Epclusa, the presence of Y93H in genotype 3 infected patients decreased the SVR12 rate to 84% compared to 97%
  - This was more impactful in those with cirrhosis and/or prior treatment
- For Mavyret, the presence of RAS had minimal impact on SVR rates in non-cirrhotic patients. There is not sufficient data to suggest that RAS effect SVR rates in these patients.
- For Paritaprevir/Ritonavir/Ombitasvir + Dasabuvir ± Ribavirin, risk of treatment failure has not been established, but use of Viekira Pak without Ribavirin in those with a history of DAA failure is not recommended.

Clinically Important RASs by Genotype and Regiment

<table>
<thead>
<tr>
<th>Drug</th>
<th>1a</th>
<th>1b</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harvoni (Ledipasvir/Sofosbuvir)</td>
<td>Q30H/R, L31M/V, Y93C/H/N</td>
<td>L31V, Y93H</td>
<td>N/A</td>
</tr>
<tr>
<td>Zepatier (Elbasvir/Grazoprevir)</td>
<td>M28A/T, Q30H/R, L31M/V, Y93C/H/N</td>
<td>Y93H</td>
<td>N/A</td>
</tr>
<tr>
<td>Epclusa (Sofosbuvir/VELpatasvir)</td>
<td>N/A</td>
<td>N/A</td>
<td>Y93H</td>
</tr>
<tr>
<td>Paritaprevir/Ritonavir/Ombitasvir +/- Ribavirin</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
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</tbody>
</table>
## NS5a RAS Testing
### Recommendations before Therapy

<table>
<thead>
<tr>
<th>Drug</th>
<th>1b TN or TE</th>
<th>1a TN</th>
<th>1a TE No Cirrhosis</th>
<th>1a TE Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harvoni (Ledipasvir/Sofosbuvir)</td>
<td>NO</td>
<td>NO</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Zepatier (Elbasvir/grazoprevir)</td>
<td>NO</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Epclusa (Sofosbuvir/velpatasvir)</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
</tr>
<tr>
<td>Paritaprevir/ritonavir/ombitasvir</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
</tr>
</tbody>
</table>

### Guideline Recommendations on the use of RAS testing

- **Zepatier (Elbasvir/Grazoprevir)**
  - NS5A RAS testing is recommended for genotype 1a-infected, treatment-naive or -experienced patients being considered for elbasvir/grazoprevir. If present, a different regimen should be considered.

- **Harvoni (Ledipasvir/Sofosbuvir)**
  - NS5A RAS testing can be considered for genotype 1a-infected, treatment-experienced patients without cirrhosis being considered for ledipasvir/sofosbuvir. If clinically important resistance is present, a different recommended therapy should be used. NS5A RAS testing can be considered for genotype 1a-infected, treatment-experienced patients with cirrhosis being considered for ledipasvir/sofosbuvir. If clinically important resistance is present, a different recommended therapy should be used.

- **Epclusa (Sofosbuvir/Velpatasvir)**
  - NS5A RAS testing is recommended for genotype 3-infected, treatment-naive patients with cirrhosis and treatment-experienced patients (with or without cirrhosis) being considered for 12 weeks of sofosbuvir/velpatasvir. If Y93H is present, weight-based ribavirin should be added or sofosbuvir/velpatasvir/voxilaprevir should be used.

- **Daclatasvir plus Sofosbuvir**
  - NS5A RAS testing is recommended for genotype 3-infected, treatment-experienced patients without cirrhosis being considered for 12 weeks of daclatasvir plus sofosbuvir. If Y93H is present, weight-based ribavirin should be added. NS5A RAS testing is recommended for genotype 3-infected, treatment-naive patients with cirrhosis being considered for 24 weeks of daclatasvir plus sofosbuvir. If Y93H is present, treatment should include weight-based ribavirin, or a different recommended therapy used.
Strategies to Manage RASs

- Characterize Patients at risk for treatment failure
  - Such as accurate assessment of liver fibrosis and clarification of prior therapy
- Virus
  - Determine adequate therapy based on genotype, subtype, and baseline RASs
- Treatment Duration
  - Shorter therapies associated with higher risk of failure whereas longer durations have lead to increased rates of SVR
- Ribavirin
  - Increases the rate of SVR in those with increased risk of failure, baseline RASs, and prior DAA treatment failure
- Multiple Combined Therapies

Clinically Important RASs by Genotype and Fold Change

<table>
<thead>
<tr>
<th>DAA</th>
<th>Genotype 1a</th>
<th>Genotype 1b</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M28T/Q30R/L31M/V/Y93H</td>
<td>L31V/I/Y93H</td>
</tr>
<tr>
<td>Ledipasvir</td>
<td>20x &gt;100x &gt;100x / &gt;100x / &gt;1000x / &gt;10,000x</td>
<td>&gt;100x / &gt;100x / &lt;10x / &gt;100x</td>
</tr>
<tr>
<td>Ombitasvir</td>
<td>&gt;1000x &gt;100x &lt;3x &gt;10,000x / &gt;10,000x</td>
<td>&lt;10x / 20x / 50x</td>
</tr>
<tr>
<td>Daclatasvir</td>
<td>&gt;100x &gt;1000x &gt;100x / &gt;1000x / &gt;10,000x</td>
<td>&lt;10x / 20x / 50x</td>
</tr>
<tr>
<td>Elbasvir</td>
<td>20x &gt;100x &gt;10x &gt;1000x / &gt;1000x</td>
<td>&lt;10x / &gt;100x / &lt;10x / &gt;100x</td>
</tr>
<tr>
<td>Velpatasvir</td>
<td>&lt;10x &lt;3x &gt;20x / 50x &gt;1000x / &gt;1000x</td>
<td>&lt;3x / &lt;3x / &lt;3x / &lt;3x / &lt;3x</td>
</tr>
</tbody>
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Color Key: light green = <3-fold change; dark green = <10-fold change; orange = >10- to 100-fold change; pink = >100-fold change
Post-Assessment Questions #1

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