Case 1: Chronic Hepatitis C

Moderator
Dawn Pease, MSN, RN, ANP-BC
Seton Healthcare Family
University Medical Center Brackenridge
Brackenridge Specialty Clinics - Gastroenterology and Endocrinology
Austin, Texas
More Common Than You Think: HCV is Nearly 4x as Prevalent as HIV and HBV

- Based on a 2015 literature search that takes into account populations excluded from NHANES, the number of US residents who have been infected with HCV is ~4.6 million (range 3.4 million-6.0 million)

Chronic Hepatitis C: A Silent Killer

• Many have no signs or symptoms
• Some have
  – Fatigue
  – Polyarthritis and polymyalgia
  – Fever
  – Nausea or anorexia
  – RUQ tenderness

http://www.cdc.gov/knowmorehepatitis/media/Posters.htm
Majority of Persons Chronically Infected With HCV Are Baby Boomers (Those Born Between 1945-1965)

Estimated Prevalence by Age Group

HCV Screening is Straightforward: Algorithm for Screening Asymptomatic Persons

Hepatitis C: Natural History

Exposure (Acute Phase)

- 15% Resolved
- 85% Chronic

Chronic

- 80% Stable
- 20% Cirrhosis

Cirrhosis

- 90% Slowly Progressive
- 6% Decompensation

Decompensation

- 4% HCC

HCC

- 90% Transplant/Death

~20 year progression rate (accelerated with HIV, HBV, alcohol)
What Leads to Faster Progression?

**Host**
- Modifiable
  - Alcohol consumption
  - Nonalcoholic fatty liver disease
  - Obesity
  - Insulin resistance
- Non-modifiable
  - Fibrosis stage
  - Inflammation grade
  - Older age at time of infection
  - Male sex
  - Organ transplant

**Viral**
- Genotype 3
- Coinfection with HBV or HIV

Basic Guidance for Patients with Active HCV

• Abstinence from alcohol
• Evaluation for other conditions that may lead to fibrosis (e.g. HIV, HBV, NASH)
• Evaluation for advanced fibrosis
  – APRI, Fib4, imaging
• Vaccination against HAV, HBV and pneumococcal infection (in patients with cirrhosis)
• Education on avoidance of transmission

Now our case...
Case 1: Patient C.B.

- 64 yo African American female with obesity, poorly controlled DM, HTN, hyperlipidemia presents with hepatitis C for evaluation

- Social History
  - No alcohol or drug or tobacco use
  - Unemployed

- Current medications
  - metformin and atorvastatin

- Examination
  - central obesity with BMI 33
Case 1: Patient C.B.

- Hx blood transfusion 1977 (postpartum hemorrhage)
- Diagnosed with chronic hepatitis C in 2012 after mildly elevated LFTs on routine screening
  - Liver biopsy: Grade 2 inflammation, Stage 2 fibrosis, moderate fatty infiltration with some features of NASH
  - Genotype 1a
- Rebekah will update us on treatment options for HCV
Chronic Hepatitis C: Current Treatment Options

Rebekah Hamner, MSN, RN, AGCNS-BC
Texas Liver Institute
Austin, Texas
HCV is Curable in Most Patients

- **SVR=Cure**
  - SVR is when there is no detectable Hepatitis C RNA in the person’s bloodstream 3 months after completing antiviral treatment.

- Unlike HIV and hepatitis B infection, HCV does not archive its genome

- There is no vaccine for HCV

- Cured patients will ALWAYS remain HCV antibody positive (Ab+) but that does not mean the infection is back.

- However, SVR ≠ immunity. Reinfection is possible if high risk factors are reintroduced.

General Concepts About Selecting HCV Regimens

• Choice of regimen, treatment duration, and use of ribavirin depends on:
  – Presence of cirrhosis
  – Prior treatment experience
    • PEG-RBV failure
    • Prior protease inhibitor failure
    • Prior sofosbuvir failure
  – Genotype
    • Genotype 1a vs 1b
    • Genotypes 2-6
Approved Treatment Options Most Often Used for Genotype 1 Infection (Most Common Genotype in US) (alphabetical)

- Daclatasvir (DCV) + Sofosbuvir (SOF) (Daklinza + Sovaldi)
- Grazoprevir (GRZ)/Elbasvir (EBR) (Zepatier)
- Ledipasvir (LDV)/Sofosbuvir (SOF) (Harvoni)
- Paritaprevir/Ritonavir/Ombitasvir (PTV/RTV/OMV) + Dasabuvir (DSV) (Viekira Pak)

- Ribavirin (RBV) required for some regimens in certain populations.
Cure (SVR12) in GT 1 Patients Treated with Daklinza + Sovaldi for 12 or 24 Weeks (FDA Approved for 12 Weeks)

Cure (SVR12) in GT 1 Patients Treated with Zepatier for 12 Weeks

Cure (SVR12) in GT 1 Patients Treated with Harvoni for 12 or 24 Weeks (FDA Approved for 12 Weeks Without RBV; 8 Weeks for Some Patients)

<table>
<thead>
<tr>
<th></th>
<th>12 Weeks</th>
<th>24 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Cirrhotic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDV/SOF</td>
<td>99/180</td>
<td>99/181</td>
</tr>
<tr>
<td>LDV/SOF + RBV</td>
<td>97/184</td>
<td>98/184</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Cirrhotic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDV/SOF</td>
<td>94/32</td>
<td>94/31</td>
</tr>
<tr>
<td>LDV/SOF + RBV</td>
<td>100/34</td>
<td>100/36</td>
</tr>
</tbody>
</table>

Cure (SVR12) in GT 1a Patients Treated with Viekira Pak for 12 Weeks

<table>
<thead>
<tr>
<th>Prior PegIFN/RBV Response</th>
<th>All Patients</th>
<th>Treatment Naïve</th>
<th>Relapse</th>
<th>Null</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Ribavirin</td>
<td>90/202</td>
<td>90/202</td>
<td>94/47</td>
<td>100/83</td>
</tr>
<tr>
<td>Ribavirin</td>
<td>90/202</td>
<td>96/202</td>
<td>100/47</td>
<td>95/87</td>
</tr>
</tbody>
</table>

p=0.004

Soon To Be Approved: Sofosbuvir/Velpatasvir (SOF/VEL) x 12 Weeks (Pangenotypic)

Side Effects

- All regimens very well-tolerated, side effects minimal
- Nothing like past treatments that included interferon
Drug Interactions

• Can still be a concern
• Valuable resource: www.hep-druginteractions.org
Special Populations

- HIV/HCV Coinfection
- ESRD
- Decompensated cirrhosis
- Post liver transplant

- These patients do have options and need to be referred to a provider that can treat them.
- [www.hcvguidelines.org](http://www.hcvguidelines.org) is living document and regularly updated
## More Pangengotypic Regimens in Development

<table>
<thead>
<tr>
<th>Combination Treatment</th>
<th>Phase</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABT-493 (NS3/4A protease inhibitor) + ABT-530 (NS5A inhibitor)</td>
<td>3</td>
<td>AbbVie</td>
</tr>
<tr>
<td>Sofosbuvir (nucleotide polymerase inhibitor) + GS-5816 (NS5A inhibitor) + GS-9857 (NS3/4A protease inhibitor)</td>
<td>3</td>
<td>Gilead</td>
</tr>
<tr>
<td>Grazoprevir (NS3/4A protease inhibitor), MK-3682 (NS5B polymerase inhibitor) and elbasvir (NS5A replication complex inhibitor)</td>
<td>2</td>
<td>Merck</td>
</tr>
<tr>
<td>Grazoprevir (NS3/4A protease inhibitor), MK-3682 (NS5B polymerase inhibitor) and MK-8408 (NS5A replication complex inhibitor)</td>
<td>2</td>
<td>Merck</td>
</tr>
</tbody>
</table>
Guidance

• Many options with high cure rates available for C.B.
• Consider concomitant medications and whether modifications must be made
• Review both www.guidelines.org and product labels when making choices
Back to Dawn
Case 1: Patient C.B.

• She was treated with SOF/LDV x 12 weeks
• Negative at EOT but relapsed at Week 4
• Admitted she missed several doses through course of therapy.
• She is now referred to another clinic to consider retreatment.
• A set of labs is done which shows she is resistant to ledipasvir and daclatasvir.
• Rossalynn will tell us a little bit about resistance and C.B.’s options...
Resistance: When and In Whom to Test

Rossalynn M. Salcido, PA-C
Texas Liver Institute
San Antonio, Texas
What is Resistance?

- These proteins are targeted by HCV medications
- Genetic variation can lead to structural changes in these proteins
- Hence, the drug may no longer bind to the protein efficiently
Ideal Situation: Enzyme Inhibition

Lock-and-Key Model

Wild Type Enzyme

HCV Drug
How Drug Resistance Arises:
Amino Acid Change (Mutation) at a Position That Decreases the Binding of a DAA

Lock-and-Key Model

Drug Resistant Enzyme

HCV Drug
Barriers to Resistance and Are Mutated Viruses Tough or Wimpy?

• Genetic barrier
  – Describes the potency of the drug being used and how unlikely it is to fail due to resistant strains. High genetic barrier means “tough” drug

• Viral fitness
  – Not all resistant strains are “healthy”
  – Some resistance mutations can compromise viral enzyme function, and that virus is easy to eradicate
  – Other mutations make the virus quite tough and hard to eradicate

Resistant Variants May Be Present Before and Can Be Selected During Treatment

- HCV is a mixture of related but distinct populations of virions in each patient\(^1\)
- Most resistant variants are unfit and may be undetectable prior to therapy\(^2,3\)

\(\text{Antiviral therapy eliminates sensitive variants}
\)

\(\text{Resistant variants expand}
\)

Two Ways to Deal with Resistance

• Use medications that have no weakness against the resistance present

• Use multiple medications, to increase chance of “covering” all the resistance strains
FDA Approved Direct-Acting Antiviral Agents (DAAs) from Multiple Classes

No Cross Resistance Between Drug Classes
Principles of all Oral Regimens for HCV

• Combine drugs from different classes
  • Hit multiple viral targets to increase efficacy
  • Diminishes risk of viral resistance

• Benefits of multi-drug strategies
  • Backbone/anchor drug plus additional agent(s)
  • Superior efficacy than expected from individual drugs

• If done properly
  • Near universal efficacy
  • Short duration of therapy
  • Side effects have minimal impact on QOL
Commercial Resistance Testing

• Widely available (Quest and LabCorp).
• Detects or reports RAVs as low as 10-20% prevalence.
• At least 2000 copies/mL must be present.
• Detects mutations associated within NS3/4a, NS5A, and NS5B in GT 1 and GT 3.
How Can Resistance Impact Efficacy?
NS5A Resistant Variants are Problematic: 12 Weeks of Potent Combo (Grazoprevir/Elbasvir) Not Enough

100% Cure Rate with Grazoprevir/Elbasvir + Ribavirin in Patients With Resistant Variants (16-18 Week Treatment; GT1a)

![Bar chart showing SVR12 rates for patients without and with RAVs.](chart.png)

<table>
<thead>
<tr>
<th>Population Sequencing</th>
<th>Next Generation Sequencing</th>
</tr>
</thead>
<tbody>
<tr>
<td>EBR RAVs</td>
<td>51/51</td>
</tr>
<tr>
<td>NS5A Class RAVs</td>
<td>1/1</td>
</tr>
<tr>
<td>EBR RAVs</td>
<td>44/44</td>
</tr>
<tr>
<td>NS5A Class RAVs</td>
<td>8/8</td>
</tr>
<tr>
<td>EBR RAVs</td>
<td>48/48</td>
</tr>
<tr>
<td>NS5A Class RAVs</td>
<td>4/4</td>
</tr>
<tr>
<td>EBR RAVs</td>
<td>38/38</td>
</tr>
<tr>
<td>NS5A Class RAVs</td>
<td>14/14</td>
</tr>
</tbody>
</table>

ABT-493/ABT-530 in Late-Stage Development: High Efficacy in Patients Who Failed DAA Regimens (12 Week Treatment)

Take Home Lesson on Resistance

• Know the genotype/subtype you are treating (eg, GT1a vs GT1b or G3)
• Know the assay the lab you order from is using (population sequencing most common in commercial labs)
• Know the specific RAVs that are most problematic and likely to affect treatment decision
Conclusion

• All viruses can become resistant
  — It’s their defense mechanism against drugs
• Our job is to not create more mutations
• We can identify resistant strains and select medications that will be effective against them
• More potent drugs are being developed that have less potential for failure
Back to Dawn
Patient C.B.

• C.B. is retreated in a clinical trial for DAA failures
• She is cured with next generation drugs
• Upon repeat biopsy to get into that study, it was noted that her biopsy stage was 3
• Now that she is cured, what should be done?
Long-term Management of Cured Patients

Yulia Lyuboslavsky, APN, ACNS-BC
Austin Gastroenterology
Austin, Texas
SVR Results in a Reduction in All-cause Mortality in Patients with Advanced Fibrosis

530 patients followed for a median of 8.4 years

• Once non-cirrhotic patients achieve SVR, the risk of liver cancer is very low and regular screening post SVR is not recommended.

El-Serag, Hepatology, 2016
Follow up: All Patients Achieving SVR

• Assessment of recurrence or reinfection ONLY if patient has ongoing risk of infection (eg, illicit drug use, high-risk sexual exposure) or unexplained hepatic dysfunction.
  – Must order HCV RNA test and not anti-HCV serology (remember: patient will always be antibody +)
• Assessment of other causes of liver disease for patients with persistently abnormal liver tests after SVR.

Follow up: Patients Achieving SVR

• No advanced fibrosis (earlier stage disease; F0-F2)
  – Manage the same as if patient was never infected with HCV

• Advanced fibrosis/cirrhosis (F3-F4)
  – Twice-yearly ultrasound for liver cancer surveillance
  – Baseline endoscopy to screen for esophageal varices if cirrhotic

Follow up: If Patient Did **Not** Achieve SVR

- Hepatic function panel, CBC, INR every 6-12 months
- Twice-yearly ultrasound for liver cancer surveillance in patients with advanced disease (F3-F4)
- Endoscopic screening for esophageal varices if cirrhosis present
- Evaluation for retreatment in a clinical trial
  - Be sure to test for HCV RAVs; may help eligibility for trial

General Advice: Keep Your Liver Healthy

- Vaccinate for HAV and HBV
- Maintain healthy BMI
- Control blood sugar and cholesterol (diabetes/HLD/metabolic syndrome)
- Limit ETOH use
- Milk Thistle?
Milk Thistle: The Jury is Still Out

- Phase III controlled clinical trial: Did not significantly reduce serum ALT levels more than placebo in participants with chronic HCV
- Clinical efficacy of milk thistle is not clearly established
  - Possible benefit has been shown most frequently, but not consistently, for improvement in aminotransferases
  - Available evidence is not sufficient to suggest whether milk thistle may be more effective for some liver diseases

Fried MW et al. JAMA. 2012 Jul 18;308(3):274-82
Patient C.B.

- Needs to be followed closely for progression of fibrosis
- She also has NASH and this could lead to advanced liver disease
- Abstain from alcohol
- Lose weight
- Control diabetes
Summary

- HCV is curable

Screening

- All baby boomers (born between 1945 and 1965) should have one time screening for hepatitis C.
- Any person with high risk behavior as defined by the CDC should be screened.

Linkage to liver experts that can assess disease progression and treatment options

Highly efficacious, short duration regimens with favorable safety profiles are available
Back to Dawn
Roundtable Discussion/Q&A