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
  – Polyarthralgia 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
- 4% Transplant/Death
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

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)

- **Treatment Naive**
  - DCV/SOF + RBV:
    - 12 Weeks: 14/14, 100%
    - 24 Weeks: 15/15, 100%
- **Prior PI/PEG/RBV Failures**
  - DCV/SOF + RBV:
    - 12 Weeks: 21/21, 100%
    - 24 Weeks: 19/20, 95%

Sułkowski MS et al., *N Engl J Med* 2014;370: 211-21
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>
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<tbody>
<tr>
<td>Non-Cirrhotic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDV/SOF</td>
<td>179/180</td>
<td>179/181</td>
</tr>
<tr>
<td>LDV/SOF + RBV</td>
<td>178/184</td>
<td>181/184</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>
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Cure (SVR12) in GT 1a Patients Treated with Viekira Pak for 12 Weeks

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 is living document and regularly updated
## More Pangenotypic Regimens in Development

<table>
<thead>
<tr>
<th>Combination Treatment</th>
<th>Phase</th>
<th>Manufacturer</th>
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<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>
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<tr>
<td>Grazoprevir (NS3/4A protease inhibitor), MK-3682 (NS5B polymerase inhibitor) and elbasvir (NS5A replication complex inhibitor)</td>
<td>2</td>
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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
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\(^2,3\)

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

5’UTR → Core → E1 → E2 → NS2 → 3’UTR

Ribavirin

- **NS3 Protease Inhibitors**
  - Boceprevir (BOC)
  - Telaprevir (TVR)
  - Simeprevir (SMV)
  - Paritaprevir (PTV)
  - Grazoprevir (GZR)

- **NS5A Replication Complex Inhibitors**
  - Daclatasvir (DCV)
  - Ledipasvir (LDV)
  - Ombitasvir (OMV)
  - Elbasvir (EBR)

- **NS5B NUC Inhibitors**
  - Sofosbuvir (SOF)

- **NS5B Non-NUC Inhibitors (NNI)**
  - Dasabuvir (DSV)

**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


Population Sequencing

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

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

![Graph showing SVR12, % Patients](chart)

**ITT**
- Low Dose: 100%
- High Dose + RBV: 91%
- High Dose - RBV: 86%

**mITT**
- Low Dose: 100%
- High Dose + RBV: 95%
- High Dose - RBV: 95%

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
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

Development of Liver Cancer After SVR Still Possible

- 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

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