Hepatitis C: The Arrival of the Interferon-Free Era

Jennifer Andres, PharmD, BCPS
Clinical Assistant Professor of Pharmacy Practice
Temple University School of Pharmacy

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Objectives

• Review epidemiology, pathophysiology, and treatment of Hepatitis C virus (HCV)
• Compare FDA-approved treatment options for genotype 1 HCV infections
• Evaluate recommended treatment strategies for genotype 1 HCV infections

Disclosures

I, Jennifer Andres, have no conflicts of interest or financial relationships to disclose

Epidemiology

• Most common blood-borne pathogen
  • 170 million people worldwide
  • 3.2 million people in the US
• Nearly 75% of infected people may not be identified yet
  • Diagnosis may be an incidental finding
  • Impact of undiagnosed and untreated HCV expected to increase dramatically
• Chronic infection likely
  • Primary cause of liver transplant and hepatocellular carcinoma (HCC)

More Americans Die From Hepatitis C Than 60 Other Infectious Diseases Combined

SR is a 52 year old African American female patient who presents for initial evaluation for chronic Hepatitis C infection. Started alcohol use at age 18. Drank up to 6 packs of beer a day. Sober for the past 5 years. Used crack/cocaine in the past stopped 5 years ago. SR weighs 70 kg and stands 5’3’’.

Allergies: NKDA

PMH: Hepatitis C (diagnosed 1 year prior), depression, GERD, acne, exercise-induced asthma

Current Medications:

- Albuterol Inhaler 1 puff PO Q4-6H PRN
- Omeprazole 40 mg PO daily
- Citalopram 40 mg PO daily

Pertinent Labs/Tests:

Hepatic Function Panel:

- Albumin 3.8
- Globulin 3.1
- Bilirubin, Total 0.3
- Bilirubin, Direct 0.1
- Bilirubin, Indirect 0.2
- Alkaline Phosphatase 98
- Aspartate Aminotransferase 23
- Alanine Aminotransferase 6

Anti-HCV +

HCV RNA PCR Q7 (IU/mL)

Genotype: 1a

NR 52239

NS5A Resistance Panel
Daclatasvir Resistance NOT PREDICTED
Ledipasvir Resistance NOT PREDICTED
Ombitasvir Resistance NOT PREDICTED
Elbasvir Resistance NOT PREDICTED

FibroTest: Fibrosis Score 0.49
Fibrosis Stage F2
Etiology

- HCV is a single-stranded RNA virus of the family *Flaviviridae*
- Lacks a proofreading polymerase
- Replicates within hepatocytes
- HCV is differentiated into **six major genotypes**
  - Genotypes are further classified into subtypes (a, b, c, etc.)
  - Therapeutic response and drug treatment is based on infecting genotype
  - All can lead to cirrhosis, end-stage liver disease, or HCC

Genotype Distribution

In the US, >70% are genotype 1 infections


Genotype Distribution


Risk Factors

- Injection-drug use
- Blood transfusion before 1992
- Healthcare-associated transmission
- Sexual contact
  - Multiple sexual partners
  - Coinfection with STDs or HIV
- ?Acupuncture, tattooing, and body piercing?

Pathophysiology

- Acute infection leads to chronic infection
- Immune response is insufficient to eradicate the virus
- Rapid viral diversification
  - Genomic mutations detectable within 1 year

Goals of Treatment

- Eradicate HCV RNA
  - Sustained virologic response (SVR)
  - Undetectable RNA 12 weeks after treatment
  - Determines “cure”
- Decrease mortality, need for liver transplant, hepatocellular carcinoma rates, and hepatic-related complications
- Improve quality of life

 Therapeutic Decisions

- AASLD and IDSA have collaborated on Practice Guidelines
- Guidelines are updated as data is released
- Available free at [www.hcvguidelines.org](http://www.hcvguidelines.org)
Who to Treat?

- ALL HCV infected patients
- Except patients with short life expectancy that could not be remediated with HCV treatment
- AASLD-IDSA Clinical Guidelines do NOT recommend prioritizing treatment for any patient group due to the overwhelming benefit of treating HCV

Back in the Day: Prior Treatment Options

<table>
<thead>
<tr>
<th>Drug</th>
<th>Abbrev</th>
<th>Approval Date</th>
<th>Therapeutic Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peginterferon (Pegasis®, PegIntron®)</td>
<td>PEG-IFN</td>
<td>2001; 2002</td>
<td>Interferon</td>
</tr>
<tr>
<td>Ribavirin (Copegus®, Ribosphere®, Modener®, Ribosphere®, others)</td>
<td>RBV</td>
<td>2001</td>
<td>Antiviral Agent</td>
</tr>
<tr>
<td>Bocaprevir (Vicitel®)</td>
<td>BOC</td>
<td>2011</td>
<td>Protease Inhibitor</td>
</tr>
<tr>
<td>Telaprevir (Incivek®)</td>
<td>TVR</td>
<td>2011</td>
<td>Protease Inhibitor</td>
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Elbasvir/Grazoprevir

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<th>Therapeutic Class</th>
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</thead>
<tbody>
<tr>
<td>Grazoprevir</td>
<td></td>
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</tr>
<tr>
<td>Elbasvir (Zepatier™)</td>
<td>ELB/GRZ</td>
<td>2016</td>
<td>NS3/4A protease inhibitor/NSSA inhibitor</td>
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Sofosbuvir/Velpatasvir

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<th>Therapeutic Class</th>
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<tbody>
<tr>
<td>Sofosbuvir</td>
<td>SMP</td>
<td>2013</td>
<td>NS3/4A protease inhibitor</td>
</tr>
<tr>
<td>Sofosbuvir/ledipasvir (Harvoni®)</td>
<td>LDP</td>
<td>2014</td>
<td>NSSA inhibitor/NSSB polymerase inhibitor</td>
</tr>
<tr>
<td>Ombitasvir/Paritaprevir/ Ritonavir and Dasabuvir (Viekira Pak™, Viekira XR™)</td>
<td>OMB/PTV/CD</td>
<td>2014, 2016</td>
<td>NSSA inhibitor/NSS3/4A protease Inhibitor/Pharmacokinetic booster/NSSB polymerase inhibitor</td>
</tr>
<tr>
<td>Daclatasvir (Daklinza®)</td>
<td>DCC</td>
<td>2015</td>
<td>NSSA inhibitor</td>
</tr>
<tr>
<td>Ombitasvir/Paritaprevir/ Ritonavir (Technivie™)</td>
<td>OMB/PTV/CD</td>
<td>2015</td>
<td>NSSA inhibitor/NSS3/4A protease Inhibitor/PK booster</td>
</tr>
<tr>
<td>Elbasvir/Grazoprevir (Zapater™)</td>
<td>ELB/GRZ</td>
<td>2016</td>
<td>NS3/4A protease inhibitor/NSSA inhibitor</td>
</tr>
<tr>
<td>Sofosbuvir/Velpatasvir (Epclusa)</td>
<td>SOF/VEL</td>
<td>2016</td>
<td>NSSA inhibitor/NSSB polymerase inhibitor</td>
</tr>
</tbody>
</table>

Treatment Response: Genotype 1

SVR 15-20%
- Interferon monotherapy
- Peg-IFN + RBV

SVR 40-55%
- Interferon free regimens (DAAs)

SVR >90%
- Triple therapy with 1st generation protease inhibitors
AASLD/IDSA Guidelines

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Treatment-naïve: Genotype 1a</th>
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<tbody>
<tr>
<td></td>
<td>No Cirrhosis</td>
</tr>
<tr>
<td>Sofosbuvir + simeprevir</td>
<td>12 wks</td>
</tr>
<tr>
<td>Sofosbuvir/ledipasvir</td>
<td>12 wks</td>
</tr>
<tr>
<td>Ombitasvir/paritaprevir/ritonavir + dasabuvir</td>
<td>12 wks + RBV</td>
</tr>
<tr>
<td>Sofosbuvir + daclatasvir</td>
<td>12 wks</td>
</tr>
<tr>
<td>Elbasvir/grazoprevir</td>
<td>12 wks (no NS5A) or 16 wks + RBV (NS5A)</td>
</tr>
<tr>
<td>Sofosbuvir/velpatasvir</td>
<td>12 weeks</td>
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Bolding indicates AASLD/IDSA-recommended regimen
Italics indicate alternative regimen.

What trials led to these recommendations?
Focus on ELB/GRZ and SOF/VEL

Clinical Trials | Design | Summary of Results |
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>C-SURFER</td>
<td>• Type of Trial: Phase 3, &quot;placebo&quot; controlled</td>
<td>• Overall SVR12~99% (115/116)</td>
</tr>
<tr>
<td></td>
<td>• Patient Population: Treatment naïve and experienced, ODX, GT1 patients</td>
<td>• Adverse events (76% vs 84%) - headache, nausea, and fatigue</td>
</tr>
<tr>
<td></td>
<td>• n = 224 (179 patients on HD)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Regimen: ELB/GRZ x 12 weeks</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Primary endpoint: SVR12</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(reference comparator of 49%)</td>
<td></td>
</tr>
<tr>
<td>C-EDGE TN</td>
<td>• Type of Trial: Phase 3, multi-center, &quot;placebo&quot; controlled</td>
<td>• Overall SVR12~99% (299/316)</td>
</tr>
<tr>
<td></td>
<td>• Patient Population: Treatment naïve, GT 1, 4, and 6 patients</td>
<td>• GT 1a - 92% (144/157)</td>
</tr>
<tr>
<td></td>
<td>• n = 316</td>
<td>• GT 1b - 99% (129/131)</td>
</tr>
<tr>
<td></td>
<td>• Regimen: ELB/GRZ x 12 weeks</td>
<td>• Virolologic failure - 13 patients (4%)</td>
</tr>
<tr>
<td></td>
<td>• Primary endpoint: SVR12</td>
<td>• Adverse events - Headache, fatigue, nausea</td>
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<table>
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<tbody>
<tr>
<td>ASTRAL-1</td>
<td>• Type of Trial: Phase 3, &quot;placebo&quot; controlled</td>
<td>• Overall SVR12~99% [95% CI, 98 to &gt;99]</td>
</tr>
<tr>
<td></td>
<td>• Patient Population: Treatment naïve or experienced patients with GT 1, 2, 4, 5, or 6 with or without cirrhosis</td>
<td>• GT 1a - 98% (95% CI, 95 to &gt;99)</td>
</tr>
<tr>
<td></td>
<td>• n = 624 (328 with GT 1)</td>
<td>• GT 1b - 99% (95% CI, 95 to 100)</td>
</tr>
<tr>
<td></td>
<td>• Regimen: SOF/VEL x 12 weeks</td>
<td>• Adverse Effects (78% vs 77%) - headache, fatigue, nasopharyngitis, and nausea</td>
</tr>
<tr>
<td></td>
<td>• Primary endpoint: SVR12</td>
<td>• Serious Adverse Effects – 19 in SOF/VEL group, 0 in placebo group</td>
</tr>
<tr>
<td></td>
<td>(superiority to prespecified performance goal of 85%)</td>
<td>• Treatment Discontinuations – 1 in SOF/VEL group, 2 in placebo group</td>
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Feld JJ et al. NEJM. 2015.
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Current Medications:
- Albuterol Inhaler 1 puff PO 4-6H PRN
- Ramipril 10 mg PO daily
- Citrato propranolol 40 mg PO daily
- Metoprolol 50 mg PO Bi-daily

Pertinent Labs/Tests:
- HCV RNA PCR Q2 (IU/mL) Genotype 1a
  - 6/10/2021
  - 1.33
- LFTs:
  - Albumin: 3.8
  - Total Bilirubin: 0.3
  - Direct Bilirubin: 0.1
  - ALT: 36
  - AST: 6
  - Alkaline Phosphatase: 38
- FibroScan: 5.8
- FibroTest: 0.15

Questions

Would elbasvir/grazoprevir be an acceptable treatment option for this patient?

Would sofosbuvir/velpatasvir be an acceptable treatment option for this patient?

Role of the Pharmacist

- Counsel patients on risk factor reduction and avoidance of factors that may worsen hepatic function
- Screen for drug interactions
- Ensure appropriate dosing and duration of drug therapy based on patient-specific factors (concomitant disease states; renal function; hepatic function; concomitant drug therapy)
- Counsel patients on side effect profile of agents
- Encourage adherence
- Stay up to date on new agents/pipeline agents

References

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