New and Emerging Interferon-free Treatments for Chronic Hepatitis C

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Learning Objectives

- At the completion of this activity, pharmacists will be able to:
  1. Recognize the pathogenesis and natural disease progression of hepatitis C.
  2. Evaluate patient characteristics for appropriate screening and treatment selection.
  3. Identify the key steps in the life cycle of hepatitis C virus (HCV).
  4. Design an individualized treatment plan for HCV patients.
  5. Develop a monitoring plan to assess clinical outcomes in HCV patients.

- At the completion of this activity, technicians will be able to:
  1. Describe the life cycle of HCV and its mechanism of chronic infection.
  2. Evaluate patient characteristics for appropriate treatment selection.
  3. Identify new and emerging direct-acting HCV treatments.

Meet Two Patients

Patient 1
BN is a 55 yo white female who has returned to her gastroenterologist for follow-up after a positive HCV antibody result from her PCP. She originally went to her PCP for mental health issues and cannot explain why he ran the HCV panel. Regardless, she is asymptomatic and has no complaints of abdominal pain, jaundice, fever, or nausea/vomiting. She does complain of fatigue and mentions a history of blood transfusions in the early 1980s secondary to "hysterectomy with bleeding complications." She presents today to review the results of her biopsy and labs, and discuss possible treatment options.

Patient 2
TL is a 68 yo African American male who was diagnosed with HCV about 15 years ago when he donated blood. HCV RNA was detected in his blood at the screening process. He received peginterferon and ribavirin for an unknown period of time. He recalls that treatment was stopped early due to lack of response and severe flu-like symptoms. Recently, he has been bruising easily and he was sent to his gastroenterologist for work up. He is otherwise asymptomatic and has no complaints of abdominal pain, jaundice, fever, or nausea/vomiting. He does complain of fatigue. He presents today to review the results of his biopsy and labs, and discuss possible new treatment options.

Labs (performed by gastroenterologist):

<table>
<thead>
<tr>
<th></th>
<th>Patient 1</th>
<th>Patient 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>BLN/Sc</td>
<td>16/1.0</td>
<td>26/1.6</td>
</tr>
<tr>
<td>AST/ALT</td>
<td>50/65</td>
<td>47/55</td>
</tr>
<tr>
<td>T. bil</td>
<td>1.4</td>
<td>1.7</td>
</tr>
<tr>
<td>Albumin</td>
<td>3.4</td>
<td>2.9</td>
</tr>
<tr>
<td>WBC</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>H/H</td>
<td>12/37</td>
<td>13/40</td>
</tr>
<tr>
<td>PL</td>
<td>250</td>
<td>150</td>
</tr>
<tr>
<td>INR</td>
<td>1.1</td>
<td>1.6</td>
</tr>
<tr>
<td>WT</td>
<td>56 kg</td>
<td>72 kg</td>
</tr>
<tr>
<td>HT</td>
<td>156 cm</td>
<td>164 cm</td>
</tr>
</tbody>
</table>

Disclosures

- New and Emerging Interferon-free Treatments for Chronic Hepatitis C is accredited by ACPE for pharmacists, ACPE 0154-0000-15-037-L01-R, and technicians, ACPE 0154-0000-15-037-L01-T, for 1.5 contact hours.
- Rebecca Brady and Alireza FakhriRavari have not disclosed any financial or conflicts of interest in relation to this program.
Introduction

- The hepatitis C virus (HCV) discovery in 1989
- "Non-A non-B hepatitis" in the mid-1970s
- HCV leading cause of chronic hepatitis
- Cirrhosis
- Liver cancer
- Primary indication for liver transplantation

Pathogenesis

- Hepatocytes predominantly affected
- Hepatic fibrosis
  - Mechanisms poorly understood
  - Immune recognition and destruction of infected hepatocytes
  - Hepatic lesions from continuous microinflammatory process
- HCV can evade the host immune response

HCV Genotypes

- 7 major HCV genotypes
  - ~30% sequence divergence
- Each genotype is grouped into a number of subtypes
  - ~10% sequence divergence

<table>
<thead>
<tr>
<th>HCV genotype</th>
<th>Prevalence of HCV</th>
<th>Geographic Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>30-55%</td>
<td>United States</td>
</tr>
<tr>
<td>1b</td>
<td>~3-10%</td>
<td>Europe, Japan, and China</td>
</tr>
<tr>
<td>1c</td>
<td>~15-16%</td>
<td>Europe, United States, and Central Africa</td>
</tr>
<tr>
<td>2</td>
<td>~6-13%</td>
<td>Southeast Asia</td>
</tr>
<tr>
<td>3</td>
<td>~1-2%</td>
<td>Middle East and Northern Africa</td>
</tr>
<tr>
<td>4</td>
<td>~1-2%</td>
<td>South Africa</td>
</tr>
<tr>
<td>5</td>
<td>&lt;1%</td>
<td>Southeast Asia</td>
</tr>
<tr>
<td>6</td>
<td>&lt;1%</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

Relative Prevalence of HCV Genotypes

United States: GT1 (~75%), GT2 (~15%), GT3 (~9%), GT4 (~1%)

Epidemiology

- Can take decades to see manifestations related to HCV infection
- Most patients are asymptomatic
Epidemiology

- Can take decades to see manifestations related to HCV infection
- Most patients are asymptomatic

Screening: 1998 CDC Recommendations

- Persons with risk behaviors
  - IV drug use
- Persons at risk of exposure
  - Long-term hemodialysis
  - Children born to HCV-infected women
  - Prior recipients of transplants or organ transplants
  - Persons who were ever incarcerated
- Persons with other medical conditions
  - HIV infection
  - Unexplained chronic liver disease
  - Chronic hepatitis

- Estimated that 45 – 85% of people infected with HCV are unaware of their infection
- 45% of people diagnosed with HCV report no known risk exposure

Screening: Current CDC Recommendations

- Persons born between 1945 and 1965
  - Accounts for 76.5% of persons infected with HCV in the U.S.
- Persons with risk behaviors
  - IV drug use
- Persons at risk of exposure
  - Long-term hemodialysis
  - Children born to HCV-infected women
  - Prior recipients of transplants or organ transplants
  - Persons who were ever incarcerated
- Persons with other medical conditions
  - HIV infection
  - Unexplained chronic liver disease
  - Chronic hepatitis

Who Should Be Treated?

- Highest priority: those at highest risk for severe complications (immediate treatment)
  - Advanced fibrosis or compensated cirrhosis
  - Liver transplant recipients
  - Severe extrahepatic manifestations
- High priority
  - Signs of disease progression (fibrosis or cirrhosis)
  - Co-infection with HIV or HBV
  - Comorbidities: NASH or type 2 diabetes
  - Extrahepatic: debilitating fatigue or porphyria cutanea tarda
- Grey area: those at highest risk for transmitting HCV
  - Counsel on ways to decrease transmission/minimize re-infection

AASLD/IDSA Guidelines: *All with Chronic HCV Infection*
Virology

- Enveloped flavivirus
- Positive-sense viral ribonucleic acid (RNA)
- Utilizes the hepatocyte ribosomes for translation

HCV Life Cycle

HCV Life Cycle – Cell Entry

HCV Life Cycle – Release and Translation

HCV Life Cycle - Processing
Goals of treatment

- Sustained virologic response (SVR)
  - SVR = undetectable serum HCV RNA 12 weeks after completion of treatment
  - A sustained virological response is equivalent to a "viral cure"
- All-cause mortality
- Liver-related mortality
- Non-liver-related mortality

"The goal of treatment of HCV-infected persons is to reduce all-cause mortality and liver-related health adverse consequences, including end-stage liver disease and hepatocellular carcinoma, by the achievement of virologic cure as evidenced by an SVR."

Important Considerations

- Important factors to consider
  - Duration of therapy
  - Need for ribavirin
  - Cost
  - Difficult to treat characteristics
- Genotype 1 subtype b
- Genotype 1 subtype a

Historically difficult to treat but no longer difficult
- IL28B non-CC genotype
- Black race

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Skin

- Adverse effects
  - Sofosbuvir: fatigue and headache
  - Simeprevir: fatigue, headache, nausea, insomnia, pruritus, rash, and photosensitivity

- Drug interactions
  - Max dose: rosuvastatin 10 mg, atorvastatin 40 mg

- Resistance
  - Sofosbuvir (SOF): high barrier to resistance
  - Simeprevir (SMV): low barrier to resistance

- Renal impairment
  - Avoid sofosbuvir in patients with eGFR < 30 mL/min/1.73m²

Sofosbuvir and Simeprevir Combination

- FDA-approved dosing
  - 12 weeks of simeprevir 150 mg daily with food plus sofosbuvir 400 mg po daily for patients without cirrhosis ($150,000)
  - 24 weeks of simeprevir 150 mg daily with food plus sofosbuvir 400 mg po daily for patients with cirrhosis ($300,000)
Sofosbuvir and Ledipasvir Combination

- **Adverse effects**
  - Fatigue and headache
- **Drug interactions**
  - Antacids (avoid within 4 hours)
  - Rifampin, St. John’s wort, carbamazepine, or tipranavir/ritonavir
  - Amiodarone
- **Resistance**
  - Sofosbuvir (SOF): high barrier to resistance
  - Ledipasvir (LDV): low barrier to resistance
- **Renal impairment**
  - Avoid sofosbuvir in patients with eGFR < 30 mL/min/1.73m²


SIRIUS

- **Phase 2 study in France**
- **155 cirrhotic patients, all treatment-experienced including treatment with boceprevir and telaprevir**
- **LDV+SOF+RBV for 12 weeks: SVR12 96% (95% CI: 89 to 99)**
- **LDV+SOF for 24 weeks: SVR12 97% (95% CI: 91 to 100)**
- **Ledipasvir-sofosbuvir plus ribavirin for 12 weeks and ledipasvir-sofosbuvir for 24 weeks provided similarly high SVR12 rates in previous non-responders with HCV genotype 1 and compensated cirrhosis**

Adverse effects
- Fatigue, nausea, pruritus, skin reactions, insomnia, and asthenia
- Serum alanine amino- transferase (ALT) elevations in 1-4% of patients

Drug Interactions
- Cyclosporine and tacrolimus may increase serum concentrations of amiodarone and flecainide
- Ethinyl estradiol or efavirenz

Hepatic impairment
- Not recommended in patients with moderate hepatic impairment (Child-Pugh B)
- Contraindicated in patients with severe hepatic impairment (Child-Pugh C)

Resistance - Low barrier to resistance

Paritaprevir/r-Ombitasvir and Dasabuvir (3D) Combination

FDA-approved dosing
- 12 weeks of PTVr+OBV+DSV for treatment of genotype 1b without cirrhosis (~$83,000)
- 12 weeks of PTVr+OBV+DSV plus RBV for treatment of genotype 1a without cirrhosis or genotype 1b with cirrhosis (~$84,000)
- 24 weeks of PTVr+OBV+DSV plus RBV for treatment of genotype 1a with cirrhosis (~$168,000)
Emerging Treatments for HCV Genotype 1

- Ribavirin-free combination
  - Sofosbuvir and daclatasvir combination (A-LASSO Phase 2 Trial, ALLY-1 Trial)
- Shorter duration of therapy
  - Sofosbuvir, grazoprevir, and elbasvir combination: treatment for 6 or 8 weeks
  - Sofosbuvir, ledipasvir, and velpatasvir (GS-5851) combination: treatment for 6 weeks
- Nucleotide-free strategy
  - Beclabuvir, daclatasvir, and asunaprevir combination (UNITY-2 Trial)
  - Grazoprevir and elbasvir combination (G-WORTHY Phase 2 Trial, C-LINTER Trial)

UNITY-2

- Phase 3 study in USA, Canada, France, and Australia
- 202 cirrhotic patients, treatment-naïve and treatment-experienced
- Daclatasvir 30 mg po BID plus asunaprevir 200 mg po BID plus beclabuvir 75 mg po BID with or without ribavirin for 12 weeks
- With RBV: SVR12 98% (97.5% CI: 88.9 to 100)
- Without RBV: SVR12 87% (97.5% CI: 75.3 to 98)
- Conclusion: Patients with chronic HCV genotype 1 infection and cirrhosis who received a 12-week oral fixed-dose regimen of daclatasvir, asunaprevir, and beclabuvir, with or without ribavirin, achieved high rates of SVR12.

C-SURFER

- Phase 3 RCT
- 224 pts with HCV GT1 + CKD4/5
- 52% GT1a; 80% TN; 6% cirrhotic; 19% CKD4; 81% CKD5; 76% HD.
- Grazoprevir (GZR) 100mg/elbasvir (EBR) 50mg once daily for 12 weeks vs placebo
- SVR12: 99%
- Serious AEs occurred in 14% and 15% in active and placebo groups
- 0% and 4% in active and placebo groups discontinued therapy due to AEs
- Conclusion: once-daily GZR/EBR for 12 weeks was highly effective and generally well tolerated in patients with HCV GT1 infection and advanced CKD

Monitoring

- Prior to starting antiviral therapy
  - Hepatic function panel and GFR
  - HCV genotype and subtype
  - Quantitative HCV viral load
- During antiviral therapy
  - Clinic visits or telephone contact
  - GFR and hepatic function panel after 4 weeks
  - Discontinue if 10-fold increase in ALT at week 4
  - Quantitative HCV viral load testing after 4 weeks and at 12 weeks following completion of therapy

Summary

- Adherence
  - Every pill counts!
- Cost
  - Prior authorizations
- Drug Interactions
  - http://www.hep-druginteractions.org/
- Renal function

Resources for Pharmacists

- IDSA-AASLD Guidelines
  - http://www.hcvguidelines.org/
- Drug Interactions
  - http://www.hep-druginteractions.org/
- Hepatitis C - Diagnosis, Treatment and Support
  - http://hepnet.liverfoundation.org/
- U.S. Department of Veterans Affairs
  - http://www.hepatitis.va.gov/