Hepatitis C

Overview
Hepatitis C Disease Overview

The Hepatitis C Virus ("HCV")

- Seven known genotypes (1 – 7), greater than 67 subtypes (1a, 1b, etc)
  - Treatment guidelines address genotypes 1 - 6
- Genotype 1b often results in the most aggressive form of liver disease and is resistant to interferon ("PEG") therapy
- Genotype 1a viruses may have a NS3 Q80K polymorphism (see below)

Acute and Chronic Disease

- Acute Hepatitis C
  - Often asymptomatic
  - Mean incubation of 50 days; virus can be detected in blood 3 weeks from infection date
  - Coinfection with Human Immunodeficiency Virus ("HIV") and/or a history of chronic alcohol use can increase the severity of acute hepatitis C
  - Acute hepatitis C may be resolved or may evolve into chronic hepatitis C
- Chronic Hepatitis C
  - Often asymptomatic until cirrhosis, end-stage liver disease and/or hepatocellular carcinoma develop, which can take years or even decades
  - Liver biopsy, not severity of symptoms or serum transaminase levels, is the best indicator of disease severity

Treatment Goals and Approaches

Acute and Chronic Hepatitis C Treatment Goals

- Increase quality of life
- Decrease acute morbidity and mortality
- Minimize the spread of infection
- Stop hepatic inflammation (normalize aminotransferases)
- Prevent end-stage liver disease
- Stop viral replication in the patient
- Eradicate the virus = cure!

Treatment Approaches

- Acute Hepatitis C
  - Supportive (symptomatic) care - may require hospitalization for severe symptoms
  - Acute hepatitis C may be resolved or may evolve into chronic hepatitis C
- Chronic Hepatitis C
  - Regular monitoring of qualitative and quantitative measures
  - Determination of disease progression
  - Pharmacologic treatment - Timing of initiation should be discussed in depth with the patient
    - It may not be best to immediately start treatment if the disease is in its early stages
    - Adverse drug effects must be considered
- Improved efficacy and reduced side effects of new and soon-to-be-released drugs may warrant waiting unless the patient needs immediate treatment
  - Liver support systems (liver dialysis)
  - Liver transplant

**Acronyms & Definitions**

**Acronyms**
- HIV = human immunodeficiency virus
- NS3 Q80K polymorphism = a particular type of Hepatitis C genotype 1a. It does not respond well to, and should not be treated with simeprevir
- PEG = pegylated interferon, a drug used to treat hepatitis C. “PEG” and “interferon” are sometimes used interchangeably
- RIBA = ribavirin, a drug used to treat hepatitis C
- RNA = ribonucleic acid = large molecules possessed by both viruses and humans that regulate genes. Viral RNA uses the human body’s normal processes to replicate and spread infection.
- SVRx = Sustained Virologic Response = a laboratory value indicating the absence of detectable hepatitis C virus in blood x weeks after discontinuing treatment (e.g. SVR12 at 12 weeks, SVR24 at 24 weeks, etc.) The current regulatory standard is SVR12. If “SVR” (with no number) is referenced, assume SVR12.
- Viral Load = the amount of detectable hepatitis C virus in the blood

**Patient Treatment History**
- Treatment-naïve = no previous Hepatitis C treatment
- Response = Hepatitis C virus is undetectable in blood and liver function tests are normal immediately after treatment and sustained for 6 months
- Nonresponse = Failure = Hepatitis C virus is detectable and/or liver function tests are abnormal as therapy progresses. Therapy is usually stopped
- Relapse = Hepatitis C virus is undetectable and liver function tests are normal immediately after treatment, but re-emerge in the 6 months following therapy
- Interferon-ineligible (PEG-ineligible) = patient is not a candidate for treatment with PEG-interferon for one or more of a variety of reasons (autoimmune disorders, decompensated hepatic disease, etc.)

**Pharmacotherapy for Hepatitis C**
- PEG (various brand names) = pegylated interferon, injected subcutaneously once weekly. Interferons decrease cell growth and increase cell death via a variety of mechanisms. Pegylated interferon is interferon to which inert polyethylene glycol has been chemically bound. Pegylated interferon remains in the body longer than non-pegylated interferon, and thus can be administered less often than non-pegylated interferon. “PEG” and “interferon” are sometimes used interchangeably.
- **RIBA** (various brand names, also available generic) = ribavirin, an oral capsule or solution taken twice daily. Ribavirin is a nucleoside which inhibits viral replication by stopping initiation and elongation of viral RNA fragments via a variety of mechanisms.

- **Boceprevir (Victrelis®)** = an oral capsule taken three times daily. Boceprevir is a first generation protease inhibitor targeted to a specific protease. It inhibits viral replication and is considered a direct-acting antiviral treatment for hepatitis C. Boceprevir became available in 2011.

- **Simeprevir (Olysio®)** = an oral capsule taken once daily. Simeprevir is a protease inhibitor targeted to a specific protease. It inhibits viral replication and is considered a direct-acting antiviral treatment for hepatitis C. It has low efficacy against, and should not be used to treat Hepatitis C genotype 1a with the NS3 Q80K polymorphism. Simeprevir became available in January (2014).

- **Sofosbuvir (Sovaldi®)** = an oral tablet taken once daily. Sofosbuvir is a polymerase inhibitor. It inhibits a specific polymerase and is considered a direct-acting antiviral treatment for hepatitis C. Sofosbuvir became available in January (2014).

- **Telaprevir (Incivek®)** = an oral tablet taken twice daily. Telaprevir inhibits viral replication. Telaprevir is a first generation protease inhibitor targeted to a specific protease. It inhibits viral replication and is considered a direct-acting antiviral treatment for hepatitis C. Telaprevir became available in 2011.

### Drugs Currently Available to Treat Hepatitis C

<table>
<thead>
<tr>
<th>Interferon</th>
<th>Nucleoside</th>
<th>First Generation Protease Inhibitor</th>
<th>Second Generation Protease Inhibitor</th>
<th>Polymerase Inhibitor</th>
</tr>
</thead>
</table>
The Evolution of Hepatitis C Standard of Care\textsuperscript{ii,vii,viii,ix,x}

- 2009 AASLD Guidelines
  - Only PEG and RIBA were available

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Treatment</th>
<th>Duration</th>
<th>SVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PEG + RIBA</td>
<td>48 weeks</td>
<td>~ 50%</td>
</tr>
<tr>
<td>2 and 3</td>
<td>PEG + RIBA</td>
<td>24 weeks</td>
<td>~ 80%</td>
</tr>
</tbody>
</table>

- 2011 AASLD Guidelines
  - PEG, RIBA, and first generation protease inhibitors were available (boceprevir, 2011 and telaprevir, 2011)

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<th>Genotype</th>
<th>Treatment</th>
<th>Duration</th>
<th>SVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PEG + RIBA + First Generation Protease Inhibitor</td>
<td>24 to 48 weeks</td>
<td>~ 60 - 79%</td>
</tr>
<tr>
<td>2 and 3</td>
<td>PEG + RIBA</td>
<td>24 weeks</td>
<td>~ 80%</td>
</tr>
</tbody>
</table>

- 2014 AASLD / IDSA Guidelines
  - PEG, RIBA, boceprevir 2011, simeprevir 2014, sofosbuvir 2014 and telaprevir 2011 are available

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Treatment</th>
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<th>SVR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>See attached document</td>
<td></td>
<td>≤ ~ 97%</td>
</tr>
</tbody>
</table>
Pause for
Public Comment

1) Dr. Laura Litzenberger, Pharm.D., M.B.A.
   Senior Liaison, Health Economics and Outcomes, Johnson & Johnson

2) Dr. Michelle Puyear, Pharm.D.
   Associate Director, Medical Sciences, Gilead Inc.

3) Dr. Michael Charlton, M.D.
   Medical Director, Intermountain Medical Center Liver Transplant Program
   Former Medical Director, Mayo Clinic Liver Transplant Program
   AASLD guideline panel member

4) Ms. Kerin Stevens, A.P.R.N.
   Hepatology and Liver Transplant, University of Utah

Resume DUR Discussion:

Treatment Costs
Hepatitis C Treatment Costs to Medicaid\textsuperscript{ii,xi}

- Drug Costs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Least Costly Complete Course of Therapy</th>
<th>Most Costly Complete Course of Therapy</th>
<th>Maximum Percentage of Patients Achieving SVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boceprevir (2011, Victrelis®)</td>
<td>$7,069.02</td>
<td>$11,680.03</td>
<td>75% \textsuperscript{xii,xi}</td>
</tr>
<tr>
<td>Simeprevir (2014, Olysio®)</td>
<td>$51,254.72</td>
<td>$114,246.32</td>
<td>95% \textsuperscript{xiv, xv, xvi}</td>
</tr>
<tr>
<td>Sofosbuvir (2014, Sovaldi®)</td>
<td>$63,915.60</td>
<td>$127,831.20</td>
<td>100% \textsuperscript{ xvii, xviii}</td>
</tr>
<tr>
<td>Telaprevir (2011, Incivek®)</td>
<td>$32,856.11</td>
<td>$34,242.11</td>
<td>88% \textsuperscript{xix, xx, xxi}</td>
</tr>
</tbody>
</table>

- Tolerability for Patients (Quality of Living Costs)
  - Older drugs
    - Boceprevir 2011 = Anemia, neutropenia, dysgeusia, must take with food, many drug-drug interactions, must take many capsules daily
    - Telaprevir 2011 = Rash, anemia, anorectal symptoms, must take with fatty food, many drug-drug interactions, must take many tablets daily
  - Newer drugs
    - Simeprevir 2014 = Rash, photosensitivity, increased bilirubin, must take with food, fewer drug-drug interactions, PEG-free treatment options, once-daily dosing. Should not be used to treat Hepatitis C genotype 1a with the NS3 Q80K polymorphism
    - Sofosbuvir 2014 = Fatigue, headache, nausea, insomnia, may take without regard to food, fewer drug-drug interactions, PEG-free treatment options, once-daily dosing, pangenotypic

- Health Care Costs
  - The economic burden of a patient with hepatitis C is estimated to be substantially greater than that of a patient without hepatitis C. Various studies have estimated the cost differences of one patient with hepatitis C per year versus one patient without hepatitis C per year, including inpatient stays
    - Before simeprevir and sofosbuvir (pre-2014): $3,200 \textsuperscript{xxii} to $15,500 \textsuperscript{xxiii}
      - A patient that is “cured” will recover the drug costs in two to eleven years
    - After simeprevir and sofosbuvir: Too early for any studies, but using the figures above…
      - A patient that is “cured” will recover the drug costs in three to forty years
Other Payers’ Policies

- Medicaid Accountable Care Organizations (ACOs)
  - Boceprevir 2011
    - All require prior authorization
  - Simeprevir 2014
    - Not yet reviewed
  - Sofosbuvir 2014
    - Not yet reviewed
  - Telaprevir 2011
    - All require prior authorization

Possible Prior Authorization Criteria for Hepatitis C Treatments

- Note: The Board discussed boceprevir and telaprevir in 2011, shortly after they came to market. It was decided that no prior authorization should be required.
  - They offered significantly better outcomes than PEG + RIBA therapy, the previous standard of care
  - Chances for abuse or misuse of hepatitis C treatments were considered very small
  - However, rebate agreements are such that if PA criteria are placed upon simeprevir and sofosbuvir, PA criteria must also be placed upon boceprevir and telaprevir.
    - Boceprevir 2011 and telaprevir 2011 are preferred on Utah Medicaid’s Preferred Drug List.
    - Simeprevir 2014 and sofosbuvir 2014 have not been reviewed by the Pharmacy and Therapeutics Committee (do not appear on the Preferred Drug List)

- Based largely upon cost considerations, Utah Medicaid is considering prior authorization requirements for simeprevir 2014 and sofosbuvir 2014. Prior authorization criteria would serve to keep use on-label, particularly concerning viral genotype and subtype.
  - Possible prior authorization criteria is attached