1 – 2pm
Advances in Chronic Hepatitis C Infection

SPEAKER
Sammy Saab, MD, MPH, AGAF, FAASLD

Presenter Disclosure Information
The following relationships exist related to this presentation:
- Sammy Saab, MD, MPH, AGAF, FAASLD: Advisory Committee, stock ownership, and speaker for Gilead, BMS, AbbVie, and Merck.

Off-Label/Investigational Discussion
- In accordance with pmiCME policy, faculty have been asked to disclose discussion of unlabeled or unapproved use(s) of drugs or devices during the course of their presentations.

Objectives
- Outline epidemiology and risk factors for chronic hepatitis C
- Review the natural history and the clinical impact of chronic hepatitis C infection
- Discuss current treatment options for chronic hepatitis C infection

Case Study

Laura
- 72 years old
- HCV genotype 1
- Treatment-naïve
- HCV RNA level >1,000,000 IU/mL
- Liver biopsy: cirrhosis
- No features of decompensated liver disease
- Normal PTT, bilirubin, and platelet count

Case Study 1 ~ Continued

Laura
- Patient wants to know prognosis and treatment options
- Afraid of adverse effects described with interferon therapy
Case Study 2

Ray
- 38 years old
- Chronic HCV infection, genotype 3
- Former illicit intravenous drug user
- Moderate depression; taking citalopram

Ray is ready to begin antiviral treatment, but is concerned about his current antidepressive therapy and also wants to know if he's a candidate for hepatitis C therapy.

Case Study 3

Joanne
- 50 years old
- Hypertension and diabetes
- HCV, genotype 1, diagnosed 10 years ago
- Results of elastography suggest cirrhosis
- Did not respond to prior course of pegylated interferon and ribavirin

Should we treat Joanne again? Can she be cured of her hepatitis C?

Hepatitis C Worldwide Prevalence

~180 Million With Hepatitis C Infection

Hepatitis C: Under Diagnosed in the United States


Natural History of Hepatitis C Infection

*20%-30% of individuals are symptomatic.

HCC=hepatocellular carcinoma.


Estimated Hepatitis C Cases

Conservative estimate
Upper limit of estimate


Chronic Hepatitis C Infection in the United States

- >5.2 million living with chronic HCV in US
  - Prevalence: 2%
- Chronic HCV cases not included in NHANES estimate
  - Homeless (n=142,761-337,610)
  - Incarcerated (n=272,754-464,826)
  - Veterans (n=1,237,461-2,452,006)
  - Active military (n=6805)
  - Healthcare workers (n=12,971-17,000)
  - Chronic hemodialysis (n=20,578)
  - Nursing home residents (n=63,609)
  - Hemophiliacs (n=372,754-664,826)
  - Active military (n=6805)
  - Healthcare workers (n=12,971-17,000)


Factors Associated with Hepatitis C Disease Progression

- Alcohol consumption
  - 30 g/day in men
  - 20 g/day in women
  ~ 2 drinks per day
- Disease acquisition at >40 years
- Male gender
- HIV coinfection
- Hepatitis B virus coinfection
- Immunosuppression


Hepatitis C-Related Cirrhosis is Projected to Peak Over the Next 10 Years

Number of patients

<table>
<thead>
<tr>
<th>Year</th>
<th>1990</th>
<th>2000</th>
<th>2010</th>
<th>2020</th>
<th>2030</th>
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<tr>
<td>25%</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>2020</td>
<td>1,000,000</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2030</td>
<td>1,200,000</td>
<td></td>
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</tbody>
</table>

25% of patients with HCV currently have cirrhosis
37% of patients with HCV are projected to develop cirrhosis by 2020, peaking at 1 million

Davis GL, et al. Gastroenterology 2010

Annual Adjusted Hepatitis C Mortality Rates in the United States

<table>
<thead>
<tr>
<th>Year</th>
<th>1990</th>
<th>2000</th>
<th>2010</th>
<th>2020</th>
<th>2030</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rate per 100,000 Patient-Years</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>


Increasing Number of Deaths Among HCV-Infected Persons, Surpassing HIV

National Center for Health Statistics 1999-2007
Annual Age-Adjusted Mortality Rates

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>


Hepatitis C Is Leading Indication of Liver Transplants in the US

Primary cause of disease among adults on the liver transplant wait list, 2011
Primary cause of disease among adult liver transplant recipients, 2011

Available at: http://srtr.transplant.hrsa.gov/annual_reports/2011/pdf/03_%20liver_12.pdf

Increasing Number of Hospitalizations related to Hepatitis C Infection in Los Angeles County, 2007-2009

Sie et al. J Viral Hepat. 2013
Extrahepatic Manifestations of Chronic Hepatitis C

- Hematologic/Oncologic:
  - Mixed cryoglobulinemia
  - Lymphoma
- Renal: Glomerulonephritis
- Dermatologic:
  - Porphyria cutanea tarda
  - Cutaneous necrotizing vasculitis
  - Lichen planus
- Diabetes
- Fatigue
- Depression

Source of Images:  

Chronic HCV Infection Increases Mortality from Both Hepatic and Extrahepatic Diseases

Follow-Up (Years)

Follow-Up (Years)

Cumulative Mortality (%)

Follow-Up (Years)

Cumulative Mortality (%)

All Causes (n=2394)

Liver Cancer (n=115)

Extrahepatic Diseases (n=2199)

Anti-HCV+, HCV RNA detectable  Anti-HCV+, HCV RNA undetectable  Anti-HCV-

All Causes Mortality

Liver-Related Mortality or Liver Transplantation (%)

Hepatocellular Carcinoma (%)

Sustained Virologic Response is Associated with Reduction in All-Cause Mortality

An international, multicenter, long-term follow-up study from 5 tertiary care hospitals in Europe and Canada of 530 advanced fibrosis/cirrhotic HCV patients treated with IFN-based regimen between 1990-2003

Non-SVR  SVR

2013 Updated USPSTF HCV Screening Recommendations

Risk Assessment:

- Those at high risk for HCV infection:
  - Most important risk factor is past or current injection drug use
  - Additional risk factors include:
    - Receiving a blood transfusion before 1992
    - Long-term hemodialysis
    - Being born to an HCV-infected mother
    - Incarceration
    - Intranasal drug use
    - Getting an unregulated tattoo, and other percutaneous exposures
  - Adults born between 1945 and 1965 ("Baby Boomers")

Screening for Chronic Hepatitis C

Hepatitis C antibodies (ELISA)

Confirm with Hepatitis C RNA Virus testing (PCR)

If treatment candidate

Determine Hepatitis C Genotype

*Grade B recommendation for persons at high risk for infection and adults born between 1945 and 1965; Moyer VA; on behalf of the USPSTF. Ann Intern Med. 2013
Serological Tests

*Hepatitis C Antibodies*

- Serologic test is the enzyme-linked immunosorbent assay (ELISA)
- Rare false positives with autoimmune hepatitis
- Rare false negatives in immunocompromised or recently exposed patients
- Molecular testing required to confirm active/ongoing infection

Molecular Tests

*Hepatitis C RNA*

- Viral load expressed as IU/ml:
  - Ranges from non-detected to near a hundred million IU
  - Mean viral load is at 1 Million IU/ml
- Different ways of testing
  - PCR (RNA), TMA, etc
- No correlation with disease severity

Molecular Tests

*Genotype*

- 6 genotypes
- Significance
  - Treatment response
  - Duration of treatment
  - Not severity of disease

Goals of therapy

- **Primary Goal**
  - Clearance of virus

- **Secondary Goal**
  - Decrease rate of decompensation
  - Decrease risk of hepatocellular carcinoma
  - Improved histology

Hepatitis C Differs from HIV and HBV

No long-term or Latent Reservoir

<table>
<thead>
<tr>
<th>HBV</th>
<th>HIV</th>
<th>HCV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Host cell</td>
<td><strong>cccDNA</strong></td>
<td><strong>Viral RNA</strong></td>
</tr>
<tr>
<td><strong>Nucleus</strong></td>
<td>Proviral DNA</td>
<td></td>
</tr>
</tbody>
</table>

TREATMENT
- Long-term suppression of viral replication

TREATMENT
- Long-term suppression of viral replication

TREATMENT
- Viral Eradication = Cure

cccDNA = covalently closed circular DNA

Options for Liver Fibrosis Assessment

- Liver Biopsy
- Serum Biomarkers
- Elastography
- Ultrasound

Liver Biopsy and Histology

- Gold standard for defining status of liver injury
- Identifies features useful in decision to embark on therapy
- May reveal advanced fibrosis or cirrhosis that necessitates surveillance for HCC or screening for varices
- Helps identify concurrent liver disease

Laboratory Assessment of Fibrosis

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>AUC</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>APRI</td>
<td>46</td>
<td>94</td>
<td>0.84</td>
<td>AST/platelet count</td>
</tr>
<tr>
<td>FIB-4</td>
<td>74</td>
<td>80</td>
<td>0.85</td>
<td>Platelet count, AST, ALT, a-fetoprotein level</td>
</tr>
<tr>
<td>Fibrotest</td>
<td>77</td>
<td>82</td>
<td>0.89</td>
<td>Haptoglobin, α2-macroglobulin, apolipoprotein A1, γGT, bilirubin, gender</td>
</tr>
<tr>
<td>Fibrosoft II</td>
<td>76</td>
<td>73</td>
<td>0.82</td>
<td>Hyaluronan, TIMP-1, α2-macroglobulin</td>
</tr>
</tbody>
</table>

2. Wai CT, Greenson JK, Fontana RJ, Hadjivassiliou JG, Marrero JA, Larion AS. Hepatology 2003

Abdominal Ultrasound

- Pros
  - Readily available
  - Noninvasive
  - Assess for liver disease complications
- Cons
  - Operator dependent
  - Cannot assess for fibrosis stage
  - Insensitive for early cirrhosis

Hepatitis C: Achieving a Cure

- Simple, Safe, And Short
- Lack of Resistance
- Broad Efficacy

Evolution of Hepatitis C Therapy

Genotype 1

<table>
<thead>
<tr>
<th>Year</th>
<th>Sustained Viral Response (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1980s</td>
<td>13–17%</td>
</tr>
<tr>
<td>1990s</td>
<td>29–39%</td>
</tr>
<tr>
<td>2002</td>
<td>38–52%</td>
</tr>
<tr>
<td>2011</td>
<td>67–70%</td>
</tr>
<tr>
<td>2014/5</td>
<td>&gt;90</td>
</tr>
</tbody>
</table>

To Treat or Not to Treat: Previous Constellation of Considerations

- Viral genotype
- Histologic stage
- Age
- Duration of infection
- Personal plans
- Patient mindset
- Benefits
- Risks
- Compliance
- Out of pocket costs
- Comorbidities
Properties of Direct Acting Agents

<table>
<thead>
<tr>
<th>Class of Drug</th>
<th>Mode of Action</th>
<th>Potency/Genotypic Activity</th>
<th>Barrier to Resistance</th>
<th>Drug-Drug Interaction Potential</th>
<th>Dosing Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protease inhibitor</td>
<td>Inhibits assembly and packaging of HCV</td>
<td>High (1a&lt;1b)</td>
<td>Low (1a&lt;1b)</td>
<td>High</td>
<td>Telaprevir, Boceprevir</td>
</tr>
<tr>
<td>NS5B nucleoside/nucleotide polymerase inhibitors</td>
<td>Directly inhibits HCV RNA chain elongation</td>
<td>High pan-genotypic activity</td>
<td>Low</td>
<td>Very low (1a&lt;1b)</td>
<td>Sofosbuvir</td>
</tr>
<tr>
<td>NS5A inhibitors</td>
<td>Regulates HCV replication</td>
<td>High (GT 1b)</td>
<td>Low (GT 1a)</td>
<td>Low to moderate</td>
<td>Ledipasvir, Ombitasvir</td>
</tr>
</tbody>
</table>

First Generation Direct Acting Agents

- Telaprevir and boceprevir previously used in HCV genotype 1 with Pegylated interferon (PEG)/Ribavirin (RBV)
- Markedly improved SVR rates and shorter duration versus PEG/RBV only
- Poor tolerability and increased severity of adverse effects

Differences in Sustained Viral Responses between African Americans and Caucasians Treated with Interferon-based Therapy

<table>
<thead>
<tr>
<th>Regiment</th>
<th>Cohort</th>
<th>Non cirrhotic</th>
<th>Cirrhotic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sofosbuvir/ledipasvir</td>
<td>Treatment naive</td>
<td>96-99% (8-12 wks)</td>
<td>94% (12 wks)</td>
</tr>
<tr>
<td></td>
<td>Treatment experienced</td>
<td>95% (12 wks)</td>
<td>100% (24 wks)</td>
</tr>
<tr>
<td>Sofosbuvir/simeprevir</td>
<td>95% (12 wks)</td>
<td>100% (24 wks)</td>
<td></td>
</tr>
<tr>
<td>3-D ± ribavirin</td>
<td>Genotype 1a</td>
<td>96% (12wks)</td>
<td>89-95% (12-24wks)</td>
</tr>
<tr>
<td></td>
<td>Genotype 1b</td>
<td>100% (12 wks)</td>
<td>99% (12 wks)</td>
</tr>
</tbody>
</table>

Treatment of Genotype 1 Patients

Sustained Viral Response Rates

<table>
<thead>
<tr>
<th>Regiment</th>
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<td>96% (12wks)</td>
<td>89-95% (12-24wks)</td>
</tr>
<tr>
<td></td>
<td>Genotype 1b</td>
<td>100% (12 wks)</td>
<td>99% (12 wks)</td>
</tr>
</tbody>
</table>

Treatment of Genotype 2 Patients

Sustained Viral Response Rates

<table>
<thead>
<tr>
<th>Regiment</th>
<th>Non cirrhotic</th>
<th>Cirrhotic</th>
<th>FDA Approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sofosbuvir/ledipasvir</td>
<td>Naive</td>
<td>97%</td>
<td>Experienced</td>
</tr>
<tr>
<td></td>
<td>Naive</td>
<td>100%</td>
<td>Experienced</td>
</tr>
<tr>
<td></td>
<td>FDA Approved</td>
<td>Yes</td>
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</table>

Treatment of Genotype 3 Patients

Sustained Viral Response Rates

<table>
<thead>
<tr>
<th>Regiment</th>
<th>Non cirrhotic</th>
<th>Cirrhotic</th>
<th>FDA Approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sofosbuvir/ledipasvir</td>
<td>Naive</td>
<td>93%</td>
<td>Experienced</td>
</tr>
<tr>
<td></td>
<td>Naive</td>
<td>92%</td>
<td>Experienced</td>
</tr>
<tr>
<td></td>
<td>FDA Approved</td>
<td>Yes</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: SOF – sofosbuvir; LED – ledipasvir; SIM – simeprevir; 3-D – ombitasvir, paritaprevir + ritonavir, dasabuvir; R-ribavirin

Adapted from: Stedman CAM. J Gastroenterol Hepatol 2013

Adapted from: Saab et al. A J Gastroenterol 2014

Adapted from: Moradpour et al.; Nat Rev Microbiol. 2007
Treatment Prioritization by AASLD/IDSA

**Highest Priority for Treatment Owing to Highest Risk for Severe Complications**
- patients with advanced fibrosis (Metavir F3)
- patient with cirrhosis (Metavir F4)
- liver transplant recipients
- patients with severe extrahepatic hepatitis C

**High Priority for Treatment Owing to High Risk for Complications**
- Fibrosis (Metavir F2)
- HIV-1 coinfection
- HBV coinfection
- Other coexistent liver disease (eg, NASH)
- Debilitating fatigue
- Type 2 Diabetes mellitus (insulin resistant)
- Porphyria cutanea tarda

Recommended assessments prior to starting antiviral therapy

Assessment of potential drug-drug interactions

Following laboratory tests recommended within 6 weeks prior to starting antiviral therapy:
- CBC, INR
- Hepatic panel
- TSH; if IFN is used
- Calculated glomerular filtration rate (GFR)

Following laboratory test recommended within 12 weeks of starting antiviral therapy:
- HCV genotype and quantitative HCV viral load

Recommended monitoring during antiviral therapy

- Every 4 weeks:
  - CBC, creatinine level, calculated GFR, and hepatic function panel
- Every 12 weeks:
  - TSH if on IFN.
  - More frequent assessment for drug-related toxic effects (eg, CBC for patients receiving RBV) is recommended as clinically indicated.
- Quantitative HCV viral load testing:
  - After 4 weeks of therapy
  - End of treatment,
  - 12 weeks following completion of therapy.

Recommended monitoring for patients in whom treatment failed to achieve an SVR

- Disease progression assessment every 6 to 12 months with hepatic panel, CBC, and INR.
- Hepatocellular carcinoma surveillance with ultrasound every 6 months for patients with advanced fibrosis (F3 or F4).
- Endoscopic surveillance for esophageal varices is recommended with cirrhosis.
- Evaluation for retreatment is recommended as effective alternative treatments become available.

Recommended monitoring for patients who achieve an SVR

- For patients without advanced fibrosis (F 0 - F2), follow-up same as if never infected with HCV.
- Assessment for HCV recurrence or reinfection is recommended only if the patient has ongoing risk for HCV infection or unexplained hepatic dysfunction develops.
- Hepatocellular carcinoma surveillance with twice yearly ultrasound for patients with advanced fibrosis (F3 or F4).
- Endoscopy to screen for varices if cirrhosis present. Patients with varices should be treated and followed up as indicated.
Decision to Start Oral Antiviral Therapy for Chronic Hepatitis C

Pros
• Safe
• Effective
• Tolerable
• Short duration

Con
• Adverse effects
  Nausea, headache, rash, fatigue
• Costs
• Drug-Drug interactions

Approximate Costs of Antiviral Therapy

<table>
<thead>
<tr>
<th></th>
<th>SOFR x 12-24 weeks</th>
<th>SOF/LED x 8-24 weeks</th>
<th>SOF/SIM x 12-24 weeks</th>
<th>3-D ± R x 12-24 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>List price</td>
<td>93-186k</td>
<td>66-198k</td>
<td>165-330k</td>
<td>90-180k</td>
</tr>
<tr>
<td>Patient Assistant Program</td>
<td>Available</td>
<td>Available</td>
<td>Available</td>
<td>Available</td>
</tr>
<tr>
<td>Co-Payment Cards</td>
<td>Available</td>
<td>Available</td>
<td>Available</td>
<td>Available</td>
</tr>
</tbody>
</table>

Abbreviations: SOF – sofosbuvir; LED – ledipasvir; SIM – simeprevir; 3-D – ombitasvir, paritaprevir +ritonavir, dasabuvir; R-ribavirin; PAP – Patient Assistant Program

Drug Development Goals

Not all needs being met

Keeping your liver healthy

• Minimize alcohol consumption
• Exercise regularly and eat healthy
• Low salt diet
• Hepatitis A and B immunization if naive

Summary

• Most individuals do not know they are infected with hepatitis C
  – Appropriate screening is essential

• Patients with hepatitis C are at risk of hepatic and extra-hepatic manifestations.
  – Hepatitis C currently the leading indication for liver transplantation in the United States

• Currently available therapy is effective, safe, and tolerable