4 – 5pm
Spotlight on Hepatitis C Infection
SPEAKER
Michael P. Curry, MD

Presenter Disclosure Information
The following relationships exist related to this presentation:
► Michael P. Curry, MD, receives consulting fees from Abbvie, Bristol-Myers Squibb, and Gilead.

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.

Advances in Chronic Hepatitis C Infection
Sammy Saab, MD, MPH, AGAF, FAASLD
Professor of Medicine and Surgery
Assistant Professor of Nursing
David Geffen School of Medicine at UCLA

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

Case Study
Laura
• 72 years old
• HCV genotype 1
• Treatment-naive
• 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

HCV=hepatitis C virus; HBV=hepatitis B virus; HIV=human immunodeficiency virus.


Natural History of Hepatitis C Infection

*20%-30% of individuals are symptomatic.
HCC=hepatocellular carcinoma

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

Davis GL, et al. Gastroenterology. 2010

Annual Adjusted Hepatitis C Mortality Rates in the United States


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


Hepatitis C Is Leading Indication of Liver Transplants in the US

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


Chronic HCV Infection Increases Mortality from Both Hepatic and Extrahepatic Diseases

Follow-Up (Years)

<table>
<thead>
<tr>
<th>Survival (%)</th>
<th>Follow-Up (Years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Causes</td>
<td>Liver Cancer</td>
</tr>
<tr>
<td>(n=2394)</td>
<td>(n=115)</td>
</tr>
<tr>
<td>30.1%*</td>
<td>12.8%</td>
</tr>
<tr>
<td>10.4%*</td>
<td>1.6%</td>
</tr>
</tbody>
</table>

* p<0.001 for comparison among all 3 groups and p<0.001 for HCV RNA detectable versus undetectable.
† p<0.001 for comparison among all 3 groups and p=0.002 for HCV RNA detectable versus undetectable.

Community-based, long-term, prospective study in Taiwan (REVEAL-HCV, Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer, 1991-2008).


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

All-Cause Mortality

p<0.001

All-Cause Mortality (%)

<table>
<thead>
<tr>
<th>Follow-Up (Years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-SVR</td>
</tr>
<tr>
<td>SVR</td>
</tr>
</tbody>
</table>


Sustained Virologic Response is Associated with a Reduction in Liver-Related Mortality and HCC

Liver-Related Mortality or Liver Transplantation

p<0.001

Liver-Related Mortality or Liver Transplantation (%)

<table>
<thead>
<tr>
<th>Follow-Up (Years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without SVR</td>
</tr>
<tr>
<td>With SVR</td>
</tr>
</tbody>
</table>

Hepatocellular Carcinoma

p<0.001

Hepatocellular Carcinoma (%)

<table>
<thead>
<tr>
<th>Follow-Up (Years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without SVR</td>
</tr>
<tr>
<td>With SVR</td>
</tr>
</tbody>
</table>


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 IUs
  - 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**

- HBV
- HIV
- HCV

- cccDNA = covalently closed circular DNA

Options for Liver Fibrosis Assessment

<table>
<thead>
<tr>
<th>Liver Biopsy</th>
<th>Serum Biomarkers</th>
<th>Elastography</th>
<th>Ultrasound</th>
</tr>
</thead>
</table>

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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, α-fetoprotein level</td>
</tr>
<tr>
<td>Fibrotest</td>
<td>77</td>
<td>82</td>
<td>0.89</td>
<td>Hepatoglobin, α2-macroglobulin, apolipoprotein A1, γGT, bilirubin, gender</td>
</tr>
<tr>
<td>Fibrospect 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, Hadziopoulos J, MacFarlane AJ, Cooperman HS, Los AL. Hepatology 2013

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

To Treat or Not to Treat: Previous Constellation of Considerations

- Benefits
- Risks
- Compliance
- Out of pocket costs
- Comorbidities

- Viral genotype
- Histologic stage
- Age
- Duration of infection
- Personal plans
- Patient mindset
- Extrahepatic features
- HIV coinfection
- ALT
Properties of Direct Acting Agents

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Protease Inhibitors</td>
<td>Inhibits assembly and packaging of HCV</td>
<td>Low (1a&lt;1b)</td>
<td>High</td>
<td>qd to tid</td>
<td>Beupeprav/ Telaprevir/ Saimeprev/ Paritaprevir</td>
<td></td>
</tr>
<tr>
<td>NS3B Non-nucleotide/ nucleotide phosphodiesters</td>
<td>Directly inhibits HCV RNA chain elongation</td>
<td>High Pan-genotypic activity</td>
<td>High</td>
<td>qd to tid</td>
<td>Simeprevir</td>
<td></td>
</tr>
<tr>
<td>NS5A Inhibitors</td>
<td>Regulates HCV replication</td>
<td>High Pan-genotypic activity</td>
<td>Low to moderate</td>
<td>qd to bid</td>
<td>Ledipasvir/ Ombitasvir</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Buxton CAM. J Gastroenterol Hepatol 2013

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

Treatment of Genotype 1 Patients

**Sustained Viral Response Rates**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Non cirrhotic</th>
<th>Cirrhotic</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOF/LED (duration)</td>
<td>96-99% (8-12 wks)</td>
<td>94% (12 wks)</td>
</tr>
<tr>
<td>Treatment naive</td>
<td>95% (12 wks)</td>
<td>100% (24 wks)</td>
</tr>
<tr>
<td>Treatment experienced</td>
<td>95% (12 wks)</td>
<td>100% (24 wks)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Non cirrhotic</th>
<th>Cirrhotic</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-D ± R (duration)</td>
<td>96% (12 wks)</td>
<td>89-95% (12-24wks)</td>
</tr>
<tr>
<td>Genotype 1a</td>
<td>96% (12wks)</td>
<td>89-95% (12-24wks)</td>
</tr>
<tr>
<td>Genotype 1b</td>
<td>100% (12 wks)</td>
<td>99% (12 wks)</td>
</tr>
</tbody>
</table>

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

Treatment Prioritization by AASLD/IDSA

**Highest Priority for Treatment Owing to Highest Risk for Severe Complications**

- Patients with advanced fibrosis (Metavir F3)
- Patients 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

Abbreviations: SOF – sofosbuvir;  LED – ledipasvir;  R-ribavirin

http://hcvguidelines.org/full-report/when-and-whom-initiatehcv-therapy

http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/204671s000lbl.pdf

http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/205834s000lbl.pdf

http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/205123s001lbl.pdf

http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/206619lbl.pdf

http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/204671s000lbl.pdf
Treatment Prioritization by AASLD/IDSA (continued)

High HCV Transmission Risk

- MSM with high-risk sexual practices
- Active injection drug users
- Incarcerated persons
- Persons on long-term hemodialysis

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 follow-up 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>Therapy</th>
<th>SOF/R 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</td>
<td>Available</td>
<td>Available</td>
<td>Available</td>
<td>Available</td>
</tr>
<tr>
<td>Assistant Program</td>
<td></td>
<td></td>
<td></td>
<td></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

Unmet Medical Need

US Prevalence

Drugs: GT3 Dialysis

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

Keeping your liver healthy

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