Treatment of Hepatitis C in Patients With Cirrhosis

Andrew J. Muir, MD, MHS
Chief, Division of Gastroenterology
Duke University School of Medicine
Durham, North Carolina
Disclosure

- Research grants
  - Abbvie, Achillion, BMS, Gilead, Hologic, Intercept, Janssen, Merck, NGM, Roche, Shire

- Advisory boards
  - Abbvie, Achillion, BMS, Gilead, Janssen, Merck

- Consultant
  - Theravance
Outline

- Definitions and diagnostic approach
- Treatment
  - Candidacy
  - Efficacy
  - Adverse events
- Decompensated cirrhosis
54-year-old man presents with new diagnosis
- History: no ascites, encephalopathy, GI bleeding
- Examination: mentally clear, no ascites or edema
- Laboratory data:
  - AST 60 U/L, ALT 75 U/L, t bili 1.2 mg/dL
  - Albumin 3.9 gm/dL, creatinine 1.0 mg/dL
  - Platelet 110 x 10^9/L
  - PT-INR 1.1
  - HCV RNA 1,100,000 IU/mL
  - Genotype 1a

Clinical questions
- Does the patient need treatment?
- What is the stage of liver disease?
Definitions and Diagnostic Approach
Faster progression with:
- older age at infection
- alcohol
- HIV infection
- post-transplant

Acute HCV

Chronic HCV 75-85 %

Cirrhosis 20 %

HCV natural history

DiBisceglie A. Hepatology 2000
Liver fibrosis staging

F1: portal fibrosis

F2: portal fibrosis with few septa

F3: septal fibrosis (bridging)

F4: cirrhosis

Bedossa P. *Hepatology* 1996
Liver biopsy

- Gold standard
- Invasive
  - Morbidity (3/1,000)
  - Mortality (1/10,000)
- Observer variability
- Sampling error
- Costly

Rockey DC. Hepatology 2009; Regev A. Am J Gastroenterol 2002
Alternatives to liver biopsy

- **Alternative approaches**
  - Serum markers
    - Standard laboratory tests: APRI, FIB-4
    - Commercial assays
  - Radiographic tests
    - Elastography

- **Limitations**
  - Ability to distinguish F1 versus F2, etc
    - Better to differentiate advanced versus early
  - Serologies impacted by inflammation
  - Indeterminable outcomes common

Recommendations

- AASLD/IDSA/IAS–USA Guidance
  - [www.hcvguidelines.org](http://www.hcvguidelines.org)

- An assessment of the degree of hepatic fibrosis, using noninvasive testing or liver biopsy, is recommended.
- Ongoing assessment of liver disease is recommended for persons in whom therapy is deferred.
Treatment
Who needs treatment?

- AASLD/IDSA/IAS–USA Guidance
  - www.hcvguidelines.org

“Treatment is recommended for all patients with chronic HCV infection, except those with short life expectancies that cannot be remediated by treating HCV, by transplantation, or by other directed therapy. Patients with short life expectancies owing to liver disease should be managed in consultation with an expert.”
### Genotype 1: AASLD/IDSA Guidance Oct 2015

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Sofosbuvir + peginterferon + ribavirin</th>
<th>Ledipasvir + sofosbuvir +/- ribavirin</th>
<th>Paritaprevir/r + ombitasvir + dasabuvir +/- ribavirin</th>
<th>Simeprevir + sofosbuvir +/- ribavirin</th>
<th>Daclatasvir + sofosbuvir +/- ribavirin</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Recommended Naïve PEG failures</td>
<td>Recommended Naïve PEG failures</td>
<td>Recommended Naïve PEG failures</td>
<td>Recommended Naïve PEG failures</td>
<td>Recommended Naïve PEG failures</td>
</tr>
<tr>
<td></td>
<td>PI failures</td>
<td></td>
<td>PI failures</td>
<td>PI failures</td>
<td>PI failures</td>
</tr>
<tr>
<td></td>
<td>SOF/PEG failure</td>
<td></td>
<td>SOF/PEG/RBV failure</td>
<td>SIM/SOF failure</td>
<td>SIM/SOF failure</td>
</tr>
<tr>
<td></td>
<td>SOF/PEG/RBV failure</td>
<td></td>
<td>SIM/SOF failures</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Ledipasvir + Sofosbuvir

- **SIRIUS**
- **Patients:**
  - Treatment-experienced, failure of both PEG/RBV and PI + PEG/RBV regimens
  - Compensated cirrhosis
- **Design**
  - Randomized, double-blinded
- **Regimens**
  - Placebo 12 weeks followed by LDV/SOF + RBV for 12 weeks
  - LDV/SOF + Placebo RBV for 24 weeks

- **Adverse events**
  - 2 AEs higher with LDV/SOF vs placebo: headache and fatigue

<table>
<thead>
<tr>
<th>Safety Outcome</th>
<th>LDV/SOF + RBV 12 wks (n = 77)</th>
<th>LDV/SOF 24 wks (n = 78)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAE</td>
<td>5%</td>
<td>10%</td>
</tr>
<tr>
<td>AE leading to d/c</td>
<td>1%</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>21%</td>
<td>35%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4%</td>
<td>17%</td>
</tr>
</tbody>
</table>

Bourlière M. Lancet Infect Dis 2015
Ledipasvir + Sofosbuvir

- **SIRIUS**
- **Patients:**
  - Treatment-experienced, failure of both PEG/RBV and PI + PEG/RBV regimens
  - Compensated cirrhosis
- **Design**
  - Randomized, double-blinded
- **Regimens**
  - Placebo 12 weeks followed by LDV/SOF + RBV for 12 weeks
  - LDV/SOF + Placebo RBV for 24 weeks

Bourlière M. Lancet Infect Dis 2015
Paritaprevir/ritonavir + ombitasvir + dasabuvir

- **Population**
  - 380 Child Pugh Class A cirrhosis (compensated)
  - Treatment naive and previously treated

- **Regimen**
  - Paritaprevir/ritonavir, dasabuvir, ombitasvir, ribavirin

- **Design**
  - Phase 3, randomized, open label
  - Duration 12 vs 24 weeks

**Efficacy: SVR (%)**

<table>
<thead>
<tr>
<th></th>
<th>12 weeks</th>
<th>24 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>91.8</td>
<td>95.9</td>
</tr>
<tr>
<td>1a</td>
<td>88.6</td>
<td>94.2</td>
</tr>
<tr>
<td>1b</td>
<td>98.5</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Poordad F. *NEJM* 2014
### Paritaprevir/ritonavir + ombitasvir + dasabuvir

<table>
<thead>
<tr>
<th>Variable</th>
<th>12-week group (N = 208)</th>
<th>24-week group (N = 172)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event</td>
<td>191 (91.8%)</td>
<td>156 (90.7%)</td>
</tr>
<tr>
<td>AE leading to discontinuation</td>
<td>4 (1.9%)</td>
<td>4 (2.3%)</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>13 (6.2%)</td>
<td>8 (4.7%)</td>
</tr>
<tr>
<td>Deaths</td>
<td>1 (0.5%)</td>
<td>0</td>
</tr>
</tbody>
</table>

Poordad F. *NEJM* 2014
Paritaprevir/ritonavir + ombitasvir + dasabuvir
Genotype 1b, cirrhosis

- Paritaprevir/r, ombitasvir + dasabuvir
- NO RIBAVIRIN
- Duration: 12 weeks
- Naïve and experienced patients (55%)
- All compensated cirrhosis
- Sample size 60

SVR12 (%)

100
80
60
40
20
0

Genotype 1b experienced

60
60

1b

Feld J. 15th International Symposium on Viral Hepatitis and Liver Disease. 2015.
Paritaprevir/ritonavir + ombitasvir + dasabuvir

- FDA letter
- 26 worldwide cases
  - 10 hepatic failure resulting in transplantation or death
  - 16 patients with liver dysfunction
- In most, liver injury within 1 to 4 weeks of starting
- Some patients contraindicated or not recommended
- “Transaminase elevations did not appear to be a predominant presentation in the cases with advanced liver disease”
- Contraindicated in Child Pugh B and C
### Genotype 2

**AASLD/IDSA/IAS–USA Guidance**
- [www.hcvguidelines.org](http://www.hcvguidelines.org)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Treatment</th>
<th>Peginterferon-α, ribavirin + sofosbuvir</th>
<th>Daclatasvir + sofosbuvir</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sofosbuvir + ribavirin</strong></td>
<td><strong>Recommended 12 wks</strong></td>
<td><strong>Recommended 12 weeks</strong></td>
<td><strong>Recommended 12 weeks</strong></td>
</tr>
<tr>
<td><strong>PEG/RBV nonresponders</strong></td>
<td><strong>Recommended 16-24 weeks</strong></td>
<td><strong>Alternative 12 weeks</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Sofosbuvir failures</strong></td>
<td></td>
<td><strong>Recommended IFN eligible 12 weeks</strong></td>
<td><strong>Recommended IFN ineligible +/- RBV 24 weeks</strong></td>
</tr>
</tbody>
</table>

www.hcvguidelines.org
Genotype 2

SVR12 in treatment experienced genotype 2 patients

- **FUSION STUDY**
  - SOF/RBV 12 weeks: 96%
  - SOF/RBV 16 weeks: 100%
  - SOF/PEG/RBV 12 weeks: 78%
  - SOF/PEG/RBV 12 weeks: 93%
  - SOF/RBV 16 weeks: 94%
  - SOF/RBV 24 weeks: 87%
  - SOF/RBV 24 weeks: 100%

- **LONESTAR-2**
  - SOF/RBV 12 weeks: 60%

- **BOSON STUDY**
  - SOF/RBV 16 weeks: 100%

*Jacobson IM. NEJM 2013; Lawitz 2015; Foster 2015*
Genotype 2

Daclatasvir + Sofosbuvir in Genotype 2

- Minimal data in genotype 2 cirrhosis
- AASLD/IDSA: consider 24 weeks and ribavirin if cirrhosis

Sulkowski *NEJM* 2014; Wyles *NEJM* 2015
### Genotype 3

- **AASLD/IDSA/IAS–USA Guidance**
  - [www.hcvguidelines.org](http://www.hcvguidelines.org)

<table>
<thead>
<tr>
<th></th>
<th>Sofosbuvir + ribavirin</th>
<th>Peginterferon-α, ribavirin + sofosbuvir</th>
<th>Daclatasvir + sofosbuvir</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment naive</strong></td>
<td>Alternative, 24 weeks</td>
<td>Recommended, 12 weeks</td>
<td>Recommended, 12 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cirrhosis: 24 wks +/- RBV</td>
</tr>
<tr>
<td><strong>PEG/RBV nonresponders</strong></td>
<td>Recommended, 12 weeks</td>
<td>Recommended, 12 weeks</td>
<td>Recommended, 12 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cirrhosis: 24 wks + RBV</td>
</tr>
<tr>
<td><strong>Sofosbuvir failures</strong></td>
<td>Recommended, 12 weeks</td>
<td></td>
<td>Recommended, 24 weeks + RBV</td>
</tr>
</tbody>
</table>
SVR12 in genotype 3 patients, ALLY-3 & BOSON

- DAC/SOF 12 weeks: 97%
- SOF/PEG/RBV 12 weeks: 58%
- SOF/PEG/RBV 12 weeks: 96%
- SOF/PEG/RBV 24 weeks: 91%
- SOF/RBV 24 weeks: 90%
- SOF/RBV 24 weeks: 82%
- SOF/RBV 24 weeks: 95%
- SOF/RBV 24 weeks: 92%
- SOF/RBV 24 weeks: 94%
- SOF/RBV 24 weeks: 94%
- SOF/RBV 24 weeks: 86%
- SOF/RBV 24 weeks: 82%
- SOF/RBV 24 weeks: 77%
- SOF/RBV 24 weeks: 87%
- SOF/RBV 24 weeks: 62%

Genotype 3

TREATMENT NAIVE

INTERFERON/RIBAVIRIN FAILURES

Lawitz 2015; Foster 2015
• **ALLY-3**

• **Population:**
  - Genotype 3
  - Treatment naïve and experienced

• **Regimen**
  - Daclatasvir 60 mg + sofosbuvir 400 mg for 12 weeks

---

**ALLY-3 Genotype 3**

<table>
<thead>
<tr>
<th>SVR12 (%)</th>
<th>Naïve</th>
<th>Experienced</th>
</tr>
</thead>
<tbody>
<tr>
<td>No cirrhosis</td>
<td>97</td>
<td>94</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>58</td>
<td>69</td>
</tr>
</tbody>
</table>

Nelson D. *Hepatology* 2015
Genotype 3: daclatasvir + sofosbuvir

- ALLY-3+
- Population:
  - 50 patients
  - Genotype 3
  - Advanced fibrosis (28%) and cirrhosis (72%)
  - Treatment naïve (26%) and experienced (74%)
- Design: RCT
- Regimen
  - Daclatasvir 60 mg + sofosbuvir 400 mg + ribavirin
- Arms: 12 vs 16 weeks

<table>
<thead>
<tr>
<th></th>
<th>12 weeks n=24</th>
<th>16 weeks n=26</th>
</tr>
</thead>
<tbody>
<tr>
<td>SVR4</td>
<td>21 (88%)</td>
<td>25 (96%)</td>
</tr>
<tr>
<td>Adv fibrosis</td>
<td>6/6 (100%)</td>
<td>8/8 (100%)</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>15/18 (83%)</td>
<td>17/18 (94%)</td>
</tr>
<tr>
<td>Breakthrough</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Relapse</td>
<td>2 (8%)</td>
<td>1 (4%)</td>
</tr>
</tbody>
</table>

Leroy V. Liver Meeting Abstract LB-3 2015.
Decompensated Cirrhosis
Decompensated cirrhosis

AASLD/IDSA: Patients with decompensated cirrhosis (Child Turcotte Pugh class B or C) should be referred to a medical practitioner with expertise in that condition (ideally in a liver transplant center).
<table>
<thead>
<tr>
<th>Regimen</th>
<th>FDA recommendation for hepatic impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sofosbuvir + ribavirin</td>
<td>No dose adjustment for CTP A, B, C</td>
</tr>
<tr>
<td>Sofosbuvir + peginterferon + ribavirin</td>
<td>Contraindicated if decompensated</td>
</tr>
<tr>
<td>Sofosbuvir/ledipasvir</td>
<td>No dose adjustment for CTP A, B, C</td>
</tr>
<tr>
<td>Paritaprevir/ritonavir + ombitasvir + dasabuvir</td>
<td>Contraindicated in CTP B, C</td>
</tr>
<tr>
<td>Simeprevir + sofosbuvir</td>
<td>Not recommended in CTP B, C</td>
</tr>
<tr>
<td>Daclatasvir + sofosbuvir</td>
<td>No dose adjustment for CTP A, B, C</td>
</tr>
</tbody>
</table>

CTP: Child Turcotte Pugh score
Decompensated cirrhosis

- **SOLAR study**
- **Patients**
  - 108 GT 1 or 4
  - Treatment naïve or experienced
  - CPT class B or C
- **Inclusion/exclusion**
  - Total bili ≤10 mg/dL
  - Creatinine clearance ≥40 mL/min
  - Platelets >30,000 x 10^3/uL
- **Design: RCT**
- **Regimen**
  - Ledipasvir + sofosbuvir
  - Ribavirin 600 mg daily, titrated up if tolerated
  - Duration: 12 or 24 weeks

Charlton M. *Gastroenterology* 2015.
What does cure of HCV mean?

- SOLAR study MELD scores
What does cure of HCV mean?

- Decompensated cirrhosis:
  - Is there a threshold where we cannot avoid a transplant?
  - Should HCV+ patients defer and take a HCV+ organ?
  - Outcomes post-transplant are excellent
Summary

- All patients with HCV need an assessment of fibrosis
  - Patients with advanced fibrosis or cirrhosis should be prioritized for treatment
- HCV treatment is safe and effective in patients with compensated cirrhosis
- Patients with decompensated cirrhosis
  - Should be referred to an experienced clinician and preferably a liver transplant center
  - Antiviral treatment can be effective but must consider transplant options
  - Some agents are not recommended or contraindicated in patients with decompensated cirrhosis