Hepatitis C Update

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Disclosures

- None
Personal Introduction

- From Pinellas County
- University of Miami Miller SOM
- University of Texas Southwestern IM Residency
- University of Alabama Birmingham GI/Hepatology Fellowship
- USF Assistant Professor
  - Focus on non-transplant hepatology
    - Treatment of hepatitis C
Aim

- Reflect on epidemiology and advances in treatment over 25 years
- Delineate assessment of patients for treatment
- Review treatment options
- Discuss special cases
Natural History

- Acute HCV Infection (100)
  - Recovery & Clearance of HCV (20)
    - Mild (24)
    - Chronic Hepatitis
  - Chronic Infection (80)
    - Moderate (32)
    - Severe (24)
    - Cirrhosis
    - End-Stage Liver Disease
    - Hepatocellular CA

Thomas DL, Seeff LB, 2005

UNIVERSITY OF SOUTH FLORIDA
Prevalence by Age Group

Pyenson B et al, 2009
Decompensated Cirrhosis and HCC

Ghany MG et al, 2009
Brief History of Treatment

1989: IFN
1998: IFN + RBV
2001: Peg-IFN + RBV
2011: PI + PegIFN + RBV
2014: IFN-free Combos

Webster DP et al, 2015
Advances in Standard of Care

Webster DP et al, 2015
Patient Assessment
Patient Case

- A 62 year-old asymptomatic female presents to you with recent diagnosis of hepatitis C, inquiring about treatment
  - Denies history of IV drug abuse
  - On routine screening, found to have positive HCV Ab
Testing for HCV

- All persons born between 1945 and 1965, regardless of risk factors
  - Why?
    - Retrospective review of >100,000 patients
    - Only 27% would be screened with risk-based criteria
    - 68% would have been tested by meeting the 1945-1965 birth cohort criteria

Mahajan R et al, 2013
Testing for HCV
Population to consider

All patients

Except those with severely limited life expectancy
History

- Factors associated with accelerated disease progression and compliance
  - Alcohol use
  - Drug abuse
  - Metabolic complications related to fatty liver
- Complications that would suggest underlying cirrhosis
- Concurrent medication use
Physical Exam

- Stigmata of advanced liver disease
- Signs of extrahepatic manifestations of HCV infection

Retamozo S et al, 2013
Physical Exam

- Stigmata of advanced liver disease
- Signs of extrahepatic manifestations of HCV infection

Lab Evaluation

- Basic Laboratory Testing
  - CBC, CMP, INR, lipid panel, U/A, pregnancy test
- HIV, HBV, HAV
- HCV RNA
- HCV genotype
- Assessment of fibrosis stage
Genotype

Messina JP et al, 2015
Assessment of Fibrosis

- Necessary in every patient
- May affect
  - Length of therapy
  - Success of therapy
  - Surveillance
  - Insurance approval
Laboratory Assessment of Fibrosis

- **Indirect**
  - AST/ALT ratio
  - APRI score
  - FIB-4

- **Direct**
  - Biomarkers
    - Fibrosure

\[
\text{FIB-4} = \frac{\text{Age (years)} \times \text{AST (U/L)}}{\text{Platelet count (10}^9/\text{L}) \times [\text{ALT (U/L)}]^{1/2}}
\]

\[
\text{APRI} = \frac{\text{AST (/ULN*)}}{\text{Platelet count (10}^9/\text{L})} \times 100
\]

Teshale E et al, 2014
Imaging Assessment of Fibrosis

- Transient elastography

Fibroscan(R) uses low-frequency ultrasound to measure hepatic transient elasticity (stiffness) and fibrosis for the staging of liver injury.
Assessment of Fibrosis

ALL markers of fibrosis are imperfect (even biopsy) None alone have adequate sensitivity A combination approach is preferred to assess concordance

- **Direct**
  - Imaging is preferred (i.e. transient elastography)
  - Biomarkers have limitations
    - Expensive, not universally covered
    - Some no more sensitive than indirect tests

- **Indirect**
  - APRI or FIB-4
Management

AASLD/ISDA Guidelines
Hcvguidelines.org
When to refer

- USF GI is accepting referrals for patients with HCV
  - Patients without cirrhosis or with compensated cirrhosis
  - Previously treated patients
  - Patients with renal failure
  - Fine print
    - Patients with decompensated cirrhosis or OLT often better served by TGMG transplant hepatology
    - Patients with concurrent HIV better served by Infectious Disease
DAA Drug Classes

- Protease inhibitors
  - NS 3/4 inhibitors
- NS5a inhibitors

- Polymerase inhibitors
  - NS5b inhibitors
  - Nucleoside
  - Non-nucleoside
Suffixes

- **“-previr”**
  - Protease inhibitors
  - Metabolized in the liver
    - Avoid in decompensated liver disease

- **“-asvir”**
  - NS5a inhibitors
  - Pangenotypic

- **“-buvir”**
  - NS5b inhibitors
  - Pangenotypic
Which combinations are which??

- Harvoni = Sofosbuvir/Ledipasvir
- Epclusa = Sofosbuvir/Velpatasvir
- Zepatier = Elbasvir/Grazoprevir
- Viekira pak:
  - Ombitasvir/Paritaprevir/Ritonavir + Dasabuvir
NOT Recommended Treatments

- **General**
  - Monotherapy with Peg-IFN, Ribavirin, or DAA
  - PegIFN + Ribavirin
  - Sofosbuvir + Ribavirin

- ** Decompensated cirrhosis**
  - Protease-inhibitor-based treatments
    - Paritaprevir
    - Simeprevir
    - Grazoprevir

- **Pregnancy**
  - Ribavirin
Current Treatment Recommendations

Treatment Naive
Of Note

- Efficacy of proposed regimens exceeds 90%
- Only the most effective recommended regimens will be discussed
Gen 1 – Non-cirrhotic

- Sofosbuvir/Velpatasvir
- Sofosbuvir/Ledipasvir
- Elbasvir/Grazoprevir*
- Paritaprevir/Ritonavir/Ombitasvir + Dasabuvir +/- Ribavirin**
- Sofosbuvir + Daclatasvir
- Sofosbuvir + Simeprevir

AASLD/IDSA 2016
Gen 1 – Cirrhotic

- Sofosbuvir/Velpatasvir
- Sofosbuvir/Ledipasvir
- Elbasvir/Grazoprevir
- Paritaprevir/Ritonavir/Ombitasvir + Dasabuvir (Gen 1b)
- Sofosbuvir + Daclatasvir
- Sofosbuvir + Simeprevir

AASLD/IDSA 2016
# Harvoni

## Table 1: LDV/SOF Phase III trials for the treatment of patients with chronic hepatitis C genotype 1 infection

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patient characteristics</th>
<th>Treatment regimen</th>
<th>Number of pts</th>
<th>Duration (weeks)</th>
<th>SVR12 (%)</th>
<th>Relapse (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ION-1&lt;sup&gt;9&lt;/sup&gt;</td>
<td>Treatment-naïve</td>
<td>LDV/SOF</td>
<td>214*</td>
<td>12</td>
<td>210/213 (99)</td>
<td>1/212 (&lt;1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LDV/SOF + RBV</td>
<td>217</td>
<td>12</td>
<td>211 (97)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LDV/SOF</td>
<td>217</td>
<td>24</td>
<td>212 (98)#</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LDV/SOF + RBV</td>
<td>217*</td>
<td>24</td>
<td>215 (99)</td>
<td>0</td>
</tr>
<tr>
<td>ION-2&lt;sup&gt;16&lt;/sup&gt;</td>
<td>Treatment-experienced</td>
<td>LDV/SOF</td>
<td>109</td>
<td>12</td>
<td>102 (94)</td>
<td>7 (6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LDV/SOF + RBV</td>
<td>111</td>
<td>12</td>
<td>107 (96)</td>
<td>4 (4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LDV/SOF</td>
<td>109</td>
<td>24</td>
<td>108 (99)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LDV/SOF + RBV</td>
<td>111</td>
<td>24</td>
<td>110 (99)#</td>
<td>0</td>
</tr>
<tr>
<td>ION-3&lt;sup&gt;17&lt;/sup&gt;</td>
<td>Treatment-naïve</td>
<td>LDV/SOF</td>
<td>215</td>
<td>8</td>
<td>202 (94)</td>
<td>11 (5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LDV/SOF + RBV</td>
<td>216</td>
<td>8</td>
<td>201 (93)</td>
<td>9 (4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LDV/SOF</td>
<td>216</td>
<td>12</td>
<td>208 (95)</td>
<td>3 (1)</td>
</tr>
</tbody>
</table>

Nkuize et al, 2016
Gen 2

- Sofosbuvir/Velpatasvir
## Table 2. Response during and after Treatment.*

<table>
<thead>
<tr>
<th>Response</th>
<th>Sofosbuvir–Velpatasvir (N = 624)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HCV RNA &lt;15 IU/ml</strong></td>
<td></td>
</tr>
<tr>
<td>During treatment period — no. (%)</td>
<td></td>
</tr>
<tr>
<td>At wk 2</td>
<td>355 (57)</td>
</tr>
<tr>
<td>At wk 4</td>
<td>564 (90)</td>
</tr>
<tr>
<td>At 12 wk after treatment period — no./total no. (%)</td>
<td></td>
</tr>
<tr>
<td>Any genotype</td>
<td>618/624 (99)</td>
</tr>
<tr>
<td>1a</td>
<td>206/210 (98)</td>
</tr>
<tr>
<td>1b</td>
<td>117/118 (99)</td>
</tr>
<tr>
<td>2</td>
<td>104/104 (100)</td>
</tr>
<tr>
<td>4</td>
<td>116/116 (100)</td>
</tr>
<tr>
<td>5</td>
<td>34/35 (97)</td>
</tr>
<tr>
<td>6</td>
<td>41/41 (100)</td>
</tr>
<tr>
<td><strong>Virologic failure — no. (%)</strong></td>
<td></td>
</tr>
<tr>
<td>During treatment</td>
<td>0</td>
</tr>
<tr>
<td>After treatment</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td><strong>Other reason for classification as failure — no. (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Loss to follow-up</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Withdrawal of consent</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Death</td>
<td>1 (&lt;1)</td>
</tr>
</tbody>
</table>
### Analysis of SOF/VEL x 12 weeks

<table>
<thead>
<tr>
<th>Patients, n (%)</th>
<th>GT1 n=328</th>
<th>GT2 n=238</th>
<th>GT3 n=277</th>
<th>GT4 n=116</th>
<th>GT5 n=35</th>
<th>GT6 n=41</th>
<th>Total N=1035</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cirrhosis</td>
<td>73 (22)</td>
<td>29 (12)</td>
<td>80 (29)</td>
<td>27 (23)</td>
<td>5 (14)</td>
<td>6 (15)</td>
<td>220 (21)</td>
</tr>
<tr>
<td>Platelets &lt;100 x 10^3/µL</td>
<td>21 (6)</td>
<td>4 (2)</td>
<td>25 (9)</td>
<td>8 (7)</td>
<td>1 (3)</td>
<td>3 (7)</td>
<td>62 (6)</td>
</tr>
<tr>
<td>Albumin &lt;3.5 mg/dL</td>
<td>6 (2)</td>
<td>1 (&lt;1)</td>
<td>8 (3)</td>
<td>6 (5)</td>
<td>0</td>
<td>0</td>
<td>21 (2)</td>
</tr>
<tr>
<td>Fibroscan ≥15 kPa</td>
<td>30 (16)</td>
<td>9 (7)</td>
<td>40 (20)</td>
<td>17 (19)</td>
<td>4 (17)</td>
<td>5 (19)</td>
<td>105 (16)</td>
</tr>
<tr>
<td>HCV RNA ≥800,000 IU/mL</td>
<td>255 (78)</td>
<td>186 (78)</td>
<td>191 (69)</td>
<td>74 (64)</td>
<td>26 (74)</td>
<td>31 (76)</td>
<td>763 (74)</td>
</tr>
<tr>
<td>Treatment experienced</td>
<td>110 (34)</td>
<td>44 (18)</td>
<td>71 (26)</td>
<td>52 (45)</td>
<td>11 (31)</td>
<td>3 (7)</td>
<td>291 (28)</td>
</tr>
<tr>
<td>Black race</td>
<td>25 (8)</td>
<td>19 (8)</td>
<td>3 (1)</td>
<td>14 (12)</td>
<td>0</td>
<td>0</td>
<td>61 (6)</td>
</tr>
<tr>
<td>Age ≥65 years</td>
<td>36 (11)</td>
<td>53 (22)</td>
<td>7 (3)</td>
<td>11 (10)</td>
<td>16 (46)</td>
<td>0</td>
<td>123 (12)</td>
</tr>
<tr>
<td>BMI ≥35 kg/m²</td>
<td>20 (6)</td>
<td>18 (8)</td>
<td>21 (8)</td>
<td>8 (7)</td>
<td>3 (9)</td>
<td>0</td>
<td>70 (7)</td>
</tr>
<tr>
<td>HbA1c ≥6.5%</td>
<td>21 (6)</td>
<td>9 (4)</td>
<td>13 (5)</td>
<td>10 (9)</td>
<td>3 (9)</td>
<td>4 (10)</td>
<td>60 (6)</td>
</tr>
<tr>
<td>NS5A RAVs (15% cut off)</td>
<td>50 (15)</td>
<td>146 (61)</td>
<td>31 (11)</td>
<td>69 (59)</td>
<td>3 (9)</td>
<td>19 (46)</td>
<td>318 (31)</td>
</tr>
</tbody>
</table>

The ASTRAL-1, -2, and -3 studies enrolled patients with baseline characteristics historically associated with poor response.
Integrated Efficacy - ASTRAL

<table>
<thead>
<tr>
<th></th>
<th>SVR12 (%)</th>
<th>Total</th>
<th>GT 1</th>
<th>GT 2</th>
<th>GT 3</th>
<th>GT 4</th>
<th>GT 5</th>
<th>GT 6</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>98</td>
<td>98</td>
<td>99</td>
<td>95</td>
<td>100</td>
<td>97</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1015</td>
<td>323</td>
<td>237</td>
<td>264</td>
<td>116</td>
<td>34</td>
<td>41</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1035</td>
<td>328</td>
<td>238</td>
<td>277</td>
<td>116</td>
<td>35</td>
<td>41</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2 relapse</td>
<td>1 D/C</td>
<td>11 relapse</td>
<td>2 D/C</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2 LTFU</td>
<td></td>
<td>1 death</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1 D/C</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 death</td>
</tr>
</tbody>
</table>
Gen 3

- Sofosbuvir/Velpatasvir
- Sofosbuvir + Daclatasvir (if cirrhotic, 24 weeks)

AASLD/IDSA 2016
Gen 4

- Sofosbuvir/Velpatasvir
- Sofosbuvir/Ledipasvir
- Elbasvir/Grazoprevir
- Paritaprevir/Ritonavir/Ombitasvir + Dasabuvir +/- Ribavirin
Current Treatment Recommendations

Treatment Experienced
Treatment Experienced

- Prior peg-IFN/Ribavirin
  - Same as treatment for naïve patients
Treatment Experienced

- Gen 1, prior NS5A Inhibitor or SOF/SIM
  - Non-cirrhotic and no urgent reason for treatment
    - Defer treatment pending availability of data
  - Cirrhotic or urgent reason for treatment
    - Test for RAVs to NS3/NS5A inhibitors

AASLD/IDSA 2016
Treatment Experienced

Test for RAVs

None

SOF/LDV or SOF/VEL x 24wk

NS5A RAVs

SOF/SIM + RBV x 24wk

NS3 & NS5A RAV

?

AASLD/IDSA 2016
SOF/VEL + Voxilaprevir (GS-9857)

Lawitz E et al, 2016
Special Considerations
Discontinue PPI OR Take 20mg >2 hours after DAA

Afdhal N et al, 2016
Medication Interactions

- **Avoid amiodarone with sofosbuvir**
  - Risk of symptomatic bradycardia

- **Caution with inducers of P-glycoprotein**
  - Rifampin
  - St. John’s Wort
  - Carbemazepine
  - Phenytoin
  - Statins
  - Digoxin

Hep-druginteractions.org
Renal Failure

- Gen 1 and 4: Elbasvir/Grazoprevir
  - 224pts, CKD 4/5, 75% on HD: SVR12 99%
- Gen 1b: Paritaprevir/Ritonavir/Ombitasvir + Dasabuvir*
- Gen 2, 3, 5, or 6: Peg-IFN and Ribavirin*

- In the works: Glecaprevir/Pibrentasvir (ABT-493/ABT-530): 98% SVR across GT 1-6

AASLD/IDSA 2016 and Gane E et al, 2016
Side Effects

- DAA side effects similar to placebo
  - Nausea
  - Headache
  - Fatigue

- Ribavirin
  - Anemia
  - Rash/pruritus
  - Irritability, insomnia, anxiety, depression
  - Teratogenic
# Cost

## Table 2 Wholesale acquisition cost of direct-acting antivirals

<table>
<thead>
<tr>
<th>Direct-acting antiviral</th>
<th>Pharmaceutical company</th>
<th>WAC for 12 week course</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sofosbuvir (Sovaldi)</td>
<td>Gilead sciences</td>
<td>$84,000</td>
</tr>
<tr>
<td>Ledipasvir/Sofosbuvir (Harvoni)</td>
<td>Gilead sciences</td>
<td>$94,500</td>
</tr>
<tr>
<td>Ombitasvir/paritaprevir/ritonavir + Dasabuvir (Viekira Pak)</td>
<td>AbbVie</td>
<td>$83,319</td>
</tr>
<tr>
<td>Daclatasvir (Daklinza) + Sofosbuvir (Sovaldi)</td>
<td>Bristol-Myers Squibb and Gilead</td>
<td>$147,000</td>
</tr>
<tr>
<td>Grazoprevir/Elbasvir (Zepatier)</td>
<td>Merck</td>
<td>$54,600</td>
</tr>
</tbody>
</table>

Rosenthal E and Graham CS, 2016
“In the US, HCV has all the attributes of an eradicable disease except sufficient public investment. Delivering care effectively, safely, and broadly to all patient populations in an economically acceptable fashion must be our goal.”

– Dr. Nezam Afdhal
Key Points

- Hepatitis C is a curable viral illness
- Estimating fibrosis is necessary
- Every patient should be considered for treatment irrespective of fibrosis
- New therapies are safe, simple, and effective
- Cost is currently a primary barrier to treatment
Acknowledgements

- Dr. Philip Henderson
- Dr. Brendan McGuire
- Dr. Omar Massoud
- Dr. John Jacobs
- Dr. Joel Richter
References


12. Teshale E, et al. APRI and FIB-4 are Good Predictors of the Stage of Liver Fibrosis in Chronic Hepatitis B. The Chronic Hepatitis Cohort Study (CHeCS). J Viral Hepat. 2014;21(12):917-920.


Thank You