Tough Cases in HIV/HCV Coinfection

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Presentation prepared by: J Scott
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Disclosures

• In the past year, JS has served on Advisory Boards for Gilead and Tibotec/Janssen; and received grant funding for clinical trials from Genentech, Merck, and Vertex.

• JS serves on the DSMB for Tacere Therapeutics, Inc
Objectives

- To discuss the pros/cons of treating Hep C now vs. waiting
- To know the efficacy for using SMV/SOF for coinfected patients
Case 1

- 55 yo W man, coinfected with HIV/HCV wants to know if he should be treated for HCV.
- Diagnosed with HIV in 1990, nadir CD4 100, on ARVs w/ good suppression for last 15 yrs. Now on RAL + TDF/FTC w/ CD4 of 500 and HIV <15 c/ml.
- Diagnosed with HCV 1995, never treated before.
- GT 1a, HCV RNA 1 million IU/ml.
- Liver Bx 2012: F4
- INR 1.1, TB 0.7, Cr 0.8, plt 100, alb 3.6
- Never had decompensation, no ascites
- Otherwise in good health: no DM, CAD, CKD or significant psych issues.
Survey: What would you recommend?

A. Treat now with Peginterferon + Ribavirin + Sofosbuvir x 12 wks
B. Treat now with Sofosbuvir + Simeprevir x 12 wks
C. Treat now with Sofosbuvir + Simeprevir + RBV x 12-24 wks
D. Treat now with Sofosbuvir + RBV x 24 wks
E. Wait for SOF/LDV or other non-IFN based therapy in next 12 mos

URL:  http://rwpoll.com
Code: uwecho
FDA label for Sofosbuvir (Sovaldi)

- GT 2 and 3 naives
- GT 2 and 3 intolerant or non-responders
- GT 1,4 naives and P/R failures (non-decompensated cirrhotics and non-cirrhotics)
- Patients with HCC and awaiting liver txp
- Both HIV+ and HIV-
Dosage and Duration

- 400 mg tablet once daily
- No food effect
- “SOVALDI in combination with ribavirin for 24 weeks can be considered for CHC patients with genotype 1 infection who are interferon ineligible.”

<table>
<thead>
<tr>
<th></th>
<th>SOF, PegIFN, &amp; RVN</th>
<th>SOF/RBV</th>
</tr>
</thead>
<tbody>
<tr>
<td>GT1: naïve, P/R failures, HIV+/-</td>
<td>12 weeks</td>
<td>-</td>
</tr>
<tr>
<td>GT 2: naïve or P/R failures</td>
<td>-</td>
<td>12 wks</td>
</tr>
<tr>
<td>GT 3: naïve or P/R failures</td>
<td>-</td>
<td>24 wks</td>
</tr>
<tr>
<td>HCC, awaiting OLT</td>
<td>-</td>
<td>48 wks</td>
</tr>
</tbody>
</table>
## PHOTON-1 Trial: Features

- **Design**: Randomized, controlled, open-label, phase 3, non-inferiority trial using sofosbuvir + ribavirin in HCV-HIV and GT 1, 2, 3

- **Setting**: United States and Puerto Rico

- **Entry Criteria**
  - HIV coinfection; HCV Genotype 1, 2, or 3
  - Treatment naïve or treatment experienced
  - Compensated cirrhosis permitted; no platelet cutoff
  - CD4 ≥ 200 if on stable ARV therapy; CD4 ≥ 500 if no ARV therapy
  - Stable antiretroviral therapy = HIV RNA < 50 copies/ml > 8 weeks

- **Patient Characteristics**
  - N = 182 HCV-HIV coinfected patients
  - Baseline mean CD4 count: range 585-658 cells/mm³
  - On ARV Rx: GT1 (98%); GT/32 naive (90%); GT/32 experienced (95%)

- **Primary End-Points**: Efficacy (SVR12), safety, and impact on HIV

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**Source:** Naggie S, et al. 21st CROI. 2014: Abstract 26. Slide courtesy of D. Spach
HIV/HCV Coinfected Patients: PHOTON-1

- Wide range of ARVs permitted
- Compensated cirrhotics permitted
- HIV RNA had to be undetectable for at least 8 wks
- CD4 >200 cells/ml if on ARVs or >500 cells/ml if untreated

Sofosbuvir and Ribavirin for HCV-HIV Coinfection
PHOTON-1 Trial: Results

# Sofosbuvir + Simeprevir +/- Ribavirin for HCV GT 1

## COSMOS Trial: Study Features

<table>
<thead>
<tr>
<th><strong>COSMOS Trial: Features</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Design</strong>: Randomized, phase 2a, open-label, using sofosbuvir + simeprevir +/- ribavirin in treatment naive or experienced, chronic HCV GT 1</td>
</tr>
<tr>
<td><strong>Setting</strong>: United States and Europe</td>
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<tr>
<td><strong>Entry Criteria</strong></td>
</tr>
<tr>
<td>- Chronic HCV Genotype 1</td>
</tr>
<tr>
<td>- Cohort 1: prior null responders; Metavir F0-F2</td>
</tr>
<tr>
<td>- Cohort 2: treatment naïve &amp; prior null responders; Metavir F3-F4</td>
</tr>
<tr>
<td><strong>Patient Characteristics (range in different treatment arms)</strong></td>
</tr>
<tr>
<td>- N = 167 (n = 80 in Cohort 1 and n = 87 in Cohort 2)</td>
</tr>
<tr>
<td>- Baseline GT1a with Q80K: Cohort 1 = 50%; Cohort 2 = 40%</td>
</tr>
<tr>
<td>- Non-CC IL28b Genotype: Cohort 1 = 94%; Cohort 2 = 79%</td>
</tr>
<tr>
<td><strong>End-Points</strong>: Primary = SVR12; Secondary = safety</td>
</tr>
</tbody>
</table>

**Cohort 1: Prior Null Responders; Metavir Scores F0-F2**

<table>
<thead>
<tr>
<th>Week</th>
<th>0</th>
<th>12</th>
<th>24</th>
<th>36</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 24</td>
<td>SOF + SMV + RBV</td>
<td>SVR12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N = 15</td>
<td>SOF + SMV</td>
<td>SVR12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N = 27</td>
<td>SOF + SMV + RBV</td>
<td>SVR12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N = 14</td>
<td>SOF + SMV</td>
<td>SVR12</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Drug Dosing**
- SOF = Sofosbuvir: 400 mg once daily
- SMV = Simeprevir: 150 mg once daily
- RBV = Ribavirin (weight-based and divided bid): 1000 mg/day if < 75 kg or 1200 mg/day if ≥ 75 kg

**Source:** Sulkowski M, et al. 49th EASL. April 2014. Abstract 07.
Sofosbuvir + Simeprevir +/- Ribavirin for HCV GT 1
COSMOS Trial: Results for Cohort 1

• COSMOS (Cohort 1): SVR 12 by Regimen


SOF = sofosbuvir; SMV = simeprevir; RBV = ribavirin

- 24-Week Treatment
- 12-Week Treatment
Sofosbuvir + Simeprevir +/- Ribavirin for HCV GT 1

COSMOS Trial: Design for Cohort 2

- **Cohort 2**: Treatment Naïve & Prior Null Responders; Metavir Scores F3-F4

<table>
<thead>
<tr>
<th>Week</th>
<th>0</th>
<th>12</th>
<th>24</th>
<th>36</th>
</tr>
</thead>
<tbody>
<tr>
<td>N =30</td>
<td>SOF + SMV + RBV</td>
<td>SVR12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N =16</td>
<td>SOF + SMV</td>
<td>SVR12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N =27</td>
<td>SOF + SMV + RBV</td>
<td>SVR12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N =14</td>
<td>SOF + SMV</td>
<td>SVR12</td>
<td></td>
<td></td>
</tr>
</tbody>
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**Drug Dosing**
- Sofosbuvir: 400 mg once daily
- Simeprevir: 150 mg once daily
- Ribavirin (weight-based and divided bid): 1000 mg/day if < 75 kg or 1200 mg/day if ≥ 75 kg

Sofosbuvir + Simeprevir +/- Ribavirin for HCV GT 1
COSMOSOS Trial: Results

- COSMOS (Cohort 2 with F3-F4 Fibrosis):
  - SVR12 by Regimen


<table>
<thead>
<tr>
<th>Regimen</th>
<th>SVR12 (%)</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOF + SMV + RBV (24 weeks)</td>
<td>93</td>
<td>28/30</td>
</tr>
<tr>
<td>SOF + SMV (24 weeks)</td>
<td>100</td>
<td>16/16</td>
</tr>
<tr>
<td>SOF + SMV + RBV (12 weeks)</td>
<td>93</td>
<td>25/27</td>
</tr>
<tr>
<td>SOF + SMV (12 weeks)</td>
<td>93</td>
<td>13/14</td>
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SOF = sofosbuvir; SMV = simeprevir; RBV = ribavirin
The Coming Pipeline for HCV

• Protease Inhibitors:
  - 2\textsuperscript{nd} Generation: MK 5172 (2015) in conjunction with MK 8742 (NS5a)
  - ABT 450/ritonavir (Nov 2014)
  - Asunaprevir (Dec 2014)

• NS5a Inhibitors
  - Daclatasvir (Dec 2014), Ledipasvir + SOF (Oct 2014), ABT 267 ombitasvir (Nov 2014)

• Non-nucleoside inhibitors
  - ABT 333 dasabuvir (Nov 2014)
Sofosbuvir + Ledipasvir Phase 3 Studies

ION-1 Trial

- **Design**: Open-label, randomized, phase 3, using fixed-dose combination of ledipasvir-sofosbuvir +/- ribavirin in treatment-naïve patients with GT1 HCV
- **Setting**: 99 sites in United States and Europe
- **Entry Criteria**
  - Chronic HCV Genotype 1 (n = 865)
  - HIV negative; 18 years or older
  - No prior HCV treatment
  - Patients with cirrhosis accepted (up to 20% of patients)
- **Primary End-Point**: SVR12

Ledipasvir-Sofosbuvir +/- Ribavirin in Treatment-Naïve HCV GT 1 ION-1 Study: Study Design

<table>
<thead>
<tr>
<th>Week</th>
<th>0</th>
<th>12</th>
<th>24</th>
<th>36</th>
</tr>
</thead>
<tbody>
<tr>
<td>GT-1 Naive</td>
<td>n = 214</td>
<td>LDV-SOF</td>
<td>SVR12</td>
<td></td>
</tr>
<tr>
<td>GT-1 Naive</td>
<td>n = 217</td>
<td>LDV-SOF + RBV</td>
<td>SVR12</td>
<td></td>
</tr>
<tr>
<td>GT-1 Naive</td>
<td>n = 217</td>
<td>LDV-SOF</td>
<td>SVR12</td>
<td></td>
</tr>
<tr>
<td>GT-1 Naive</td>
<td>n = 217</td>
<td>LDV-SOF + RBV</td>
<td>SVR12</td>
<td></td>
</tr>
</tbody>
</table>

**Drug Dosing**

Ledipasvir-sofosbuvir (90/400 mg): fixed dose combination; one pill once daily
Ribavirin (weight-based and divided bid): 1000 mg/day if < 75 kg or 1200 mg/day if ≥ 75 kg

**Abbreviations**: LDV = ledipasvir; SOF = sofosbuvir; RBV = ribavirin

Ledipasvir-Sofosbuvir +/- Ribavirin in Treatment-Naïve HCV GT 1
ION-1 Study: Results

- ION-1: SVR 12 by Treatment Duration and Regimen


LDV= ledipasvir; SOF = sofosbuvir; RBV = ribavirin
Ledipasvir-Sofosbuvir +/- Ribavirin in Treatment-Naïve HCV GT 1
ION-1 Study: Results

<table>
<thead>
<tr>
<th></th>
<th>Without Cirrhosis</th>
<th>With Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>12-Week Treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDV-SOF</td>
<td>179/179</td>
<td>32/33</td>
</tr>
<tr>
<td>LDV-SOF + RBV</td>
<td>178/178</td>
<td>33/33</td>
</tr>
<tr>
<td><strong>24-Week Treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDV-SOF</td>
<td>181/182</td>
<td>31/32</td>
</tr>
<tr>
<td>LDV-SOF + RBV</td>
<td>179/179</td>
<td>36/36</td>
</tr>
</tbody>
</table>

Patients (%) with SVR 12

Treat Now or Wait?

**Treat Now:**
- 80-90% chance of cure right now
- Insurance will likely pay for it
- Side effects from IFN/RBV are not as major a consideration with 12 wks

**Treat Later:**
- 90-95% chance of cure in next year
- Better tolerated
- Insurance will still likely pay for it

Stay tuned! HCV Guidelines from IDSA/AASLD to address decision of **when** to treat late Jun/early July 2014