Treatment of Chronic HCV Genotype 2

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Treatment of Chronic HCV Genotype 2

• Background and Definitions
• Initial Treatment
• Retreatment of Patients with Prior Treatment Failure
• Disappearance of Issues and Controversies
• Is There a Need for Future Therapies?
• Summary
TREATMENT OF CHRONIC HEPATITIS C: GENOTYPE 2

Background and Definitions
Treatment of Chronic HCV Genotype 2

Background

• Genotype 2 is second most common HCV genotype in US
• Up to 85% of patients have contraindications for interferon therapy
• Small proportion of untreated patients are genotype 2 today due to historically high treatment and cure rates
Sustained Virologic Response (SVR12) = Undetectable HCV RNA 12 Weeks Post Treatment
TREATMENT OF CHRONIC HEPATITIS C: GENOTYPE 2

Initial Treatment
## Genotype 2 HCV: Initial Treatment

| Recommended Regimen, Patients without Cirrhosis | Sofosbuvir + Ribavirin x 12 weeks |
| Recommended Regimen, Patients with Cirrhosis   | Sofosbuvir + Ribavirin x 16 weeks |
| Recommended Regimen, Patients Not Able to Tolerate Ribavirin | Daclatasvir + Sofosbuvir x 12 weeks (consider 24 weeks with cirrhosis) |
Treatment-Naïve with Genotype 2 Chronic HCV

Key Studies

- **Sofosbuvir + Ribavirin**
  - FISSION
  - POSITRON
  - VALENCE

- **Daclatasvir + Sofosbuvir**
  - A144040
  - ALLY-2
Initial Therapy: Genotype 2
Sofosbuvir plus Ribavirin
Sofosbuvir + Ribavirin for Treatment-Naïve HCV GT 2 or 3
FISSION Trial: Design

<table>
<thead>
<tr>
<th>Week</th>
<th>0</th>
<th>12</th>
<th>24</th>
<th>36</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>256</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>243</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Sofosbuvir + RBV (weight-based)**

**Peginterferon + RBV (fixed-dose)**

**Drug Dosing**

- Sofosbuvir: 400 mg once daily
- Peginterferon alfa-2a: 180 µg once weekly
- Weight-based Ribavirin (in 2 divided doses): 1000 mg/day if < 75 kg or 1200 mg/day if ≥ 75 kg
- Fixed-dose Ribavirin (in 2 divided doses): 800 mg/day

Sofosbuvir + Ribavirin for Treatment-Naïve HCV GT 2 or 3 FISSION Trial: Results

SVR12 by Genotype

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Sofosbuvir + RBV</th>
<th>PEG + RBV</th>
</tr>
</thead>
<tbody>
<tr>
<td>GT 2 and 3 (n=496)</td>
<td>67/170/253</td>
<td>67/162/243</td>
</tr>
<tr>
<td>GT 2 (n=137)</td>
<td>97/68/70</td>
<td>78/52/67</td>
</tr>
<tr>
<td>GT 3 (n=359)</td>
<td>63/110/176</td>
<td>56/102/183</td>
</tr>
</tbody>
</table>

RBV = Ribavirin; PEG = Peginterferon

Sofosbuvir + Ribavirin for HCV GT 2 or 3 (PEG-IFN not an option)

POSITRON Trial: Design

<table>
<thead>
<tr>
<th>Week</th>
<th>0</th>
<th>12</th>
<th>24</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 207</td>
<td>Sofosbuvir + RBV 12 weeks</td>
<td>SVR12</td>
<td></td>
</tr>
<tr>
<td>N = 71</td>
<td>Placebo 12 weeks</td>
<td>SVR12</td>
<td></td>
</tr>
</tbody>
</table>

**Drug Dosing**
- Sofosbuvir: 400 mg once daily
- Weight-Based Ribavirin (in 2 divided doses): 1000 mg/day if < 75 kg or 1200 mg/day if ≥ 75 kg

Sofosbuvir + Ribavirin for HCV GT 2,3 (PEG not an option) POSITRON: Results with Sofosbuvir + Ribavirin

SVR12 by HCV Genotype

Placebo arm = 0% SVR12

Sofosbuvir + Ribavirin for Treatment Naïve & Experienced HCV GT 2 or 3

**VALENCE: Treatment Arms**

<table>
<thead>
<tr>
<th>Week</th>
<th>0</th>
<th>12</th>
<th>24</th>
<th>36</th>
</tr>
</thead>
<tbody>
<tr>
<td>GT 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Sofosbuvir + RBV</strong> (n = 73)</td>
<td></td>
<td></td>
<td>SVR12</td>
</tr>
<tr>
<td>GT 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Sofosbuvir + RBV</strong> (n = 250)</td>
<td></td>
<td></td>
<td>SVR12</td>
</tr>
</tbody>
</table>

Note: 85 patients enrolled in placebo arm

**Original Study Protocol**: Placebo versus 12 weeks treatment for GT 2 and 3.

**Amended Protocol**: GT3 treatment extended from 12 to 24 weeks; Placebo arm offered alternative treatment

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

Sofosbuvir + Ribavirin for Treatment Naïve & Experienced HCV GT 2 or 3

VALENCE: Results for Treatment-Naïve GT 2

SVR12 for Treatment-Naïve GT 2

Initial Therapy: Genotype 2
Daclatasvir plus Sofosbuvir
Daclatasvir + Sofosbuvir +/- Ribavirin for HCV GT 1-3
A1444040 Design: Treatment-Naïve 24 Week Rx (Part 1)

**Drug Dosing**
Daclatasvir (DCV): 60 mg once daily
Sofosbuvir (SOF): 400 mg once daily
Ribavirin (RBV): GT1, given weight-based and divided bid (1000 mg/day if < 75kg or 1200 mg/day if ≥ 75kg)
Ribavirin (RBV): GT 2,3 (800 mg/day)

Daclatasvir + Sofosbuvir +/- Ribavirin for HCV GT 1-3 Treatment-Naïve 24 Week Rx: Results (Part 1)

DCV = daclatasvir; SOF = sofosbuvir; RBV = ribavirin

Daclatasvir + Sofosbuvir for HCV GT 1-4 and HIV Coinfection
ALLY-2 Trial: Design

**Drug Dosing**
Daclatasvir: 60 mg once daily; with efavirenz and nevirapine the dose was increased to 90 mg once daily and with ritonavir-boosted protease inhibitors the dose was decreased to 30 mg once daily
Sofosbuvir: 400 mg once daily

Daclatasvir + Sofosbuvir for HCV GT 1-4 and HIV Coinfection
ALLY-2 Trial: Results for Genotype 2

SVR12, Genotype 2

<table>
<thead>
<tr>
<th>Treatment Status</th>
<th>Duration</th>
<th>Patients with SVR12 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment Naïve</td>
<td>DCV + SOF x 12 weeks</td>
<td>100 (11/11)</td>
</tr>
<tr>
<td></td>
<td>DCV + SOF x 8 weeks</td>
<td>83 (5/6)</td>
</tr>
<tr>
<td>Treatment Experienced</td>
<td>DCV + SOF x 12 weeks</td>
<td>100 (2/2)</td>
</tr>
</tbody>
</table>


Abbreviations: DCV = daclatasvir; SOF = sofosbuvir
TREATMENT OF CHRONIC HEPATITIS C: GENOTYPE 2
Retreatment of Persons in Whom Prior Therapy Failed
### Genotype 2 HCV: Retreatment, Prior Failure with Peginterferon + Ribavirin

<table>
<thead>
<tr>
<th>Recommended Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sofosbuvir + Ribavirin x 16 or 24 weeks*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Alternative Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sofosbuvir + Ribavirin + Peginterferon x 12 weeks (if patient interferon eligible)</td>
</tr>
</tbody>
</table>

*The decision to use 16 or 24 weeks should be made on an individual patient basis*
**Genotype 2 HCV: Retreatment, Prior Failure with Sofosbuvir + Ribavirin**

<table>
<thead>
<tr>
<th>Recommended Regimen for Patients NOT Eligible to Receive Interferon</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daclatasvir + Sofosbuvir +/- Ribavirin x 24 weeks</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommended Regimen for Patients Eligible to Receive Interferon</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sofosbuvir + Ribavirin + Peginterferon x 12 weeks</td>
</tr>
</tbody>
</table>
### AASLD/IDSA/IAS-USA 2015 HCV Treatment Recommendations

#### Criteria for Interferon Ineligible

**NOT Eligible to Receive Interferon Defined as one or more of the following:**

- Intolerance to interferon
- Autoimmune hepatitis and other autoimmune disorders
- Hypersensitivity to peginterferon or any of its components
- Decompensated hepatic disease
- Major uncontrolled depressive illness
- A baseline neutrophil count below 1500/μL, a baseline platelet count below 90,000/μL or baseline hemoglobin below 10 g/dL
- A history of preexisting cardiac disease

Source: AASLD/IDSA/IAS-USA ([www.hcvguidelines.org](http://www.hcvguidelines.org)).
Retreatment of Genotype 2 Chronic HCV

Key Studies

• Prior Failure with Peginterferon + Ribavirin
  - FUSION
  - VALENCE
  - LONESTAR-2
  - BOSON

• Prior Failure with Sofosbuvir + Ribavirin
  - Retreatment of prior Sofosbuvir Failure
Sofosbuvir + RBV in Treatment-Experienced HCV GT 2 or 3
FUSION Trial: Design

<table>
<thead>
<tr>
<th>Week</th>
<th>0</th>
<th>12</th>
<th>16</th>
<th>24</th>
<th>28</th>
</tr>
</thead>
</table>

N =103

Sofosbuvir + RBV 12 weeks

Placebo

SVR12

N =98

Sofosbuvir + RBV 16 weeks

SVR12

Drug Dosing
Sofosbuvir: 400 mg once daily
Weight-Based Ribavirin (in 2 divided doses): 1000 mg/day if < 75 kg or 1200 mg/day if ≥ 75 kg

Sofosbuvir + RBV in Treatment-Experienced HCV GT 2 or 3 FUSION Trial: Results for GT2

SVR12 for Treatment-Experienced GT2

<table>
<thead>
<tr>
<th>Treatment</th>
<th>GT 2 (All)</th>
<th>Without Cirrhosis</th>
<th>With Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOF + RBV (12 wks)</td>
<td>86/36</td>
<td>96/25</td>
<td>60/9</td>
</tr>
<tr>
<td>SOF + RBV (16 wks)</td>
<td>94/32</td>
<td>100/23</td>
<td>78/9</td>
</tr>
</tbody>
</table>

SOF = Sofosbuvir; RBV = Ribavirin

Sofosbuvir + Ribavirin for Treatment Naïve & Experienced HCV GT 2 or 3

VALENCE: Treatment Arms

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<tr>
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Note: 85 patients enrolled in placebo arm

Original Study Protocol: Placebo versus 12 weeks treatment for GT 2 and 3.
Amended Protocol: GT3 treatment extended from 12 to 24 weeks; Placebo arm offered alternative treatment

Drug Dosing
Sofosbuvir 400 mg once daily
Ribavirin (weight-based and divided bid): 1000 mg/day if < 75 kg or 1200 mg/day if ≥ 75 kg

Sofosbuvir + Ribavirin for Treatment Naïve & Experienced HCV GT 2 or 3

Treatment Experienced GT2: 12 weeks of treatment

SVR12 for Treatment-Experienced GT 2

Sofosbuvir + PEG + RBV in Treatment-Experienced HCV GT 2 or 3
LONESTAR-2 Trial: Design

**Drug Dosing**
- Sofosbuvir: 400 mg once daily
- Peginterferon alfa-2a: 180 µg once weekly
- Ribavirin (weight-based and in 2 divided doses): 1000 mg/day if < 75 kg or 1200 mg/day if ≥ 75 kg

Sofosbuvir + PEG + RBV for 12 weeks in Treatment-Experienced HCV GT 2 or 3
LONESTAR-2 Trial: Results

SVR12 in Treatment-Experienced by HCV Genotype

Sofosbuvir + PEG + RBV for 12 weeks in Treatment-Experienced HCV GT 2 or 3
LONESTAR-2 Trial: Results

LONESTAR-2 Trial: SVR12 by Cirrhosis Status

<table>
<thead>
<tr>
<th>Patients (%) with SVR12</th>
<th>Genotype 2</th>
<th>Genotype 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Cirrhosis</td>
<td>9/9 (100%)</td>
<td>10/12 (83%)</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>13/14 (93%)</td>
<td>10/12 (83%)</td>
</tr>
</tbody>
</table>

Sofosbuvir + Ribavirin +/- Peginterferon for HCV GT 2 or 3
BOSON: Treatment Arms

**Drug Dosing**
Sofosbuvir 400 mg once daily
Ribavirin (weight-based and divided bid): 1000 mg/day if < 75 kg or 1200 mg/day if ≥ 75 kg
Peginterferon alfa-2a: 180 ug/week
Sofosbuvir + Ribavirin +/- Peginterferon for HCV GT 2 or 3

BOSON: Results

SVR12 by Regimen and Genotype

Retreatment of SOF + RBV Failure with SOF-Containing Regimens in GT 2 or 3

**Study Design**

N = 73

N = 34

GT2 or GT3

Sofosbuvir + RBV

Drug Dosing
Sofosbuvir: 400 mg once daily
Peginterferon alfa-2a: 180 µg once weekly
Weight-based Ribavirin (in 2 divided doses): 1000 mg/day if < 75 kg or 1200 mg/day if ≥ 75 kg

Retreatment of SOF + RBV Failure with SOF-Containing Regimens in GT 2 or 3
Preliminary Results, by Genotype

SVR12 by Regimen and HCV Genotype

TREATMENT OF CHRONIC HEPATITIS C: GENOTYPE 2

Issues and Controversies
## Hepatitis C Genotype 2
### Estimated Medication Costs for Treatment-Naïve & Prior Relapsers

### Patients with GT 2 HCV: Initial Treatment

<table>
<thead>
<tr>
<th>Recommended Regimen and Duration</th>
<th>AWAC Regimen Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sofosbuvir + Ribavirin x 12 weeks</td>
<td>$85,000</td>
</tr>
<tr>
<td>Sofosbuvir + Ribavirin x 16 weeks</td>
<td>$113,000</td>
</tr>
<tr>
<td>Daclatasvir + Sofosbuvir x 12 weeks</td>
<td>$147,000</td>
</tr>
<tr>
<td>Daclatasvir + Sofosbuvir x 24 weeks</td>
<td>$295,000</td>
</tr>
</tbody>
</table>

**AWAC** = Average Wholesale Acquisition Cost

*Note: health care systems may receive substantial discounts*
## Hepatitis C Genotype 2
### Estimated Medication Costs for Treatment-Naïve & Prior Relapsers

<table>
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<td>Sofosbuvir + Ribavirin x 16 weeks</td>
<td>$113,000</td>
</tr>
<tr>
<td>Sofosbuvir + Ribavirin x 24 weeks</td>
<td>$170,000</td>
</tr>
<tr>
<td>Sofosbuvir + Ribavirin + Peginterferon x 12 weeks</td>
<td>$97,000</td>
</tr>
<tr>
<td>Daclatasvir + Sofosbuvir +/- Ribavirin x 24 weeks</td>
<td>$295,000</td>
</tr>
</tbody>
</table>

**AWAC = Average Wholesale Acquisition Cost**

Note: health care systems may receive substantial discounts
Treatment of Genotype 2 Chronic HCV
Issues and Controversies

• Cost of Therapy: what is actual discounted cost and is there a need to wait for price competition?

• With cure rates as high as 96%, are we over-treating most patients by treating patients for 12-24 weeks?
  - Can we shorten therapy to 4 or 6 weeks to save treatment costs?
  - Can we revitalize response guided therapy or find pretreatment predictors of SVR with short therapy?

• When to Defer or Decline Therapy:
  - Decisions on when to warehouse?
  - Based on mild histology or lack of evidence of systemic disease
  - Short lifespan
  - Noncompliance

• (Non) Role of IL-28b Testing, now obviated

• For treatment purposes, liver fibrosis staging primarily used to meet insurance requirements and determine HCC surveillance strategy
## HCV Therapy for Genotype 2 Chronic HCV
Cost Analysis Based on Cost per SVR

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Regimen Options</th>
<th>SVR</th>
<th>Cost per SVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naïve, no cirrhosis</td>
<td>SOF + RBV x 12 wks</td>
<td>92-98%</td>
<td>$95,263</td>
</tr>
<tr>
<td>Naïve, cirrhosis</td>
<td>SOF + RBV x 16 wks</td>
<td>91-94%</td>
<td>~$154,658</td>
</tr>
<tr>
<td>Treatment experienced, no cirrhosis</td>
<td>SOF + RBV x 12 wks</td>
<td>91-96%</td>
<td>$96,276</td>
</tr>
<tr>
<td>Treatment experienced, cirrhosis</td>
<td>SOF + RBV x 16 wks</td>
<td>78%</td>
<td>$154,658</td>
</tr>
<tr>
<td></td>
<td>SOF + PEG + RBV x 12 wks</td>
<td>93%</td>
<td>$113,269</td>
</tr>
</tbody>
</table>

Source for Figure: Camilla Graham, MD, MPH. Beth Israel Deaconess Medical Center

Data Sources:
(3) Antiviral Drugs Advisory Committee Meeting, FDA and Gilead reviews, 10/25/2013.
How is cost of therapy impacting treatment decisions?
HEPATITIS C: GENOTYPE 2

Treatment Regimens Under Study
Possible Future Regimens for GT-2

• Unlikely
  - Ledipasvir-Sofosbuvir
  - Ombitasvir-Paritaprevir-Ritonavir

• Likely
  - ABT-493 plus ABT-450
  - Regimens with 5816
Treat now or defer therapy?
Factors Favoring Urgent GT2 Treatment

- Advanced Fibrosis (F3-F4)
  - Platelet count < 150,000/uL
  - Large spleen and/or portal vein
  - Esophageal varices

- Synthetic dysfunction, decompensated disease

- Systemic disease
  - Cryoglobulinemia ([+] Rheumatoid Factor)
Summary Points for Treatment of Chronic HCV GT-2

• Genotype 2 highly responsive to 12 weeks of all-oral therapy
• Relatively little retreatment data since high SVR rates with therapy in naïve patients
• Few GT2 studies moving forward with new therapies
• Will be difficult to enroll large studies required for licensing trials
• New pangenotypic drugs will be used for genotype 2 off-label (prediction)
This slide deck is from the University of Washington’s *Hepatitis C Online* and *Hepatitis Web Study* projects.

**Hepatitis C Online**

[www.hepatitisc.uw.edu](http://www.hepatitisc.uw.edu)

**Hepatitis Web Study**


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