Case 2: Current Issues in Hepatitis C Virus (HCV) Management: Treat Now or Wait

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Learning Objectives
After attending this presentation, learners will be able to:
- Assess fibrosis stage in HCV
- Determine who needs treatment now and who can wait
- Understand current Protease inhibitor therapy with Pegylated interferon and ribavirin
- Know what all oral drugs are being studied

Case 2
45 y/o man with HCV GT-1b infection, he has known about his HCV for 10 years

History of depression

Never had a liver biopsy or treatment

He has heard of the new HCV medications and wants to know if he should be treated?
What do you need now?

1. History including ETOH use
2. Assessment of fibrosis: biopsy, transient elastography or non-invasive marker of liver fibrosis
3. EGD
4. Ultrasound
5. IL28b
6. Something else

Case 2

• He has a history of moderate ETOH use but now abstains
• He has diagnosis of DM, well controlled
• His Labs are:
  – Platelet count 200,000/L
  – INR 1.0
  – Albumin 4.1 g/dL
  – HCV RNA 2.1 x 10^6 IU/mL

What now?

Which factor is the most predictive of this patient’s long-term prognosis?

1. ALT
2. HCV RNA
3. Stage of liver fibrosis
4. IL28B haplotype
SVR Substantially Decreased Risk of All-Cause Mortality in Patients With Common Comorbidities

- In a large study by the US Department of Veterans Affairs, SVR improved survival in patients with common comorbidities.

Risk factors for poor outcomes

- Severe fibrosis
- Diabetes
- Obesity
- IL28 TT
- Prior null response (NR) vs Responder relaper (RR)

Interferon λ in HCV Innate Immunity?

Biologically Plausible
Case 2

- His Labs are:
  - Platelet count 200,000/L
  - INR 1.0
  - Albumin 4.1 g/dL
  - HCV RNA 2.1 x 10^6 IU/mL
- He has a serum marker (fibrosure) F2
- He has a liver biopsy F0

What now?
How do you proceed?

1. Start PI plus pegIFN/ribavirin
2. Wait until there are two different DAAs in combination
3. Start with lead-in of pegIFN/RBV to decide role of DAA
4. Enroll in study with all DAA

Different Types of “Non-Response”

EVR: Partial versus Complete
RGT = response guided therapy
Similarities/Differences in Phase III Studies of TVR and BOC in GT1 Naive Pts

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>PR lead-in?</td>
<td>No</td>
<td>Yes: 4 wks</td>
</tr>
<tr>
<td>PegIFN alfa formulation</td>
<td>2a</td>
<td>2b</td>
</tr>
<tr>
<td>PI dosing requirements</td>
<td>TID; administer with fatty meal</td>
<td>TID with food not low fat</td>
</tr>
<tr>
<td>Duration of PI triple therapy</td>
<td>8-12 wks followed by 12-40 wks PR</td>
<td>24-44 wks after 4 wks PR lead-in</td>
</tr>
<tr>
<td>Qualification for shortened therapy (response guided)</td>
<td>Undetectable HCV RNA Wk 4 and 12 of triple therapy</td>
<td>Undetectable HCV RNA W8 and w24 of triple therapy</td>
</tr>
<tr>
<td>Qualified for shortened therapy, %</td>
<td>58 (24 wks)</td>
<td>44 (28 wks)</td>
</tr>
<tr>
<td>SVR, %</td>
<td>69-75</td>
<td>63-66</td>
</tr>
<tr>
<td>Relapse, %</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Adverse events more frequent in PI arms</td>
<td>Rash, anemia, pruritus, nausea</td>
<td>Anemia, dysgeusia</td>
</tr>
</tbody>
</table>


Response Guided Therapy

1. All patients are candidate for RGT
2. Only naïve to treatment patients are candidates for RGT
3. RGT is the same for Boceprevir and telaprevir
4. HCV HIV patients are candidates for RGT
5. Non responders are candidates for RGT
6. Cirrhotic patients are not candidates for RGT

TELAPREVIR (ADVANCE Study):
Study Design & Results

<table>
<thead>
<tr>
<th>Treatment</th>
<th>SVR</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR48 (control) n=330*</td>
<td>44%</td>
<td>65%</td>
</tr>
<tr>
<td>T8PR24 or T12PR48 n=330*</td>
<td>75%</td>
<td>75%</td>
</tr>
<tr>
<td>Peg IFN + RBV</td>
<td>No further treatment</td>
<td>Peg IFN + RBV</td>
</tr>
<tr>
<td>Peg IFN + RBV</td>
<td>Peg IFN + RBV</td>
<td>Peg IFN + RBV</td>
</tr>
</tbody>
</table>

Jacobson et al., AASLD 2010

IAS–USA
**Response-Guided Therapy: Telaprevir**

- **Naives, relapsers**
  - eRVR+ (ud w 4 and 12)
  - 24 weeks (TPR12/PR12)
  - eRVR-
  - 48 weeks (TPR12/PR36)
- **Nonresponders** (Partial and null), cirrhotics
  - 48 weeks (TPR12/PR36)

**Stopping Rules for Telaprevir**

*Treatment Naïve & Experienced*

<table>
<thead>
<tr>
<th>Week</th>
<th>HCV RNA</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>&gt;1000 IU/ml</td>
<td>Stop all therapy</td>
</tr>
<tr>
<td>12</td>
<td>&gt;1000 IU/ml</td>
<td>Stop all therapy</td>
</tr>
<tr>
<td>24</td>
<td>Detectable</td>
<td>Stop all therapy</td>
</tr>
</tbody>
</table>

**SPRINT-2 TRIAL DESIGN**

Poordad et al. AASLD Nov 2010 LB-4
BOC PR Primary Outcome SVR

Cohort 1 – non-AA

Cohort 2 – AA

Role of 4 week LI phase

Group 1 – non-AA

Response Guided Therapy

Group 1 – non-AA
Response-Guided Therapy: Boceprevir

- **Naives**: 28 or 48 weeks total therapy
  - HCV RNA undetectable at weeks 8, 24
    - 28 weeks (PR4/BPR24)
  - HCV detectable at w 8, undetectable w 24
    - 48 weeks (PR4/BPR32/PR12)

- **Relapsers, partial responders**: 36 or 48 weeks total therapy
  - HCV RNA detectable weeks 8, 24
    - 36 weeks (PR4/BPR32)
  - HCV RNA detectable w 8, undetectable w 24
    - 48 weeks (PR4/BPR32/PR12)

- **Null responders, cirrhotics**: 48 weeks total therapy
  - 48 weeks (PR4/PRB44)
  - Consider 4/44 regimen for patients with poor IFN response at 4 wks (Boceprevir Package Insert)

**Stopping Rules for Boceprevir**
*Treatment Naive & Experienced*

- **Week 12**
  - HCV RNA ≥100 IU/ml
    - Stop all therapy

- **Week 24**
  - HCV RNA detectable
    - Stop all therapy
PI + PEG/RBV Efficacy Data

Treatment-naive

- Telaprevir: 72-75% SVR
  - 58-65% eligible for shortened therapy
- Boceprevir: 63-66% SVR
  - 44% eligible for shortened therapy

Treatment-experienced

- Telaprevir: 47% (31-57-86)
- Boceprevir: 63% (x-46-72)

Case

- He elects to await newer therapies as he is uninterested in interferon therapy

Targets for Direct Acting Antivirals (DAA)

Telaprevir or Boceprevir with Peg/RBV produce superior SVR in naïve HCV-1

<table>
<thead>
<tr>
<th>TVR (ADVANCE)</th>
<th>BOC (SPRINT-2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TVR12/PR</td>
<td>BOC12/PR</td>
</tr>
<tr>
<td>750 mg q8h</td>
<td>(non-AA/AA)</td>
</tr>
<tr>
<td>Peg/R</td>
<td>Peg/R (non-AA/AA)</td>
</tr>
<tr>
<td>800 mg tid</td>
<td>800 mg tid</td>
</tr>
</tbody>
</table>

SVR: 75% 44% 67/42% 40/23%

Poordad F et al, NEJM 2011; 364:1195-1206
Jacobson I et al, NEJM 2011; 364:2405-2416

Issues with 1st Gen PIs PR in G1: Toxicities

<table>
<thead>
<tr>
<th></th>
<th>ADVANCE (TVR)</th>
<th>SPRINT-2 (BOC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>D/C for AEs</td>
<td>10%</td>
<td>7%</td>
</tr>
<tr>
<td>D/C for rash</td>
<td>7%</td>
<td>1%</td>
</tr>
<tr>
<td>Anemia (&lt;10/&lt;8.5 g/dL)</td>
<td>36%/9%</td>
<td>14%/2%</td>
</tr>
</tbody>
</table>

Jacobson I et al, Poordad F et al, NEJM 2011

The Promise of Triple Therapy Does Not Reach to All Groups


IAS–USA
April 23, 2013

M. G. Peters, MD
DAA therapy

1. BOC and TPV can only be used in genotype 1 patients
2. Second generation protease inhibitors have less resistance
3. Interferon will not be used with new DAA’s
4. Drug drug interactions will not be a problem with new DAA’s

Characteristics of HCV DAA Classes

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Protease inhibitors</th>
<th>Nucleos(t)ide Polymerase inhibitors</th>
<th>Non-nucleoside Polymerase inhibitors</th>
<th>NS5A inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potency</td>
<td>High; Variable among HCV genotypes</td>
<td>Moderate-high; Consistent across genotype, subtype</td>
<td>Variable; Variable among HCV genotypes</td>
<td>High; multiple HCV genotypes</td>
</tr>
<tr>
<td>Barrier to Resistance</td>
<td>Low 1a &lt; 1b</td>
<td>High 1a = 1b</td>
<td>Very Low 1a = 1b</td>
<td>Low 1a = 1b</td>
</tr>
<tr>
<td>Drug Interaction Potential</td>
<td>High</td>
<td>Low</td>
<td>Variable</td>
<td>Low to moderate</td>
</tr>
<tr>
<td>Toxicity</td>
<td>Rash, Anemia, TBilirubin</td>
<td>Mitochondrial, Nuc. interactions (ART, RBV)</td>
<td>Variable</td>
<td>Variable</td>
</tr>
<tr>
<td>Pharmacokinetics</td>
<td>Variable; QD to TID</td>
<td>QD</td>
<td>Variable; QD to TID</td>
<td>QD</td>
</tr>
<tr>
<td>Comments</td>
<td>2nd gen PI; better barrier; pangenotypic</td>
<td>Single target; Active site</td>
<td>Allergic; Many targets</td>
<td>Multiple enrolled MOA</td>
</tr>
</tbody>
</table>

Triple Therapy: PEG + RBV + DAA
ATOMIC: High Rate of SVR With 12 Wks of Sofosbuvir (GS-7977) + PegIFN/RBV

- SOF 400 mg qd
- Virologic relapse rare to date and not associated with primary resistance
  - No S282T observed
  
80 100 94 98 94 90 98 99 94 97 99 93
Wk EOT SVR4 SVR12

- SOF generally well tolerated in combination with PEG/RBV
  - No SAE attributed to GS-7977


PEG/RBV + Daclatasvir (NS5A) in Gt 1 or 4: COMMAND

- RCT of PEG-2a + RBV + DCV 20 mg/d, DCV 60 mg/d or PLA
- Week 12: PDR (week 4 <LOQ and W10 <LOD) re-randomized to receive P/R/D or P/R to week 24

<table>
<thead>
<tr>
<th></th>
<th>Gt 1 Overall (n=365)</th>
<th>Gt 1a (n=275)</th>
<th>Gt 1b (n=88)</th>
<th>Gt 4 (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SVR12 (&lt;LOQ)</td>
<td>65</td>
<td>64</td>
<td>38</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>64</td>
<td>64</td>
<td>38</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>36</td>
<td>36</td>
<td>36</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>59</td>
<td>59</td>
<td>31</td>
<td>31</td>
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<tr>
<td></td>
<td>75</td>
<td>75</td>
<td>87</td>
<td>87</td>
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<tr>
<td></td>
<td>67</td>
<td>67</td>
<td>67</td>
<td>67</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

P/R/Simeprevir (TMC435) in gt1 naïve and experienced: SVR24 by prior response to PR in F3/F4 patients

<table>
<thead>
<tr>
<th></th>
<th>ASPIRE treatment-experienced: F3/F4 pooled</th>
<th>ASPIRE treatment-experienced: F4 only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responder</td>
<td>65</td>
<td>67</td>
</tr>
<tr>
<td>Partial Responder</td>
<td>43</td>
<td>31</td>
</tr>
<tr>
<td>Null Responder</td>
<td>21</td>
<td>31</td>
</tr>
<tr>
<td>Relapser</td>
<td>20</td>
<td>31</td>
</tr>
</tbody>
</table>

Interferon-Free Regimens

Dual DAA Interferon-Free Therapy in Prior Null Responders

Daclatasvir (NS5A) 60 qd + Asunaprevir 200 bid (PI) x 24 wks (IFN-Free)

US Study
9/11 GT1a
Japanese Study
10/10 GT1b
AASLD 2012
GT1b only


SOUND-C2: Faldaprevir (BI 201335) + BI 207127 (NNI) +/- RBV in gt1 naive

SOUND-C2 BID Dosing Group: Higher SVR12 in Pts With GT1b or GT1a-IL28B CC

SVR According to IL28B and HCV Subtype: BID 28 Wks + RBV (ITT)


Daclatasvir (NS5A) + Asunaprevir (PI) + BMS-791325 (NNI) in GT1 Naive Pts: 12 vs 24 wks (Part 1)

Freedom from IFN and RBV

• No premature D/C for AE; HA, diarrhea > 10%


Daclatasvir + Sofosbuvir ± RBV in Tx-Naive GT1, 2/3 Pts

Treatment-naive patients with GT1a or 1b HCV infection (n = 44)

Follow-up

GS-7977 dosed 400 mg OD. Daclatasvir dosed 60 mg OD. RBV dosed by body weight for GT1 pts (1000 – 1200 mg/day); 800 mg/day for GT 2/3 pts.

Daclatasvir + Sofosbuvir ± RBV x 24W: Efficacy Analysis According to Genotype

Genotype 1a/1b HCV

Genotype 2/3 HCV


Background: AVIATOR Study Design

Methods (2): Treatment Arms Included in Analysis

Patients Included in Analysis
Null Responder: Dual vs Quadruple PI + NS5A ± pegIFN/RBV

- Group A: No PegIFN/RBV, n = 11
- Group B: PegIFN/RBV, n = 10

Electron
- Sofosbuvir (pol I) once daily, pangenotypic
- Ledipasvir (NS5A I) gen 1a 1b
- RBV
- Non cirrhotic
Study Design: Genotype 1 Cohorts

- n = 28: SOF + RBV (treatment-naive) • 84%, SVR12
- n = 18: SOF + RBV (null responders) • 16%, SVR12

We hypothesized that adding a second direct-acting antiviral would enhance response.

- n = 28: SOF + LDV + RBV (treatment-naive)
- n = 18: SOF + LDV + RBV (null responders)

LDV, ledipasvir; RBV, ribavirin; SOF, sofosbuvir.

Results: Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>SOF + RBV</th>
<th>SOF + LDV + RBV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean ± SD)</td>
<td>49 (34–68)</td>
<td>45 (30–63)</td>
</tr>
<tr>
<td>Male (%)</td>
<td>60%</td>
<td>50%</td>
</tr>
<tr>
<td>Caucasian (%)</td>
<td>97%</td>
<td>92%</td>
</tr>
<tr>
<td>Mean BMI (kg/m²)</td>
<td>26.7</td>
<td>26.1</td>
</tr>
<tr>
<td>IL28B genotype</td>
<td>CT</td>
<td>CT</td>
</tr>
<tr>
<td>GT1a (%)</td>
<td>95%</td>
<td>90%</td>
</tr>
<tr>
<td>HCV RNA, log E/R</td>
<td>6.1 (4.4–7.2)</td>
<td>6.9 (6.5–7.3)</td>
</tr>
</tbody>
</table>

Absence of cirrhosis was determined by transient elastography or biopsy.
RACE, rapid access early assessment cirrhosis; RBV, ribavirin.

Results: Efficacy

<table>
<thead>
<tr>
<th>Week</th>
<th>SOF + RBV</th>
<th>SOF + LDV + RBV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treatment-naive</td>
<td>Null responder</td>
</tr>
<tr>
<td>Week 1</td>
<td>8/25 (22)</td>
<td>8/10 (80)</td>
</tr>
<tr>
<td>Week 2</td>
<td>7/25 (28)</td>
<td>7/10 (70)</td>
</tr>
<tr>
<td>Week 4</td>
<td>23/25 (92)</td>
<td>10/10 (100)</td>
</tr>
<tr>
<td>SVR12</td>
<td>23/25 (92)</td>
<td>11/10 (100)</td>
</tr>
</tbody>
</table>

*Represents "Talobat" HCV Test 2.0 with limit of detection (LOD) of 15 IU/mL. HCV GT1a patient who did not achieve treatment response to SOF + RBV at week 12 was SVR at week 12.
Various Paradigms Being Developed Simultaneously

- IFN-free regimens
  - PEG IFN + Ribavirin + Single DAA
    - PI
    - NS3
    - NS5A
    - Cyclophilin antagonist
  - PEG IFN + Ribavirin + DAA-1 + DAA-2
  - Some trials involve more than one of these designs
  - PEG IFN lambda being evaluated
  - Proof of concept for curative potential of IFN-free regimens had been established

Studies of DAA + P/R

<table>
<thead>
<tr>
<th>PI</th>
<th>NS3A</th>
<th>Pol I</th>
<th>P/R</th>
<th>SVR12/24</th>
<th>HIV SVR12</th>
</tr>
</thead>
<tbody>
<tr>
<td>TPV</td>
<td>+</td>
<td></td>
<td></td>
<td>75%</td>
<td>75%(+29%)</td>
</tr>
<tr>
<td>BOC</td>
<td>+</td>
<td></td>
<td></td>
<td>67%</td>
<td>61%(+34%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SOF</td>
<td>+</td>
<td></td>
<td></td>
<td>90%</td>
<td></td>
</tr>
<tr>
<td>DAA</td>
<td>+</td>
<td></td>
<td>1a-58%</td>
<td>1b-87%</td>
<td>4-100%</td>
</tr>
<tr>
<td>SMV</td>
<td>+</td>
<td></td>
<td>31-81%</td>
<td>77%</td>
<td></td>
</tr>
</tbody>
</table>

Studies of DAA + RBV (g1 unless stated)

<table>
<thead>
<tr>
<th>PI</th>
<th>NS3A</th>
<th>Pol I</th>
<th>SVR 12/24 naive</th>
<th>SVR12/24 NA</th>
<th>HIV SVR12</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDV</td>
<td>SOF</td>
<td></td>
<td>100%</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SOF</td>
<td></td>
<td>84%</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>DAC</td>
<td>SOF</td>
<td></td>
<td>G 1-100%</td>
<td>G2/3 100%</td>
<td></td>
</tr>
<tr>
<td>BI FDV</td>
<td>BI NNI</td>
<td></td>
<td>69%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABT 450</td>
<td>ABT 267</td>
<td>NNI</td>
<td>97%</td>
<td>93%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ABT 267</td>
<td>NNI</td>
<td>90%</td>
<td>89%</td>
<td></td>
</tr>
<tr>
<td>ABT 450</td>
<td>ABT 333</td>
<td>NNI</td>
<td>85%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
In Deciding to Wait or Treat: what is important?

- Patient choice
- Fibrosis stage
- Whether new DAA’s are available
- Whether interferon free regimens are available
- Level of HCV RNA