HCV Case Study

Treat Now or Wait for New Therapies
Program Disclosure

• This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the sponsorship of Annenberg Center for Health Sciences at Eisenhower and the Chronic Liver Disease Foundation. Annenberg Center for Health Sciences at Eisenhower is accredited by the ACCME to provide continuing medical education for physicians.

• This program is supported by educational grants from Kadmon and Merck Pharmaceuticals.
Learning Objectives

• Describe current data on approved and experimental DAA’s used in combination with Pegylated Interferon and Ribavirin

• Define the benefits and risks of treating now versus delaying therapy for different patient populations
Glenn: Patient Characteristics

- 55 year old male
- Shift worker
- History/risk factors
  - BMI=34
  - Hypertension and dyslipidemia
  - Moderate drinker/cigarette smoker
- Concomitant medications
  - Simvastatin 20 mg/day
  - Lisinopril 10 mg/day
Glenn: Baseline Labs

- Hemoglobin: 15.6 g/dL
- Neutrophils: 1400 cells/mm³
- Platelets: 210,000 cells/mm³
- AST/ALT: 55/75 IU/L
- Albumin: 4.1 g/dL
- Bilirubin: 0.7 mg/dL
Glenn: Disease Characteristics

- Treatment naïve
- Genotype 1a
- *IL28B* CC
- METAVIR F3
- BL viral load 1,300,000 IU/mL
Clinical Decision 1

• How would you manage this patient?

1. Continue to monitor patient but do not start treatment

2. Start patient on first generation protease inhibitor/PEG-IFN/RBV
Modeling of Liver Fibrosis in Chronic Hepatitis C

n=1157 Patients

Rapid progressors
Intermediate progressors
Slow progressors

Poynard et al, Hepatology 1999
Cumulative Proportion of Patients Transitioning from Compensated to Decompensated Stage Over Time

Impact According to Response of 10 Different Treatment Regimens on Evolution of Activity* in 3010 Patients with Paired Biopsies

* Necrosis and Inflammation.
**ADVANCE: IL28B Genotype Effect on Telaprevir Therapy**

<table>
<thead>
<tr>
<th></th>
<th>In Patients Tested for <em>IL28B</em> (%)</th>
<th>In All ADVANCE Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CC</td>
<td>CT</td>
</tr>
<tr>
<td><strong>T12PR</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>90</td>
<td>71</td>
</tr>
<tr>
<td><strong>T8PR</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>87</td>
<td>58</td>
</tr>
<tr>
<td><strong>PR</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>64</td>
<td>25</td>
</tr>
</tbody>
</table>

*T12PR = T+PR12 weeks, then PR12 or 36 weeks depending on eRVR status
**T8PR = T+PR8 weeks, then PR16 or 40 weeks depending on eRVR status

Jacobson et al.  EASL 2011
SVR Rates in F1/2 vs F3/4 Naïve Patients

Jacobson IM et al, NEJM, 2011; 364: 2405-2416
Poordad F et al, NEJM, 2011; 364: 1195-1206
OPTIMIZE Trial: Telaprevir BID vs TID

• PR + TVR 1125 mg BID versus 750 mg TID
• Response-guided therapy
• 740 patients
• 29% bridging fibrosis or cirrhosis
• 57% G1a, IL28B CC 29%

Buti M et al, Abstract LB-8, AASLD 2012
OPTIMIZE Trial: Results

Buti M et al, Abstract LB-8, AASLD 2012
Should Glenn Be Treated Now?

- F3 disease – risk of progression with waiting
- *IL28B* CC
- Potential BID option is attractive
The Case for Waiting

- Multiple issues with current therapy
  - Compliance – pill burden
  - Co-morbidities
  - Adverse effects
  - New treatments on the horizon
Compliance

Pill Burden

BOC = 18/d
RBV 4-7/d

TVR = 12/d
RBV 4-7/d

Food Requirement
Co-Morbidities

• Cardiac Risk Factors
  – Hypertension, hyperlipidemia, smoker

• Pre Treatment
  – DDI – Statin with TVR/BOC → likely just stop it

• On Treatment
  – Anemia management → consider pre-treatment cardiac testing
Drugs with the Potential to Interact with First Generation Protease Inhibitors are Commonly Used by HCV Patients

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Percent</th>
<th>Drug Name</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zolpidem *</td>
<td>17.4</td>
<td>Diazepam</td>
<td>7.9</td>
</tr>
<tr>
<td>Codeine</td>
<td>16.0</td>
<td>Bupropion *</td>
<td>7.2</td>
</tr>
<tr>
<td>Prednisone</td>
<td>15.4</td>
<td>Trazodone</td>
<td>7.1</td>
</tr>
<tr>
<td>Tramadol *</td>
<td>14.3</td>
<td>Fluconazole</td>
<td>6.8</td>
</tr>
<tr>
<td>Citalopram</td>
<td>13.5</td>
<td>Sertraline</td>
<td>6.4</td>
</tr>
<tr>
<td>Fluticasone</td>
<td>13.1</td>
<td>Clarithromycin</td>
<td>6.1</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>13.0</td>
<td>Sildenafil (Viagra)</td>
<td>5.4</td>
</tr>
<tr>
<td>Alprazolam *</td>
<td>11.8</td>
<td>Clonazepam</td>
<td>5.3</td>
</tr>
<tr>
<td>Amlodipine *</td>
<td>10.2</td>
<td>Simvastatin</td>
<td>5.2</td>
</tr>
<tr>
<td>Escitalopram *</td>
<td>8.1</td>
<td>Venlafaxine</td>
<td>5.0</td>
</tr>
</tbody>
</table>

* One of the 20 most frequently filled
No clinically significant interactions

- Boceprevir
  - Prednisone (abstract #1896)
  - Omeprazole (abstract #1808)
  - Ethinyl estrodiol/norethidrone (abstract #1901)

- Simeprevir (TMC-435)
  - Cyclosporine/tacrolimus (abstract #80)
  - Ethinyl estrodiol/norethidrone (abstract #773)
Anemia is a Known Side Effect with First Generation Protease Inhibitor Based Therapies


Future Options for Waiting? (Short-Term)

PILLAR (G1 Naïve)\(^1\)

- Simeprevir 150 mg OD x 12 wks + PR x 24-48
- PR x 48

<table>
<thead>
<tr>
<th>%</th>
<th>n/N =</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>81</td>
<td>62/77</td>
<td>0.013</td>
</tr>
<tr>
<td>65</td>
<td>50/77</td>
<td></td>
</tr>
<tr>
<td>79</td>
<td>61/77</td>
<td></td>
</tr>
<tr>
<td>93</td>
<td>57/61</td>
<td></td>
</tr>
</tbody>
</table>

SILEN C1 (G1 Naïve)\(^2\)

- Faldaprevir 240 mg OD x 24 wks + PR x 24-48
- PR x 48

<table>
<thead>
<tr>
<th>%</th>
<th>n/N =</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>83</td>
<td>118/142</td>
<td>0.001</td>
</tr>
<tr>
<td>56</td>
<td>40/71</td>
<td></td>
</tr>
<tr>
<td>87</td>
<td>124/142</td>
<td></td>
</tr>
<tr>
<td>93</td>
<td>53/57</td>
<td></td>
</tr>
</tbody>
</table>

1. Fried et al. AASLD 2011
2. Sulkowski et al. EASL 2011
No Incremental Decline in Hemoglobin or Neutrophils with Simeprevir or Faldaprevir

Anemia with Simeprevir + P/R


Anemia with Faldaprevir + P/R

2. Sulkowski et al, EASL 2011
Select Oral Directing Acting Antivirals in Development for the Treatment of Chronic Hepatitis C, 2012

<table>
<thead>
<tr>
<th>Compound</th>
<th>Sponsor</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABT-267</td>
<td>Abbott</td>
<td>NS5A inhibitor</td>
</tr>
<tr>
<td>ABT-333</td>
<td>Abbott</td>
<td>Non-nucleoside NS5B polymerase inhibitor</td>
</tr>
<tr>
<td>ABT-450</td>
<td>Abbott</td>
<td>NS3/4A protease inhibitor</td>
</tr>
<tr>
<td>Faldaprevir</td>
<td>Boehringer Ingelheim</td>
<td>NS3/4A protease inhibitor</td>
</tr>
<tr>
<td>(BI201335)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BI207127</td>
<td>Boehringer Ingelheim</td>
<td>Non-nucleoside NS5B polymerase inhibitor</td>
</tr>
</tbody>
</table>
## Select Oral Directing Acting Antivirals in Development for the Treatment of Chronic Hepatitis C, 2012 (cont)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Sponsor</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asunaprevir</td>
<td>Bristol-Myers Squibb</td>
<td>NS3 protease inhibitor</td>
</tr>
<tr>
<td>(BMS-650032)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daclatasvir</td>
<td>Bristol-Myers Squibb</td>
<td>NS5A replication complex inhibitor</td>
</tr>
<tr>
<td>(BMS-790052)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMS-791325</td>
<td>Bristol-Myers Squibb</td>
<td>Non-nucleoside NS5B polymerase inhibitor</td>
</tr>
<tr>
<td>Sofosbuvir</td>
<td>Gilead</td>
<td>Uridine nucleotide analog NS5B polymerase inhibitor</td>
</tr>
<tr>
<td>(GS-7977)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GS-5885</td>
<td>Gilead</td>
<td>NS5A protein inhibitor</td>
</tr>
</tbody>
</table>

*Not all-inclusive, but indicates drugs covered in this presentation*
Should Glenn Delay Treatment?

- **IL28B CC** → ~80% chance of shortened therapy
  - 80-90% chance of SVR
- F3 disease – risk of progression with waiting
- No clear issues with IFN
- Seems anxious and willing to be treated now
- I would suggest treatment
Glenn: On Treatment Response

- Glenn was started on TVR/PEG/RBV
- TW4 and TW12
  - HCV RNA undetectable
Clinical Decision 2

- Which regimen should Glenn receive?
  1. 12 weeks TVR/PEG/RBV
  2. 12 weeks TVR/PEG/RBV + 12 weeks PEG/RBV
  3. 12 weeks TVR/PEG/RBV + 24 weeks PEG/RBV
  4. 12 weeks TVR/PEG/RBV + 36 weeks PEG/RBV
  5. 24 weeks TVR/PEG/RBV
# Recommended Treatment Duration

<table>
<thead>
<tr>
<th>HCV-RNA</th>
<th>Triple Therapy TVR/Peg-IFN/RBV</th>
<th>Dual Therapy Peg-IFN/RBV</th>
<th>Total Treatment Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Undetectable at TW4 and TW12</td>
<td>First 12 weeks</td>
<td>Additional 12 weeks</td>
<td>24 weeks</td>
</tr>
<tr>
<td>Detectable ($\leq 1000$ IU/mL) at TW4 and/or TW12</td>
<td>First 12 weeks</td>
<td>Additional 36 weeks</td>
<td>48 weeks</td>
</tr>
</tbody>
</table>

HCV-RNA Levels and Lab Assays

- “Undetectable” (or “target not detected”) result is required for assessing RGT eligibility
- Below LLOQ but still “detectable” is not sufficient to shorten therapy—ie, patient should continue for full 48 wks

<table>
<thead>
<tr>
<th>Assay Name</th>
<th>LLOQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roche COBAS® AmpliPrep/COBAS® Taqman® HCV Test</td>
<td>43 IU/mL</td>
</tr>
<tr>
<td>Roche COBAS® Taqman® HCV Test, v2.0</td>
<td>25 IU/mL†</td>
</tr>
<tr>
<td>Abbott RealTime HCV Assay</td>
<td>12 IU/mL</td>
</tr>
</tbody>
</table>

LLOQ Values for Various Assays*

*Package Inserts state the “the assay should have a lower limit of HCV-RNA quantification ≤ 25 IU/mL and a limit of HCV-RNA detection of approximately 10-15 IU/mL.
† Usually considered 25 IU/mL, but 23 IU/mL per FDA-approved label.

Conclusions

• Many chronic hepatitis C patients are good candidates for treatment today
• The HCV pipeline is promising with potential new treatment modalities in the near future
• Physicians should carefully consider individual patient characteristics when deciding whether to initiate or delay treatment