Hepatitis C Treatment 2014

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UAB Liver Center

Outline

• Epidemiology/National History
• Terminology for Treatment
• Treatment Considerations
• Current Treatment Options
  – Genotype 1 (GT 1)
  – Genotype 2 (GT 2)
  – Genotype 3 (GT 3)
• Future Therapies
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Epidemiology of HCV

• ≈ 170 M persons infected worldwide
• 2.7 - 4 M Americans infected
• High prevalence rates in USA
  – 2.5% of males
  – 3.2% of African Americans
  – 2.1% of Hispanic Americans
  – Peak age of persons born between 1946 - 1964

Two-Thirds of Those With Chronic HCV in the U.S. Were Born 1946 - 1964

Estimated Prevalence by Age Group

Individuals (n)

<table>
<thead>
<tr>
<th>Birth Year Group</th>
<th>0</th>
<th>200,000</th>
<th>400,000</th>
<th>600,000</th>
<th>800,000</th>
<th>1,000,000</th>
<th>1,200,000</th>
<th>1,400,000</th>
<th>1,600,000</th>
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<tbody>
<tr>
<td>&lt;1920</td>
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<td>1920-1929</td>
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<td>1930-1939</td>
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<td>1940-1949</td>
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<td>1950-1959</td>
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<td>1970-1979</td>
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<td></td>
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<tr>
<td>1980-1989</td>
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<td></td>
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<td></td>
<td></td>
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<tr>
<td>1990+</td>
<td></td>
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</tr>
</tbody>
</table>

Estimation Prevalence by Age Group


Natural History of HCV Infection

Acute HCV Infection (100)

Recovery & Clearance of HCV (20) Chronic Infection (80)

Mild (24) Moderate (32) Severe (24)

Chronic Hepatitis Cirrhosis

End-Stage Liver Disease Hepatocellular CA

Aging of HCV-Infected Persons in the US: Disease Progression

Projected Cases of Hepatocellular Carcinoma & Decompensated Cirrhosis Due to HCV

Patient Survival Rates with HCV (+) & HCV (−) After Liver Transplantation

<table>
<thead>
<tr>
<th></th>
<th>HCV (+)</th>
<th>3035</th>
<th>1951</th>
<th>1134</th>
<th>519</th>
<th>98</th>
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</thead>
<tbody>
<tr>
<td>HCV (-)</td>
<td>6597</td>
<td>4784</td>
<td>3343</td>
<td>2117</td>
<td>1003</td>
<td>220</td>
</tr>
</tbody>
</table>

Gastroenterology 2002;122:889.

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Prevalence of HCV Genotypes (GT) in the USA

- 1a (36%)
- 1b (39%)
- 2a
- 2b
- 3
- 4
- 1a & 1b
- 1 & 2


Patterns of Virologic Response

- RVR: rapid virological response
- eRVR: extended RVR & EVR: early virological response
- ETR: end of treatment response
- SVR: sustained virological response

4 weeks - RVR
12 weeks - eRVR
24 - 48 weeks - ETR
24 weeks after treatment - SVR

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Treatment Evolution of HCV

**Sustained Viral Response (SVR)**

- 1991: 6%
- 1999: 16%
- 2001: 34%
- 2011: 54-56%
- 2014: >90%

IFN: Interferon; m: months; RBV: Ribavirin; Peg: Pegylated; PI: Protease inhibitor; DAA: Direct Acting Antiviral
SVR & Reduced Risk of All-Cause Mortality
US VA Study: Treatment with PegIFN/RBV

P (log-rank) < 0.0001

<table>
<thead>
<tr>
<th>Genotype</th>
<th>N</th>
<th>SVR</th>
<th>Hazard Ratio for Death with SVR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12,166</td>
<td>35%</td>
<td>0.70</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>2</td>
<td>2904</td>
<td>72%</td>
<td>0.64</td>
<td>0.006</td>
</tr>
<tr>
<td>3</td>
<td>1794</td>
<td>62%</td>
<td>0.51</td>
<td>0.0002</td>
</tr>
</tbody>
</table>


HCV Life Cycle
HCV Life Cycle & DAA Targets

Receptor binding and endocytosis
Fusion and uncoating
Transport and release
(+) RNA
Translation and polyprotein processing
RNA replication
Membranous web
ER lumen
LD
Virion assembly
NS5A inhibitors
Block replication complex formation, assembly
NS3/4 protease inhibitors
NS5B polymerase inhibitors
Nucleoside/nucleotide
Nonnucleoside

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First Generation Protease Inhibitors (PI)
Telaprevir (TEL) & Boceprevir (BOC)


HCV Therapies

Interferon Free Therapies

Interferon & Ribavirin Based Therapies
**BOC & TEL + PegIFN/RBV (P/R)**

**GT1 Treatment-Naive Patients**

<table>
<thead>
<tr>
<th>PegIFN/RBV</th>
<th>BOC or TEL + PegIFN/RBV</th>
</tr>
</thead>
<tbody>
<tr>
<td>38-44</td>
<td>63-75</td>
</tr>
</tbody>
</table>


**BOC & TEL + PegIFN/RBV (P/R)**

**GT1 Treatment Failures**

<table>
<thead>
<tr>
<th>Relapsers$^{[1,2]}$</th>
<th>Partial Responders$^{[1,2]}$</th>
<th>Null Responders$^{[2,3]}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-29</td>
<td>7-15</td>
<td>5</td>
</tr>
<tr>
<td>69-83</td>
<td>40-59</td>
<td>29-40</td>
</tr>
</tbody>
</table>

Side Effects from BOC & TEL

Treatment is more effective but much more difficult

Other Issues With BOC & TEL

Pill burden
- BOC 12/day
- RBV 4-7/day
- TEL 6/day
- RBV 4-7/day

Drug-drug interactions
- PI CYP3A4 metabolites

Food requirement

Resistance
HCV-TARGET: Safety Assessment of P/R + BOC/TEL in Patients

<table>
<thead>
<tr>
<th>Event, %</th>
<th>Cirrhotic (n = 550)</th>
<th>Noncirrhotic (n = 787)</th>
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<tbody>
<tr>
<td>SAE</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Death, n</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Early discontinuation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Due to adverse event</td>
<td>44</td>
<td>33</td>
</tr>
<tr>
<td>• Due to lack of efficacy</td>
<td>31</td>
<td>38</td>
</tr>
<tr>
<td>Decompensation</td>
<td>11</td>
<td>1</td>
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<tr>
<td>Infection</td>
<td>21</td>
<td>24</td>
</tr>
<tr>
<td>Severe rash (grade 3/SCAR)</td>
<td>2</td>
<td>1</td>
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<tr>
<td>Hemoglobin &lt; 8.5 g/dL</td>
<td>20</td>
<td>14</td>
</tr>
<tr>
<td>RBV dose reduction</td>
<td>42</td>
<td>31</td>
</tr>
<tr>
<td>EPO</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Transfusion</td>
<td>11</td>
<td>5</td>
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Second Generation Protease Inhibitors (PI)

*Simeprevir (SIM) & Faldaprevir (FAL)*

**HCV Therapies**

**Interferon Free Therapies**

<table>
<thead>
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</thead>
<tbody>
<tr>
<td>Protease Inhibitor</td>
<td>Telaprevir G1</td>
<td>Simeprevir G1</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>NS5B Polymerase Inhibitor</td>
<td>Faldaprevir</td>
<td></td>
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</tr>
<tr>
<td>NS5A Inhibitor</td>
<td>Boceprevir G1</td>
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**Interferon & Ribavirin Based Therapies**

**QUEST-1/2: Simeprevir (SIM) + P/R**

**RGT in Treatment-Naive GT1 HCV**

- **Stratified by GT1 subtype, IL28B genotype**
- **SIM 150 mg QD + P/R**
  - **Wk 12: RGT**
  - **Wk 24**
  - **Wk 48**

- **Treatment-naive patients with GT1 HCV**
  - **(N = 394)**

- **Placebo + P/R**
  - **(n = 130)**

*Response-guided therapy: Patients with HCV RNA < 25 IU/mL at Week 4 & undetectable at wk 12 received a 24 wks of therapy. Patients not achieving this on-treatment response received 48 wks of therapy.*


**QUEST-1, QUEST-2, PROMISE: SIM + P/R in GT1 Treatment-Naive Patients/Relapsers**

**QUEST: 88% Qualified for Shortened Therapy in SIM Phase III Studies**

Pts who did not meet RGT→SVR 25%; therefore, RGT not recommended in US label

**QUEST Studies: GT 1a ≠ 1b**

- **Simeprevir + P/R (RGT 12 + 12)**
- **Placebo + P/R**

Likely relates to presence of Q80K polymorphism in GT1a

**QUEST: No Benefit of SIM if Q80K +**

Q80K present in 34% of GT1a patients
No benefit of SIM if Q80K positive

---

SIM in Treatment-Experienced Patients

FDA extended indication to partial & null responders


SIM Is Well Tolerated

- Mild unconjugated hyperbilirubinemia → transporter
- No anemia signal beyond P/R
- Rash up to 25% (mild)

SIM + P/R for GT1 HCV: Approved Indications

- Simeprevir 150 mg/day with food, administered with P/R
  - Fixed duration
- Treatment-naive patients & relapsers (including cirrhotic patients)

12 weeks 12 weeks
Simeprevir + P/R P/R $86,000

- Previous partial or null responders (including cirrhotic patients)

12 weeks 36 weeks
Simeprevir + P/R P/R $105,400

Stopping rules

<table>
<thead>
<tr>
<th>Treatment Wk</th>
<th>HCV RNA (IU/mL)</th>
<th>Action</th>
</tr>
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<tbody>
<tr>
<td>4</td>
<td>≥ 25</td>
<td>Discontinue simeprevir, pegIFN, &amp; RBV</td>
</tr>
<tr>
<td>12</td>
<td>≥ 25</td>
<td>Discontinue pegIFN &amp; RBV (SIM stops at 12 wks)</td>
</tr>
<tr>
<td>24</td>
<td>≥ 25</td>
<td>Discontinue pegIFN &amp; RBV</td>
</tr>
</tbody>
</table>


NS5B (Nucleotide) Polymerase Inhibitor

Sofosbuvir (SOF)

NEUTRINO: 12 Wks Sofosbuvir (SOF) + P/R in Treatment-Naive GT 1/4/5/6 HCV Pts

- Open-label, single-arm study of sofosbuvir 400 mg QD + P/R for 12 wks in treatment-naive patients with GT 1/4/5/6 HCV
  - 17% had cirrhosis; 89% had GT 1, 9% had GT 4, < 1% had GT 5, 2% had GT 6 HCV

P/R: pegIFN alfa-2a 180 µg/wk + RBV 1000-1200 mg/day

NEUTRINO Study: SVR12 by Pre-specified Subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>SVR12 Rate, % (95% CI)</th>
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<tbody>
<tr>
<td>Overall</td>
<td>—</td>
</tr>
<tr>
<td>HCV GT</td>
<td>—</td>
</tr>
<tr>
<td>1 (1a, 1b, 1a/b)</td>
<td>—</td>
</tr>
<tr>
<td>1a</td>
<td>—</td>
</tr>
<tr>
<td>1b</td>
<td>—</td>
</tr>
<tr>
<td>4, 5, 6</td>
<td>—</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>—</td>
</tr>
<tr>
<td>No</td>
<td>—</td>
</tr>
<tr>
<td>Yes</td>
<td>—</td>
</tr>
<tr>
<td>Race</td>
<td>—</td>
</tr>
<tr>
<td>Black</td>
<td>—</td>
</tr>
<tr>
<td>Non-black</td>
<td>—</td>
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<tr>
<td>HCV RNA level</td>
<td>—</td>
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<tr>
<td>&lt; 6 log_{10} IU/mL</td>
<td>—</td>
</tr>
<tr>
<td>≥ 6 log_{10} IU/mL</td>
<td>—</td>
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<tr>
<td>IL28B</td>
<td>—</td>
</tr>
<tr>
<td>CC</td>
<td>—</td>
</tr>
<tr>
<td>Non-CC</td>
<td>—</td>
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</table>

SOF + RBV for 24 Weeks in 60 GT 1 Pts Intolerable to PegIFN

- No one discontinued treatment due to adverse events.
- Most frequent adverse events were headache, anemia, fatigue & nausea


SOF + P/R for GT1 HCV: Approved Indications

- SOF 400 mg/day with or without food, administered with P/R
- All GT1 patients receive same regimen, regardless of previous treatment history or fibrosis level
  - Same regimen approved for GT4 HCV

12 weeks

Sofosbuvir + P/R $ 91,500

- Additional option for GT1 patients ineligible for IFN therapy
  - Sofosbuvir + ribavirin for 24 weeks $ 168,000

- If drugs combined with sofosbuvir must be permanently discontinued, sofosbuvir should also be discontinued

COSMOS: SIM + SOF \pm RBV in GT 1 HCV Patients

- Planned interim analysis of randomized phase IIa study
- 2 cohorts with same study design evaluating impact of duration & RBV
- Primary endpoint: SVR12

Patients With GT1 HCV

Randomized 2:1:2:1

- **Cohort 1:** Previous null responders, F0-F2 (N = 80)
- **Cohort 2:** Naives & previous null responders, F3-F4 (N = 87)

SIM 150 mg QD; SOF 400 mg QD; weight-based RBV 1000-1200 mg/day.

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FISSION: SOF/RBV vs P/R in Treatment-Naive GT 2/3 HCV Patients

- Randomized, controlled, open-label phase III noninferiority trial
  - 21% had cirrhosis; 72% had GT 3 HCV

**Stratified by HCV GT**
(2 vs 3), HCV RNA
(< vs ≥ 10⁶ IU/mL),
cirrhosis (yes vs no)

**Treatment-naive patients with GT 2/3 HCV**
(N = 499)

- PegIFN alfa-2a 180 µg/wk + RBV 800 mg/day
  (n = 243)

- SOF 400 mg QD + RBV 1000-1200 mg/day
  (n = 256)

Gane E, et al. NEJM 2013;368:34-44.
FISSION: SOF/RBV Noninferior to P/R in Tx-Naive GT 2/3 HCV Patients

Gane E, et al. NEJM 2013;368:34-44.

FISSION: SVR12 According to GT & Fibrosis Level

Gane E, et al. NEJM 2013;368:34-44.
**FISSION: Better Tolerability Profile With SOF/RBV vs P/R**

- Grade ≥ 3 AEs: 7% with SOF/RBV vs 19% for pegIFN/RBV
- Discontinuations due to AEs: 1% for SOF/RBV vs 11% for pegIFN/RBV

<table>
<thead>
<tr>
<th>AEs Occurring in ≥ 15% in Either Arm, %</th>
<th>SOF/RBV (n = 256)</th>
<th>PegIFN/RBV (n = 243)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>36</td>
<td>55</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Headache</td>
<td>25</td>
<td>44</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Nausea</td>
<td>18</td>
<td>29</td>
<td>.0057</td>
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<tr>
<td>Insomnia</td>
<td>12</td>
<td>29</td>
<td>&lt; .0001</td>
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<tr>
<td>Rash</td>
<td>9</td>
<td>17</td>
<td>.0052</td>
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<tr>
<td>Diarrhea</td>
<td>9</td>
<td>17</td>
<td>.0075</td>
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<tr>
<td>Irritability</td>
<td>10</td>
<td>17</td>
<td>.0328</td>
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<tr>
<td>Decreased appetite</td>
<td>7</td>
<td>18</td>
<td>.0001</td>
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<tr>
<td>Myalgia</td>
<td>8</td>
<td>17</td>
<td>.0060</td>
</tr>
<tr>
<td>Pruritus</td>
<td>7</td>
<td>17</td>
<td>.0009</td>
</tr>
<tr>
<td>Influenzalike symptoms</td>
<td>3</td>
<td>18</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Chills</td>
<td>3</td>
<td>18</td>
<td>&lt; .0001</td>
</tr>
</tbody>
</table>

Gane E, et al. NEJM 2013;368:34-44.

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**FUSION: SOF + RBV for 12 or 16 Wks in Tx-Experienced GT 2/3 HCV Pts**

- Randomized, double-blind, placebo-controlled phase III trial
  - 62% to 64% had GT 3 HCV, 33% to 35% had cirrhosis, 75% to 76% were previous relapsers

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**Stratified by HCV GT (2 vs 3), cirrhosis (yes vs no)**

- Wk 12: SOF 400 mg QD + RBV 1000-1200 mg/day (n = 103)
- Wk 16: SOF 400 mg QD + RBV 1000-1200 mg/day (n = 98)
- Placebo

**FUSION: Overall Efficacy Outcomes of SOF + RBV in GT 2/3**

- **HCV RNA < LLOQ (%):**
  - Wk 4: 97/100, 98/100
  - End of Treatment: 100/100, 100/100
  - SVR12: 50/100, 73/100

- **SOF + RBV 12 wks:**
  - No Cirrhosis: 96/100, 60/100
  - Cirrhosis: 100/100, 78/100

- **SOF + RBV 16 wks:**
  - No Cirrhosis: 25/26, 6/10
  - Cirrhosis: 23/23, 7/9

**FUSION: SVR by GT & Cirrhosis in Treatment-Experienced Patients**

- **GT2:**
  - 12 weeks sufficient for GT2
  - 16 weeks better than 12 weeks for GT3… so what about 24 weeks?

- **GT3:**
  - No Cirrhosis: 37/38, 25/40
  - Cirrhosis: 19/26, 14/23

VALENCE: SOF + RBV for 12 or 24 Weeks in Naive & Exp’d GT2/3 HCV Pts

- Phase III study in Europe
- Original protocol amended to lengthen treatment for all GT3 pts when emerging data suggested benefit of additional treatment for this group*
- Primary endpoint: SVR12


*Small number of GT3 patients (n = 11) who had already completed 12 wks at time of protocol amendment were included in safety analysis with GT2 but analyzed separately for efficacy. Patients randomized to placebo in original protocol offered alternative treatment protocol.

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VALENCE: SVR12 With 12 or 24 Wks of SOF + RBV in GT2 & GT3 Pts

- No increase in AEs seen with longer duration treatment
  - AEs seen consistent with RBV

### VALENCE: Efficacy With 24-Week SOF + RBV in GT3 Patients

- **Treatment Naive**
  - SVR12 (%): 94/92 (24 Wks) vs 87/100 (24 Wks)
- **Treatment Experienced**
  - SVR12 (%): 60/45 (16 Wks)

- **FUSION**
  - SVR12 (%): 61/23 (16 Wks)

- **24 weeks better for treatment-naive patients**
- **Not ideal for cirrhotic treatment failures**


### POSITRON: SOF + RBV for 12 Wks in GT 2/3 IFN- Unwilling/Intolerant/Ineligible

- **Randomized, double-blind, placebo-controlled phase III trial**
  - Stratified by cirrhosis (yes vs no)
  - **SOF 400 mg QD + RBV 1000-1200 mg/day**
    - (n = 207)
  - **Placebo**
    - (n = 71)

<table>
<thead>
<tr>
<th>Baseline Factor, n (%)</th>
<th>Sofosbuvir + RBV (n = 207)</th>
<th>Placebo (n = 71)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GT 2</td>
<td>109 (53)</td>
<td>34 (48)</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>31 (15)</td>
<td>13 (18)</td>
</tr>
<tr>
<td>Interferon unwilling</td>
<td>102 (49)</td>
<td>30 (42)</td>
</tr>
<tr>
<td>Interferon ineligible</td>
<td>88 (43)</td>
<td>33 (47)</td>
</tr>
<tr>
<td>Interferon intolerant</td>
<td>17 (8)</td>
<td>8 (11)</td>
</tr>
</tbody>
</table>

**POSITRON: Virologic Response in GT 2/3 IFN-Unwilling/Intolerant/Ineligible**

**Overall Outcomes**

- **SVR12 0% for placebo**


---

**Sofosbuvir + RBV for GT 2 & 3**

**HCV: Approved Indications**

- All GT2 patients receive same regimen, regardless of previous treatment history or fibrosis level
  
  ![12 weeks](SOF + RBV) $ 86,300

- All GT3 patients receive same regimen, regardless of previous treatment history or fibrosis level
  
  ![24 weeks](SOF + RBV) $ 172,600

- If drugs combined with sofosbuvir must be permanently discontinued, sofosbuvir should also be discontinued

LONESTAR-2: SOF + P/R for 12 Wks in Treatment-Exp’d GT2/3 HCV Pts

- Single-arm trial of pts with treatment failure on P/R
- Approximately 50% with compensated cirrhosis
- Primary endpoint: SVR12

Pts with GT2 or GT3 HCV & previous treatment failure with P/R (N = 47)

SOF 400 mg QD + PegIFN 180 µg once wkly + RBV 1000 mg or 1200 mg/d

SVR12 (%)

GT2: 96%
GT3: 83%

~ Similar rates of SVR12 in pts with & without cirrhosis


Do We Still Need PegIFN for GT3?

LONESTAR-2: SOF + PegIFN + RBV x 12 wks

SVR12 (%)

GT 2: No cirrhosis
- 100%
- 9/9
- 13/14

GT 3: Cirrhosis
- 83%
- 10/12

85% previous treatment failures

- Small single-center study but looks promising...
- PegIFN is not dead yet!

Outline

- Epidemiology/National History
- Terminology for Treatment
- Treatment Considerations
- Current Treatment Options
  - Genotype 1 (GT 1)
  - Genotype 2 (GT 2)
  - Genotype 3 (GT 3)
- Future Therapies

Future DAA to Treat HCV

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>NS3/4A protease inhibitor</td>
<td>ABT-450/RTV</td>
<td>150/100 mg</td>
</tr>
<tr>
<td>NS3 protease inhibitor</td>
<td>Asunaprevir</td>
<td>200 mg BID</td>
</tr>
<tr>
<td>NS3/4A protease inhibitor</td>
<td>Faldaprevir</td>
<td>120 mg or 240 mg QD</td>
</tr>
<tr>
<td>NS3 protease inhibitor</td>
<td>GS-9451</td>
<td>200 mg QD</td>
</tr>
<tr>
<td>NS3/4A protease inhibitor</td>
<td>MK-5172</td>
<td>100 mg QD</td>
</tr>
<tr>
<td>NS5B nonnucleoside polymerase inhibitor</td>
<td>ABT-333</td>
<td>400 mg BID</td>
</tr>
<tr>
<td>NS5B nonnucleoside polymerase inhibitor</td>
<td>BMS-791325</td>
<td>75 mg or 150 mg BID</td>
</tr>
<tr>
<td>NS5B nonnucleoside polymerase inhibitor</td>
<td>Deleobuvir</td>
<td>600 mg BID</td>
</tr>
<tr>
<td>NS5B nonnucleoside polymerase inhibitor</td>
<td>GS-9669</td>
<td>500 mg QD</td>
</tr>
<tr>
<td>NS5A inhibitor</td>
<td>ABT-267</td>
<td>25 mg QD</td>
</tr>
<tr>
<td>NS5A inhibitor</td>
<td>Daclatasvir</td>
<td>30 mg BID or 60 mg QD</td>
</tr>
<tr>
<td>NS5A inhibitor</td>
<td>Ledipasvir</td>
<td>90 mg QD</td>
</tr>
<tr>
<td>NS5A inhibitor</td>
<td>MK-8742</td>
<td>20 or 50 mg QD</td>
</tr>
<tr>
<td>NS5A inhibitor</td>
<td>PI-688</td>
<td>200 mg QD</td>
</tr>
</tbody>
</table>
Future of HCV Therapies

Interferon Free Therapies

- **Ledipasvir + SOF**
- **ABT 450/RTV + ABT 267 + ABT 333 + RBV**
- **Asunaprevir + Daclatasvir**
- **SOF + Riba G2,3**
- **Protease Inhibitor**
  - **NS5B Polymerase Inhibitor**
  - **NS5A Inhibitor**
  - **Non-nuclease Inhibitor**

Interferon & Ribavirin Based Therapies

- **Boceprevir G1**
- **Telaprevir G1**
- **SOF G1, 4-6, Naive**
- **Simeprevir G1**
- **Faldaprevir**

Potential Targets for Direct Acting Antiviral (DAA) Agents Against HCV Gene Products

NS5A Inhibitors

SOF + Ledipasvir (NS5A) + RBV

- Treatment-naive pts (noncirrhotic)
- PI failures (50% cirrhotic)

<table>
<thead>
<tr>
<th></th>
<th>8 wks</th>
<th>12 wks</th>
<th>12 wks</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOF/LDV</td>
<td>95/19</td>
<td>95/18</td>
<td>95/18</td>
</tr>
<tr>
<td>SOF/LDV + RBV</td>
<td>100/21</td>
<td>100/21</td>
<td></td>
</tr>
<tr>
<td>SOF/LDV + RBV</td>
<td>8 wks</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- No breakthrough; 2 relapses, both without RBV
- 1 case of resistance – retreated with SOF/LDV + RBV x 24 weeks → SVR


ELECTRON: SOF/Ledipasvir + RBV for 6 Wks in Naive GT1 HCV Pts

- Open-label phase II trial in GT1 HCV pts
- 68% SVR12 rate with 6 wks of SOF/LDV + RBV lower\(^1\) than SVR rates previously achieved with 8 wks\(^2\) or 12 wks\(^3\) treatment with this regimen

SYNERGY: SOF/Ledipasvir (LDV) ± GS-9669 (NS5Bnns) or GS-9541 (NS3) in GT1 HCV Pts

- NIAID nonrandomized parallel-arm phase II trial GT 1
- Primary endpoint: SVR12

SOF/LDV + GS-9669

SOF/LDV + GS-9451

SOF 400 mg QD/LDV 90 mg QD; GS-9669 500 mg QD; GS-9451 80 mg QD.


SYNERGY: High Response Rates With 6-Wk Triple-Drug Regimens

- Very high response rates with all-oral therapy without RBV
- 1 pt in SOF/LDV + GS-9669 arms relapsed & 1 missed SVR4 visit
- No serious AEs leading to discontinuation

ELECTRON: SOF/Ledipasvir ± RBV or GS-9669 (NS5Bnns) in Cirrhotic GT1 HCV Pts

- Open-label phase II trial
- SVR12 rate enhanced with addition of RBV or GS-9669

<table>
<thead>
<tr>
<th>Treatment-experienced pts with HCV GT1, F4 (N = 20)</th>
<th>SOF/LDV (n = 10)</th>
<th>SOF/LDV + RBV (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment-experienced pts with HCV GT1, F3 or F4 (N = 50)</td>
<td>SOF/LDV + RBV (n = 25)</td>
<td>SOF/LDV + GS-9669 (n = 25)</td>
</tr>
</tbody>
</table>

SOF 400 mg QD/ledipasvir 90 mg QD; GS-9669 500 mg QD; weight-based RBV 1000-1200 mg/day

SVR12, %


Protease, NS5a, & Nonnucleoside Polymerase Inhibitor + RBV for 12 wks

GT1 treatment-naive noncirrhotic pts: ABT-450/RTV/ABT-267 FDC + ABT-333 + RBV

GT1 treatment-experienced noncirrhotic pts (49% null responders): ABT-450/RTV/ABT-267 FDC + ABT-333 + RBV

5 drugs (3 pills daily) with < 1% discontinuing treatment

Summary

- GT 1 patients can be treated with
  - SOF + P/R x 12 weeks in GT1
  - Off label with SOF + SIM x 12 weeks in GT1
- GT 2 patients can be treated with
  - SOF + RBV x 12 weeks
- GT 3 patients can be treated with
  - SOF + RBV x 24 weeks
  - SOF + PegIFN + RBV x 12 weeks
- Within the next year we should be PegIFN free
Hepatitis C Treatment 2014

Conclusions