HCV TREATMENT IN 2011:
INTEGRATING NEW THERAPIES INTO CURRENT TREATMENT ALGORITHMS
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Disclosures:

Advisory Board or Speakers Bureau: Genentech, Gilead, Merck, Salix, Vertex, Bayer

No off-label discussion

No conflicts of interest
Banner Liver Disease Center
Liver Transplantation Program

• Largest comprehensive liver program in the region
  • 5 hepatologists, 3 surgeons, NP, PA
  • Arizona’s first liver transplant in 1983
  • 500 liver transplants by mid-2011
  • 5 regional satellite clinics
  • Major focus on HCV, HBV, NAFLD, HCC, ALF
Burden of the HCV Epidemic
HCV Infection Worldwide

- 170 million persons with HCV
- 3-4 million newly infected each year

Prevalence of infection

- > 10%
- 2.5% to 10%
- 1% to 2.5%
- < 1%
- NA

HCV Prevalence in High-Risk US Populations

- Incarcerated: ~310,000 (15%)
- IDUs: ~300,000 (80%-90%)
- Alcoholics: ~250,000 (11%-36%)
- HIV Infected: ~300,000 (30%)
- Homeless: ~175,000 (22%)
- Veterans: ~280,000 (8%)

HCV Infection: Natural Disease Progression

Exposure (Acute Phase)
- 15%Resolved
- 85%Chronic

Cirrhosis (20-year progression rate accelerated with HIV, HBV, etoh)
- 20%
- 6%ESLD
- 4%HCC (5-year survival <5%)
- 3-4%Transplant/Death

Time (years)
- 10
- 20
- 30

The Changing Face of HCV in the US

- Ever HCV Infected
- All Chronic HCV
- Acute HCV Infection
- Cirrhosis

Peak Incidence

Peak Cirrhosis

Sustained Virologic Response (SVR) Leads to Improved Outcome

- SVR
  - Viral Eradication
  - Improved Clinical Outcomes
  - Improved Liver Histology
  - Decreased Decomplementation
  - Hepatocellular Carcinoma
  - Mortality

SVR is Associated with Lower Incidence of ESLD, HCC or Death: Results from the HALT-C Trial

Treatment of prior nonresponders with advanced fibrosis pegIFN alfa-2a + RBV
Among Respondents (N=133) to the National Health and Nutrition Evaluation Survey (NHANES) Hepatitis C Follow-Up Questionnaire

- Unaware of diagnosis: 49%
- Clinician did not recommend treatment: 24%
- Received treatment: 12%
- Did not follow-up with clinician: 9%
- Refused treatment: 6%

Burden of HCV Disease

• Liver disease due to chronic HCV is a major cause of morbidity and mortality
  – Impact is expected to peak in ~ 2020

• Sustained virologic response (SVR) = cure
  – Decreased risk of liver complications
  – Decreased risk of death

• In 2010, Institute of Medicine report noted limited awareness and called for more action to address viral hepatitis in the US

## Recommendations for Viral Hepatitis in the US

<table>
<thead>
<tr>
<th>Surveillance</th>
<th>Knowledge &amp; Awareness</th>
<th>Viral Hepatitis Services</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDC should:</td>
<td></td>
<td>Federally funded health insurance programs should:</td>
</tr>
<tr>
<td>➢ Evaluate HCV public health surveillance system</td>
<td>CDC should work with key stakeholders to:</td>
<td>➢ Incorporate guidelines for risk-factor screening as required component of preventive care</td>
</tr>
<tr>
<td>➢ Develop agreements with state health departments to support HCV surveillance</td>
<td>➢ Develop HCV educational programs for providers</td>
<td></td>
</tr>
<tr>
<td>➢ Support targeted surveillance</td>
<td>➢ Develop and evaluate innovative and effective outreach programs</td>
<td></td>
</tr>
<tr>
<td></td>
<td>to 1) target at-risk populations, and 2) increase public awareness</td>
<td></td>
</tr>
</tbody>
</table>

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HCV Treatment Issues and Guidelines
Favorable IL28B Genotype is more Common Among Caucasians than African-Americans

Caucasian (n=871)  African American (n=191)

- CC: 50% 12%
- CT: 38% 37%
- TT: 12% 16%

Clark PJ  Am J Gastroenterol 2011; 106:38–47
IL28B Less Common in African-Americans and Affects SVR

Caucasians

- Genotype C/C: 39%
- Genotype C/T: 12%
- Genotype T/T: 50%

African Americans

- Genotype C/C: 37%
- Genotype C/T: 16%
- Genotype T/T: 48%

Clark PJ, Am J Gastroenterol 2011; 106:38–47
HCV TREATMENT IN 2011: INTEGRATING NEW THERAPIES INTO CURRENT TREATMENT ALGORITHMS

HCV Protease Inhibitor: Treatment-naïve Patients
ADVANCE: Telaprevir + PegIFN/RBV in Treatment-Naïve, Genotype 1 HCV Patients

**T12PR**
- TVR + PR
- PR
- eRVR + Follow-up
- SVR
- Follow-up

**T8PR**
- TVR + PR
- Pbo + PR
- PR
- eRVR + Follow-up
- SVR
- Follow-up

**PR48**
- Pbo + PR
- PR
- Follow-up

eRVR = undetectable HCV RNA by Taqman v2.0 at weeks 4 and 12

Jacobson IM, et al. 61st AASLD; Boston, MA; October 29-November 2, 2010; Abst. 211.
ADVANCE: Achievement of SVR

T12PR and T8PR vs. PR: P<0.0001

75% 69% 44%

Jacobson IM, et al. 61st AASLD; Boston, MA; October 29-November 2, 2010; Abst. 211.
ADVANCE: RVR and eRVR

Week 4 (RVR) - 68% T12PR, 66% T8PR, 9% PR
Weeks 4 and 12 (eRVR) - 58% T12PR, 57% T8PR, 8% PR

RVR = Undetectable HCV RNA at Week 4
eRVR = Undetectable HCV RNA at Weeks 4 and 12

Jacobson IM, et al. 61st AASLD; Boston, MA; October 29-November 2, 2010; Abst. 211.
ADVANCE: High SVR with eRVR

Jacobson IM, et al. 61st AASLD; Boston, MA; October 29-November 2, 2010; Abst. 211.
ADVANCE: SVR Rates By Fibrosis/Cirrhosis

Jacobson IM, et al. 61st AASLD; Boston, MA; October 29-November 2, 2010; Abst. 211.

No, Mild or Portal Fibrosis
- T12PR: 78%
- T8PR: 73%
- PR: 47%

Bridging Fibrosis or Cirrhosis
- T12PR: 62%
- T8PR: 53%
- PR: 33%
ADVANCE: SVR By Race/Ethnicity

<table>
<thead>
<tr>
<th>Race/Ethnicity</th>
<th>T12PR</th>
<th>T8PR</th>
<th>PR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasian</td>
<td>75%</td>
<td>70%</td>
<td>46%</td>
</tr>
<tr>
<td>Black/African American</td>
<td>62%</td>
<td>58%</td>
<td>25%</td>
</tr>
<tr>
<td>Hispanic/Latino</td>
<td>74%</td>
<td>66%</td>
<td>39%</td>
</tr>
</tbody>
</table>

Jacobson IM, et al. 61st AASLD; Boston, MA; October 29-November 2, 2010; Abst. 211.
ADVANCE: Adverse Events

*No difference regarding fatigues, headache, insomnia, influenza-like illness, pyrexia

Jacobson IM, et al. 61st AASLD; Boston, MA; October 29-November 2, 2010; Abst. 211.
ADVANCE: Rash During TVR/Placebo Phase

Jacobson IM, et al. 61st AASLD; Boston, MA; October 29-November 2, 2010; Abst. 211.
ILLUMINATE: Telaprevir + PegIFN/RBV for 24 or 48 Weeks in Treatment-Naïve, Genotype 1 HCV Patients with eRVR

- \( T12PR \) (N=540)
- \( PR \) (N=162)

Follow-up

SVR

Non-inferiority (margin:-10.5%)

Sherman KE, et al. 61st AASLD; Boston, MA; October 29-November 2, 2010; Abst. LB-2.
ILLUMINATE: SVR Rates

Sherman KE, et al. 61st AASLD; Boston, MA; October 29-November 2, 2010; Abst. LB-2.
ILLUMINATE: SVR Rates in All Treatment Groups

Δ 4.5%  
(2-sided 95% CI = -2.1% to +11.1%)

|          | SVR  
|----------|------
| ITT      | 72%  
| eRVR+ T12PR24 | 92%  
| eRVR+ T12PR48 | 88%  
| eRVR- T12PR48 | 64%  
| Other    | 23%  

ILLUMINATE: Common AEs Leading to TVR Discontinuation

<table>
<thead>
<tr>
<th>Discontinuation of All Study Drugs During TVR Treatment</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Adverse Event</td>
<td>7%</td>
</tr>
<tr>
<td>Rash</td>
<td>1%</td>
</tr>
<tr>
<td>Anemia</td>
<td>1%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Discontinuation of TVR During TVR Treatment</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Adverse Event</td>
<td>21%</td>
</tr>
<tr>
<td>Rash</td>
<td>7%</td>
</tr>
<tr>
<td>Anemia</td>
<td>2%</td>
</tr>
</tbody>
</table>

Sherman KE, et al. 61st AASLD; Boston, MA; October 29-November 2, 2010; Abst. LB-2.
SPRINT-2: Study Design

**Control Group**: 48 P/R, N = 363
- **Week 4**: PR lead-in
- **Week 28**: PR + Placebo
- **Week 48**: Follow-up

**BOC RGT Group**: N = 368
- **Week 4**: PR lead-in
- **Week 28**: PR + Boceprevir
- **Follow-up**

**BOC PR48 Group**: N = 366
- **Week 4**: PR lead-in
- **Week 28**: PR + Boceprevir
- **Follow-up**

– **TW 8-24 HCV-RNA Undetectable**
– **Follow-up**
– **TW 8-24 HCV-RNA Detectable**
– **PR + Placebo Follow-up**

Poordad F, et al. 61st AASLD; Boston, MA; October 29 – November 2, 2010; Abst. LB-4.
**SPRINT-2: Potential Rationale for Lead-in Phase**

- **Avoidance of use of cost and unnecessary drug use**
  - Identify interferon-sensitive patients who may not need DAA

  4 weeks
  
  Peg-IFN/RBV

  RVR

  Peg-IFN/RBV

  no RVR

  Peg-IFN/RBV + protease inhibitor

- **Optimization of DAA**
  - Decrease viral resistance development at time of DAA introduction and enhance response-guided therapy strategy
  - Inform on-treatment decision-making based on likelihood of response

  4 weeks

  Peg-IFN/RBV

  Peg-IFN/RBV + protease inhibitor

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SPRINT-2: SVR and Relapse Rates (ITT)

- **Non-Black Patients**
  - SVR:
    - 48 P/R: 40% (23% relapse rate)
    - BOC RGT: 67% (9% relapse rate)
    - BOC/PR48: 68% (8% relapse rate)
  - **p < 0.0001**

- **Black Patients**
  - SVR:
    - 48 P/R: 23% (14% relapse rate)
    - BOC RGT: 42% (12% relapse rate)
    - BOC/PR48: 53% (17% relapse rate)
  - **p = 0.044, p = 0.004**

Poordad F, et al. 61st AASLD; Boston, MA; October 29 – November 2, 2010; Abst. LB-4.
SPRINT-2: SVR Based on Week 4 PR Lead-in in Non-Black Patients

Poordad F, et al. 61st AASLD; Boston, MA; October 29 – November 2, 2010; Abst. LB-4.
SPRINT-2: Virologic Response Rates for Undetectable HCV RNA Levels Weeks 8 to 24

Poordad F, et al. 61st AASLD; Boston, MA; October 29 – November 2, 2010; Abst. LB-4.
SPRINT-2: SVR Rates Based on Week 8 HCV RNA

<table>
<thead>
<tr>
<th></th>
<th>Non-Black Patients</th>
<th>Black Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BOC RGT</strong></td>
<td>89%</td>
<td>78%</td>
</tr>
<tr>
<td>Undetectable</td>
<td>91%</td>
<td>82%</td>
</tr>
<tr>
<td><strong>BOC/PR48</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Detectable</td>
<td>37%</td>
<td>32%</td>
</tr>
<tr>
<td><strong>BOC RGT</strong></td>
<td>43%</td>
<td>28%</td>
</tr>
<tr>
<td>Detectable</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Poordad F, et al. 61st AASLD; Boston, MA; October 29 – November 2, 2010; Abst. LB-4.
## SPRINT-2: Common Treatment-Related Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>PR48</th>
<th>RGT</th>
<th>BOC/PR48</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>29%</td>
<td>49%</td>
<td>49%</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>18%</td>
<td>37%</td>
<td>43%</td>
</tr>
</tbody>
</table>

No difference between arms in: Fatigue, headache, nausea, chills, pyrexia, insomnia, alopecia, decreased appetite, pruritis, neutropenia, influenza-like illness, myalgia, rash, irritability, depression, diarrhea, dry skin, dyspnea, dizziness

Treatment Paradigm for HCV Genotype 1 Naïve Patients

- Telaprevir (12 weeks) + PegIFN/RBV
  - HCV RNA at week 4
  - Response Guided Therapy (RGT) based on HCV RNA at week 4 (Treatment for 24 or 48 weeks)
  - Common AEs: rash, anemia

- Boceprevir (24 weeks) + PegIFN/RBV
  - PegIFN/RBV lead-in for 4 weeks
  - HCV RNA at week 4 and 8
  - RGT based on HCV RNA at week 8 (Treatment for 28 or 48 weeks)
  - Common AE: anemia
HCV PROTEASE INHIBITOR: Treatment-experienced Patients
Study to assess safety/efficacy of BOC plus PegIFN (P) and RBV (R) in re-treatment of previous non-responders (NRs) and relapsers to P/R therapy

- **Control**: 48 P/R (N=80)
  - Week 4: PR lead-in
  - Week 36: PR + Placebo
  - Week 48: Follow-up
  - Week 72: Follow-up
  - TW 8-24 HCV-RNA Undetectable

- **BOC RGT**: N=162
  - Week 4: PR lead-in
  - Week 36: PR + Boceprevir
  - Week 48: Follow-up
  - Week 72: Follow-up
  - TW 8-24 HCV-RNA Detectable

- **BOC/PR48**: N=161
  - Week 4: PR lead-in
  - Week 36: PR + Boceprevir
  - Week 48: Follow-up

SVR and Relapse Rates (ITT)

SVR rates in BOC RGT and BOC/PR48 arm not statistically different (OR, 1.4; 95% CI [0.9, 2.2])

12-week HCV RNA level used if 24-week post-treatment level was missing. A sensitivity analysis where missing data was considered as non-responder, SVR rates for Arms 1, 2 and 3 were 21% (17/80), 58% (94/162) and 66% (106/161), respectively.

46% of patients in the BOC RGT arm were eligible for shorter therapy

~6 times as many patients on BOC regimens (46%-52%) achieved undetectable HCV RNA at week 8 compared to control (9%)
### SVR by Historical Response: Non-responders and Relapsers

<table>
<thead>
<tr>
<th></th>
<th>48 P/R</th>
<th>BOC RGT</th>
<th>BOC/PR48</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-responder, n/n</td>
<td>2/29 (6.9%)</td>
<td>23/57 (40.4%)</td>
<td>30/58 (51.7%)</td>
</tr>
<tr>
<td>Relapser, n/n</td>
<td>15/51 (29.4%)</td>
<td>72/105 (68.6%)</td>
<td>77/103 (74.8%)</td>
</tr>
</tbody>
</table>

RESPOND-2: SVR by Week 4 PR Lead-In Response

In Response to <1 $\log_{10}$ Viral Load Decline

- PR 48: 0%
- BOC RGT: 32.6%
- BOC/PR48: 34.1%

In Response to $\geq 1$ $\log_{10}$ Viral Load Decline

- PR 48: 25%
- BOC RGT: 72.7%
- BOC/PR48: 79%

**RESPOND-2: Adverse Events**

<table>
<thead>
<tr>
<th>Adverse Events (%)</th>
<th>PR48</th>
<th>RGT</th>
<th>BOC/PR48</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>20</td>
<td>43</td>
<td>46</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>11</td>
<td>43</td>
<td>45</td>
</tr>
</tbody>
</table>

No significant difference between arms in: Fatigue, headache, nausea, chills, influenza-like illness, myalgia, pyrexia, insomnia, dyspnea, pruritis, decreased appetite, alopecia, asthenia, cough, diarrhea, arthralgia, irritability, dry skin

# REALIZE: Telaprevir in Genotype-1 Prior Nonresponders

<table>
<thead>
<tr>
<th>Weeks</th>
<th>0</th>
<th>4</th>
<th>12</th>
<th>16</th>
<th>48</th>
<th>72</th>
</tr>
</thead>
<tbody>
<tr>
<td>T12/PR48 (N=266)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>T + P + R</td>
<td>P + R</td>
</tr>
<tr>
<td>T12(DS)/PR48 (N=264)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>P + R</td>
<td>T + P + R</td>
</tr>
<tr>
<td>PR48 (N=132)</td>
<td></td>
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</tbody>
</table>

P = PegIFN α-2a 180 µg/week; R = Ribavirin 1000-1200 mg/d; T = Telaprevir 750 mg q8h.

REALIZE: SVR by Prior Response

- **Relapsers**: 86% TVR Combined, 24% PR Control
- **Partial Responders**: 57% TVR Combined, 15% PR Control
- **Null Responders**: 31% TVR Combined, 5% PR Control
- **Overall, ITT**: 65% TVR Combined, 17% PR Control

REALIZE: Similar SVR in Simultaneous and Delayed Start TVR Arms

Percent Achieving SVR (ITT)

- Relapsers: T12/PR48 83, T12(DS)/PR48 88
- Partial Responders: T12/PR48 59, T12(DS)/PR48 54
- Null Responders: T12/PR48 29, T12(DS)/PR48 33

REALIZE: Safety and Tolerability

• Most common AEs in order of frequency
  – Fatigue, pruritis, headache, rash, flu-like symptoms, nausea, and anemia

• Majority of AEs mild to moderate

<table>
<thead>
<tr>
<th>Discontinuation Rates of All Study Drugs Due to AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adverse Event</strong></td>
</tr>
<tr>
<td>-------------------</td>
</tr>
<tr>
<td>Any</td>
</tr>
<tr>
<td>Anemia</td>
</tr>
<tr>
<td>Rash</td>
</tr>
</tbody>
</table>

Treatment-experienced

• Prior treatment response is an important factor
  – SVR rate: Relapsers > partial non-responder
  > non-responder

• Lead-in with PegIFN/RBV indicates interferon responsiveness and likelihood of SVR

• Treatment regimens:
  – Telaprevir (12 weeks) + PegIFN + RBV for 48 weeks
  – Boceprevir (36 weeks) + PegIFN + RBV for 36 weeks
  (if HCV RNA undetectable at week 8) or 48 weeks
Strategies to Minimize Risk of Viral Breakthrough

- Maximize adherence to all 3 drugs in the regimen
  - Thrice-daily dosing with protease inhibitors
- Multidisciplinary team, including pharmacists
- Aggressive management of side effects
- Careful assessment of viral response kinetics and application of “stopping rules” for protease inhibitors
  - Assess HCV RNA at treatment week 4 of protease inhibitor-based therapy
- HCV eradication = no resistance
DRUG INTERACTIONS

- Contraindicated with drugs highly dependent on CYP3A4/5 for clearance
  - INCREASED TOXICITY of concomitant med
  - Potential for loss of Protease activity

MANY COMMON MEDS ARE IN THE Contraindicated, Not Recommended, or Use with Caution Categories.
INDICATIONS

• Genotype 1 only (for now)
• Never as Monotherapy
• Prior Null responders will not have as robust of response
• Retreatment with other protease not recommended
• No HIV or transplant patients (for now)
• Compensated Liver Disease, treatment naïve or previously treated.
DOSING

• Victrelis (boceprevir)
  – 800 mg (four 200 mg pills) 3 x daily (7-9 hours apart with light snack or meal)

Incivek (telaprevir)
  750 mg (two 375 mg tabs) 3x daily (7-9 hours apart with meal or snack containing 20 gms fat)
Side Effects and AEs due to PEG/RBV

1. PEGIFN: Flu-like symptoms
2. PEGIFN: Mood alteration (depression, SI/SA)
3. PEGIFN: Autoimmune reactions (thyroid, other)
4. PEGIFN: Leucopenia and thrombocytopenia
4. PEGIFN: Infection risk (especially in pts with cirrhosis)
5. RBV: Hemolytic anemia
6. RBV: Rash, mucosal irritation
7. Black box warnings
Side Effects and AEs due to Protease Inhibitors

1. TPV: Rash (management protocol(strategy)
2. TPV: Anemia (transient, usually not requiring EPO)
3. TPV: Anal pain
4. BCP: Anemia (may require EPO)
5. BCP: Dysgeusia
SAFETY

• Same rules as applied to Interferon/RVN
• PAY ATTENTION TO DRUG -DRUG INTERACTIONS
• FUTILITY RULES
• WEEK 4, 12: > 1000 IU (Incivek)
• Week 12: > 100 IU (Victrelis)
• Week 24: Any detectable virus (Both)
Hepatitis C: The Perfect Storm
Hepatitis C: “The Perfect Storm”

- Affects over 4 million Americans
- Major cause of Hepatocellular Carcinoma, Cirrhosis, and Liver Failure
- Population with HCV aging, presenting with more advanced disease
- New treatments promising, but increasingly complex to use and difficult to tolerate
- Very high cost of treatment
Hepatitis C: “The Perfect Storm”

- Large percentage of patients on public insurance
- Number of experienced “treaters” inadequate and expected to diminish
- Availability of new therapies expected to cause many more patients to seek treatment
- Lack of public awareness and disease advocacy
Hepatitis C:

- Stakeholders need to consolidate efforts to raise awareness and develop advocacy
- Stakeholders: Patients, Physicians, Pharmaceutical Companies, Hospitals and Healthcare Organizations, Government
- Programs to train providers to properly treat HCV
- Optimize role of NP/PA and/or PCP
- HIV treatment model?
Thank you!

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