HCV Treatment: SOTA: where are we today?

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San Diego ACCP 2012
Concepts in HCV

• HCV is curable
• 20-30% of HCV infected patient develop cirrhosis

• HCV is a systemic disease:
  – note cyroglobulinemia
  – HCV increases overall mortality rates

• Liver biopsy or indirect fibrosis assessment is required to triage patients in 2012
# To Treat or not to Treat: A Constellation of Considerations

<table>
<thead>
<tr>
<th>Genotype virus Genotype Patient (IL28)</th>
<th>Histologic stage 20%+ life time risk Of cirrhosis</th>
<th>Duration of infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personal plans (marriage, pregnancy)</td>
<td>Age</td>
<td>Family and other support</td>
</tr>
<tr>
<td>Patient &quot;mindset&quot;</td>
<td>ALT</td>
<td>Occupation</td>
</tr>
<tr>
<td>Extrahepatic Features (Fatigue, EMC, PCT)</td>
<td>HIV coinfection</td>
<td>Contraindications &amp; comorbidities Insulin Resistance</td>
</tr>
</tbody>
</table>

PinK AALSD CME 2009
HCV Subtype Distribution: A Mosaic of Overlapping Sub-Epidemics

Mandell, 6th Edition, 2005
## 2 Protease Inhibitors Approved for Genotype 1 HCV Infection

<table>
<thead>
<tr>
<th>Protease Inhibitor</th>
<th>Additional Regimen Components</th>
<th>Considerations</th>
</tr>
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<tbody>
<tr>
<td>Boceprevir 800 mg TID (q7-9hrs)[1,2]</td>
<td>PegIFN alfa + weight-based RBV</td>
<td>Naive to previous therapy, Previous treatment failure, Compensated cirrhosis, RGT</td>
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<tr>
<td>Telaprevir 750 mg TID (q7-9hrs)[2,3]</td>
<td>PegIFN alfa + weight-based RBV</td>
<td>Naive to previous therapy, Previous treatment failure, Compensated cirrhosis, RGT</td>
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For patients with genotype 2/3 infection, HCV therapy with pegIFN/RBV remains the standard of care

What can we tell our patients?

Significantly Higher SVR rates in Telaprevir-Treated Patients Compared to Peg IFN/Ribavirin Alone

**Percent of patients with SVR**

- **T12PR**:
  - n/N = 271/363
  - SVR: 75%

- **PR**:
  - n/N = 158/361
  - SVR: 44%

**P < 0.0001**

Telaprevir + PegIFN/RBV: Genotype 1 Treatment-Naive Patients

Dosage and Administration

- 750 mg (two 375-mg tablets) TID (every 7-9 hrs) with food (standard fat meal 20 g., e.g., ½ cup nuts or 2 oz cheddar cheese)
- Must be administered with both pegIFN and RBV
- Telaprevir dose must not be reduced or interrupted

Treatment duration

- Patients with extended RVR (eRVR, undetectable* HCV RNA at Week 4 and 12) receive 24 wks of therapy
- Patients without eRVR continue on pegIFN + RBV for a total of 48 wks
- Treatment-naive patients with compensated cirrhosis and eRVR may benefit from additional 36 wks of pegIFN + RBV (i.e., to Week 48)

F/u 24 wks

Week 4 HCV RNA > 1000 IU/ml
Week 12 HCV RNA > 1000 IU/ml
Week 24 HCV RNA detectable


*Assay should have a lower limit of HCV RNA quantification ≤ 25 IU/mL.
Boceprevir for genotype 1 naïve HCV

Milestones: Weeks 8, 12, 24

Week 4
PR + BOC (24 weeks)
Non-cirrhotic

Week 12
Week 24

Week 28
TW 8-24 HCV-RNA Undetectable*

Follow-up

Week 36

PR + BOC (32 weeks)
PR
Follow-up

TW 8-24 HCV-RNA Detectable/
TW 24 undetectable

Week 48
Week 72

PR + BOC (44) weeks for cirrhotic patients/
poorly responsive pts

Follow-up

Week 12 Futility
HCV > 100 IU/ml

Week 24 Futility
Detectable HCV RNA

*assay should have a lower limit of HCV-RNA quantification \( \leq 25 \text{ IU/mL} \), and limit of HCV-RNA detection of approximately 10-15 IU/mL
SPRINT 2: SVR* and Relapse Rates

*SVR was defined as undetectable HCV RNA at the end of the follow-up period. The 12-week post-treatment HCV RNA level was used if the 24-week post-treatment level was missing (as specified in the protocol). A sensitivity analysis was performed counting only patients with undetectable HCV RNA documented at 24 weeks post-treatment and the SVR rates for Arms 1, 2 and 3 in Cohort 1 were 39%, 66% and 68%, respectively and in Cohort 2 were 21%, 42% and 51%, respectively.
Use of Predictors to Decide to Treat Now or Wait for INF free regimens—Current Issues

**Treatment duration**
- At least 24 weeks for HCV GT1?
- Studies in Asia should be for 12 week triple therapy total or less with TVR or 12 +12 with BCP for IL28 CC?
- Suboptimal results for non-RVR patients after 48 weeks of treatment

**Safety profile**
- Several IFN-related AEs
- Current PIs: anemia, rash, etc
- DDI

**Low efficacy in certain patients**
- History of null response
- *IL28B*: TT
- Liver cirrhosis
Clinical Pharmacology and Drug Interactions

- **Boceprevir**
  - Strong inhibitor of CYP3A4/5
  - Partly metabolized by CYP3A4/5
  - Potential inhibitor of and substrate for P-gp

- **Telaprevir**
  - Substrate of CYP3A
  - Inhibitor of CYP3A
  - Substrate of P-gp

- Must perform DDI survey or work with clinic pharmacology


P-gp = p-glycoprotein
There is a paucity of data in Asians. There is a dearth of ethnicity reporting in all trials.
A Polymorphism on Chromosome 19 Predicts SVR


SVR Rates in ADVANCE Patients Genotyped for IL28B

12 weeks of Telaprevir, Peg-IFNα and Ribavirin for CC Patients

SVR rates in 156 genotype 1 patients included in PROVE2 who gave informed consent for IL28B genotyping

<table>
<thead>
<tr>
<th>IL28B genotype</th>
<th>T12PR12 (n=44)</th>
<th>T12PR24 (n=37)</th>
<th>T12P12 (n=29)</th>
<th>PR48 (n=31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CC</td>
<td>100%</td>
<td>94%</td>
<td>75%</td>
<td>64%</td>
</tr>
<tr>
<td>CT</td>
<td>44%</td>
<td>67%</td>
<td>18%</td>
<td>31%</td>
</tr>
<tr>
<td>TT</td>
<td>20%</td>
<td>33%</td>
<td>0%</td>
<td>25%</td>
</tr>
</tbody>
</table>

(Bronowicki et al.)
SPRINT-2 Boceprevir: IL28B CC Polymorphism Predicts Week 8 Response

Patients negative at Week 8 were eligible for a shorter treatment duration

BOC = boceprevir; EOT = end of treatment response, PR = peginterferon alfa-2b + ribavirin; SVR = sustained virologic response.

*Intent-to-treat analysis: efficacy analyses yielded nearly identical results; no Asian patients were randomized but not treated in these studies.

- At treatment week 8, 80% of Asian patients receiving BOC/PR had undetectable HCV RNA (consisting of PR lead-in for 4 weeks and BOC/PR for 4 weeks) (Figure 4)
  - 80% of patients eligible for shortened (24-week) treatment duration
- Most Asian patients receiving PR had undetectable HCV RNA at week 8 (PR for 8 weeks)
<table>
<thead>
<tr>
<th>Treatment Options</th>
<th>SVR Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triple therapy with Peg-IFN$_\alpha$, ribavirin and a</td>
<td></td>
</tr>
<tr>
<td>low barrier to resistance DAA</td>
<td>SVR strongly depends on the patient’s responsiveness to IFN</td>
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<td>Triple therapy with Peg-IFN$_\alpha$, ribavirin and a</td>
<td></td>
</tr>
<tr>
<td>high barrier to resistance DAA/HTA</td>
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<tr>
<td>Quadruple therapy with Peg-IFN$_\alpha$, ribavirin 2</td>
<td></td>
</tr>
<tr>
<td>DAAs/HTAs</td>
<td>SVR is less dependent on the patient’s responsiveness to IFN</td>
</tr>
<tr>
<td>IFN-free regimens</td>
<td>SVR depends on the potency and barrier to resistance of the combination</td>
</tr>
</tbody>
</table>
## Characteristics of HCV DAA Classes

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Protease inhibitors</th>
<th>Nucleos(t)ide Polymerase inhibitors</th>
<th>Nonnucleoside 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 &lt; 1b</td>
<td>Low 1a &lt; 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>Toxicty</td>
<td>Rash Anemia ↑Bilirubin</td>
<td>Mitochondrial Nuc interactions (ART, QBV)</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 PIs: better barrier, pangenotypic</td>
<td>Single target Active site</td>
<td>Allosteric; Many targets</td>
<td>Multiple antiviral MOA</td>
</tr>
</tbody>
</table>
Virologic Response
QUAD Therapy: B1 and B2 (GT 1a/1b, mITT)

- No viral breakthrough
- 2 patients relapsed—1 at PT week 4 (B1); 1 at PT week 12 (B2)

\[N = \begin{array}{c|c|c|c|c|c|c|c|c|c} \\
Week 4 & Week 12 & EOT (Week 24) & SVR_4 & SVR_{12} & SVR_{24} \\
\hline
20 & 21 & 20 & 21 & 20 & 21 & 20 & 21 & 20 & 21 \\
\end{array} \]

- B1: DCV + ASV 200 mg BID + pegIFN-alfa/RBV
- B2: DCV + ASV 200 mg QD + pegIFN-alfa/RBV

% of patients with HCV RNA < LLOQ-TND

*1 patient missing an HCV RNA measurement; LLOQ, 25 IU/mL; LOD, 10 IU/mL.
ATOMIC Trial: Virologic Response

- Rapid reduction in HCV RNA in first 2 weeks of therapy regardless of IL28B status
- SVR4 rates were comparable between GS-7977 regimens of 12 and 24 week duration
- Virologic relapse was rare to date, 4 patients sequenced
  - No S282T mutation (population sequencing)
  - Deep sequencing results are pending for all patients with relapse

Genotype 2/3: Virologic Response During and After Treatment (mITT)

- **Group B**: 1 “viral breakthrough” (<LLOQ-TD) at Week 8 and 1 relapse at PT Week 4 (both GT3)
- **Group F**: 2 lost to follow-up after EOT; 1 returned at PT Week 24 with HCV RNA < LLOQ-TND

*End-of-treatment (EOT) includes patients who discontinued early, with last visit considered EOT; TD, target detected; TND, target not detected*
• There was an association between IL28B genotype and undetectable HCV RNA at week 2
  – This association disappeared at week 4 due to high RVR rates across all IL28B genotypes (83% to 100%)

Genotype 1: Virologic Response During and After Treatment, 12- and 24-Week Groups (mITT)

- **Group G**: 1 patient missing at PT Week 4—achieved SVR$_{12}$
- **Group H**: 1 patient missing at PT Week 4—achieved SVR$_{12}$; 1 patient undetectable at PT Week 2 and with HCV RNA = 54 IU/mL at PT Week 4 (not confirmed)—also achieved SVR$_{12}$
- **Groups G and H**: 68 patients have reached PT Week 12—all 68 have achieved SVR$_{12}$

$^a$End-of-treatment (EOT) includes patients who discontinued early, with last visit considered EOT; TND, target not detected
Interferon-Free: PILOT and Co-PILOT

**Pilot**: G1, treatment naïve, *IL28B* CC, non-cirrhotic

- **ABT-450/r + ABT-072 + RBV**

**Co-Pilot**: G1, non-cirrhotic

- **Naive**
  - ABT-450 250mg/r + ABT-333 + RBV
  - ABT-450 150mg/r + ABT-333 + RBV

- **Treatment Experienced**
  - ABT-450 250 mg/r + ABT-333 + RBV

**SVR12 (%)**

<table>
<thead>
<tr>
<th></th>
<th>Pilot¹</th>
<th>Co-Pilot²</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=11</td>
<td>91</td>
<td>95</td>
</tr>
<tr>
<td>n=19</td>
<td>95</td>
<td>93</td>
</tr>
<tr>
<td>n=14</td>
<td>93</td>
<td>47</td>
</tr>
<tr>
<td>n=17</td>
<td>47</td>
<td></td>
</tr>
</tbody>
</table>


**ABT-450**: NS3 inhibitor
**ABT-072 and ABT-333**: non-nucleoside inhibitor
**r**: ritonavir
**BMS: INF Free, Riba Free, triple therapy PI, NS5A, Pol Inh**

**HCV RNA Endpoints**  
Modified Intention-to-Treat Analysis

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**24-Week Treatment**  
Group 1, N = 16

- **HCV RNA < LLOQ\textsubscript{TD} or TND**
- **Missing data**

<table>
<thead>
<tr>
<th>Study Week</th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>12</td>
<td>94</td>
<td>88</td>
</tr>
<tr>
<td>EOT\textsuperscript{b}</td>
<td>94\textsuperscript{a}</td>
<td>100</td>
</tr>
<tr>
<td>PT 4 (SVR\textsubscript{4})</td>
<td>94</td>
<td>94</td>
</tr>
</tbody>
</table>

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**12-Week Treatment**  
Group 2, N = 16

- **HCV RNA < LLOQ\textsubscript{TD} or TND**
- **Missing data**

<table>
<thead>
<tr>
<th>Study Week</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>100</td>
</tr>
<tr>
<td>12</td>
<td>88</td>
</tr>
<tr>
<td>EOT\textsuperscript{b}</td>
<td>94</td>
</tr>
<tr>
<td>PT 4 (SVR\textsubscript{4})</td>
<td>94</td>
</tr>
<tr>
<td>PT 12 (SVR\textsubscript{12})</td>
<td>94</td>
</tr>
</tbody>
</table>

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\textsuperscript{a} Includes 1 patient with HCV RNA 118 IU/mL at last on-treatment visit but < LLOQ\textsubscript{TND} 2 and 4 weeks posttreatment (SVR\textsubscript{4}).

\textsuperscript{b} EOT, end of treatment; includes patients who discontinued prior to the protocol-defined last treatment visit.

< LLOQ\textsubscript{TD} or TND\textsubscript{TD} or TND\textsubscript{TP}: HCV RNA below assay lower limit of quantitation (25 IU/mL) and target detected (LLOQ\textsubscript{TD}) or target not detected (LLOQ\textsubscript{TND}; HCV RNA < LOD \approx 10 IU/mL, previously reported as HCV RNA undetectable); PT, posttreatment.

Towards a Future for the Asian Patient
Treatment Personalized Medicine for HCV Therapy

Direct Acting Antivirals
8-12 weeks therapy or shorter

Nuc + RBV
NNI + PI ± RBV
Nuc + NS5A ± RBV ± PI
PEG-IFN + RBV + DAA (s)
To shorten Rx time to ≤4 weeks

Nuc: nucleotide polymerase inhibitor
NNI: non-nucleotide polymerase inhibitor
PI: protease inhibitor
NS5A: NS5A replication complex inhibitor
Treat now? Yes
DAAs provisional “yes” with current PIs as part of triple therapy INF + Riba

• Advanced fibrosis by
  – Liver biopsy
  – Fibroscan
  – Imaging

• Cryoglobulinemia

• Patient demand

• 1st Gen PIs in Asian patients, off label:
  – Shorten Rx with TVR to 8 weeks if 2 week vRVR
  – Shorten Rx with BCP to 12 to 18 weeks if 2 week vRVR
Will week 1 or 2 become the new assessment of seRVR or vRVR?

- For Asia
- Ready for DAA s now
  - Qualified yes
  - Cost: estimates will be the cost of 50 000 $ use for a 12 week course, dual triple or quad
  - Use of INF as back bone to save cost? Shorten Rx to 4-6 weeks for some favorable>
    - G 1b
    - No metabolic Syndrome
    - IL28 CC
HCV Treatment : SOTA : Asia: where are we today?

Robert G. Gish MD

Hong Kong SLD meeting 2012: Thank you !@