Goals for Treatment and Predicting Response

Raymond T. Chung, MD
Director of Hepatology and Liver Center
Massachusetts General Hospital
Boston, Massachusetts
Disclosure Information

- Dr Chung has received grants or research support from Gilead Sciences, Inc, and has served as a consultant to Idenix Pharmaceuticals, Inc, and Abbvie.
Outline

- Rationale and goals for treatment (SVR, disease progression, survival)
- Viral factors that predict response to therapy (HCV genotype, HCV RNA level)
- Host factors that predict response to therapy (race, age, sex, *IL28B* genotype)
- Combined factors (degree of fibrosis)

HCV = hepatitis C virus; SVR = sustained virologic response
Rationale and Goals for Treatment (SVR, Improve Histology, Survival)
Rationale and Goals for Treatment

- Chronic HCV is a progressive disease that can produce significant morbidity and mortality if left untreated
- HCV RNA virus without latent, stable intermediate
- Requires continuous replication
- SVR is possible and connotes clinical cure
- Defined as clearance of HCV RNA 24 weeks after completion of a course of antiviral therapy
  - SVR 12 weeks after discontinuation of treatment equates to SVR 24 weeks after discontinuation of treatment
Natural History of Chronic HCV

- **Exposure (Acute phase):**
  - 20% (20) Resolved
  - 80% (80) Chronic

- **Chronic:**
  - 80% (64) Stable or variably progressive
  - 20% (16) Cirrhosis

- **Cirrhosis:**
  - 75% (12) HCC
  - 25% (4) Death

- **HCC Transplant Death**
  - 20 yrs
  - 25 yrs

HCC = hepatocellular carcinoma
An SVR is Truly Sustained

- Cohort study
- Patients from 9 trials
- HCV: 1243 patients
- HIV/HCV: 100 patients
- Follow-up: mean 3.9 yrs (range, 0.8-7.1 yrs)
- 0.9% HCV RNA positive after treatment ended

HCV RNA during follow-up period after SVR

- 99% Negative
- 0.9% Positive

Swain MG. Gastro, 2010
Impact of SVR on Natural History in Patients With Advanced Fibrosis

- Improved outcomes in patients who achieve SVR
  - All-cause mortality
  - Liver-related mortality
  - Liver cancer
  - Liver failure or need for liver transplantation
  - Reduce insulin resistance and diabetes mellitus
SVR Reduces Liver-Related Complications

- HALT-C Cohort (patients with bridging fibrosis/cirrhosis)
- Median follow-up 85.8 months (SVR) and 78.4 months (non-SVR)

SVR Reduces All-Cause and Liver-Related Mortality

van der Meer A, JAMA, 2013

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Events, No.</th>
<th>Observation Period, Person-Years</th>
<th>Rate per 100 Person-Years (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any event&lt;sup&gt;a&lt;/sup&gt;</td>
<td>18</td>
<td>1260</td>
<td>1.43 (0.77-2.09)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>13</td>
<td>1283</td>
<td>1.01 (0.46-1.56)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Liver-related mortality or liver transplantation</td>
<td>3</td>
<td>1283</td>
<td>0.23 (&lt;0.01-0.50)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

<sup>a</sup> Includes all-cause mortality and liver-related mortality or liver transplantation.

<sup>b</sup> Calculated using log-rank test.
Baseline Factors Predictive of SVR With an HCV PI Plus PegIFN and RBV therapy

Viral factors
- HCV RNA level
- HCV genotype (GT; 1 vs 2,3)
- GT 1 subtype (1a vs 1b)

Host factors
- Race and ethnicity
- Gender
- Interleukin 28B genotype (CC vs CT or TT)
- Body mass index (BMI)

Combined
- Liver histology

PI = protease inhibitor; PegIFN = peginterferon alfa; RBV = ribavirin
## Baseline Predictors of SVR: SPRINT-2

<table>
<thead>
<tr>
<th>Effect</th>
<th>Odds Ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline HCV RNA: ≤ 400,000 vs &gt; 400,000</td>
<td>11.6 (1.5, 87.8)</td>
<td>.02</td>
</tr>
<tr>
<td><em>IL28B</em> rs12979860: CC vs TT</td>
<td>2.6 (1.3, 5.1)</td>
<td>.006</td>
</tr>
<tr>
<td><em>IL28B</em> rs12979860: CC vs CT</td>
<td>2.1 (1.2, 3.7)</td>
<td>.01</td>
</tr>
<tr>
<td><em>IL28B</em> rs12979860: CT vs TT</td>
<td>1.2 (0.7, 2.2)</td>
<td>.48</td>
</tr>
<tr>
<td>Cirrhosis: no vs yes</td>
<td>4.3 (1.6, 11.9)</td>
<td>.004</td>
</tr>
<tr>
<td>Genotype: 1b vs 1a</td>
<td>2.0 (1.2, 3.4)</td>
<td>.005</td>
</tr>
<tr>
<td>Race: non-black vs black</td>
<td>2.0 (1.1, 3.7)</td>
<td>.03</td>
</tr>
<tr>
<td>BMI: ≤ 30 vs &gt; 30</td>
<td>1.6 (1.0, 2.5)</td>
<td>.07</td>
</tr>
</tbody>
</table>

CI = confidence interval
Viral Factors that Predict Response to Therapy (HCV Genotype, HCV RNA level)
### Viral Factors

<table>
<thead>
<tr>
<th><strong>Genotype</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>- Current therapies (PegIFN/RBV/PI) centered on GT 1</td>
</tr>
<tr>
<td>- Standard of care for GT 2,3: PegIFN and RBV</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Subtype</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>- SVR rates higher for GT 1b vs 1a</td>
</tr>
<tr>
<td>- 1a - lower barrier to emergence of resistant variants for HCV PIs</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>HCV RNA level</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>- Higher HCV RNA associated with slightly diminished SVR</td>
</tr>
<tr>
<td>- Effect strong</td>
</tr>
</tbody>
</table>
Host Factors that Predict Response to Therapy (Race, Age, Sex, *IL28B* Genotype)
Host Factors

- Race (non-black > black)
- Age (younger > older)
- Sex (F > M)
- $IL28B$ GT (CC > CT, TT for the rs12979860 single nucleotide polymorphism [SNP])
  - Strongest predictor of PegIFN and RBV response in GT 1, but effect less stark with PegIFN and RBV plus a PI
SVR to PegIFN and RBV Profoundly Influenced by *IL28B* Genotype

SVR According to *IL28B*: PegIFN, RBV, and Telaprevir

Jacobson et al. EASL, 2011; PR = peginterferon alfa and ribavirin; T = telaprevir
Degree of Fibrosis and Predicting Treatment Response
Combined Factors

• Extent of fibrosis
  o Patients without cirrhosis more responsive than patients with cirrhosis
• Mechanism unclear
  o Pharmacokinetic and pharmacodynamic considerations with distorted architecture
  o Cirrhosis associated with innate and adaptive immune deficits
• Decision to treat patients with cirrhosis must be weighed against projected response rate and potential for adverse effects
• Similarly, deferral of treatment may be considered in patients without cirrhosis with the impending approval of direct-acting antivirals (DAAs)
Summary

- Cure of HCV achievable
- SVR associated with significant clinical benefit
  - Slows or reverses disease progression
  - Reduces hepatic and all-cause mortality
  - Improves extrahepatic manifestations
- Host, viral, and mixed factors all influence success of treatment with PegIFN, RBV, and a PI
- Discussion of these factors should take place in preparation for treatment
- Availability of potent DAA combination regimens will dilute the effect of these predictors
This presentation is brought to you by the International Antiviral Society-USA (IAS-USA) in collaboration with Hepatitis Web Study & the Hepatitis C Online Course

Funded by a grant from the Centers for Disease Control and Prevention