ASSAYS UTILIZED TO MONITOR HCV AND ITS TREATMENT

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Liver Institute of Virginia
Bon Secours Health System
Richmond and Newport News, VA
FINANCIAL RELATIONSHIPS WITH INDUSTRY

<table>
<thead>
<tr>
<th>Company</th>
<th>Roles</th>
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<tbody>
<tr>
<td>Abbott</td>
<td>Data safety monitoring board, grant support</td>
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<td>Achillion</td>
<td>Advisor meeting, grant support</td>
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<td>Anadys</td>
<td>Advisor meeting, data safety monitoring board, grant support</td>
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<tr>
<td>Bayer</td>
<td>Speaker, advisor meetings</td>
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<td>Bristol Myers-Squibb</td>
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<td>Boehringer-Ingelheim</td>
<td>Advisor meetings, grant support</td>
</tr>
<tr>
<td>Conatus</td>
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</tr>
<tr>
<td>Gilead</td>
<td>Advisor meetings, speaker, grant support</td>
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<td>Globeimmune</td>
<td>Grant support, advisor meetings</td>
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<tr>
<td>Human Genome Sciences</td>
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<tr>
<td>Idenix</td>
<td>Grant support</td>
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<tr>
<td>Novartis</td>
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<tr>
<td>Pfizer</td>
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<td>Roche/Genentech</td>
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<td>Romark</td>
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<tr>
<td>Schering-Plough/Merck</td>
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<td>Vertex</td>
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<tr>
<td>Zymogenetics</td>
<td>Advisor meetings, grant support</td>
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</table>
CHRONIC LIVER DISEASE MORTALITY

• 12 most common cause of death
• Only chronic medical disorder with increasing mortality over past 5 years
• Chronic HCV accounts for 44% of all patients with chronic liver disease
  • Most common cause of:
  • Cirrhosis
  • Liver failure
  • Liver cancer
  • Liver transplantation

J Xu et al.
USE OF HCV ASSAYS
OUTLINE

• Antibody testing
• RIBA
• HCV RNA testing
• Treatment of HCV
• IL28B testing
• Anti-viral therapy
TESTING FOR HEPATITIS C VIRUS anti-HCV

- Screening test
- ELISA
- Sensitivity 97%
- Detects circulating HCV antibodies
- False positive reactions may occur
  - Cross reacting circulating antibodies
  - Non-specific binding of anti-HCV antibodies
- Positive predictive value:
  - 95% with risk factors and elevated ALT
  - 50% without risk factors and normal ALT
anti-HCV TESTING
LIMITATIONS

• False positives:
  ▪ Autoimmune disorders
  ▪ Spontaneous resolution of viral infection

• False negatives:
  ▪ Chronically immune suppressed
  ▪ Transplant recipients
  ▪ Chronic renal failure on dialysis
  ▪ HIV positive
TESTING FOR HEPATITIS C VIRUS
RIBA

- Supplemental assay
- Detects circulating antibodies to 4 HCV proteins
- Antigen-antibody reaction
- More specific than anti-HCV
- False positive reaction can still occur
- Replaced by HCV-RNA
- Only use – define spontaneous resolution
CHRONIC HCV INFECTION
ROLES FOR MOLECULAR TESTING

- Diagnose acute infection
- Confirm chronic infection
- Assess severity of disease
- Assess risk for disease progression
- Identify which patients require treatment
- Monitor response to treatment
- Define duration of treatment

<table>
<thead>
<tr>
<th>Roles</th>
<th>Yes</th>
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<tr>
<td>Diagnose acute infection</td>
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<td>Confirm chronic infection</td>
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<tr>
<td>Assess severity of disease</td>
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<tr>
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<tr>
<td>Monitor response to treatment</td>
<td>Yes</td>
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<tr>
<td>Define duration of treatment</td>
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HEPATITIS C VIRUS RESPONSE TO ACUTE INFECTION

<table>
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<tr>
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<th>Resolution</th>
<th>Chronic</th>
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<tbody>
<tr>
<td>Anti-HCV</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>HCV RNA</td>
<td>+</td>
<td>-</td>
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</table>
ACUTE HCV INFECTION
INTERMITTENT VIREMIA

S Glynn et al.
Transfusion 2005; 45:994-1002.
SERUM HCV RNA LEVEL REMAINS STABLE OVER TIME

SERUM HCV RNA LEVEL REMAINS STABLE OVER TIME

HCV RNA AND LIVER HISTOLOGY

FIBROSIS

A Ferreira-Gonzalez et al.
HCV RNA AND LIVER HISTOLOGY
INFLAMMATION

A Ferreira-Gonzalez et al.
TREATMENT OF CHRONIC HCV
SVR RATES OVER TIME

YEAR

0 20 40 60 80 100

SVR (%)


$5,000 $24,000 >$40,000+

12-fold increase
In 2 decades!!!

INF INF PEG PEG

RBV RBV RBV RBV

DAA
VIROLOGIC PATTERNS TO TREATMENT NON-RESPONSE

Log HCV RNA (IU/ml) vs. WEEKS

Peginterferon/Ribavirin

2-log decline

Limit of detection

SVR
VIROLOGIC PATTERNS TO TREATMENT NON-RESPONSE

Log HCV RNA (IU/ml) vs WEEKS

- Peginterferon/Ribavirin
- 2-log decline
- Limit of detection
- SVR
## TREATMENT OF CHRONIC HCV: A SVR IS DURABLE = "CURE"

<table>
<thead>
<tr>
<th>Treatment</th>
<th>SVR (N)</th>
<th>Duration (Years)</th>
<th>Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEGINF</td>
<td>166</td>
<td>5.2</td>
<td>2 (1.2%)</td>
</tr>
<tr>
<td>PEGINF/RBV</td>
<td>998</td>
<td>4.2</td>
<td>9 (0.9%)</td>
</tr>
<tr>
<td>PEG/RBV Normal ALT</td>
<td>79</td>
<td>4.7</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>PEG ± RBV HIV Co-infection</td>
<td>100</td>
<td>4.6</td>
<td>1 (1.0%)</td>
</tr>
<tr>
<td>Total</td>
<td>1343</td>
<td>4.7</td>
<td>12 (0.9%)</td>
</tr>
</tbody>
</table>

Swain et al, Gastroenterol 2010; 139:1593-1601.

2 patients with recurrence were RNA + at end of treatment or during follow-up. True recurrence = 0.7%
TREATMENT OF CHRONIC HCV

ACHIEVING SVR

Affected by:

- Rate of virologic response
- Interferon sensitivity of the host
- Racial factors
- Adverse events – anemia
- Viral factors
- Other factors:
  - Body weight
  - Serum level of HCV RNA
  - Insulin resistance
  - Degree of fibrosis
IL28B POLYMORPHISM
THE INTERFERON SWITCH

• Host gene
• Modulates the interferon response
• Chromosome 19
• SNP at loci rs12979860
• CC haplotype (cure):
  • Highly interferon sensitive
  • High rates of spontaneous resolution
  • High rates of RVR
  • High rates of virologic response
  • High rates of SVR

D Ge et al.
IL28B POLYMORPHISM
THE INTERFERON SWITCH

• Host gene
• Modulates the interferon response
• Chromosome 19
• SNP at loci rs12979860
• TT haplotype (terrible):
  • Minimally interferon sensitive
  • No spontaneous resolution
  • Low rates of RVR
  • Low rates of virologic response
  • Low rates of SVR

IL28B POLYMORPHISM
THE INTERFERON SWITCH

- Host gene
- Modulates the interferon response
- Chromosome 19
- SNP at loci rs12979860
- CT halotype:
  - Lower interferon sensitivity
  - Low rates of spontaneous resolution
  - Low rates of RVR
  - Low rates of virologic response
  - Low rates of SVR

D Ge et al.
IL28 B POLYMORPHISM AND SVR IMPACT OF RACE AND ETHNICITY

# IL28 B POLYMORPHISM IMPACT OF RESPONSE AND RACE

<table>
<thead>
<tr>
<th></th>
<th>Caucasian</th>
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<th>African American</th>
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<tbody>
<tr>
<td></td>
<td>CC</td>
<td>Non-CC</td>
<td>CC</td>
</tr>
<tr>
<td>RVR</td>
<td>28%</td>
<td>5%</td>
<td>15%</td>
</tr>
<tr>
<td>cEVR</td>
<td>87%</td>
<td>33%</td>
<td>50%</td>
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<tr>
<td>ETR</td>
<td>92%</td>
<td>54%</td>
<td>70%</td>
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<tr>
<td>SVR</td>
<td>69%</td>
<td>30%</td>
<td>48%</td>
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<tr>
<td>Relapse</td>
<td>14%</td>
<td>34%</td>
<td>23%</td>
</tr>
</tbody>
</table>

A Thompson et al.  
Gastroenterology 2010; 139:120-129.
TREATMENT OF HCV
IMPACT OF GOOD RESPONSE FACTORS

Peginterferon/Ribavirin

- IL28B-cc
- Caucasian race
- Less fibrosis
- Low HCV RNA level
- Low body weight
- No insulin resistance

WEEKS

Log HCV RNA (IU/ml)
TREATMENT OF CHRONIC HCV
DIRECT ACTING ANTI-VIRAL (DAA)

HW Reesink et al.  Gastroenterol 2006; 131:997-1002.
TELAPREVIIR PHASE 3 - ADVANCE NAÏVE: 8 vs 12 WEEKS

Week of TPV

If eRVR:
PEGINF + Ribavirin

83% 89%

If NO eRVR:
PEGINF + Ribavirin

50% 54%

PEGINF-2a + Ribavirin

44%

Weeks

0  8  12  24  48

IM Jacobson et al. AASLD 2010.
<table>
<thead>
<tr>
<th>HCV RNA</th>
<th>UD</th>
<th>UD</th>
<th>UD</th>
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<tr>
<td>RVR</td>
<td>Telaprevir</td>
<td>PEGINF</td>
<td>Ribavirin</td>
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<td>No RVR</td>
<td>PEGINF</td>
<td>Ribavirin</td>
<td>PEGINF-RBV</td>
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<td>&lt; 3</td>
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<tr>
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<tr>
<td>Week</td>
<td>4</td>
<td>8</td>
<td>12</td>
</tr>
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</table>

ML Shiffman, R Estaban
Liver Intl 2012; (in press)
BOCEPREVIR PHASE 3 – SPRINT 2
RGT vs 48 WEEKS

If eRVR:
BOC + PEGINF + Ribavirin

If NO eRVR:
BOC + PEGINF + Ribavirin

PEGINF-2b + Ribavirin

PEGINF-2b
Ribavirin

F Poordad et al.
## BOCEPREVIR TREATMENT NAIVE

<table>
<thead>
<tr>
<th>HCV RNA</th>
<th>RVR</th>
<th>No RVR</th>
<th>Log HCV</th>
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<th>Week</th>
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<tr>
<td>*</td>
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<td>UD</td>
<td>&gt;2</td>
<td>4</td>
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<td>36</td>
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<td>Boceprevir PEGINF + Ribavirin</td>
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<td></td>
<td>PEG Ribavirin</td>
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</tr>
</tbody>
</table>

**Stop Rule**
- RVR: 2
- Log HCV: ><2
- Week: 4

ML Shiffman, R Estaban
Liver Intl 2012; (in press)
TREATMENT OF CHRONIC HCV EMERGENCE OF RESISTANCE

[Graph showing the decline of HCV RNA (IU/ml) over weeks. Key points include:
- DAA/PEGINF/RBV
- Loss of Response
- Breakthrough
- 2-log decline
- Limit of Detection]
BOCEPREVIR + PEGINF + RIBAVIRIN IMPACT OF IL28B STATUS ON SVR

F Poordad et al.
EASL 2011
POTENT LOW RESISTANCE POLYMERASE
HOW MUCH INF IS NEEDED?

- PEGINF 100%
- PEGINF 100%
- PEGINF 100%
- PSI-7977 Ribavirin 100%

Weeks 0 to 24

E Gane et al.
AASLD 2011.
CHRONIC HCV SUMMARY

- RIBA is only useful in defined spontaneous resolution
- HCV RNA can be misleading during acute infection
- The level of HCV RNA does not correlate with disease severity
- Patients with a SVR are “cured” of chronic HCV
- Host genetics play a major role in defining which patients with chronic HCV can be cured
The addition of a protease inhibitor to peginterferon and ribavirin significantly enhances SVR.

Patients who are not genetically sensitive to peginterferon have a lower rate of SVR even with protease inhibitors and high rate of developing resistance to the anti-viral agent.

Potent anti-viral agents with low resistance may be able to cure HCV without peginterferon in the future.