The Coming Revolution in the Assessment and Treatment of Hepatitis C

Presented By:
David R. Hillyard, MD
Medical Director, Molecular Infectious Disease, ARUP Laboratories

Learning Objectives:
1. Discuss recent advances in the management of HCV
2. Discuss the likely impact of new therapeutic agents for HCV
3. Discuss the role of human genotyping for prediction of HCV outcomes
### 10 Leading Causes of Infectious Disease Deaths Worldwide (2000)

<table>
<thead>
<tr>
<th>Disease</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower respiratory tract infections</td>
<td>~3.5 million</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>~3.0 million</td>
</tr>
<tr>
<td>Diarrheal diseases</td>
<td>~2.2 million</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>~2.0 million</td>
</tr>
<tr>
<td>Malaria</td>
<td>~1-3 million</td>
</tr>
<tr>
<td>Malaria</td>
<td>~888,000</td>
</tr>
<tr>
<td>Measles</td>
<td>~888,000</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>~500,000-750,000</td>
</tr>
<tr>
<td>Pertussis</td>
<td>~355,000</td>
</tr>
<tr>
<td>Neonatal tetanus</td>
<td>~300,000</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>~250,000</td>
</tr>
</tbody>
</table>


From Clinical Care Options
Discovery HCV

- Search for basis of non-A, non-B hepatitis
  - 85% of blood transfusion hepatitis
  - DNA or RNA virus?
- Purify nucleic acid from infected chimpanzee
- Copy and clone into bacteriophage \( \lambda \text{gt}11 \)
- Identify clones expressing viral proteins using antibodies from non-A, non-B patient

“It is not unrealistic to expect that other elusive agents may now be recognized using similar approaches”

Harvey Alter  Annals of Internal Medicine 1991
**HCV Infection**  
most common indication for liver transplantation  

Acute HCV Infection → 15% Recovery  
↓ 85%  

Chronic HCV Infection  
↓ 20% - 80%  

Cirrhosis → Hepatocellular Carcinoma  
(1-3% per year in setting of cirrhosis)  

End Stage Liver Disease
The Changing Face of HCV in the US


Assuming no changes in standard of care

- Liver transplantation
- Hepatocellular carcinoma
- Decompensated cirrhosis

- Total number of patients with advanced liver disease in 20 yrs projected to be > 4-fold higher than today


From Clinical Care Options
The Coming HCV Revolution

• New therapies with dramatically improved outcomes
• Improved technologies for molecular testing
  – HCV quantitation (Viral Load)
  – HCV genotyping
• Genetic markers for host response
• Advanced management algorithms
Hepatitis C Virus

- Flaviviridae (RNA genome)
- Discovered 1989 (molecular approach)
- Cause of “non-A, non-B” viral hepatitis
- Affects 3.8 million in U.S. (most still undiagnosed)
- Medical risk due to chronic infection
- Most common chronic blood-borne infection
- Causes cirrhosis and hepatocellular carcinoma
- ~12,000+ deaths annually (U.S.)
HVC Genome

• Most conserved
  – Detection & quantitation (viral load)
  – Genotyping (1-6)

Interferon sensitivity

Serine protease
NS3/4A

HCV genome does not integrate into host DNA
Patients can be cured!
HCV Genotypes

- 1a: 58%
- 1b: 22%
- 2a: 2%
- 2b: 12%
- 3a: 4%
- 4a: 1%
- 4b: 1%

HCV Sub-classification

<table>
<thead>
<tr>
<th>GENOTYPE</th>
<th>SUBTYPE (total=84)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>a, b, c, d, e, f, g, h, i, j, k, l, m (13)</td>
</tr>
<tr>
<td>2</td>
<td>a, b, c, d, e, f, g, h, i, j, k, l, m, n, o, p, q, r (18)</td>
</tr>
<tr>
<td>3</td>
<td>a, b, c, d, e, f, g, h, i, k (10)</td>
</tr>
<tr>
<td>4</td>
<td>a, b, c, d, e, f, g, h, i, j, k, l, m, n, o, p, q, r, s, t, u (21)</td>
</tr>
<tr>
<td>5</td>
<td>a (1)</td>
</tr>
<tr>
<td>6</td>
<td>a, b, c, d, e, f, g, h, i, j, k, l, m, n, o, p, q, r, s, t (20)</td>
</tr>
<tr>
<td>7</td>
<td>a (1)</td>
</tr>
</tbody>
</table>

Confirmed subtypes

Provisional subtypes added since 2005

Disease severity, drug resistance, treatment responsive

Combet et al. 2007; http://euhcvdb.ibcp.fr/euHCVdb
“Standard” Treatment

- Peginterferon-alpha-2b and Ribavirin
- Genotype dependent
  - Types 2, 3 best outcome Type 1 worst outcome
- Issues
  - Cost ~$17K/yr
  - Toxicity (bone marrow, CNS)
  - Current overall cure rates ~50%
- Critical need for improved cure rates!
Sustained Viral Response (SVR) (HCV undetectable 6 months post therapy)

- Genotype 1: 21% (PEG-IFN α-2a + Placebo), 37% (IFN α-2b + RBV), 46% (PEG-IFN α-2a + RBV)
- Genotype 2, 3: 45% (PEG-IFN α-2a + Placebo), 61% (IFN α-2b + RBV), 76% (PEG-IFN α-2a + RBV)

P-values:
- P = 0.001
- P = 0.001
- P = 0.016
- P = 0.054
- P = 0.008
- P = 0.001
- P = 0.001
- P = 0.016

Genotype Driven Therapy

- 1. Diagnosis (EIA, Viral Load, Genotyping)
- 2. Therapeutic monitoring (stopping rules for failed response class)
- 3. End-treatment assessment
# Stopping Rules “traditional”

<table>
<thead>
<tr>
<th>Condition</th>
<th>NPV</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>$&lt; 2 \log_{10}$ drop by wk 12</td>
<td>NPV = 97%</td>
<td>Fried et al., 2002. <em>N. Eng. J. Med.</em> 347(13):975-982</td>
</tr>
<tr>
<td>$&lt; 2 \log_{10}$ drop by wk 8 and $&gt;615$ IU/mL; $&gt;96,000$ IU/mL at wk 4</td>
<td>NPV = 97%</td>
<td>Terrault et al., 2002. <em>Hepatology</em> 36(4; pt 2 of 2): 523</td>
</tr>
<tr>
<td>Viral load $&lt; 130,000$ IU/mL at baseline</td>
<td>PPV = 72%</td>
<td>Berg et al., 2003. <em>Hepatology</em> 37(5):600-609</td>
</tr>
<tr>
<td>$&gt;540,000$ IU/mL at wk 4 or $&gt;30,000$ IU/mL at wk 12</td>
<td>NPV = 100%</td>
<td></td>
</tr>
</tbody>
</table>
Which Molecular Confirmation Method? (diagnosis)

• Most sensitive test method “recommended” although average viral load of untreated patients is high
  – PCR qualitative vs TMA vs PCR quantitative

• Use of quantitative test also establishes viral load baseline
  – New generation PCR quantitative tests are now very sensitive
Direct Acting Antivirals (DAA)  
Basis for New Therapies

- Receptor binding and endocytosis
- Fusion and uncoating
- (+) RNA
- Translation and polyprotein processing
- RNA replication
- Virion assembly
  - Membranous web
  - ER lumen

**NS3/4 protease inhibitors**

**NS5B polymerase inhibitors**
- Nucleoside/nucleotide
- Nonnucleoside

**NS5A* inhibitors**

*Role in HCV life cycle not well defined

Protease Inhibitors
(approved 5-2011)

• Peptidomimetics (protease cleavage peptides)

• Telaprevir

• Boceprevir

• Issues (Resistance and side-effects)
SVR Rates With BOC and TPV in GT1 Treatment-Naive and -Experienced Pts

Current Standard of Care

- Treatment-Naive Pts: 38-44\(^{[1-2]}\)
- Treatment-Experienced Pts: 17-21\(^{[3-4]}\)

SOC + Protease Inhibitors (Approval Anticipated in 2011)

- Treatment-Naive Pts: 63-75\(^{[1-2]}\)
- Treatment-Experienced Pts: 59-66\(^{[3-4]}\)

Polymerase Inhibitors

• Nucleoside
  – Bind highly conserved NS5B active site
  – Lower rates resistance
  – Good genotype coverage

• Non-Nucleoside Inhibitors (NNI)
  – Bind multiple non-active sites to destabilize NS5B

• Available 3-5 years?
Laboratory Testing and Test Issues (Era of DAAs)

- Viral load
  - Document treatment failure (stopping rules)
  - Document treatment success (SVR)
  - Rate of response (personalized treatment)

- Genotyping (1-6)
  - Likelihood response
  - Duration of therapy
  - Association with drug resistance
Viral Load Testing as Measure of Kinetics of Response

HCV RNA

Limit of Detection ≤50 (IU/ml)

Clearance of infected cells

0 1 4 12 24 48 72 weeks

Phase 1 (24-48 h)

Phase 2

RVR EVR DVR

Likelihood of SVR

DVR, delayed virological response; EVR, early virological response; RVR, rapid virological response.

EASL Clinical Practice Guidelines
RVR is best predictor SVR (all therapies)

AASLD Guidelines 2009

shorter treatment

longer treatment

Peginterferon and Ribavirin

RVR

EVR

ETR

SVR

Weeks After Start of Therapy

HCV RNA Log_{10} IU/ml

Undetectable

Non-Response

Partial

Relapse

Null
Required Sensitivity?

• Undetectable at what level?
• Continuous improvement in assay sensitivity
  – International standard is WHO I & II & III (I.U.)
  – Several hundred I.U to << 100 I.U./ml
• Qualitative assays previously most sensitive
  – Roche Cobas Qualitative 50 I.U./ml
  – TMA (7-10 I.U.)
• Current real-time quantitative assays offer broad dynamic range and sensitivity
Viral Load Testing in Setting of DAA Therapy

• Sensitivity
  – Limit of detection (LOD) vs Limit of quantification (LOQ)
  – Protease inhibitors approval trials conducted with RUO Roche COBAS TaqMan assay (LOQ 25 I.U./ml)
  – Abbott
    • LOD (9 I.U./ml)
    • LOQ (9 I.U./ml)
  – Roche COBAS TaqMan FDA approved assay
    • LOD 15 I.U./ml (type 1 virus 7.1 I.U./ml)
    • LOQ 43 I.U./ml (types 1-6 overall)
Viral Genotyping for Analysis of Resistance to Protease Inhibitors

• Sequence-based testing of NS3 to detect resistance mutations is now commercially available (6-2011)
  – Mutations commonly emerge during therapy
• Existing “viral genotyping” reveals subtype-specific resistance patterns
Telaprevir Resistance in GT1a vs GT1b

- R155K NS3 protease mutation does not emerge upon selection in GT1b
  
  Explained by codon usage differences
  - GT1b requires 2 nucleotide changes in arginine codon
  - GT1a uses different codon requiring only 1 change

**TABLE 2. Genotypic characterization of the NS3 protease from GT-1b and GT-1a replicons after telaprevir treatment**

<table>
<thead>
<tr>
<th>Replicon (no. of expts)</th>
<th>3</th>
<th>6</th>
<th>9</th>
<th>13</th>
<th>16</th>
<th>21</th>
</tr>
</thead>
</table>

Sarrazin

*McCowan ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, May 2009, p. 2129–2132*
Host Genetic Factors (IL28B)

- Genome-Wide Association Study

- Sequence polymorphisms identified linked to interferon $\gamma$ genes (CC, CT, TT genotypes defined)

- IFNs classified into three groups based on sequence and receptor binding
  - Type I: $\alpha$, $\beta$, $\varepsilon$, $\kappa$, $\omega$, (τ, δ, ζ)
  - Type II: $\gamma$
  - Type III: $\lambda 1$ (IL29), $\lambda 2$ (IL28A), $\lambda 3$ (IL28B)

Chromosome 9
Geographic frequency of the protective C allele

Spontaneous clearance and response to INF/RBV therapy

Response to therapy

Spontaneous clearance


**IL28B Polymorphisms and Response to PegIFN/RBV by HCV Genotype**

**Graphs**

- **Genotype 1**: SVR (%) 85, CC 45, CT 41, TT 32
- **Genotype 2/3**: SVR (%) 79, CC 50, CT 25, TT 25
- **Genotype 4**: SVR (%) 88, CC 32, CT 25, TT 25

Variants Associated with HCV Clearance/Treatment response -Studies Results

rs12979860 C/T

<table>
<thead>
<tr>
<th>CC</th>
<th>favorable</th>
</tr>
</thead>
<tbody>
<tr>
<td>TT</td>
<td>risk</td>
</tr>
</tbody>
</table>

Spontaneous clearance of HCV infection
Higher response to treatment
Strongest effect in HCV genotype 1

rs 8099917 T/G

<table>
<thead>
<tr>
<th>TT</th>
<th>favorable</th>
</tr>
</thead>
<tbody>
<tr>
<td>GG</td>
<td>risk</td>
</tr>
</tbody>
</table>

Higher risk of hep C chronicity
Increased risk of treatment failure
Strongest effect in HCV genotype 1

TC TT

risk of treatment failure

TG GG
Outcome Predictors

- VL < 400,000 I.U./ml
- Age
- Sex
- Race
- Weight
- Fibrosis
- Steatosis
- Insulin resistance
- Alcohol consumption
- All above less predictive than IL28 during treatment
- All above less predictive than RVR (kinetics)
Evolution of HCV Therapy

2001
- PegIFN/RBV

2011
- Protease inhibitor
- Nucleos(t)ide polymerase inhibitor
- Nonnucleoside polymerase inhibitor
- NS5A inhibitor

Beyond
- PegIFN/RBV
- Protease inhibitor
- Nucleos(t)ide polymerase inhibitor
- Nonnucleoside polymerase inhibitor
- NS5A inhibitor

From Clinical Care Options
Technology Driven HCV Revolution

- Discovery
- 1st generation therapy
- Genotype guided therapy
- Kinetic guided therapy
- Advanced therapies
- Host genetics
- HCV sequence guided therapy