Treatment Of Viral Hepatitis: An Evolving Armamentarium.

Rafael J Pastrana, M. D.
April 11, 2013
Outline

- HCV epidemiology
- Risk factors
- Natural history
- Current treatment strategies
- On the horizon
The available data suggest that the prevalence of HCV infection is approximately 2.2–3.0% worldwide (130–170 million people).
**Global death rate**

[Diagram showing global death rates caused by viruses and other causes.]

**FIGURE 1-1** Approximate global preventable death rate from selected infectious diseases and other causes, 2003

- Caused by viruses:
  - HIV
  - HBV + HCV
  - Measles
  - RSV, Rota
  - Flu
  - Dengue
  - HPV
  - West Nile
  - SARS
  - Ebola
  - Polio
  - Hanta
  - vCJD

- Other causes:
  - Tobacco
  - Malaria
  - Road accidents
  - Non-HIV TB
  - Hospital infection
  - Suicide

Abbreviations: HIV, human immunodeficiency virus; HBV, hepatitis B virus; HCV, hepatitis C virus; RSV, respiratory syncytial virus; HPV, human papilloma virus; SARS, severe acute respiratory syndrome; TB, tuberculosis; vCJD, variant Creutzfeldt-Jakob disease.


IOM, Hepatitis and Liver Cancer. Jan 2010
Hepatitis C: US Prevalence

- 4.1 million infected
  - general prevalence 1.6%
  - non-Hispanic whites 1.5%
  - Non-Hispanic blacks 3.0%
  - Mexican-Americans 1.3%

### Projected HCV-related morbidity, mortality and cost in the US, 2010-2019*

<table>
<thead>
<tr>
<th>HUMAN COSTS</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths from HCV-related CLD</td>
<td>165,900</td>
</tr>
<tr>
<td>Deaths from HCC</td>
<td>27,200</td>
</tr>
<tr>
<td>Years from advanced liver disease</td>
<td>960,000</td>
</tr>
<tr>
<td>Years of life lost</td>
<td>3.1 million</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SOCIETAL AND FISCAL COSTS</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct medical expenditures</td>
<td>10.7 billion</td>
</tr>
<tr>
<td>Cost of lost of productivity due to disability</td>
<td>21.3 billion</td>
</tr>
<tr>
<td>Cost of lost of productivity due to premature death</td>
<td>54.2 billion</td>
</tr>
</tbody>
</table>

Leading causes of death in PR, 2004 (N=29,066)

<table>
<thead>
<tr>
<th>RANK</th>
<th>CAUSE</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Diseases of the heart</td>
<td>17.3</td>
</tr>
<tr>
<td>2</td>
<td>Malignant neoplasms</td>
<td>16.6</td>
</tr>
<tr>
<td>3</td>
<td>Diabetes mellitus</td>
<td>8.8</td>
</tr>
<tr>
<td>4</td>
<td>Cerebrovascular diseases</td>
<td>5.3</td>
</tr>
<tr>
<td>5</td>
<td>Alzheimer’s disease</td>
<td>4.2</td>
</tr>
<tr>
<td>6</td>
<td>Chronic lower respiratory diseases</td>
<td>4.0</td>
</tr>
<tr>
<td>7</td>
<td>Hypertensive disease</td>
<td>3.9</td>
</tr>
<tr>
<td>8</td>
<td>Accidents (unintentional injuries)</td>
<td>3.8</td>
</tr>
<tr>
<td>9</td>
<td>Pneumonia and Influenza</td>
<td>3.5</td>
</tr>
<tr>
<td>10</td>
<td>Nephritis, nephrotic syndrome and nephrosis</td>
<td>2.9</td>
</tr>
<tr>
<td>11</td>
<td>Chronic liver disease and cirrhosis</td>
<td>2.6</td>
</tr>
<tr>
<td>12</td>
<td>Homicides</td>
<td>2.6</td>
</tr>
</tbody>
</table>

Source: Department of Health, Auxiliary Secretariat for Planning and Development, Division of Statistical Analysis, San Juan, PR, 2007.
Risk factors associated with transmission of HCV

- Illegal injection drug use
- Transfusion or transplant from infected donor
- Occupational exposure to blood
  - Mostly needle sticks
- Iatrogenic (unsafe injections)
- Birth to HCV-infected mother
- Sexual/household exposure to anti-HCV positive contact
- Multiple sex partners
HCV testing routinely recommended (based on risk for infection)

- Persons who ever injected illegal drugs

- Persons with selected medical conditions
  - received clotting factor concentrates produced before 1987
  - ever on chronic hemodialysis
  - evidence of liver disease

- Prior recipients of transfusion/organs
  - before July 1992
  - notified that donor later tested positive

- All baby boomers ????
Baby boomers: 1945-1965

- NHANES data
- More than 2 million infected (3.25% prevalence)
- 800,000 undiagnosed
- 45% of infected report no risk factor
- “Don’t ask, don’t tell”

Recommendations for the Identification of Chronic Hepatitis C Virus Infection Among Persons Born During 1945–1965
http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6104a1.htm
HCV Prevalence (NHANES)

http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6104a1.htm
Natural history of HCV infection

100 People

- Resolve (15) (15%)
- Chronic (85)
  - Stable (68) (80%)
  - Cirrhosis (17) (20%)
    - Slow progression (13) (75%)
    - HCC/Transplant/Death (4) (25%)

Leading Indication for Liver Transplant
Chronic Hepatitis C factors promoting progression or severity

- Increased alcohol intake
- Age > 40 years at time of infection
- HIV co-infection
- Other
  - Male gender
  - Chronic HBV co-infection
Natural History of Hepatitis C Virus (HCV) Infection.

Aging of Hepatitis C Virus (HCV)-Infected in the United States: A Multiple Cohort Model of HCV Prevalence and Disease Progression

Figure 1
Aging of Hepatitis C Virus (HCV)-Infected in the United States: A Multiple Cohort Model of HCV Prevalence and Disease Progression

Figure 4


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Hepatitis C – clinical features

- **Incubation period**
  - Average 6 - 7 wks
  - Range 2 - 26 wks

- **Acute illness (jaundice)**
  - Mild (≤20%)

- **Case fatality rate**
  - Low

- **Chronic infection**
  - 60%-85%

- **Chronic hepatitis**
  - 70%

- **Cirrhosis**
  - 20%-30%

- **Mortality from CLD**
  - 3%
Pattern of acute HCV infection with recovery

- **HCV RNA**
- **Symptoms +/-**
- **Anti-HCV**
- **ALT**
- **Titer**

**Time after Exposure**

- **0**
- **1**
- **2**
- **3**
- **4**
- **5**
- **6**
- **1**
- **2**
- **3**
- **4**

- **0 Years**
- **1 Years**
- **2 Years**
- **3 Years**
- **4 Years**

**Normal**
Serologic pattern of acute HCV infection with progression to chronic infection

Time after Exposure

Titer

Anti-HCV

Symptoms +/-

HCV RNA

ALT

Normal

0 1 2 3 4 5 6

Years

0 1 2 3 4

Months
Treatment evolution

Graph showing the evolution of treatment duration and sustained virological response (SVR) from 1996 to 2015, with milestones including IFN, IFN-RBV, PEG-IFN-RBV, PEG-IFN-RBV-PI or Poli, and PEG-IFN-RBV-PI-Poli.
Many Factors Contribute To Response

Patient

Virus

Regimen
Table 1. Predictors of a Favorable Response to Treatment with Peginterferon and Ribavirin.

<table>
<thead>
<tr>
<th>General characteristics</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV genotype other than 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low baseline viral level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White race</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Interleukin-28B genotype</strong>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absence of fibrosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body weight &lt;85 kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &lt;40 yr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT quotient ≥3†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCV-specific immune response</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Before treatment**

- Absence of both insulin resistance and steatosis
- Statin use

**During treatment**

- Response during treatment (RVR or EVR)‡
- Adherence to treatment
- Standard dose of ribavirin

* C (vs. T) allele is advantageous for single-nucleotide polymorphism (SNP) rs12979860; T (vs. G) allele is advantageous for SNP rs8099917.
† The alanine aminotransferase (ALT) quotient is the average of the serum ALT level divided by the upper limit of the normal range.
‡ A rapid virologic response (RVR) is defined as an undetectable HCV RNA level (<50 IU per milliliter) at week 4 of treatment. An early virologic response (EVR) is defined as a decrease in the HCV RNA level of at least 2 log_{10} IU per milliliter or the complete absence of serum HCV RNA at week 12 of treatment.

Host IL28B genotype (rs12979860)

<table>
<thead>
<tr>
<th>T/T</th>
<th>C/T</th>
<th>C/C</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Other important pretreatment factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genotype 1</td>
<td>Viral genotype</td>
<td>Genotypes 2 and 3</td>
</tr>
<tr>
<td>&gt;600,000 IU/ml</td>
<td></td>
<td>&lt;600,000 IU/ml</td>
</tr>
<tr>
<td>African American (AA)</td>
<td>Race</td>
<td>Non-AA</td>
</tr>
<tr>
<td>F3 and F4 fibrosis (METAVIR grade)</td>
<td>F0 and F1</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>Gender</td>
<td>Female</td>
</tr>
<tr>
<td>&gt;40</td>
<td>Age (years)</td>
<td>&lt;40</td>
</tr>
</tbody>
</table>

Less likely to respond More likely to respond

Clark, Thompson and McHutchinson, AJG 2011

SVR by IL28b genotype

Clark, Thompson and McHutchinson, AJG 2011
Life cycle of hepatitis C virus

Hepatitis C Virology, Intracellular Innate Immune Response and Evasion Tactics, and Hepatic Immune Lymphocyte Response to Infection

Definitions of response

- **RVR** = Rapid Virological Response
  - VL undetected at week 4

- **eRVR** = extended Rapid Virological Response
  - VL undetected at weeks 4 and 12

- **EVR** = Early Virological Response
  - VL drop $\geq$ 2 log at week 12

- **SVR** = Sustained Virological Response
  - VL negative 24 wks post-therapy

- **Viral breakthrough** = return of detectable HCV RNA during therapy (resistant mutations)
More terms

- **RGT** = response guided therapy
- **Null responder** = VL drop < 2 logs at week 12
- **Partial responder** = VL drop > 2 logs at wk 12, positive at week 24
- **Relapser** = VL negative at end of therapy, + 24 wks after end of treatment
HCV Therapy

- SOC until summer 2011
  - PEG-interferon + Ribavirin
  - G1 and 4 – 48 wks
  - G2 and 3 – 24 wks

- New SOC for some G1
  - PEG-IFN + Riba + NS3 PI
Telaprevir
(Incivek®, Vertex)
Telaprevir naive studies

ADVANCE
Jacobson, AASLD 2010

PROVE-1 and 2

62% SVR in bridging fibrosis, blacks
FDA approved indications: telaprevir

- G1 treatment naive with compensated liver disease including cirrhosis
- G1 previously treated with interferon-based regime and are null or partial responders or relapsers
- Must be used with peginterferon plus ribavirin
- No data for OLT, HCV/HIV or HCV/HBV
- 750 mg (2 tabs) po tid with food
## Tela: Treatment scheme

<table>
<thead>
<tr>
<th>HCV-RNA</th>
<th>Tela, Peg + Riba</th>
<th>Peg + Riba</th>
<th>Total tx duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neg at wk 4 and 12</td>
<td>First 12 wks</td>
<td>Addtl 12 wks</td>
<td>24 wks</td>
</tr>
<tr>
<td>+ ≤ 1000 IU wk 4 and/or 12</td>
<td>First 12 wks</td>
<td>Addtl 36 wks</td>
<td>48 wks</td>
</tr>
</tbody>
</table>

### Partial and null responders

| All pts | First 12 wks | Addtl 36 wks | 48 wks |

## Tela: futility rules

<table>
<thead>
<tr>
<th>HCV RNA</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wk 4 or 12 &gt; 1000 IU/ml</td>
<td>dc all treatment</td>
</tr>
<tr>
<td>Wk 24 detectable</td>
<td>dc peg and riba</td>
</tr>
</tbody>
</table>
Boceprevir
(Victrelis®, Merck)
Boceprevir: SPRINT-2

SPRINT 2: SVR and Relapse Rates (ITT)

Non-Black Patients

48 P/R | BOC RGT | BOC/PR48
---|---|---
40 | 211 | 213
37 | 316 | 311
23 | 9 | 8
12 | 2 | 2
3 | 12 | 8
162 | 21/32 | 18/20
311 | 22/14 | 3/25
23 | 52 | 35

Black Patients

48 P/R | BOC RGT | BOC/PR48
---|---|---
23 | 42 | 53
14 | 22 | 55
12 | 12 | 17
9 | 52 | 35
8 | 3 | 12
18 | 21 | 8

Figure 6. SVR Rates Based on Week 8 HCV-RNA

*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 treatment level was missing (as specified in the protocol). A sensitivity analysis was performed counting only patients with undetectable HCV documented at 24 weeks post-treatment and the SVR rates for Arms 1, 2, and 3 in Cohort 1 were 39% (122/311), 66% (207/316) and 68% (215/315), respectively and in Cohort 2 were 21% (115/52), 42% (22/85) and 51% (29/58), respectively.
Boce: FDA approved indications

- G1 naive or previously treated with interferon and riba
  - Null responders not studied
- Compensated liver disease
- 800 mg (4 tabs) tid with food
- Lead-in with Peg + Riba x 4 wks
## Boce treatment scheme

<table>
<thead>
<tr>
<th></th>
<th>HCV RNA</th>
<th>Recommendation</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Wk 8</td>
<td>Wk 24</td>
</tr>
<tr>
<td>Naive</td>
<td>Neg</td>
<td>Neg</td>
</tr>
<tr>
<td></td>
<td>Pos</td>
<td>Neg</td>
</tr>
<tr>
<td>Part responders or relapsers</td>
<td>Neg</td>
<td>Neg</td>
</tr>
<tr>
<td></td>
<td>Pos</td>
<td>Neg</td>
</tr>
</tbody>
</table>
# Table 1. Discontinuation or Futility or Stopping Rules

<table>
<thead>
<tr>
<th>ASSESSMENT* (HCV-RNA Results)</th>
<th>RECOMMENDATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>At Treatment</td>
<td></td>
</tr>
<tr>
<td>Week 8</td>
<td>Week 24</td>
</tr>
<tr>
<td>Undetectable</td>
<td>Undetectable</td>
</tr>
<tr>
<td>Detectable</td>
<td>Undetectable</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Previous Partial Responders or Relapsers</th>
<th>RECOMMENDATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>At Treatment</td>
<td></td>
</tr>
<tr>
<td>Week 8</td>
<td>Week 24</td>
</tr>
<tr>
<td>Undetectable</td>
<td>Undetectable</td>
</tr>
<tr>
<td>Detectable</td>
<td>Undetectable</td>
</tr>
</tbody>
</table>

*TREATMENT FUTILITY
If the patient has HCV-RNA results greater than or equal to 100 IU/mL at TW12, then discontinue three-medicine regimen.
If the patient has confirmed, detectable HCV-RNA at TW24, then discontinue three-medicine regimen.

*In clinical trials, HCV-RNA in plasma was measured using a Roche COBAS® TaqMan® assay with a lower limit of quantification of 25 IU/mL and a limit of detection of 9.3 IU/mL. See Warnings and Precautions (5.5) for a description of HCV-RNA assay recommendations.
Response guided therapy

- HCV RNA determination at specific points in therapy will determine duration
  - 4 wk RVR
  - 8 wk for boceprevir
  - 12 wk EVR
  - 24 wk
Peg-IFN/RBV Treatment Experienced Patients Can Be Re-treated

Relapsers
New regimen: NS3 Protease Inhibitor + Peg-IFN+RBV

Viral breakthroughs
SVR~69%

Non-responders
Peg-IFN/RBV treatment failure

SVR~57%

SVR~39%
Previously treated

REALIZE: SVR in Prior Relapsers, Partial Responders and Null Responders

<table>
<thead>
<tr>
<th>Prior relapsers</th>
<th>Prior partial responders</th>
<th>Prior null responders</th>
</tr>
</thead>
<tbody>
<tr>
<td>SVR (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>83*</td>
<td>88*</td>
<td>59*</td>
</tr>
<tr>
<td>24</td>
<td>54*</td>
<td>29*</td>
</tr>
<tr>
<td>16</td>
<td></td>
<td>6</td>
</tr>
</tbody>
</table>

T12/PR48 121/145  T12(DS)/PR48 124/141  Pbo/PR48 18/68
29/49 28/48 4/27
21/72

for 12 wk, followed by telaprevir-matched placebo plus peginterferon alpha-2a and ribavirin for 12 wk
113 Received at least one dose of study drugs
1 Did not receive study drugs
24 wk, followed by peginterferon alpha-2a and ribavirin alone for 24 wk
113 Received at least one dose of study drugs
4 Did not receive study drugs
Dose of study drugs
and ribavirin followed by placebo
114 Received at least one dose of study drugs
3 Did not receive study drugs

RESPOND-2 SVR and Relapse Rates

Intention to treat population

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

**Telaprevir**
- Rash *
- Anemia
- Anorectal symptoms

**Boceprevir**
- Anemia
- Neutropenia
- Dysgeusia *
Drug interactions

- Boceprevir: CYP3A4/5 and P-gp
- Telaprevir: CYP3A and P-gp
- Drugs that clear through CYP3A or substrate for P-gp
  - Risk of elevated or longer levels
- Drugs that induce CYP3A or P-gp lower protease inhibitor levels
- Drug dose readjustment after stopping PI
Drug interactions

**Contraindicated**

- Atorvastatin, lovastatin, simvastatin
- Sildenafil, tadalafil
- Midazolam (po), triazolam
- St John’s wort

**Caution**

- Digoxin, amiodarone
- Clarithro, erythro
- Warfarin
- Phenytoin, PB, carbamazepine
- Ketoconazole
- Alprazolam, Midazolam im/iv
- Ca channel blockers
- Corticosteroids
- HIV PI’s and RTI
- Contraceptives
- Methadone
Telaprevir vs boceprevir: similarities

- High rate of SVR
- Effective in cirrhotics and previously treated
- Similar extensive drug interactions
- Expensive
- Response guided therapy
- Higher rate of AE than PEG-Riba alone
- Chance for shorter duration of therapy
# Telaprevir vs Boceprevir: Differences

<table>
<thead>
<tr>
<th>Telaprevir</th>
<th>Boceprevir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wk 0-12</td>
<td>Wk 4-28/36</td>
</tr>
<tr>
<td>Effective in null responders</td>
<td>Less data in null responders</td>
</tr>
<tr>
<td>Min therapy 24 wks</td>
<td>Min therapy 28 wks</td>
</tr>
<tr>
<td>6 tabs daily</td>
<td>12 tabs daily</td>
</tr>
<tr>
<td>More expensive</td>
<td></td>
</tr>
</tbody>
</table>
On the horizon....

- A 12-Week Interferon-free Treatment Regimen with ABT-450/r, ABT-267, ABT-333 and Ribavirin Achieves SVR12 Rates (Observed Data) of 99% in Treatment-Naïve Patients and 93% in Prior Null Responders with HCV Genotype1 Infection (ABT)

- An Interferon-free, Ribavirin-free 12-Week Regimen of Daclatasvir (DCV), Asunaprevir (ASV), and BMS-791325 Yielded SVR4 of 94% in Treatment-Naïve Patients with Genotype (GT) 1 Chronic Hepatitis C Virus (HCV) Infection (BMS)

AASLD Nov 2012, late breaking abstracts
In this preliminary study, a combination of a protease inhibitor, a non-nucleoside polymerase inhibitor, and ribavirin was effective for the treatment of HCV genotype 1 infection.

This preliminary study suggests that 12 weeks of therapy with a combination of a protease inhibitor, a non-nucleoside polymerase inhibitor, and ribavirin may be effective for treatment of HCV genotype 1 infection.
Hepatitis C Virus (HCV) RNA Values through 12 Weeks of Treatment and 12 Weeks of Follow-up in Previously Untreated Patients and in Patients with a Null or Partial Response to Previous Therapy.

Groups 1 & 2 – naive
Group 3 – partial or null responders


48 wk SVR – 18/18
48 wk SVR – 11/13
## Table 2. Virologic Response Rates.

<table>
<thead>
<tr>
<th>Response</th>
<th>Group 1 (N=19)</th>
<th>Group 2 (N=14)</th>
<th>Group 3 (N=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid virologic response*</td>
<td>19/19†</td>
<td>13/14</td>
<td>15/17</td>
</tr>
<tr>
<td></td>
<td>100 (82–100)</td>
<td>93 (66–100)</td>
<td>88 (64–99)</td>
</tr>
<tr>
<td>Extended rapid virologic response‡</td>
<td>17/19</td>
<td>11/14</td>
<td>10/17</td>
</tr>
<tr>
<td></td>
<td>89 (67–99)</td>
<td>79 (49–95)</td>
<td>59 (33–82)</td>
</tr>
<tr>
<td>Response at week 12 of treatment</td>
<td>19/19†</td>
<td>13/14</td>
<td>11/17</td>
</tr>
<tr>
<td></td>
<td>100 (82–100)</td>
<td>93 (66–100)</td>
<td>65 (38–86)</td>
</tr>
<tr>
<td>Sustained viral response 12 wk after treatment§</td>
<td>18/19</td>
<td>13/14</td>
<td>8/17</td>
</tr>
<tr>
<td></td>
<td>95 (74–100)</td>
<td>93 (66–100)</td>
<td>47 (23–72)</td>
</tr>
</tbody>
</table>

Response to previous therapy

<table>
<thead>
<tr>
<th>Response</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial</td>
<td>—</td>
<td>—</td>
<td>5/10</td>
</tr>
<tr>
<td>Null</td>
<td>—</td>
<td>—</td>
<td>3/7</td>
</tr>
<tr>
<td></td>
<td>50 (19–81)</td>
<td>43 (10–82)</td>
<td></td>
</tr>
</tbody>
</table>

IL28 genotype

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>CC</td>
<td>9/10</td>
<td>4/5</td>
<td>0/0</td>
</tr>
<tr>
<td></td>
<td>90 (56–100)</td>
<td>80 (28–99)</td>
<td>—</td>
</tr>
<tr>
<td>CT</td>
<td>7/7</td>
<td>7/7</td>
<td>6/12</td>
</tr>
<tr>
<td></td>
<td>100 (59–100)</td>
<td>100 (59–100)</td>
<td>50 (21–79)</td>
</tr>
<tr>
<td>TT</td>
<td>2/2</td>
<td>2/2</td>
<td>2/5</td>
</tr>
<tr>
<td></td>
<td>100 (16–100)</td>
<td>100 (16–100)</td>
<td>40 (5–85)</td>
</tr>
</tbody>
</table>

* Rapid virologic response was defined as an HCV RNA level of less than 25 IU per milliliter at week 4.
† One patient who discontinued the study treatment early had a suppressed level of HCV RNA 1 week after treatment. We therefore imputed HCV RNA values for this patient that represented a rapid virologic response and a response at week 12. If this patient were counted as having had a treatment failure, the rates for rapid virologic response and response at week 12 would both be 95% (18 of 19 patients).
‡ Extended rapid virologic response was defined as an undetectable level of HCV RNA from week 4 through week 12.
§ Sustained virologic response 12 weeks after treatment was defined as an HCV RNA level of less than 25 IU per milliliter 12 weeks after treatment.

Nucleotide Polymerase Inhibitor Sofosbuvir plus Ribavirin for Hepatitis C

Edward J. Gane, M.D., Catherine A. Stedman, M.B., Ch.B., Ph.D., Robert H. Hyland, D.Phil., Xiao Ding, Ph.D., Evguenia Svarovskaia, Ph.D., William T. Symonds, Pharm.D., Robert G. Hindes, M.D., and M. Michelle Berrey, M.D., M.P.H.

• In this small, preliminary study of sofosbuvir, a nucleotide inhibitor of HCV polymerase, treatment with sofosbuvir and ribavirin, without peginterferon, was effective in achieving a sustained virologic response in patients with HCV genotype 1, 2, or 3 infection.

• Sofosbuvir plus ribavirin for 12 weeks may be effective in previously untreated patients with HCV genotype 1, 2, or 3 infection.
Mean Change from Baseline in Hepatitis C Virus (HCV) RNA Level during Treatment.

Personalized medicine and HCV

- “Genetic variations in the innate immune system and differences in outcome of hepatitis C virus infection: a candidate gene association study”
  - Clausen et al, abs # 991, AASLD Nov 2012

- “A genome wide association study of HCV induced liver cirrhosis identified novel susceptibility loci at MHC region”
  - Kato et al, abs # 183, AASLD Nov 2012
Predicting response: IFNL4

- INFL4 region variant with 2 forms: deltaG results in deletion that produces IFNL4 protein
- Expression of INFL4 protein associated with poorer clearance of HCV and poorer response to PEG + Riba
- Deletion more common in African Americans
- Prokunina-Olsson et al: A variant upstream of IFNL3 (IL28B) creating anew interferon gene IFNL4 is associated with impaired clearance of hepatitis C virus. Nature Genetics, 2013; DOI 10.1038/ng.2521
Treatment of genotypes other than 1 has not changed
Improving the outcomes: the real problem
Reasons for lack of treatment in NHANES

Population unawareness of serostatus, PR 2005-2008

- HIV: 36.4%
- HCV: 80.0%
- HAV: 96.4%
- HSV-2: 97.8%
- HBV: 98.3%

Source: Pérez CM et al. BMC Infectious Diseases 2010, 10:76
Adequate knowledge (Score≥70%)

Population knowledge of viral infections
PR 2005-2008

- HCV 5%
- HAV 9.3%
- HIV 65.8%
- HSV-2 55.3%
- HBV 14.8%

Source: Soto M et al. J Comm Health 2010
Take home points

● HCV is prevalent in PR

● Anybody with a risk factor or abnormal liver enzymes should be tested plus ‘‘baby boomers’’

● Cirrhosis and HCC are already a health problem

● New therapies have a much better SVR rate
  ● IFN free regimes are coming soon

● Diagnose and refer all patients with HCV to a skilled specialist
Thank you!