Chronic Hepatitis C Natural History and Current Treatment 2013

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Financial Disclosures

Research Support from Anadys, BMS, Gilead, Globeimmune, Merck, Novartis, Roche, Vertex
Consulting: Cumberland, Novartis
AND
My presentation may possibly include discussion of off-label use of DAAs
Outline of this talk

• Review Hep C 101: basic statistics
• Review the CDC Baby Boomer Directive
• Provide an overview to current Rx with the new DAAs
• Give a glimpse of the future, which happens to be just around the corner

Hepatitis C Virus (HCV)

• Discovered in 1989 as a small RNA blood-borne virus with a large reservoir of chronic carriers worldwide
• Major cause of post-transfusion hepatitis prior to 1992
• Major cause of chronic liver disease, cirrhosis, and hepatocellular carcinoma worldwide
• Prevalence is 1.8% of the US population, 4 million
• 1990-2015: estimated 4-fold increase in the number of patients diagnosed with HCV in the United States

Hepatitis C: A Global Health Problem

170 Million Carriers Worldwide, 3-4 MM new cases/year


Sources of Infection for Hepatitis C (1995-2000)

Injecting drug use 68%

Sexual 18%

Other* 5%

Unknown 9%

*Nosocomial; Health-care work; Perinatal

Recommendations for Identification of Chronic Hepatitis C Virus Infection Among Persons Born During 1945–1965

• Adults born during 1945-1965 should receive one-time testing for HCV without prior ascertainment of HCV risk.

• All persons with identified HCV infection should receive a brief alcohol screening and intervention as clinically indicated, followed by referral to appropriate care and treatment services for HCV infection and related conditions.


### Recommendations and Reports


<table>
<thead>
<tr>
<th>Birth cohort</th>
<th>U.S. population (in millions)*</th>
<th>No. (in millions)</th>
<th>(Weighted %)</th>
<th>No. (in millions)</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1945–1965</td>
<td>84.2</td>
<td>2.74</td>
<td>(3.25)</td>
<td>2.06</td>
<td>76.6</td>
</tr>
<tr>
<td>1950–1970</td>
<td>89.2</td>
<td>2.89</td>
<td>(3.24)</td>
<td>2.17</td>
<td>80.6</td>
</tr>
<tr>
<td>1945–1970</td>
<td>105.1</td>
<td>3.15</td>
<td>(3.00)</td>
<td>2.36</td>
<td>87.3</td>
</tr>
<tr>
<td>1950–1965</td>
<td>68.3</td>
<td>2.47</td>
<td>(3.61)</td>
<td>1.85</td>
<td>69.9</td>
</tr>
<tr>
<td>1950–1960</td>
<td>45.6</td>
<td>1.83</td>
<td>(4.01)</td>
<td>1.37</td>
<td>52.3</td>
</tr>
<tr>
<td>1945–1949</td>
<td>13.2</td>
<td>0.21</td>
<td>(1.58)</td>
<td>0.16</td>
<td>6.7</td>
</tr>
<tr>
<td>1966–1970</td>
<td>20.9</td>
<td>0.41</td>
<td>(1.94)</td>
<td>0.30</td>
<td>10.8</td>
</tr>
</tbody>
</table>

**Abbreviations:** HCV = hepatitis C virus; anti-HCV = antibody to hepatitis C virus.


† Not adjusted by age or other covariates.


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<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>4.34</td>
<td>4.12</td>
<td>3.89</td>
</tr>
<tr>
<td>Female</td>
<td>2.19</td>
<td>2.34</td>
<td>2.14</td>
</tr>
<tr>
<td><strong>Race/ethnicity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White, non-Hispanic</td>
<td>2.89</td>
<td>3.01</td>
<td>2.77</td>
</tr>
<tr>
<td>Black, non-Hispanic</td>
<td>6.42</td>
<td>5.73</td>
<td>5.60</td>
</tr>
<tr>
<td>Mexican American</td>
<td>3.26</td>
<td>2.56</td>
<td>2.71</td>
</tr>
</tbody>
</table>

**Abbreviation:** anti-HCV = antibody to hepatitis C virus.

* Not adjusted by age or other covariates.

The prevalence data in 1965 is lower than that of birth cohorts 1945–1965 due to lower testing rates. By 1970, testing rates had increased, resulting in a higher prevalence of anti-HCV. Complicating health outcomes among HCV-infected persons born during 1945–1965 are a lack of health insurance (31.5%) and use of alcohol (34.1%). Of all anti-HCV-positive
Summary of new CDC Recs

• Current estimates are ca. 4 million Americans with HCV
• Between 45 and 85% of HCV infected are unaware of it
• Risk-based strategies have failed
• Baby boomers (1945-1965) represent 27% of the population but 75% of those infected
• 1990-2015: estimated 4-fold increase in the number of patients diagnosed with HCV in the United States


Natural History Hepatitis C

100 patients

- Resolve 15%
- Chronic Hepatitis 85%
- Stable 68%
- Cirrhosis 17%
- Stable 13%
- Mortality 4%
Modeling of Liver Fibrosis in Chronic Hepatitis C, n=1157 Patients

Rapid progressors
Intermediate progressors
Slow progressors

Poynard et al, Hepatology 1999
Factors Which Might Influence The Outcome Of Hepatitis C

**Virus**
- Load
- Genotype
- Quasispecies

**Host**
- Sex
- Age
- Race
- Genetics
- Immune-response

**Environment**
- Alcohol
- HBV
- HIV
- Drugs
- Steatosis
- Iron


Advances in HCV Therapy

**Average SVR**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Average SVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFN x 6 mo</td>
<td>10%</td>
</tr>
<tr>
<td>IFN x 12 mo</td>
<td>30%</td>
</tr>
<tr>
<td>IFN +RBV</td>
<td>50%</td>
</tr>
<tr>
<td>PEG-IFN +RBV</td>
<td>60%</td>
</tr>
</tbody>
</table>
Treatment of Chronic HCV

Type of Response

- Peginterferon/Ribavirin
- Breakthrough
- Relapse
- Null Response
- Partial Response
- Limit of Detection
- SVR

HCV RNA (IU/mL)

WEEKS

HCV Kinetics: Key to Viral Clearance

1st phase – Reduction in Viral Production

2nd phase – Clearance of Hepatitis

Lag

Cutoff

Days

Viral load (log IU/mL)

Neumann et al. Science. 1998;282:103,
Virological Response Terms

- EVR = minimum $2 \log_{10}$ decrease in HCV RNA during first 12 wk of therapy
- ETR = undetectable HCV RNA at the completion of therapy
- SVR = persistently undetectable HCV RNA for $\geq 6$ months following completion of therapy
- RVR = negative at wk 4
- eRVR = extended RVR, neg wk 4 + wk 12, 20
- VRVR = negative at wk 1

Genotype 1: Relationship of SVR rate and time to undetectable HCV RNA.

Likelihood of RVR:
- 34% low VL vs. 23% with high VL

Both viral load and early response make a difference

Overall response of Genotype 1: ca. 40%
- But ca. 25% in A-A patients

Ferenci et al Data based on Pegasys licensing trial
HCV Polyprotein Processing and Viral Protein Function


Potential HCV Targets

Adapted from Bartenschlager RJ. Presented at 43rd EASL Milan, Italy, April 2008.
Graveyard for HCV Compounds is Filling Up Quickly!

- ISIS 14803 (Antisense)
- UT-231B (Imino sugar)
- Heptazyme (Ribozyme)
- VX-497 (IMPDH inhibitor)
- ANA976 (TLR agonist)
- CPG 10101 (TLR agonist)
- ACH-806/GS-9132 (NS4a)
- R7025 (Interferon-alpha)

BILN 2061 (Protease)
JTK-003 (Polymerase)
HCV-796 (Polymerase)
NM-283 (Polymerase)
R803 (Polymerase)

Emergence of Resistance Underlies Breakthrough and Plateau Response

Data have not been reviewed or approved by FDA.
**Major HCV Therapy Trials 2006-2011**

**MERCK: Boceprevir, Victrelis®**
- SPRINT-1: Naïve, Phase 2: Boceprevir: dose finding
- SPRINT-2: Naïve, Phase 3: Boceprevir: RGT/Blacks/Non-Black
- RESPOND-2: Experienced, Phase 3: Boceprevir, length Rx experienced

**VERTEX: Telaprevir, Incivek®**
- PROVE-1: Naïve, Phase 2: Telaprevir, dose/duration
- PROVE-2: Naïve, Phase 2: Telaprevir, leave off RBV?
- ADVANCE: Naïve 8 vs 12 wk, Phase 3: Telaprevir, shorten Rx to 8 wk
- ILLUMINATE: Naïve RGT, Phase 3: Telaprevir: RGT: 24 vs. 48
- REALIZE: Experienced, Phase 3: Telaprevir: Lead-in

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**Add on to SOC: Phase 2 Trials of HCV NS3-4A protease inhibitors in HCV-1**

<table>
<thead>
<tr>
<th>Response</th>
<th>PROVE1 (24 wks)</th>
<th>PROVE2 (24 wks)</th>
<th>SPRINT-1 (28 wks) (no leadin/leadin)</th>
<th>SPRINT-1 (48 wks) (no leadin/leadin)</th>
<th>SOC Peg/RBV (48 wks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RVR</td>
<td>81%</td>
<td>69%</td>
<td>39%</td>
<td>37%</td>
<td>8-15%</td>
</tr>
<tr>
<td>SVR</td>
<td>61%</td>
<td>68%</td>
<td>54/56%</td>
<td>67/75%</td>
<td>38-48%</td>
</tr>
</tbody>
</table>

* PROVE1: TPV + Peg-2a / RBV × 12 wks then Peg/ RBV × 12 wks if RVR (24W)
* PROVE2: TPV + Peg-2a / RBV × 12 wks then Peg RBV × 12 wks (24W)
* SPRINT-1: Boceprevir + Peg-2b + RBV for 24/28 weeks or 44/48 weeks with or without a 4-wk lead in period of PEG-2b + RBV

Hezode C et al, NEJM 2009;360:1839-50
SPRINT-2: Boceprevir in G1 Naïve CHC

Control
48 P/R
n = 363

PR
lead-in

PR + Placebo
Follow-up

Week 4
Week 28
Week 48
Week 72

BOC
RGT
n = 368

PR
lead-in

PR + Boceprevir
Follow-up

Week 28
Week 72

TW 8-24 HCV RNA Undetectable

Follow-up

TW 8-24 HCV RNA Detectable

PR + Placebo
Follow-up

BOC/
PR48
n = 366

PR
lead-in

PR + Boceprevir
Follow-up

Peginterferon (P) administered subcutaneously at 1.5 μg/kg once weekly, plus ribavirin (R) using weight-based dosing of 600-1400 mg/day in a divided daily dose
Boceprevir dose of 800 mg thrice daily
Poordad F et al. NEJM 2011;364:1195-1206

SPRINT-2: SVR and Relapse Rates (ITT)

Non-Black Patients

SVR*
Relapse Rate

p < 0.0001

p < 0.0001

% Patients
0 20 40 60 80 100

48 P/R BOC RGT BOC/PR48

23 40 23 12

211 37 162 116

211 116 162 37

211 116 162 37

211 116 162 37

211 116 162 37

Black Patients

% Patients
0 20 40 60 80 100

48 P/R BOC RGT BOC/PR48

23 14 42* 53

52 22 3/25 3/25

52 22 3/25 3/25

52 22 3/25 3/25

52 22 3/25 3/25

52 22 3/25 3/25

*(mITT in 47% vs 53%)

Poordad F et al NEJM 2011;1195-1206
SPRINT-2 Study Outcomes Based on Week 4 Lead-In (Nonblack Patients)

SVR and HCV RNA at wk 4

- **>1 log\(_{10}\) HCV RNA decline**
- **<1 log\(_{10}\) HCV RNA decline**

**Week 4--1 log response is similar to:**
Week 12--2 log response

### LI/B44/PR
(n=218/79)
- SVR (%): 82
- 1 log response: 39

### LI/B24/PR
(n=228/73)
- SVR (%): 82
- 1 log response: 29

### PR48
(n=234/62)
- SVR (%): 52
- 1 log response: 5

RAVs: resistance-associated variants. Boceprevir RAVs determined with population sequencing.
Poordad F, et al. NEJM 2011;364:1195-1206

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PROVE2 Study Design

**Study Arms**

- **Control Arm**
  - Placebo + Peg-IFN-2a (Peg-IFN) + Ribavirin (RBV)
- **24 Wk Arm**
  - Telaprevir + Peg-IFN + RBV
- **12 Wk Arm**
  - Telaprevir + Peg-IFN + RBV
- **No RBV Arm**
  - Telaprevir + Peg-IFN

**Follow Up**

- 0
- 12
- 24
- 48

36 Weeks Interim Analysis

Hezode C et al, NEJM 2009;360:1839-50
**PROVE2**

**Undetectable HCV RNA at Weeks 4 and 12**

![Graph showing undetectable HCV RNA at Weeks 4 and 12.](image)

*Percent with Undetectable HCV RNA (<10 IU/mL)*

<table>
<thead>
<tr>
<th></th>
<th>Week 4</th>
<th>Week 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control Arm</td>
<td>13%</td>
<td>41%</td>
</tr>
<tr>
<td>24 Wk Arm</td>
<td>89%</td>
<td>73%</td>
</tr>
<tr>
<td>12 Wk Arm</td>
<td>51%</td>
<td>79%</td>
</tr>
<tr>
<td>No RBV Arm</td>
<td>62%</td>
<td>*</td>
</tr>
</tbody>
</table>

* p<0.001 compared to control arm

Hezode C et al, NEJM 2009;360:1839-50

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**ADVANCE: Most Common Adverse Events**

<table>
<thead>
<tr>
<th>% of Patients with</th>
<th>T12PR N=363</th>
<th>T8PR N=364</th>
<th>PR (control) N=361</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Adverse Event*</td>
<td>99</td>
<td>99</td>
<td>98</td>
</tr>
<tr>
<td>Fatigue</td>
<td>57</td>
<td>58</td>
<td>57</td>
</tr>
<tr>
<td>Pruritus</td>
<td>50</td>
<td>45</td>
<td>36</td>
</tr>
<tr>
<td>Headache</td>
<td>41</td>
<td>43</td>
<td>39</td>
</tr>
<tr>
<td>Nausea</td>
<td>43</td>
<td>40</td>
<td>31</td>
</tr>
<tr>
<td>Rash</td>
<td>37</td>
<td>35</td>
<td>24</td>
</tr>
<tr>
<td>Anemia</td>
<td>37</td>
<td>39</td>
<td>19</td>
</tr>
<tr>
<td>Insomnia</td>
<td>32</td>
<td>32</td>
<td>31</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>28</td>
<td>32</td>
<td>22</td>
</tr>
<tr>
<td>Influenza-like illness</td>
<td>28</td>
<td>29</td>
<td>28</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>26</td>
<td>30</td>
<td>24</td>
</tr>
</tbody>
</table>

*Shaded areas: 10% or greater incidence in either TVR groups vs control*
REALIZE: SVR in Prior Relapsers, Prior Partial Responders and Prior Null Responders

Prior relapsers: 86%
Prior partial responders: 56%
Prior null responders: 31%


REALIZE: SVR by Baseline Fibrosis Stage and Prior Response

Conclusions: HCV Therapy as of 2011

Durability of therapy
- SVR is a cure
- Tailor therapy to early viral response: RGT is effective

Protease inhibitors
- High rates of RVR in naive patients, ca. 65%
  - Can shorten Rx to 24-28 weeks Rx for RVR’s
  - Treatment-limiting adverse effects include rash, diarrhea
- More side effects, limiting responses but few relapses
- Virological failure occurs with mutations, ? significance
- Cirrhosis, high VL, genotype less predictive; 1b > 1a
- Prior IFN/RBV response determines 3-drug response
- Need IFN and RBV so far!!
- Watch for earlier and more severe anemia!

Results
857 HCV patients were identified.

498 HCV genotype 1 patients were analyzed.

407 deferred HCV treatment.

91 started on triple therapies.

19 discontinued before 12 weeks.

72 did not discontinue early.

67 had negative HCVRNA, were seen outside date range, or were already on a treatment protocol.

174 were not genotype 1 or had unknown genotype.

57 genotype 1 were on dialysis, HIV-co-infected, or post-transplant.

61 were waiting for clinical trial, treated with another protocol, or were unsure of treatment plan.
Discussion

- Triple therapy initiation rate was only 18%
- Reasons to defer triple therapy included medical and psych contraindications, too early or too late
- Probably more HCV patients in academic practices have advanced fibrosis and/or are prior treatment non-responders. “Hard-to-treat”
- Triple therapy discontinuation rate (20.8%) higher than the 7-9% reported in clinical trials

HCV Enzymes Provide Good Targets for Drug Development

- HCV Replicase
  - Structural
  - Protease
  - RNA Polymerase

- Telaprevir, Boceprevir, TMC435
- Daclatasvir (BMS-790052)
- Alisporivir
**Examples of > 80% SVR Rates in Phase II, DAA + PegIFN + RBV Trials in HCV GT1, Rx Naive Patients**

<table>
<thead>
<tr>
<th>Direct Acting Antiviral</th>
<th>Target</th>
<th>SVR rates (DAA /PR vs. PR)</th>
<th>Unique Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daclatasvir 10 mg, 48 wk, N=12</td>
<td>NS5A Replication Complex</td>
<td>92% vs. 25%</td>
<td>First in class Once daily dosing No new side effects</td>
</tr>
<tr>
<td>TMC435, 150 mg X 24 wk, N=79</td>
<td>NS3/4A protease</td>
<td>86% vs. 65%</td>
<td>Macro cyclic Higher resistance barrier Once daily dosing</td>
</tr>
<tr>
<td>PSI-7977 400 mg, 24 wk, N=47</td>
<td>NS5B polymerase</td>
<td>91% vs. &lt; 50%</td>
<td>Pangenotypic Once daily dosing No resistance observed</td>
</tr>
</tbody>
</table>

**Phase 2a Study of Double or Quadruple Therapy of Null Responder, Genotype 1 HCV Infection with Daclatasvir (BMS-790052) and Asunaprevir (BMS-650032) +/- PR**

<table>
<thead>
<tr>
<th>CHC G1 null responder to PegIFN, no cirrhosis, N=21</th>
<th>IL28B CT/TT</th>
<th>1a/1b</th>
<th>RVR</th>
<th>EOT</th>
<th>SVR12</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMS-790052 60 mg qd + BMS-650032 600 mg bid</td>
<td>90.4%</td>
<td>9/2</td>
<td>63.6%</td>
<td>45%</td>
<td>36%</td>
</tr>
<tr>
<td>BMS-790052 60 mg qd + BMS-650032 600 mg bid + Peg-IFN 2a + RBV</td>
<td>9/1</td>
<td>60%</td>
<td>100%</td>
<td>100%</td>
<td></td>
</tr>
</tbody>
</table>

The ATOMIC Study; 7977 plus P/R for geno 1 HCV

PSI-7977 ELECTRON
Nucleotide Analogue in Genotype 2/3

<table>
<thead>
<tr>
<th>Time Wk</th>
<th>PSI-7977 + RBV + Peg-IFN</th>
<th>PSI-7977 + RBV + Peg-IFN</th>
<th>PSI-7977 + RBV</th>
<th>PSI-7977 + RBV</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>8</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>12</td>
<td>9/10</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>24</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HCV GT2 or GT3, open-label

Week 0 12 24 36

25 treatment-naive patients with HCV GT2 or GT3; one pt lost to F/U after Day 1
24/25 RVR, SVR 12 and SVR 24 (EASL 2011, Lalezari et al.)


The ATOMIC Study; 7977 plus P/R for geno 1 HCV

RESULTS: 98% SVR in subjects who received at least 8 weeks of PSI-7977 400 mg QD + PEG/RBV

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n</th>
<th>% AT*</th>
</tr>
</thead>
<tbody>
<tr>
<td>200 mg + PEG/RBV</td>
<td>48</td>
<td>98</td>
</tr>
<tr>
<td>400 mg + PEG/RBV</td>
<td>48</td>
<td>98</td>
</tr>
<tr>
<td>PEG/RBV</td>
<td>48</td>
<td>98</td>
</tr>
</tbody>
</table>

As treated: Patients who received >8 wks PSI-7977


Cure of Genotype 1b, Prior Null-Responder HCV Infections with an Interferon-Free Regimen

Chayama, K. et al, Hepatology, 2011; 54:1428A

*One patient completed only 8 weeks RX but still HCV RNA negative 24 wks later
## Summary: Current State of Play 2013

- Triple therapy is superior to Peg/RBV
- But is not successful in many patients with established cirrhosis
- Interferon/RBV still needed so far
- New agents hold great promise/not here yet
- We will be able to treat all sorts of HCV patients within the next 3 years: HIV, cirrhosis, post-transplantation

## Unanswered Questions

- 2nd generation agents are not yet here but seem amazing
- Will they work as well in the ‘hard to treat?’
- How will we treat HIV/HCV? Or transplant patients?
- When will we have an approved IFN-free regimen?
- What will be the cost of a ‘sure cure?’
Public Health Concerns

- Medications very expensive, currently up to $70,000 for a course of treatment
- No vaccination available
- Large number of unrecognized cases, probably around 50%
- Need to develop strategies to identify new cases
- Increasing numbers with end-stage liver disease being recognized: HCC
- Large burden on health care system

Taking the CDC Recs to Heart

- CDC recs represent a watershed
- How to implement them?
- How about employee screening for HCV?
- HIPAA considerations?
- The drugs will soon be available, fall 2013?
- Conquering Hep C is in sight!!
Ohio State Liver Care/Transplant Group

Chronic/end stage liver disease, hepatitis B and C, clinical trials, drug-induced liver injury, acute liver failure.

Phone: 614-293-6255 Fax Referrals To: 614-293-8518
Long-Distance: 800-293-8965 After business hours, call: 900-293-5123