Disclosures

Jay H. Hoofnagle

• I am an employee of the Federal Government and have no personal conflicts of interest to report
• I supervise several extramural and intramural projects that have varying degrees of industry support via Clinical Trial Agreements or CRADA with the NIH: Gilead, BMS, Roche & Merck
• I will discuss off-label used of new agents for hepatitis C and will mention when this is the case
Elimination and Prevention

*Three Forms*

- **Primary:** prevent the infection
  - Vaccine, Public Health, Decrease exposures
- **Secondary:** prevent the disease
  - Screening, Management, Therapy
- **Tertiary:** prevent complications/death
  - Nonspecific and Specific Therapies
Antiviral Therapy of Hepatitis C

Two Eras

• Interferon (1986-2012)
  • Mono or combined therapy, Ribavirin, Direct Acting Agents

• Direct Acting Agents (2012-present)
  • Initially with interferon, Later DAAs alone

• Future? Direct host acting agents
  • Perhaps more applicable to HBV and HDV
Therapy of Hepatitis C

The Interferon Era

- Began with demonstration that interferon alfa had beneficial effects (1986) and could induce long-term remissions (1988).
- With identification of HCV (1989), interferon was shown to reduce HCV RNA levels and lead to long-term loss of virus in a proportion of cases.
- Approved for use in hepatitis C in U.S. in 1991
- Rapidly became clear that interferon alfa by itself had very limited efficacy and applicability
- A second or even third drug was needed

- **1991**: 25% sustained response
  - 6-10% IFN high dose
- **1995**: 25% sustained response
  - 15-20% IFN
- **1997**: 35% sustained response
  - 15-20% IFN high dose

- **SVR**
- **E-o-T**
- **Relapse**
Ribavirin

Guanosine analogue with potent activity against several flaviviruses in cell culture
Ribavirin Markedly Increases the Response Rate to Interferon in Chronic Hepatitis C

McHutchison Poynard
SVR Rate

0%
10%
20%
30%
40%
50%
60%
70%
80%

n = 912
n = 832

IFN & Rbv 12 mo
IFN & Rbv 6 mo

NEJM 1998
Lancet 1998

IFN 12 mo

13%
31%
38%

19%
35%
43%

19%
6 mo

12 mo
Peginterferon Further Increases the Response Rate in Chronic Hepatitis C

**NEJM 2002**
- IFN & Rbv 48 wks: 44%
- Peg & Rbv 48 wks: 56%

**Lancet 2001**
- IFN & Rbv 48 wks: 47%
- Peg & Rbv 48 wks: 54%

Fried
- n = 1121
- alfa-2a

Manns
- n = 1530
- alfa-2b

Sustained Response

- 1991: 6%
- 1995: 16%
- 1998: 34%
- 2002: 55%

IFN/R, PegIFN/R
A sustained virologic response (SVR) appeared to presage a long-term clearance of HCV.

Late relapses uncommon (1-2% after 10 years).

The liver disease does not progress.

Hepatocellular carcinoma occurs, but largely among those with cirrhosis at the time of treatment.

Appears to be a cure of the chronic viral infection.

Initially SVR defined by 24 week follow up, later 12 weeks found adequate for clinical trials.
Lack of Progress in Therapy of Hepatitis C
2002-2010: End of the Interferon Era

Sustained Response

<table>
<thead>
<tr>
<th>Year</th>
<th>Treatment</th>
<th>Duration</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1991</td>
<td>IFN</td>
<td>6 mo</td>
<td>6%</td>
</tr>
<tr>
<td>1995</td>
<td>IFN</td>
<td>12 mo</td>
<td>16%</td>
</tr>
<tr>
<td>1998</td>
<td>IFN/R</td>
<td>6 mo</td>
<td>34%</td>
</tr>
<tr>
<td>1998</td>
<td>IFN/R</td>
<td>12 mo</td>
<td>42%</td>
</tr>
<tr>
<td>2002</td>
<td>PegIFN/R</td>
<td>12 mo</td>
<td>55%</td>
</tr>
<tr>
<td>2010</td>
<td>PegIFN/R</td>
<td>6-18 mo</td>
<td>55%</td>
</tr>
</tbody>
</table>
HCV Genome Organization

~9.6 kb Single-stranded, positive-sense RNA genome

Structural Proteins

Nonstructural Proteins (Enzymes)
Three HCV Protease Inhibitors
Efficacy in Chronic Hepatitis C, genotype 1

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>Poordad Peg &amp; Rbv 48 wks</th>
<th>Jacobson Peg &amp; Rbv 48 wks</th>
<th>Manns &amp; Jacobson Peg &amp; Rbv 48 wks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boceprevir</td>
<td>40%</td>
<td>44%</td>
<td>50%</td>
</tr>
<tr>
<td>NEJM 2011</td>
<td>68%</td>
<td>75%</td>
<td>80%</td>
</tr>
<tr>
<td>Telaprevir</td>
<td>40%</td>
<td>44%</td>
<td>50%</td>
</tr>
<tr>
<td>NEJM 2011</td>
<td>68%</td>
<td>75%</td>
<td>80%</td>
</tr>
<tr>
<td>Simeprevir</td>
<td>50%</td>
<td>50%</td>
<td>80%</td>
</tr>
<tr>
<td>Lancet 2014</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

n = 938
n = 1088
n = 785
Problems with Interferon Based Therapy

- Response rates of 70-80% are achieved with protease inhibitors added to peginterferon & ribavirin
- But the tolerability of interferon remains a limiting factor
- And addition of protease inhibitors worsens tolerability
- Up to half of patients do not qualify for treatment
- Only half can tolerate the side effects or will accept therapy
- In a community practice situation, sustained responses are achieved in only 10-15% of infected patients
- The solution is an all-oral, interferon-free regimen
The Era of Direct Acting Antiviral Agents for Hepatitis C

Interferon-free regimens
2012 to the Present
HCV Non-Structural Regions

HCV Protease Inhibitors

Protease/Helicase

- Telaprevir
- Boceprevir
- Simeprevir
- Paritaprevir
- Grazoprevir
- Asunaprevir
- Faldaprevir

RNA polymerase

- Proteomimetic drugs
- Genotype specific: 1a and 1b
- Resistance rapidly develops
- Can have difficult side effects
- Drug-drug interactions common

-FDA approved: 2015
Telaprevir

Complex macromolecule that mimics the amino acid sequence cleaved by genotype 1 protease
HCV Non-Structural Regions

NS5A Replication Complex Inhibitors

- Block formation of the HCV replication complex
- Varying genotypic restriction
- Well tolerated
- Potent activity
  “-asvir”

Protease/Helicase

RNA polymerase

| NS2 | NS3 | NS4A | NS4B | NS5A | NS5B |

FDA approved: 2015

- Daclatasvir
- Ledipasvir
- Ombitasvir
- Elbasvir
- Velpatasvir
Daclatasvir

*DimERIC molecule that blocks HCV NS5A*
HCV Non-Structural Regions

HCV RNA Polymerase Inhibitors

Protease/Helicase
- NS2
- NS3
- NS4A
- NS4B

RNA polymerase
- NS5A
- NS5B

Nucleoside
- Pan-genotypic
- Well Tolerated

Non-Nucleoside*
- More restricted activity
- Side effects
  - "-buvir"

Sofosbuvir
Dasabuvir*
Deleobuvir*
[Ribavirin?]

FDA approved: 2015
Sofosbuvir

2’deoxy-2’fluoro-2’methyl uridine monophosphate with an alaninate cap
Therapy of Hepatitis C
All Oral Regimens: DAAs

- Daclatasvir & Asunaprevir (2012)
- Daclatasvir & Sofosbuvir (2013)
- Simeprevir & Sofosbuvir (2013)
- Ledipasvir & Sofosbuvir (*Harvoni*: 2014)
- Dasabuvir, Ombitasvir & Paritaprevir/r with or without ribavirin (*Viekira Pak*: 2014)
- Velpatasvir & Sofosbuvir (2015)
- Grazoprevir & Elbasvir (2016)

*(Year of first publication of results)*
Ledipasvir & Sofosbuvir for Genotype 1 HCV

Response Rate

99% [n=214] (12 weeks, Naïve)
94% [n=109] (12 weeks, Experienced)

Afdahl et al 2014: NEJM
Ledipasvir & Sofosbuvir for 8 vs 12 wks
Genotype 1, Treatment Naïve Patients

Response Rate

8 weeks [n=215] 94%
12 weeks [n=216] 95%

Kowdley et al 2014: NEJM
Ledipasvir & Sofosbuvir for 8 vs 12 wks
Genotype 1, Treatment Naïve Patients

Post-hoc, per protocol analysis: Kowdley et al 2014: NEJM
Dasabuvir, Ombitasir, Paritaprevir/ritonavir and Ribavirin for Genotype 1 HCV

Zeuzem et al 2014: NEJM
Feld et al 2014: NEJM

Response Rate

96%
96%
70%
80%
90%
100%

Naïve

12 weeks
[n=473]

Experienced

12 weeks
[n=297]
Non-Response Rates
12 Weeks of Therapy: Naïve Patients

- S-L: Afdahl n=214
  - Non-Viral n=2
  - Relapse n=1
  - Failure n=1
  - Overall Rate: 1.5%

- S-L: Kowdley n=216
  - Non-Viral n=7
  - Relapse n=3
  - Failure n=1
  - Overall Rate: 4.6%

- D-O-Pr/R: Feld n=473
  - Non-Viral n=10
  - Relapse n=7
  - Failure n=1
  - Overall Rate: 3.8%

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Response Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>98%</td>
</tr>
<tr>
<td>1b</td>
<td>99%</td>
</tr>
<tr>
<td>2</td>
<td>99%</td>
</tr>
<tr>
<td>3</td>
<td>95%</td>
</tr>
<tr>
<td>4</td>
<td>100%</td>
</tr>
<tr>
<td>5</td>
<td>97%</td>
</tr>
<tr>
<td>6</td>
<td>100%</td>
</tr>
</tbody>
</table>

Feld et al
Foster et al
NEJM: 2015
Sofosbuvir and Velpatasvir
Non-SVR Rates

Feld et al
Foster et al
NEJM: 2015
[n=901]
A Challenging Cohort: Decompensated Cirrhosis

- Patients with cirrhosis and decompensation (Childs-Pugh Class B & C) are particularly challenging to treat.
  - A beneficial response may be very valuable
  - Restoring health and disability
  - Avoiding death or liver transplantation
  - Response rates are less optimal
  - Adverse events are more frequent and more likely to be serious and even life-threatening
  - Interferon-based therapies were associated with considerable morbidity and mortality
Chronic Hepatitis C and Cirrhosis
Phase III Trials of DAAs

Response Rate

Childs Pugh Class A

Childs Pugh Class B & C

<table>
<thead>
<tr>
<th>Treatment</th>
<th>12 weeks</th>
<th>24 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>D-O-Pr/Rbv</td>
<td>92%</td>
<td>96%</td>
</tr>
<tr>
<td>Poordad 2014</td>
<td>[n=208]</td>
<td>[n=172]</td>
</tr>
<tr>
<td>S-L</td>
<td>92%</td>
<td>98%</td>
</tr>
<tr>
<td>Reddy 2015</td>
<td>[n=118]</td>
<td>[n=133]</td>
</tr>
<tr>
<td>S-V</td>
<td>94%</td>
<td>86%</td>
</tr>
<tr>
<td>Curry 2014</td>
<td>[n=90]</td>
<td>[n=90]</td>
</tr>
</tbody>
</table>

- 12 weeks
- 24 weeks
- [n=x]
What are the side effects of the all-oral direct acting antiviral agents?

- Most publications have stated that the all oral DAA regimes are “generally well tolerated”
- The controlled trials of new DAA regimens have generally compared different treatment regimens
- Few studies have included placebo control
- Ribavirin has a well defined spectrum of adverse events (anemia, lymphopenia, itching, rash).
- Only one study of DAA therapy without ribavirin has included untreated, placebo controls
Sofosbuvir & Velpatasvir vs Placebo for Chronic Hepatitis C for 12 weeks: Adverse Events

Feld et al
NEJM: 2015

19 SAEs occurred in 15 of 624 Sof-Vel but none of the 116 placebo recipients ($p = 0.15$)
Serious Adverse Event Rates
Clinical Trials of DAAs for Chronic Hepatitis C

Eight Phase III trials published in the New England Journal Medicine: 12 week regimens only
Chronic Hepatitis C and Cirrhosis Adverse Events

Adverse Event Rate

Childs Pugh Class A

- Any Adverse Event
  - [n=380]
  - 91%
  - 1 death
  - Poordad 2014

Childs Pugh Class B & C

- Any Adverse Event
  - [n=251]
  - 76%
  - No reported
  - Reddy 2015

- Any Adverse Event
  - [n=180]
  - 94%
  - 6 deaths
  - Curry 2014
Will the excellent response rates in clinical trials be reproduced in clinical practice?

- SVR rates to interferon-based regimens are often not reproducible in clinical practice: “the real world”.
- HCV-TARGET: an investigator initiated registry of patients treated in community & academic practice.
- Initial evaluation of S-L in 942 patients with hepatitis C.

Terrault et al: AASLD 2015
Limiting Factors: Barriers

<table>
<thead>
<tr>
<th></th>
<th>Interferon Based</th>
<th>Direct Acting Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Host Factors</td>
<td>Age</td>
<td>Cirrhosis (decompensated)</td>
</tr>
<tr>
<td></td>
<td>Gender</td>
<td>End-stage renal disease ?</td>
</tr>
<tr>
<td></td>
<td>Race</td>
<td></td>
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<tr>
<td></td>
<td>IL28b</td>
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<tr>
<td></td>
<td>Obesity</td>
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<tr>
<td></td>
<td>Fibrosis</td>
<td></td>
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<tr>
<td></td>
<td>Cirrhosis</td>
<td></td>
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<tr>
<td></td>
<td>Comorbidities (many)</td>
<td></td>
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<tr>
<td>Viral Factors</td>
<td>Genotype</td>
<td>Genotype</td>
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<tr>
<td></td>
<td>HCV RNA level</td>
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<td></td>
<td>Genetic diversity</td>
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<tr>
<td></td>
<td>Viral kinetics</td>
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<tr>
<td>Extraneous Factors</td>
<td>Previous therapy</td>
<td>Costs</td>
</tr>
<tr>
<td></td>
<td>Costs</td>
<td></td>
</tr>
</tbody>
</table>
Successful Therapy of Hepatitis C

• Newer regimens of oral direct acting antivirals have response rates of 95-99%
• Twelve weeks of treatment
• Minimal side effects
• Little need for intense monitoring
• Highly effective, short-term, well tolerated therapy that can be administered easily
• Promises to make a real impact on the morbidity and mortality of this disease
Progress in Therapy of Hepatitis C

Sustained Response Rate

- IFN 6 mo: 6%
- IFN 12 mo: 16%
- IFN/R 6-12 mo: 42%
- PegIFN/R 6-12 mo: 55%
- P/R/PI 6-12 mo: 75%
- DAAs 3 mo: >95%
The Costs of Success

• The remaining major barrier is its cost
• Harvoni (L-S) for 12 weeks: $96,000
• Viekira Pak (D-O-Pr) for 12 weeks: $83,000
• Burden to the health care system in the next few years: in excess of $100,000,000,000
• In the United States only ~25% of persons with hepatitis C have private insurance; the rest are in public health care programs or uninsured
• Enormous burden to an already overburdened medical care system
The Costs of Success

- The costs of HCV agents are unreasonable
- Prices charged are unjustified
- Estimated costs of production: $200-300/ course
- Costs of development: millions not billions
- Highly effective and life-extending
- Therapy will not decrease medical care costs in the United States, and may increase them
- Part of an accelerating excessive pricing of life-sustaining and life-extending medications
Elimination and Prevention

*Three Forms*

- **Primary**: prevent the infection
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