New Antiviral Therapy for HCV: Progress Toward Cure

Raymond T. Chung, MD
Director of Hepatology
Vice Chief, GI Unit
MGH

Worldwide Prevalence of HCV

HCV Genomic Organization

**HCV life cycle**

Moradpour, Nat Rev Microbiol 2007;5:453

**HCV Genotypes and Subtypes**

Simmonds P, Journal of Hepatology, 1999

- Americas + Western Europe
- South Africa
- Middle East
- North Africa
- Asia
- IVDU
- U.S.
  - 1.75% (45% SVR)
  - 3.25% (80% SVR)

**What’s in Our Therapeutic Armamentarium?**

- PEG-interferon-α and ribavirin
- Agents directly targeting viral functions (DAAs)
  - NS3/4A protease inhibitors
  - NS5B polymerase inhibitors
    - Nucleoside
    - Nonnucleoside
  - NS5A inhibitors
- Other viral targets
- Other interferons
- Agents targeting host cofactors
  - Lipid synthesis inhibitors
  - Cyclophilin antagonists
  - miRNA inhibitors
- Pharmacogenomics (IL28B)
Proposed antiviral effects of interferon-alpha

- Hundreds of ISGs induced
- Include PKR, OAS, ISG15
- Inhibit viral protein, RNA synthesis
- HCV has evolved multiple subversive mechanisms

Ribavirin: proposed mechanisms of action

- Guanosine analogue with antiviral properties against RNA and DNA viruses
- Only minimal antiviral effects on HCV as monotherapy
- Augments IFN’s antiviral effects
- Best available evidence supports independent immunomodulatory effects
  - Enhances IFN-stimulated genes
- Clinically minimizes IFN relapse rates

PEG-IFN-α and RBV Produce SVR in About Half of Patients with HCV

- IFN
- IFN/RBV
- Peg-IFN
- Peg-IFN/RBV


- PEG-IFN-α and RBV Produce SVR in About Half of Patients with HCV

1991 1999 2001 2002

Sustained Viral Response (%)
The good news: a sustained response is truly sustained

SVR Postpones Liver Complications in Persons with Advanced HCV Fibrosis
n=479, median f/u 2.1Y (0.8-4.9)

Liver Failure, %  Hepatocellular Carcinoma, %

The bad news: limited effectiveness

- Multiple adverse effects
  - Neuropsychiatric
  - Hematologic
  - Autoimmune
- Limited tolerability
- Contraindications
- Promise of therapy therefore elusive to many
- Challenge to find shorter duration, inherently more tolerable regimens
The NS3-4A Protease

- Chymotrypsin-like serine protease (vs. HIV-1 aspartyl protease)
- Activation by NS4A
- Cleavage of viral downstream targets at cys/tyr – ser/ala boundary
- Shallow substrate-binding cleft poses challenges to small molecule development

Peptidomimetics Act to Inhibit NS3-4A

End product inhibition of NS3-4A enzymatic activity
P6-P1 hexapeptide can be mimicked

Peptidomimetic NS3-4A Inhibitors

- BILN 2061 (Macro cyclic, also Danoprevir, TMC435350)
- VX-950 (Telaprevir, Linear)
- SCH 503034 (Boccaprevir, Linear)
Potent Antiviral Effect of an HCV Protease Inhibitor

Low Barrier to Resistance of an HCV Protease Inhibitor

Dynamics of Viral Variants
Plateau Group

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

- 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 period of PEG-2b + RBV

<table>
<thead>
<tr>
<th></th>
<th>PROVE1 (24 wks)</th>
<th>PROVE2 (24 wks)</th>
<th>SPRINT-1 (24 wks)</th>
<th>SPRINT-2 (24 wks)</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>


PROVE2: Truncation of therapy is feasible with addition of a PI

ADVANCE: Telaprevir with Response Guided Therapy in naïve HCV-1
eRVR = HCV RNA(–) @W4,12: Yes 24W, No 48W
TPV 750 mg q8h, PEG-2a; WB RBV

Jacobson I et al. AASLD 2010; abstract 211
ADVANCE: Telaprevir with Response Guided Therapy in naïve HCV-1

eRVR = HCV RNA(-) @W4,12; Yes 24W, No 48W
TPV 750 mg q8h; PEG-2a; WB RBV

<table>
<thead>
<tr>
<th>Treatment</th>
<th>SVR (%)</th>
<th>eRVR, %</th>
<th>Relapse, %</th>
<th>DC rash, T or Prall %</th>
<th>DC any AE, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>PegIFN/RBV + Placebo 48w</td>
<td>44</td>
<td>9</td>
<td>28</td>
<td>1/0</td>
<td>4</td>
</tr>
<tr>
<td>TPV 12w+ PegIFN/RBV RGT (n=363)</td>
<td>76</td>
<td>56</td>
<td>9</td>
<td>7/1.4</td>
<td>7</td>
</tr>
<tr>
<td>TPV 8w+ PegIFN/RBV RGT (n=384)</td>
<td>69</td>
<td>57</td>
<td>9</td>
<td>5/0.5</td>
<td>8</td>
</tr>
</tbody>
</table>

P < 0.0001

Jacobson I et al, AASLD 2010; abstract 211

ILLUMINATE: Randomized trial of short vs. long duration Rx after eRVR

GT1 naïve (N=540)

Wk 4, 12 HCV RNA (-) 65.2% (n=352)

+12 wks P/R (n=162)

Randomized

SVR 32%

+36 wks P/R (n=160)

SVR 87%

Sherman K et al, AASLD 2010; abstract LB-2

SPRINT-2: Boceprevir Response Guided Therapy in naïve HCV-1

Ph-3, BOC 800 tid, PEG-2b, WB RBV

<table>
<thead>
<tr>
<th>Treatment</th>
<th>SVR (%)</th>
<th>WB-24RNA(-), %</th>
<th>PPV for SVR, %</th>
<th>Relapse, %</th>
<th>Anemia, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>LI + Peg/RBV + Placebo 48w</td>
<td>40</td>
<td>NR</td>
<td>NR</td>
<td>23</td>
<td>29</td>
</tr>
<tr>
<td>(n=311/52)</td>
<td>23</td>
<td>47</td>
<td>23</td>
<td>9</td>
<td>49</td>
</tr>
<tr>
<td>LI+24 Peg/RBV BOC +/- 20 Peg/RBV</td>
<td>67</td>
<td>46</td>
<td>96</td>
<td>8</td>
<td>49</td>
</tr>
<tr>
<td>(n=316/52)</td>
<td>42</td>
<td>46</td>
<td>46</td>
<td>8</td>
<td>49</td>
</tr>
<tr>
<td>LI+44 Peg/RBV BOC</td>
<td>68</td>
<td>44</td>
<td>46</td>
<td>8</td>
<td>49</td>
</tr>
<tr>
<td>(n=311/55)</td>
<td>63</td>
<td>46</td>
<td>46</td>
<td>8</td>
<td>49</td>
</tr>
</tbody>
</table>

P < 0.0001

Non-black

Black


NR

23

29

47

46

97

96

23

9

49

49

46

46

49

49

P = 0.044

P = 0.004

P = 0.044
### RESPOND-2: Boceprevir in treatment-experienced HCV-1

**Ph 3, BOC 800 tid, PEG-2b, WB RBV**

<table>
<thead>
<tr>
<th>Previous Response</th>
<th>TMC435 LI +TPR12</th>
<th>SOC (PR48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>65%* (346/530)</td>
<td>17% (22/132)</td>
</tr>
<tr>
<td>Null Response (&lt;2log ↓ @ W12)</td>
<td>31%* (46/147)</td>
<td>5% (2/37)</td>
</tr>
<tr>
<td>Partial Response (&gt;2log ↓ @ W12, but RNA+ W24)</td>
<td>57%* (55/97)</td>
<td>15% (4/27)</td>
</tr>
<tr>
<td>Relapse</td>
<td>86%* (245/286)</td>
<td>24% (16/68)</td>
</tr>
</tbody>
</table>

*P<0.0001 vs SOC

Bacon B et al, AASLD 2010; Abstract 216

### REALIZE: Phase 3 Trial of Telaprevir in treatment-experienced HCV-1

<table>
<thead>
<tr>
<th>Previous Response</th>
<th>TMC435 LI +TPR12</th>
<th>SOC (PR48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>65%* (346/530)</td>
<td>17% (22/132)</td>
</tr>
<tr>
<td>Null Response (&lt;2log ↓ @ W12)</td>
<td>31%* (46/147)</td>
<td>5% (2/37)</td>
</tr>
<tr>
<td>Partial Response (&gt;2log ↓ @ W12, but RNA+ W24)</td>
<td>57%* (55/97)</td>
<td>15% (4/27)</td>
</tr>
<tr>
<td>Relapse</td>
<td>86%* (245/286)</td>
<td>24% (16/68)</td>
</tr>
</tbody>
</table>

*P<0.0001 vs SOC

Vertex Press Release, Sept 7, 2010

### PILLAR Study: TMC435 + PegIFN/RBV

Proportion of Patients Achieving Virologic Response

<table>
<thead>
<tr>
<th>Week 4</th>
<th>Week 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMC12/12 PR24 75 mg (n=78)</td>
<td>77%</td>
</tr>
<tr>
<td>TMC12/12 PR24 150 mg (n=77)</td>
<td>84%</td>
</tr>
<tr>
<td>TMC24/24 PR24 75 mg (n=73)</td>
<td>91%</td>
</tr>
<tr>
<td>TMC24/24 PR24 150 mg (n=77)</td>
<td>94%</td>
</tr>
<tr>
<td>Pbo 24/48 PR48 (n=75)</td>
<td>11%</td>
</tr>
</tbody>
</table>

<25 IU/mL undetectable, <25 IU/mL detectable, >25 IU/mL

Fried MW, et al. AASLD 2010; Abst. 318
PILLAR Study: Role of IL28B Genotype

Mean (± SE) Change in Plasma HCV RNA (log10 IU/mL) from Baseline

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Placebo</th>
<th>All TMC 435 (75 mg)</th>
<th>All TMC 435 (150 mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Fried MW, et al. AASLD 2010; Abst. 1301

SILEN-C1: BI-1335 + PegIFN/RBV with or without 3-day lead-in

<table>
<thead>
<tr>
<th>Outcome</th>
<th>BI1335 120 mg LI</th>
<th>BI1335 240 mg LI</th>
<th>BI1335 240 mg No LI</th>
</tr>
</thead>
<tbody>
<tr>
<td>eRVR</td>
<td>80</td>
<td>78</td>
<td>55</td>
</tr>
<tr>
<td>SVR</td>
<td>88</td>
<td>71</td>
<td>73</td>
</tr>
<tr>
<td>Relapse</td>
<td>83</td>
<td>24</td>
<td>15</td>
</tr>
</tbody>
</table>

Subhawirod, et al. EASL 2011

NS5B RNA-dependent RNA Polymerase

Multiple Sites of Action

Nuc: high barrier, high fitness cost
NNI: low barrier, low fitness cost

Sulkowski et al. JHEP 2011
PROPEL: 12 wk interim analysis of PEG/RBV/RG7128
Phase 2, PEG-2a, WB RBV

- No excess AEs over SOC
- No rebound or resistance observed

JENSEN D et al. AASLD 2010; Abstract 81; Pockros P et al. EASL 2011

An NS5A inhibitor has potent activity against HCV

- NS5A: no known enzymatic function, indispensable for RNA replication, viral assembly
- Chemical screening \rightarrow BMS-790052
- single ascending dose study in gt 1 naïve pts \rightarrow 3.6 log @48h after 100 mg dose
- non-overlapping resistance profile with PI, pol-inhibitors

Gao M et al. Nature 2010;465:96-100

NS5A inhibitor + PegIFN/RBV

NS5A 1 mg (n=12)
NS5A 10 mg (n=12)
NS5A 60 mg (n=12)

Pol et al. EASL 2011
IFNs alpha and lambda

- IFN-λα: type III IFN vs type I IFN-α
- Share convergent signal transduction
- Limited receptor distribution (hepatocytes, immune cells)
- More limited AE profile? PEG-IFN-λ1 as therapeutic

Virologic response by IL28B Genotype in patients with HCV Genotypes 1, 4

Changes in Hematologic Parameters Over Time and PegIFN and RBV Dose Reductions
Pros, Cons of Direct Acting Antivirals

<table>
<thead>
<tr>
<th>Class</th>
<th>Potency</th>
<th>Barrier to Resistance</th>
<th>Toxicity and Interactions</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protease inhibitors</td>
<td>High</td>
<td>Low</td>
<td>Rash, Anemia</td>
<td>2nd gen PI: better barrier, pangenotypic</td>
</tr>
<tr>
<td>Nuc Polymerase inhibitors</td>
<td>Moderate-high</td>
<td>High</td>
<td>Mitochondrial Nuc interactions (ART, RBV)</td>
<td>Single target</td>
</tr>
<tr>
<td>Nonnuc Polymerase inhibitors</td>
<td>Low-Moderate</td>
<td>Low</td>
<td>variable</td>
<td>Many targets</td>
</tr>
<tr>
<td>NS5A inhibitors</td>
<td>Moderate-High</td>
<td>Moderate</td>
<td>Multiple antiviral MOA</td>
<td></td>
</tr>
</tbody>
</table>

Ideal DAA cocktail will combine high potency with high barrier to resistance

A Combination of DAAs Could Eliminate Resistant Variants

<table>
<thead>
<tr>
<th>Target</th>
<th>Variant</th>
<th>NS3</th>
<th>NS3</th>
<th>NS3</th>
<th>NS3</th>
<th>NS3</th>
<th>NS5A</th>
<th>NS5A</th>
<th>NS5A</th>
<th>IFN</th>
<th>RBV</th>
</tr>
</thead>
<tbody>
<tr>
<td>NS3</td>
<td>V176A</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>NS3</td>
<td>V176A</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>NS3</td>
<td>V176A</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>NS3</td>
<td>V176A</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>NS3</td>
<td>V176A</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>NS3</td>
<td>V176A</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>NS3</td>
<td>V176A</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>NS3</td>
<td>V176A</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>NS3</td>
<td>V176A</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>NS3</td>
<td>V176A</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
</tbody>
</table>

S = Susceptible (<4 fold shift in HCV replicon EC50)
R = Resistant (>4 fold increase in EC50)

Proof of concept for combining two DAAs: INFORM-1

RG7128 + danoprevir (n=73)

LLOQ = lower limit of quantification by TaqMan Assay (<40 IU/mL)
LLOD = lower limit of detection by TaqMan Assay (<15 IU/mL)

Other DAA combinations in early trials

- **Rationale**: exploit replication dependence of HCV
  - RG7128 (Nuc) + danoprevir (PI)
    (Gane, Lancet 2010)
  - Telaprevir (PI) + VX222 (NN) +/- PEG/RBV
  - BMS650032 (PI) + BMS790052 (NS5A) +/- PEG/RBV
    (Lok, AASLD LB-8)
  - GS9190 (NN) + GS9256 (PI) +/- RBV
    (Zeuzem, AASLD LB-1)
  - BI201335 (PI) + BI207127 (NN) + RBV
    (Zeuzem, AASLD LB-7)
  - IDX184 (Nuc) + IDX320 (PI)

- **Modeling**: SVR possible with DAAs if barrier high

---

A Full Pipeline: Other DAAs in Clinical Testing (Phase)

- **Protease inhibitors**
  - TMC435 (2)
  - Danoprevir (2)
  - MK7009 (2)
  - BI201335 (2)
  - BMS650032 (2)
  - GS9256 (2)
  - ACH1625 (2)
  - IDX320 (2)
  - PHX1766 (1)

- **Nuc pol inhibitors**
  - IDX184 (2)
  - PS7977 (2)
  - RG7348 (1)

- **Nonnuc pol inhibitors**
  - GS9190 (2)
  - ANA598 (2)
  - VCH759 (2)
  - Filibuvir (2)
  - VX222 (2)
  - ABT333, 072 (2)
  - BI207127 (1)
  - ABT837093 (1)

- **NS4B inhibitors**
  - clemizole (1)

- **NS5A inhibitors**
  - BMS 790052 (2)
  - PP1461 (1)

- **NS4B inhibitors**
  - clemizole (1)

- **Entry**
  - ITX5061 (2)
  - MBL-HCV1 (2)

---

At least 4 proteins participate in HCV entry

- At least 4 proteins participate in HCV entry

---

- Poleschmidt T Nature 2009;457:797
Other viral targets: HCV Entry Inhibitors

- In development: inhibitors of CD81, claudin-1, occludin-1
- Possible role in cell-to-cell spread
- Potentially promising approach to prevent *de novo* HCV infection
- Phase 2 study of MBL-HCV-1: MAb vs. HCV E2 protein to prevent allograft reinfection


Other Targets: Host Cofactors for Viral Replication

- Exploit strategies to block host accessory factors in the viral lifecycle
- Advantage: high barrier to viral resistance
- Disadvantage: host cellular toxicity
- Growing list of potential targets
  - Cyclophilin A
  - MicroRNAs
  - Lipid biosynthesis

Cyclophilin Antagonists

- Cyclophilin A blocks incorporation of NS5B into replication complex
- CsA active vs HCV in culture models
- CsA blocks cyclophilin A but also inhibits calcineurin → immunosuppression
- Non-immunosuppressive antagonists
  - DEBIO 025 (-3.6 log w/ monotherapy in HCV/HIV)
  - SCY635 (-2.3 log w/ monotherapy in HCV)
  - high barrier to resistance
  - broadly active across genotypes
- Phase 2 studies

miR122 Antagomirs

- microRNAs regulate host mRNAs
- miR122 is predominant liver miRNA, required for HCV replication
- SPC3649: miR122 antagomir reduced HCV by 2-3 log in chimpanzees
- No breakthrough, resistance observed during 12 weeks of Rx
- Suggests utility for nonresponders and DAA failures
- Phase 1 studies

Lanford RE et al, Science 2010; 327:198-201

Host factors: HCV replication requires cholesterol intermediates


Statins exert strong antiviral effect in vitro

- HMGK inhibitors: strong antiviral effect in replicon
  - Reversible with geranylgeraniol
  - However, no HCV activity alone at std clinical doses
  - Best IC50 vs HCV = 1μM (vs IC50 for HMGR = 1nM)
- Higher concentrations may be necessary for GG depletion
- Synergy with IFN in replicon
- Combo with DAA agents additive, and prevents or delays resistance
- Rationale for combination trial

Kim SS et al, Gastroenterology 2007;132:311
O'Leary JG et al, Hepatology 2007;45:895
A SNP in *IL28B* (IFNα3) predicts treatment response in HCV


IFNs alpha and lambda

O’Brien TR, Nature Genetics 2009;41:1048

The new waves of HCV therapy

- **Wave 1 (2011-2014): add-on Rx**
  - 1st generation PIs + SOC: naïve and experienced
  - Naives: consider empiric Rx (as with gt 2/3)
  - Experienced: offer Rx (particularly R/R, PR)
  - Nulls: stratify by stage
- **Wave 2 (2014-2016): the better mousetrap**
  - Substitution of 2nd generation PIs, nucs (better PK, tolerability)
  - Substitution of better tolerated IFNs
  - 4 drug regimens for P/R/PI failures
- **Phase 3 (2016-2020): the holy grail**
  - Oral cocktails of DAAs, host cofactor inhibitors, RBV
  - Many roads to the same destination!
Summary

• DAAs are the future of HCV therapy
  • Protease inhibitors have potent activity but select resistant variants
  • Nucleosides have potent activity and high genetic barrier but potential interaction concerns
  • Nonnucrs have moderate activity, many sites, but low barrier to resistance
  • NSSA inhibitors also potent, nonoverlapping resistance
• Host cofactor inhibitors have high barrier to resistance, but may have greater toxicity concerns
• Selection of agents with complementary MOA and resistance profiles will be desirable
  • Must provide rapid suppression, minimize resistance
  • Combine high barrier compounds with potent low barrier compounds
• IFN-sparing regimens will be possible in future (6-10yr)
• Role of pharmacogenomics in decision making