Assessing the Evolving Evidence of HCV Treatment Options

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Objective

- Review the evolving evidence on current and emerging treatment options for HCV including efficacy, safety, and therapeutic options
Current Status of Response-guided Therapy: 2011

- Genotype 2 or 3 infection RVR
- Genotype 1 with RVR
  - Low viral load
- Genotype 1 with Late virologic response (week 12 to 24)

Treatment Duration (Weeks):
- Baseline
- 12-16
- 24
- 72

RVR = rapid virological response.

Rates of SVR are not significantly different between the two available PEG IFN–RBV regimens or between doses of PEG IFN alfa-2b.

SVR = sustained virologic response.
HCV RNA = hepatitis C virus-ribonucleic acid.
PEG-IFN = pegylated interferon.
RBV = ribavirin.

Multiple Host Factors Are Predictive of Response to Treatment

Age, Gender, Ethnicity, Genomics, Immune Status, Severity of Liver Disease, Hepatic Steatosis, Insulin Resistance, Adherence
Pharmacogenomics Hold Promise for Predicting Responders to HCV Treatment

"-Omics" Technologies

Responder  Adverse Event  Non-responder

Allows for rationale selection of patients for different treatment strategies
Recent Evidence Suggest a Polymorphism on Chromosome 19 Predicts SVR

SVR=sustained virologic response.


Chromosome 19 graphic courtesy of Oak Ridge National Laboratory.

C Allele Is Associated With Sustained Virologic Response

Treatment-associated Decline in HCV Is Influenced by the IL28B SNP Genotype Present

Caucasian Patients Infected With HCV-2 or -3

Mean HCV RNA Decline (Log UI/ml)

rs12979860 genotype:
- CC (N=37)
- CT (N=21)
- TT (N=4)

Days on Peg-IFN and RBV Therapy

SNP=single nucleotide polymorphism. HCV gen 2-3=hepatitis C virus genotype 1 or 2. Peg-IFN=pegylated interferon.

Factors That Predict SVR in Patients With HCV Genotype 1

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio</th>
<th>IC 95 %</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>Genotype CC <em>IL28B</em> vs non-CC</td>
<td>5.2</td>
<td>4.1</td>
<td>6.7</td>
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<tr>
<td>Change Viral ≤600,000 IU/mL</td>
<td>3.1</td>
<td>2.3</td>
<td>4.1</td>
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<tr>
<td>Caucasian vs Black</td>
<td>2.8</td>
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<td>4.0</td>
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<tr>
<td>Hispanic vs Black</td>
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<td>1.3</td>
<td>3.6</td>
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<tr>
<td>METAVIR F012</td>
<td>2.7</td>
<td>1.8</td>
<td>4.0</td>
</tr>
<tr>
<td>Fasting Glucose &lt;5.6 mmol/L</td>
<td>1.7</td>
<td>1.3</td>
<td>2.2</td>
</tr>
</tbody>
</table>

SVR=sustained virologic response.
METAVIR scoring systme graded liver fibrosis on a 5-point scale (0 to 4).

CC IL28 Genotype Predicts SVR in Non-RVR CC Genotype HCV Patients

SVR=sustained virologic response.
RVR=rapid virologic response.

Pretreatment Serum Levels of IP-10 Improves Predictive Value for SVR of IL28B Polymorphism

- Data from the VIRA-HEP C cohort
- Determination of IP-10 level (n=272) and IL28B (n=210)

Combination of IP-10 and IL28B genotypes improve predictive value for SVR particularly in patients with CT/TT genotypes

SVR = sustained virologic response.
IP-10 = inducible protein 10.
The HCV Treatment Landscape Continues to Evolve

Preclinical
- Nucleoside DAA combinations
  - Gilead
  - Vertex
  - Roche
  - BMS/Pharmasset
  - Others
- Polymerase inhibitors
  - Nitazoxanide (Romark)
  - INF lambada (Zymogen / NovoNordisk)
  - Taribavirin (Valeant)

Phase I
- Phase I
  - Boceprevir (MSD)
  - TMC435 (J&J/Vertex)
  - BI201127 (BI)

Phase II
- Phase II
  - Telaprevir (J&J/Vertex)
  - GS9256 (Gilead)
  - MK7009 (MSD)
  - MK5172 (MSD)
  - ITMN-191/R7227 (Roche/Intermune)

Phase III
- Phase III
  - GS9190 (Gilead)
  - ANA598 (Anadys)
  - VX222 (Vertex)
  - PSI-7977 (Pharmasset)

Filed
- R7128 (Roche/Pharmasset)
- Biocryst
- INX189 (Inhibitex)

Non Nucleoside Polymerase inhibitors
- ABT450 (ABT)
- ABT33, ABT7072 (ABT)
- IDX375 (Idenix/NVS)

Protease inhibitors
- BI201335 (BI)
- VX222 (Vertex)
- Bi201135 (BI)

NS5A inhibitor
- MSD
- GSK
- Enanta
- Vertex
- Presidio
- Idenix
- ACH1625 (Achillion)

DAA combinations
- Others
- DEB025 cyclophilins
- BMS-791325 (nuc/non-nuc BMS))
ADVANCE: a Phase III Study of Telaprevir in Combination With Peg-interferon and Ribavirin

- Efficacy and safety of telaprevir + PEG IFN alfa-2a and RBV vs standard care
- Primary endpoint: Proportion of patients with SVR 24 weeks after last dose

n=1088

(T) TVR=telaprevir 750 mg q8h.
(P) Peg-IFN=pegylated interferon alfa-2a (40 kD) 180 µg/wk.
(R) RBV=ribavirin 1,000 or 1,200 mg/day.

(T) TVR=telaprevir 750 mg q8h.
(P) Peg-IFN=pegylated interferon alfa-2a (40 kD) 180 µg/wk.
(R) RBV=ribavirin 1,000 or 1,200 mg/day.

Pbo=Placebo.
eRVR=extended RVR defined as HCV RNA undetectable at Week 4 and Week 12.

Telaprevir Elicited Significantly Higher SVR Rates Vs Current Standard of Care

SVR = sustained virologic response.
T12PR = telaprevir + pegylated-interferon + ribavirin for 12 wks followed by pegylated-interferon and ribavirin.
T8PR = telaprevir + pegylated-interferon + ribavirin for 8 wks followed by pegylated-interferon and ribavirin.
PR = pegylated-interferon and ribavirin alone for 48 weeks.

Telaprevir-treated Patients Had Undetectable HCV RNA at Week 4 (RVR) and Weeks 4 and 12 (eRVR)

RVR=rapid virologic response.
eRVR=HCV RNA undetectable at Week 4 and Week 12.
T12PR=telaprevir + pegylated-interferon + ribavirin for 12 wks followed by pegylated-interferon and ribavirin.
T8PR=telaprevir + pegylated-interferon + ribavirin for 8 wks followed by pegylated-interferon and ribavirin.
PR=pegylated-interferon and ribavirin alone for 48 weeks.

Higher SVR Rates Were Observed in Telaprevir-treated Patients Regardless of Race or Ethnicity*

Race and ethnicity were self-reported.

*SVR=sustained virologic response.

T12PR=telaprevir + pegylated-interferon + ribavirin for 12 wks followed by pegylated-interferon and ribavirin.

T8PR=telaprevir + pegylated-interferon + ribavirin for 8 wks followed by pegylated-interferon and ribavirin.

PR=pegylated-interferon and ribavirin alone for 48 weeks.

Telaprevir Was Generally Well-tolerated in the ADVANCE Trial

- Adverse events occurring in ≥25% of patients:
  - Fatigue, pruritus,* headache, nausea,* rash,* anemia,* insomnia, diarrhea,* flulike symptoms, pyrexia

- Rash events primarily eczematous and resolved with discontinuation of therapy

- Sequential discontinuation of drugs if rash moderate or severe

- Telaprevir followed 7 days later by RBV then by PEG IFN if rash progressed

*Adverse event rates ≥10% higher in telaprevir arms vs PEG FN/RBV.

ILLUMINATE: a Phase III Non-inferiority Trial Comparing a Short Vs Long Course of Telaprevir

- To evaluate differences in SVR between a 24-week and 48-week TVR in patients who achieved eRVR and Safety of TVR in combination with PEG IFN and RBV

n=540

Patients discontinued for any reason before Wk 20 were categorized as “Other”

Stopping Rules:
- Week 4 HCV RNA >1000 IU/mL patients were to discontinue TVR and continue PR
- Week 12 HCV RNA <2 log_{10} decrease vs baseline, patients were to discontinue all study drugs
- Weeks 24–36 Detectable HCV RNA >10 IU/mL patients were to discontinue all study drugs

*eRVR=extended RVR.

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(P) Peg-IFN=pegylated interferon alfa-2a (40 kD) 180 µg/wk.
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T12PR=telaprevir + pegylated-interferon + ribavirin for 12 wks followed by pegylated-interferon and ribavirin. PR=pegylated-interferon and ribavirin alone for 48 weeks.

Non-inferior Virologic Responses to Telaprevir Treatment in the Intent-to-treat Population

**Undetectable HCV RNA Over Time**

- RVR: 72% (n/N=389/540)
- eRVR: 65% (n/N=352/540)
- EOT: 87% (n/N=469/540)
- SVR: 72% (n/N=388/540)

**SVR Rates: Non-inferiority of 24-week Regimen**

- T12PR24: 92% (n/N=149/162)
- T12PR48: 88% (n/N=140/160)

Δ 4.5% (2-sided 95% CI=-2.1% to +11.1%)

SVR=sustained virologic response.
RVR=rapid virologic response.
eRVR=extended RVR.
EOT=end of treatment.
SVR was comparable regardless of race or ethnicity and liver fibrosis stage.

ILLUMINATE Trial: Summary

- 24-week telaprevir-based regimen is non-inferior to a 48-week regimen in patients with eRVR (92% vs 88% SVR)

- 65% of patients were eligible for a shorter duration of treatment

- 72% overall SVR observed in the intent-to-treat population
  - 63% SVR in patients with bridging fibrosis and cirrhosis
  - 60% SVR in African American patients
  - 67% SVR in Hispanic/Latino patients

- Most common adverse events included: rash (primarily eczematous), fatigue, pruritus, nausea, and anemia

- An 18% overall rate of discontinuation was noted for all study drugs due to adverse events
  - 1% and 2% overall treatment discontinuation rates due to rash and anemia, respectively

REALIZE: Phase III Trial of Telaprevir in Genotype 1 HCV Patients

n=662 Genotype 1 patients who failed to achieve SVR with prior pegylated interferon-based therapy

<table>
<thead>
<tr>
<th>Category</th>
<th>Combined TVR Arms</th>
<th>Control</th>
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</thead>
<tbody>
<tr>
<td>Relapsers</td>
<td>86%*</td>
<td>24%</td>
</tr>
<tr>
<td>Partial Responders</td>
<td>57%*</td>
<td>15%</td>
</tr>
<tr>
<td>Null Responders</td>
<td>31%†</td>
<td>5%</td>
</tr>
</tbody>
</table>

*P<.0001
†P<.001 TVR vs Control

Overall population:
- Cirrhotics: 26%
- Null Responders: 33%

HCV RNA (>800,000 IU/mL):
- Overall: 89%
- Null Responders: 95%

Study to compare safety/efficacy of two treatment strategies with boceprevir added to peginterferon/ribavirin (PR) versus PR alone in treatment-naïve HCV genotype 1 patients.

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 3x/daily.

Two-thirds of Boceprevir-treated Patients Achieved SVR* in the SPRINT 2 Trial

*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 24-week post-treatment level was missing (as specified in the protocol). A sensitivity analysis was performed counting only patients with undetectable HCV RNA documented at 24 weeks post-treatment and the SVR rates for Arms 1, 2, and 3 in Cohort 1 were 39%, 66% and 68%, respectively and in Cohort 2 were 21%, 42%, and 51%, respectively.

BOC RGT=boceprevir response-guided therapy.
P/R=peglyated interferon + ribavirin/
BOC/PR=boceprevir + peglyated interferon + ribavirin.

Boceprevir Elicited SVR Following 4 Weeks of P/R Lead-in Therapy

- ≥1 log 10 HCV RNA decline from baseline
- <1 log 10 HCV RNA decline from baseline

**Non-Black Patients**
- 48 P/R: 52 SVR (%), 121/234
- BOC RGT: 82 SVR (%), 187/228
- BOC/PR48: 82 SVR (%), 178/218

**Black Patients**
- 48 P/R: 46 SVR (%), 12/26
- BOC RGT: 67 SVR (%), 16/24
- BOC/PR48: 61 SVR (%), 22/36

BOC RGT = boceprevir response-guided therapy.
P/R = peglyated interferon + ribavirin.
BOC/PR = boceprevir + peglyated interferon + ribavirin.

SVR in Patients With Undetectable HCV RNA Between Weeks 8-24

47% of patients in Cohort 1 RGT arm were treated with short duration

SVR in Patients With Detectable HCV RNA at Least Once Between Weeks 8-24

22% of patients in Cohort 1 RGT arm were treated with >28 weeks of therapy

BOC RGT=boceprevir response-guided therapy.
P/R=peglyated interferon + ribavirin.
BOC/PR=boceprevir + peglyated interferon + ribavirin.

Boceprevir Generally Well-tolerated by Patients in the SPRINT 2 Trial

- Anemia and dysgeusia occurred more often in the boceprevir groups than the control groups (20% and 19-25% higher, respectively)
- EPO was used in 19% more boceprevir recipients compared to controls; discontinuation due to anemia occurred in <2% of patients
- No other novel adverse events were noted

EPO=erythropoietin.
RESPOND 2: Phase III Study of Boceprevir in Patients Who Failed Prior Therapy

**Arm 1**
- **Control**
  - PEG + RBV 4 wk
  - Follow-up 24 wk

**Arm 2**
- **Response-guided Therapy**
  - PEG + RBV 4 wk
  - Boceprevir + PEG + RBV 32 wk
  - Follow-up 24 wk

**Arm 3**
- PEG + RBV 4 wk
- Boceprevir + PEG + RBV 44 wk
- Follow-up 24 wk

Genotype 1 HCV Patients Who Experienced a Relapse or Non-response to Prior Therapy (n=403*)

*Patient distribution was 67% male, 12% black, and 12% cirrhotic.

Boceprevir-treated Patients Had Significant Increases in SVR Rates

- **End of therapy response**
- **Relapse rates**
- **SVR**

### Graph Details:

**P/R 48 Wk**
- 31% End of therapy response
- 21% Relapse rates

**BOC RGT*: P/R 4 Wk + P/R/BOC 32 Wk +/- P/R 12 Wk**
- 70% End of therapy response
- 15% Relapse rates

**P/R 4 Wk + P/R/BOC 44 Wk**
- 77% End of therapy response
- 12% Relapse rates

*RGT based on HCV negativity at week 8: a) Patients with undetectable HCV RNA received 28 more weeks of P/R/BOC; b) Patients with detectable HCV RNA received 28 more weeks of P/R/BOC followed by 12 weeks of P/R.

†P<.0001 vs control.

BOC RGT=boceprevir response-guided therapy.
P/R=peglyated interferon + ribavirin.
BOC/PR=boceprevir + peglyated interferon + ribavirin.

**RESPOND-2 Trial: Summary**

- The combination of boceprevir, peglyated interferon, and ribavirin leads to high SVR rates in G1 previous non-responders/relapsers to P/R therapy, with significant but lower response rates in poor responders.

- This therapy was generally well tolerated, and offers substantial benefit to patients who failed prior P/R therapy.

Additional HCV Therapies in Development
Direct Antiviral Agents for HCV: Overview

**Overview**

- **Moderate-to-high potency**
  - +/- Multi-genotypic coverage
  - Intermediate barrier to resistance

- **High-potency**
  - Multi-genotypic coverage
  - Low barrier to resistance

**NS5B Non-nucleoside Polymerase Inhibitors (NNPI)**

- Low potency
- Limited-genotypic coverage
- Low barrier to resistance

**NS5B Nucleoside Inhibitors (NI)**

- Intermediate to high potency
- Pan genotypic coverage
- High barrier to resistance
## Combination Therapies With 2 or More Direct Antiviral Agents: Lessons Learned

<table>
<thead>
<tr>
<th>Drug Combinations</th>
<th>Class</th>
<th>Manufacturer</th>
<th>Phase of Development</th>
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<tbody>
<tr>
<td>BMS-650032+ BMS-790052</td>
<td>PI+NS5a</td>
<td>BMS</td>
<td>2a</td>
</tr>
<tr>
<td>Danoprevir (RG7227)+ RG7128</td>
<td>PI+NPI</td>
<td>Genentech</td>
<td>2b</td>
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<tr>
<td>GS-9190+ GS-92568</td>
<td>PI+NNPI</td>
<td>Gilead</td>
<td>2a</td>
</tr>
<tr>
<td>BI-201335+ BI-207127</td>
<td>PI+NNPI</td>
<td>Boehringer Ingelheim</td>
<td>2a</td>
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</table>

**Abbreviations:**
- NNPI = non-nucleoside polymerase inhibitors.
- NPI = nucleoside polymerase inhibitor.
- NS5a = non-structural 5A protein of HCV.
- PI = protease inhibitor.
Multiple Anti-HCV Potential Combinations

**Linear class**
- Telaprevir
- Boceprevir
- Narlaprevir

**Macrocyclic class**
- RG7227/ITMN-191
- TMC 435350
- MK 7009
- BI 201335
- BMS-650032

**NS3 Protease**
- BMS-790052
- ABT-267

**NS5A**

**NS5B Polymerase**
- Palm
  - ABT-333
  - ABT-072
  - GS 9190
  - ANA598
- Thumb
  - VCH-759
  - VCH-916
  - VX-222
  - BI 207127
  - Filibuvir

**Active site**
- RG7128
- IDX184
- PSI-7977

**Cyclophilin**
- Alisporivir
- SCY635
Therapies Anticipated After 2015

- **GT1**

- **Cost restrained markets: IL28CC + RVR:**
  - Peg IFN + RBV

- **Triple Therapy With P/R + DAA or Host Targeting Agent**

- **Quadruple Combination of P/R and DAAs and/or Host Targeting Agent**

- **Positive baseline predictors of response**
  - **Triple or Quadruple all oral therapy, including ribavirin**

**Abbreviations:**
- GT1 = genotype 1
- RVR = rapid virologic response
- RBV = ribavirin
- Peg IFN = Peginterferon alfa-2b
- P/R = Peginterferon alfa-2b/Ribavirin
- DAA = direct antiviral agent
Evolution of Therapy in HCV Genotype 1

*Difficult to treat populations
Future Individualized Standard of Care

• **Patient demographics**
  – Age, ethnicity, histology, compliance, genomics, treatment history

• **Regimen selection**
  – Based on above criteria and ease of regimen, expected duration, adverse events, payer preferences, emerging newer therapies

• **Better SVR rates with greater toxicity**

• **With 1st generation protease inhibitors, must monitor for resistance**