Evolution of HCV Therapy in the Era of Direct Acting Antivirals

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Our Challenge

A fraction of those with HCV are diagnosed

A fraction of those diagnosed are treated

A fraction of those treated are cured

The Need to Cure Cirrhosis: Survival in Patients With HCV and Cirrhosis


![Survival Probability Graph]

- **Compensated**
- **After first major complication**

### Pts at Risk, n

<table>
<thead>
<tr>
<th>Mos</th>
<th>0</th>
<th>12</th>
<th>24</th>
<th>36</th>
<th>48</th>
<th>60</th>
<th>72</th>
<th>84</th>
<th>96</th>
<th>108</th>
<th>120</th>
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<tbody>
<tr>
<td></td>
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<td>384</td>
<td>376</td>
<td>342</td>
<td>288</td>
<td>236</td>
<td>165</td>
<td>126</td>
<td>79</td>
<td>52</td>
<td>39</td>
</tr>
</tbody>
</table>

Evolution of HCV Therapy: Where Are We in 2012?

2001

2011

Beyond

From Clinical Care Options – Chung RF, HCV the Road Ahead

PegIFN/RBV
Protease inhibitor
Nucleos(t)ide polymerase inhibitor
Nonnucleoside polymerase inhibitor
NS5A inhibitor
Host targeting agent
CURRENT THERAPIES
Study 110: SVR24 With TVR + PegIFN/RBV in HCV GT1/HIV-Coinfected Patients

- Higher SVR24 rate with TVR-based therapy
- No significant drug–drug interactions with TVR and ART
  - TVR plasma levels similar in patients with or without ART
  - EFV and ATV/RTV plasma levels similar in patients with or without TVR
- No HIV breakthroughs in patients using ART during HCV treatment
- Safety and tolerability similar to treatment in patients with HCV monoinfection

Sulkowski MS, et al. AASLD 2012. Abstract 54
Higher SVR12 Rates With BOC + P/R vs P/R Alone in HIV/HCV Coinfection

- Interim data reported (3 pts in BOC arm had not reached SVR12)

- HIV-1 RNA breakthrough observed in 7 pts
  - BOC plus P/R: n = 3 (all receiving boosted PIs)
  - Placebo plus P/R: n = 4

Sulkowski MS, et al. CROI 2012. Abstract 47
Adverse Events of BOC + P/R vs P/R Alone in HIV/HCV Coinfection

• Overall and serious AE rates similar between arms
  – Anemia, pyrexia, asthenia, decrease appetite, diarrhea, dysgeusia, vomiting, neutropenia more common among BOC recipients
    • Most cases of anemia and neutropenia mild (WHO grade 1/2)
    – Flu-like illness more common among placebo recipients
• More patients discontinued study because of toxicity in BOC vs placebo arm
  – BOC plus pegIFN/RBV: 20%
  – Placebo plus pegIFN/RBV: 9%

Pharmacokinetic Effects of RTV-Boosted HIV PIs on BOC and TVR

- Similar reductions in BOC and TVR exposures observed with coadministration of ATV/RTV, DRV/RTV, and LPV/RTV
- Prescribing information for TVR does not recommend coadministering TVR with DRV/RTV, FPV/RTV, or LPV/RTV; prescribing information for BOC does not recommend coadministering BOC with any HIV PI

Pharmacokinetic Effects of BOC and TVR on RTV-Boosted HIV PIs

BOC Plus PegIFN alfa-2b/RBV: Adverse Events

- Higher rates of anemia, neutropenia, and dysgeusia in BOC arms vs control

<table>
<thead>
<tr>
<th>Adverse Event, %</th>
<th>PR48 (n = 467)</th>
<th>BOC + PR RGT/48* (n = 1225)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia*</td>
<td>30</td>
<td>50</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>19</td>
<td>25</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>16</td>
<td>35</td>
</tr>
</tbody>
</table>

*Anemia was managed with RBV reduction and/or epoetin alfa (43% of BOC + PR and 24% of PR).

TVR Plus PegIFN alfa-2a/RBV: Adverse Events

- Higher rates of rash, anemia, and anorectal signs and symptoms in TVR arms vs control

<table>
<thead>
<tr>
<th>Adverse Event, %</th>
<th>PR48 (n = 493)</th>
<th>TVR + PR RGT/48*† (n = 1797)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash</td>
<td>34</td>
<td>56</td>
</tr>
<tr>
<td>Anemia‡</td>
<td>17</td>
<td>36</td>
</tr>
<tr>
<td>Anorectal events</td>
<td>7</td>
<td>29</td>
</tr>
</tbody>
</table>

*Pooled results from TVR arms.
†Anemia was managed with RBV dose modification; epoetin alfa was not permitted.

- In most subjects, rash was mild to moderate
  - Severe rash in 4%; discontinuation due to rash in 6% of subjects

Improved Dosing With Current Therapy: TVR BID Noninferior to TID in Tx-Naive GT1

- Adverse events similar between treatment arms
- No differences in efficacy with 2 strategies in patients with more advanced disease

Limited Efficacy With Telaprevir and Boceprevir in Some Patient Groups

*Pooled TVR arms of REALIZE trial.

Likelihood of SVR With Current Therapies Related to IFN Responsiveness

HCV RNA Reduction After 4-Wk Lead-in

- < 1 log decline
- ≥ 1 log decline


*Pooled data from RGT and arm 3.

ANEMIA AND RIBAVIRIN DOSE
SVR Rates With RBV Dose Reduction or Erythropoietin for Anemia Management

• Similar SVR rates (71%) with both strategies\(^1,2\)
  – Similar SVR rates regardless of timing of anemia management, number of RBV dose reductions, or lowest RBV dose received
  – Lower SVR rates if < 50% of per protocol total RBV dose received
• Higher SVR rate if anemia management initiated with undetectable HCV RNA\(^2\)

No Association Between Degree of Hb Decline and SVR in Pts Developing Anemia

INVESTIGATIONAL AGENTS
HCV DAA Agents in Late Stage Development

<table>
<thead>
<tr>
<th>NS3/4A Pis</th>
<th>NS5A replication complex inh</th>
<th>Nucleotide NS5B poly inh</th>
<th>Non-nuc NS5B Pol inh</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABT-450/r</td>
<td>ABT-267</td>
<td>Sofosbuvir</td>
<td>ABT-333</td>
</tr>
<tr>
<td>Asunaprevir</td>
<td>Daclatasvir</td>
<td>Mericitabine</td>
<td></td>
</tr>
<tr>
<td>Faldaprevir</td>
<td>GS5885</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simeprevir</td>
<td></td>
<td></td>
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</table>
DAAS WITH INTERFERON AND RIBAVIRIN
Safety and Efficacy of Simeprevir QD + PegIFN/RBV in GT1 Treatment-Naive Pts

• Addition of simeprevir (TMC435) to pegIFN/RBV significantly improved SVR rates vs pegIFN/RBV alone at Wk 24

Safety and Efficacy of PegIFN lambda-1a vs PegIFN alfa-2a in GT 2/3 Tx-Naive Pts

- EMERGE study: each group received pegIFN + RBV for 24 wks

![Bar chart showing SVR24 (%) for different dosages of PegIFN lambda-1a and PegIFN alfa-2a.]

2 DAAs + PegIFN/RBV in GT1 Previous Null Responders

Daclatasvir (NS5A) + Asunaprevir (PI) + PegIFN/RBV x 24 Wks

Danoprevir/RTV (PI) + Mericitabine (Nuc) + PegIFN/RBV x 24 Wks

<table>
<thead>
<tr>
<th></th>
<th>SVR24 (%)</th>
<th>SVR12 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daclatasvir</td>
<td>90[1]</td>
<td>62/74</td>
</tr>
<tr>
<td>Asunaprevir</td>
<td>93*[2]</td>
<td>84</td>
</tr>
</tbody>
</table>

*Asunaprevir QD and BID combined.

INTERFERON SPARING REGIMENS
Daclatasvir Plus Sofosbuvir in GT1 Treatment-Naive Patients

- Pts with poor prognostic indicators: GT1a (73%), male (52%), black (20%), *IL28B* CT/TT (64%); advanced liver disease: 14%

- Mean HCV RNA: 6.6 logs

- No impact of RBV on viral response

<table>
<thead>
<tr>
<th>Treatment-naive, noncirrhotic patients</th>
<th>Sofosbuvir</th>
<th>Daclatasvir + Sofosbuvir</th>
<th>Daclatasvir + Sofosbuvir</th>
<th>Daclatasvir + Sofosbuvir + RBV</th>
</tr>
</thead>
<tbody>
<tr>
<td>GT1a or 1b (n = 44)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GT2 or 3 (n = 44)</td>
<td></td>
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</tbody>
</table>

Sofosbuvir dosed 400 mg QD. Daclatasvir dosed 60 mg QD. RBV dosed by body weight for GT1 patients (1000-1200 mg/day); 800 mg/day for GT2/3 patients.

ELECTRON: Sofosbuvir ± GS-5885 + RBV in Naive and Previous Null Responders

- Pts with poor prognostic indicators: GT1a (86%), male (54%), nonwhite (12%), *IL28B* CT/TT (68%)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>SVR4</th>
<th>SVR12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sofosbuvir + RBV 1000/1200 mg (GT1; naive) (n = 25)</td>
<td>84</td>
<td></td>
</tr>
<tr>
<td>Sofosbuvir + RBV 1000/1200 mg (GT1; null responders) (n = 10)</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Sofosbuvir + GS-5885 + RBV 1000/1200 mg (GT1; naive) (n = 25)</td>
<td>100</td>
<td>N/A</td>
</tr>
<tr>
<td>Sofosbuvir + GS-5885 + RBV 1000/1200 mg (GT1; nulls) (n = 9)</td>
<td>100*</td>
<td>N/A</td>
</tr>
</tbody>
</table>

*Data reported for 3 pts only. Data collection ongoing.*

IFN-Free Therapy in Previous Null Responders

Daclatasvir (NS5A) + Asunaprevir (PI) x 24 Wks (IFN Free)

US Study
9/11 GT1a
Japanese Study
10/10 GT1b
US 2012
GT1b only

IFN-Free Regimens With ABT-450/RTV, ABT-267, ABT-333, and RBV

Cohort 1: Treatment-naive pts, GT1 HCV

- ABT-450/RTV 150/100 mg + ABT-267 + ABT-333 + RBV (n = 80)
- ABT-450/RTV 100/100 mg + ABT-267 + ABT-333 + RBV
- ABT-450/RTV 150/100 mg + ABT-267 + ABT-333 + RBV
- ABT-450/RTV 100/100 mg + ABT-267 + ABT-333 + RBV

SVR12, %

- 87.5
- 97.5
- NR

Cohort 2: Tx-exp’d pts, GT1 HCV, with previous null response

- ABT-450/RTV 100/100 mg + ABT-267 + ABT-333 + RBV (n = 80)
- ABT-450/RTV 150/100 mg + ABT-267 + ABT-333 + RBV
- ABT-450/RTV 100/100 mg + ABT-267 + ABT-333 + RBV
- ABT-450/RTV 150/100 mg + ABT-267 + ABT-333 + RBV

- 93.3
- NR

INFLUENCE OF IL28B GENOTYPE
### SPRINT-2: Influence of Baseline Patient and Virus Factors on SVR With BOC

<table>
<thead>
<tr>
<th>Genotype</th>
<th>HCV RNA (IU/mL)</th>
<th>Fibrosis</th>
<th>IL28B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤ 800,000</td>
<td>&gt; 800,000</td>
<td></td>
</tr>
<tr>
<td>1b</td>
<td>70/66</td>
<td>63/59</td>
<td>85/76</td>
</tr>
<tr>
<td>1a</td>
<td>85/76</td>
<td>67/67</td>
<td>41/52</td>
</tr>
</tbody>
</table>

- **BOC + pegIFN-α2b/RBV 48 wks**
- **BOC + pegIFN-α2b/RBV RGT**

<table>
<thead>
<tr>
<th>Genotype</th>
<th>n/ N =</th>
</tr>
</thead>
<tbody>
<tr>
<td>1b</td>
<td>93/133</td>
</tr>
<tr>
<td>1a</td>
<td>89/134</td>
</tr>
<tr>
<td></td>
<td>118/187</td>
</tr>
<tr>
<td></td>
<td>63/106</td>
</tr>
<tr>
<td></td>
<td>63/179</td>
</tr>
</tbody>
</table>

ADVANCE: Influence of Baseline Patient and Virus Factors on SVR With TVR

*IL28B* testing was in whites only.

**IL28B Genotype Predicts Likelihood of Eligibility for Shortened Therapy**

**SPRINT-2: BOC + PegIFN-α2b/RBV** [1]

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Eligibility for RGT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CC</td>
<td>89</td>
</tr>
<tr>
<td>CT/TT</td>
<td>52</td>
</tr>
</tbody>
</table>

| n/ N = | 117/132 | 158/304 |

**ADVANCE: T12 + PegIFN-α2a/RBV** [2]

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Eligibility for RGT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CC</td>
<td>78</td>
</tr>
<tr>
<td>CT</td>
<td>57</td>
</tr>
<tr>
<td>TT</td>
<td>45</td>
</tr>
</tbody>
</table>

| n/ N = | 39/50 | 39/68 | 10/22 |

*IL28B* testing in ADVANCE was in whites only.

Summary

• HCV therapy for monoinfected and HIV-coinfected patients has revolutionized therapy
• Data regarding drug efficacy, toxicity and drug-drug interactions is helping to refine the role of the HCV PIs in treatment of coinfected patients
• New regimens including RBV and IFN sparing regimens create new questions about timing of treatment