New Hepatitis C Wonder Drugs: Who Is Worth the Cost?

"Riddle me this, riddle me that, your HCV treatment, who will pay for that?"

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October 17, 2014

Objectives

1. Review the epidemiology, pathophysiology, and disease progression of Hepatitis C Virus (HCV)
2. Discuss the evolution of pharmacotherapeutic options for the treatment of HCV and the genotype variance
3. Evaluate the current literature for treating cirrhotic and HIV co-infected patients with HCV
4. Examine the criteria for prioritization of treatment set forth by third party insurers along with the controversy surrounding treatment onset
BACKGROUND

I. Hepatitis C Virus
   A. Definition and epidemiology\textsuperscript{1-3}
      i. Small single-stranded RNA virus that is spread through the blood from person-to-person
      ii. Discovered in 1989
      iii. Patients with increased risk for infection
          a. Men who have sex with men with high-risk sexual practices
          b. Active drug injection users
          c. Incarcerated persons
          d. Persons on long-term hemodialysis
      iv. Chronically affects approximately 185 million people worldwide and 3.2 million people in the United States
   B. Symptoms\textsuperscript{1,5}
      i. Clinical manifestations
         a. Asymptomatic
         b. Fatigue and malaise
         c. Increased alanine aminotransferase (ALT)
         d. Detectable circulating HCV virus
      ii. Extrahepatic manifestations
         a. Diabetes mellitus
         b. Rheumatoid arthritis
         c. Keratoconjunctivitis sicca
         d. Immunologic abnormalities
            1. Mixed cryoglobulinemia
            2. Membranoproliferative glomerulonephritis
            3. Nephrotic syndrome
            4. Porphyria cutanea tarda
   C. Untreated Disease\textsuperscript{1,2}
      i. Spontaneous viral clearance
      ii. Development of chronic HCV – typically associated with persisting or fluctuating ALT levels in \textgreater 70\% of cases
         a. Cirrhosis
         b. Hepatocellular carcinoma (HCC)
         c. Liver transplant – the primary reason for liver transplantation in the US
   D. Disease progression\textsuperscript{1,2}

Figure 1 - Progression of Untreated HCV

100 patients acutely infected
80 progress to chronic disease
52 slowly progress
16 develop cirrhosis
4 progress to liver failure, cancer, transplant or death
E. Definitions (Appendix 1)\textsuperscript{1, 6-8}

i. Fibrosis: first stage of scar tissue development that occurs from liver damage
ii. Cirrhosis: development of scar tissue that takes over most of the liver
iii. Genotype: various genetic polymorphism that exist within HCV to include subtypes within the genotype
   a. Genotypes 1-6
   b. Most common in the US: 1 (70%), 2, and 3
iv. HCV RNA: viral burden of circulating HCV; viral load
v. Sustained virologic response (SVR): time point after completion of treatment whereby the virus is suppressed
vi. Methods of determining fibrosis
   a. Metavir scale: scoring system utilized to quantify the degree of fibrosis and inflammation present at liver biopsy
      1. F0: No fibrosis
      2. F1: Portal fibrosis without septa
      3. F2: Portal fibrosis with a few septa
      4. F3: Numerous septa without cirrhosis
      5. F4: Cirrhosis

Figure 2 - Metavir Score

b. Fibrosis-4 Score (FIB-4)
   1. Scoring system that estimates the amount of liver scarring
   2. FIB-4 \( >3.25 \) correlates to 97% specificity and positive predictive value of 65% fibrosis

Figure 3 – FIB-4 Equation

\[
\text{FIB-4} = \frac{\text{Age (years)} \times \text{AST (U/L)}}{\text{Platelet count (}10^9/\text{L}) \times \sqrt{\text{ALT (U/L)}}}
\]
c. AST-to-Platelet Ratio Index (APRI)
   1. Scoring system that aids in the staging of liver cirrhosis
   2. Score >1 correlates to 76% sensitivity and 72% specificity for predicting cirrhosis

**Figure 4 – APRI Equation**

\[
\text{APRI} = \frac{\text{ULN AST (U/L)}}{\text{Platelet count (10^9/L)}} \times 100
\]

vii. Virologic response

**Figure 5 - Virologic Response**

F. Treatment Goals\(^1,2\)
   i. Main goal is eradication of the virus
      a. Measured by obtaining an undetectable HCV RNA viral load during treatment
      b. SVR 24 versus SVR 12
         1. SVR 24: endpoint for older therapies containing pegylated interferon (pegIFN) and ribavirin (RBV)
         2. SVR 12: endpoint for newer treatments
         3. Most patients will relapse within the first 12 weeks
   ii. Benefit of attaining SVR
      a. Histologic improvement: seen on imaging
      b. Improved laboratory values: platelet production, liver function tests
      c. Decreasing risk for HCC, liver failure, and need for transplant
      d. Patients have increased overall survival and improved quality of life

G. Predictors of Poor Response\(^1,2\)

**Table 1 – Predictors of poor response**

<table>
<thead>
<tr>
<th>Genotype 1</th>
<th>African American/Black race</th>
<th>Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV Co-infection</td>
<td>Prior null/poor responders</td>
<td>High HCV RNA level</td>
</tr>
<tr>
<td>Age &gt;40 years old</td>
<td>Heavier body weight</td>
<td>IL28B CT or TT</td>
</tr>
</tbody>
</table>

i. Genotype 1 historically much lower SVR 24 rates with traditional therapies
ii. HIV co-infection and cirrhosis had very poor SVR 24 rates
iii. Patients not responding or those with vastly poor response to pegIFN and RBV
I. Initial Therapy\textsuperscript{9-11}
   A. Interferon as monotherapy
      i. SVR rate extremely low
         a. Standard IFN – 3-19%
         b. pegIFN – 30%
      ii. 48 weeks of therapy
      iii. Multiple injections per week versus once-weekly injections
   B. pegIFN plus RBV
      i. PegIFN allowed for weekly injections due to slower release and excretion from the body
      ii. Dosing
         a. pegIFN: 180 mcg injected weekly
         b. RBV: 1000 mg (<75 kg); 1200 mg (>75 kg)
      iii. SVR 24 rates
         a. Improved for genotypes 2 and 3: 24 weeks of therapy
         b. Lower rates for genotype 1 and 4: at least 48 weeks of therapy
      iv. Additive toxicities with ribavirin

II. Barriers to Historical Therapy\textsuperscript{9-11}
   A. IFN/pegIFN
      i. Flu-like symptoms, depression
      ii. Significant leukopenia, thrombocytopenia
      iii. Injections multiple times per week
      iv. SVR24: 3-19% standard IFN and 10-39% with pegIFN
   B. RBV
      i. Significant anemia
      ii. Multiple doses per day with multiple tablets
      iii. Weight-based dosing
      iv. SVR24: up to 42%

III. First Directly-Acting Agents (DAA)
   A. Boceprevir (BOC) and telepravir (TVR)\textsuperscript{2,12-15}
      a. NS3/4A protease inhibitors
      b. Complicated regimens
1. Must be taken every 8 hours
2. Significant pill burden: 2-4 pills at each dose
   c. Drug interactions: very strong CYP 3A4 inhibitors
   d. Significant additive toxicities associated with all three drugs – anemia, neutropenia, birth defects, and hypersensitivity reactions
   e. Cross resistance occurred between BOC and TVR
   f. Place in therapy: American Association for the Study of Liver Diseases/Infectious Diseases Society of America/International Antiviral Society-USA (AASLD/IDSA/IAS-USA) guidelines no longer recommend using these agents

B. Summary of trials (Appendix 2)

Figure 7 - Treatment - Historical Agents\textsuperscript{14,15}

![Percentage of Patients Achieving SVR](image)

**CURRENT THERAPY**

I. Next Generation of DAAAs
   A. Simeprevir (SIM)\textsuperscript{16}
      i. HCV NS3/4A protease inhibitor
      ii. FDA approved for use in combination with RBV and pegIFN for GT1
      iii. 150 mg once daily administration but must be taken with food
      iv. Patients must be cautioned to avoid/limit sun exposure
      v. Increased the rate of overall SVR; however, there was significant cross-resistance to BOC and TVR
      vi. GT1a with Q80K polymorphism
         a. Decreased SVR
         b. Testing required prior to initiating therapy
      vii. Summary of trials (Appendix 2)
B. Sofosbuvir (SOF)\textsuperscript{19}
   
   i. Novel agent: NS5B polymerase inhibitor
   
   ii. Activity against GT 1-4, HCC, awaiting liver transplant, and HIV/HCV co-infection
   
   iii. Can be used in patients who have failed previous therapy with BOC or TVR
   
   iv. Dosing: 400 mg tablet once daily taken with or without food
      
      a. In combination with pegIFN/RBV
      
      b. Co-formulated with ledipasvir (LDV)
   
   v. Summary of trials (Appendix 2)

**Figure 9 - Treatment with SOF**

<table>
<thead>
<tr>
<th>Percentage of Patients Achieving SVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFN</td>
</tr>
<tr>
<td>-----</td>
</tr>
<tr>
<td>11</td>
</tr>
</tbody>
</table>

II. Genotypes 2 and 3 (Appendix 2)\textsuperscript{9,20,21}

A. Historically had higher rates of SVR with the traditional treatments

B. SVR rates with SOF/RBV
   
   i. GT2: >90% when treated for 12 weeks
   
   ii. GT3: 93% when treated for 24 weeks

C. pegIFN/RBV: SVR of 82% when treated with pegIFN/RBV for 48 weeks

D. Longer durations of therapy may be required to improve SVR rates for GT3
SPECIAL POPULATIONS

I. Treatment Experienced (Appendix 2)\textsuperscript{22-24}
   A. Historically more difficult to treat
      i. Patients have already failed a prior regimen
      ii. pegIFN and RBV non-responders are less likely to have a response with BOC/TVR
   B. Consideration of therapy failure
      i. Intolerance to pegIFN or RBV due to adverse drug reactions $\rightarrow$ no pegIFN-free regimens
      ii. Treatment failure
      iii. Relapse of the virus
   C. Patients achieving SVR
      i. Continue to see increase in percentage of patients achieving SVR
      ii. Until the addition of SOF, patients still fared worse than the treatment-naïve patients
      iii. Less separation of SVR rates in those with IL28B CT or TT genotypes – no longer considered as much of a hindrance for achieving treatment cure

Figure 10 - Treatment Experienced

![Percentage of Patients Achieving SVR](image)

Table 2 - IL28B SVR Rates

<table>
<thead>
<tr>
<th></th>
<th>Overall SVR (%)</th>
<th>IL28 SVR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RESPOND2 BOC44/PR48</td>
<td>63</td>
<td>CC 78</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CT 67</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TT 66</td>
</tr>
<tr>
<td>REALIZE TVR12/PR48</td>
<td>65</td>
<td>CC 79</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CT 60</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TT 61</td>
</tr>
<tr>
<td>PROMISE SIM12/PR24/48</td>
<td>79</td>
<td>CC 89</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CT 78</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TT 65</td>
</tr>
</tbody>
</table>
D. Addition of SOF\textsuperscript{20} 
   i. Dramatically increased SVR rates in the treatment experienced 
   ii. Option for a pegIFN-free regimen with SOF/SIM with or without RBV 

**Figure 11 - Treatment Experienced - SOF**

![Bar chart showing SVR rates](image)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>pegIFN/RBV + BOC</td>
<td>63</td>
</tr>
<tr>
<td>pegIFN/RBV + TVR</td>
<td>65</td>
</tr>
<tr>
<td>pegIFN/RBV + SIM</td>
<td>79</td>
</tr>
<tr>
<td>SOF/SIM +/- RBV x24 wks</td>
<td>92.9</td>
</tr>
<tr>
<td>RBV SOF/SIM +/- RBV x12 wks</td>
<td>95</td>
</tr>
</tbody>
</table>

II. Cirrhotic Patients (Appendix 2)\textsuperscript{15,15,17,18,20} 
   A. Historically dismal rates of SVR with some improvement with the addition of the DAAs 

**Figure 12 - Cirrhotic Patients**

![Bar chart showing SVR rates](image)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>pegIFN/RBV + BOC</td>
<td>47</td>
</tr>
<tr>
<td>pegIFN/RBV + TVR</td>
<td>62</td>
</tr>
<tr>
<td>pegIFN/RBV + SIM</td>
<td>68</td>
</tr>
<tr>
<td>pegIFN/RBV + SOF</td>
<td>80</td>
</tr>
</tbody>
</table>

B. All Oral Regimen – SOF/SIM +/- RBV: Lawitz, et al – COSMOS\textsuperscript{26} 
   i. First all oral regimen without the use of pegIFN 
   ii. Study design 
      a. Randomized, open-label trial 
      b. Conducted in the US from November 2011 through January 2014 
   iii. Inclusion criteria 
      a. >18 years old 
      b. Chronic HCV GT1: previous non-responders to pegIFN + RBV 
      c. HIV negative
iv. Patient populations
   a. Cohort 1: Noncirrhotics
   b. Cohort 2: Cirrhotics
      1. Group 1: SIM/SOF/RBV x24 weeks; n=30
      2. Group 2: SIM/SOF x24 weeks; n=16
      3. Group 3: SIM/SOF/RBV x12 weeks; n=27
      4. Group 4: SIM/SOF x12 weeks; n=14

Figure 13 - All Oral Regimen - SOF/SIM/RBV

<table>
<thead>
<tr>
<th>Percentage of Patients Achieving SVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOF/SIM + RBV x24 wks</td>
</tr>
<tr>
<td>SOF/SIM x24 wks</td>
</tr>
<tr>
<td>SOF/SIM + RBV x12 wks</td>
</tr>
<tr>
<td>SOF/SIM x12 wks</td>
</tr>
<tr>
<td>Overall</td>
</tr>
</tbody>
</table>

- Noncirrhotic
- Cirrhotic

c. Q80K Subpopulation: with the addition of SOF, the presence of the Q80K polymorphism did not affect SVR even when treated with SIM

d. Relapses
   1. Six total relapsed – noncompliant with the treatment
   2. Five of the six developed resistance to SIM

e. No virologic breakthrough or treatment failures

f. Adverse events (Table 3)
   1. High percentage adverse events – questionable relevance
   2. Clinically important increase in anemia associated with RBV

v. Conclusions
   a. Combination of SIM/SOF in HCV GT1 resulted in high rates of SVR in cirrhotic and previous non-responders
   b. The addition of RBV or treating for 24 weeks did NOT improve SVR
   c. More anemia in patients with RBV

Table 3 - All Oral Regimen - ADRs

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Adverse Event</td>
<td>51 (94%)</td>
<td>29 (94%)</td>
<td>46 (85%)</td>
<td>20 (71%)</td>
<td>146 (87%)</td>
</tr>
<tr>
<td>Death</td>
<td>1 (2%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Most Common</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased bili</td>
<td>6 (11%)</td>
<td>1 (3%)</td>
<td>5 (9%)</td>
<td>0</td>
<td>12 (7%)</td>
</tr>
<tr>
<td>Rash</td>
<td>10 (19%)</td>
<td>5 (16%)</td>
<td>11 (20%)</td>
<td>3 (11%)</td>
<td>29 (17%)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>9 (17%)</td>
<td>1 (3%)</td>
<td>5 (9%)</td>
<td>4 (14%)</td>
<td>19 (11%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>0</td>
<td>1 (3%)</td>
<td>0</td>
<td>0</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>16 (30%)</td>
<td>1 (3%)</td>
<td>7 (13%)</td>
<td>0</td>
<td>24 (14%)</td>
</tr>
<tr>
<td>Photosensitivity</td>
<td>2 (4%)</td>
<td>2 (7%)</td>
<td>3 (6%)</td>
<td>2 (7%)</td>
<td>9 (5%)</td>
</tr>
</tbody>
</table>
III. **HIV Co-Infected**\(^{27,28}\)  
A. Why do we care?  
   i. Up to 7 million patients are co-infected with HIV and HCV  
   ii. Chronic HCV/hepatic decompensation is accelerated (Figure 5)  
      a. More rapid progression to liver fibrosis and cirrhosis  
      b. Increased rates of HCC and mortality  
   iii. In patients previously treated with BOC or TVR  
      a. SVR of 62-70%  
      b. Drug interactions with HIV antiretrovirals (ARV) and the HCV protease inhibitors  
      c. Complex dosing with the HCV agents added to the already potentially complex HIV regimens  
      d. Additive toxicities with HCV regimens including neutropenia and anemia  

Figure 14 - HCV/HIV Hepatic Decompensation

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   i. Study design: multicenter, open-label, nonrandomized, uncontrolled phase III trial  
   ii. Inclusion criteria  
      a. >18 years old and BMI >18 kg/m2 with HIV  
      b. If on HIV treatment, patients had to be on a stable HIV regimen  
      c. If untreated, CD4 count must be above 500  
   iii. Cohorts  
      a. Treatment naïve, GT1: SOF/RBV x24 weeks, n=114  
      b. Treatment naïve, GT2, 3: SOF/RBV x12 weeks, n=68  
      c. Previously treated, GT2, 3: SOF/RBV x24 weeks, n=41
iv. Conclusions
   a. GT1 SVR rates were similar to previous studies with mono-infected patients
   b. This regimen was better tolerated than those containing pegIFN
   c. SOF is not metabolized by CYP450 system, there were fewer drug interactions
   d. Simpler regimen than with previous agents – decreased pill burden
   e. Higher SVR seen in GT2; GT3 had higher SVR when treated for 24 weeks
   f. HIV virologic relapse occurred in two patients - ARV noncompliance

IV. Summary of Current Therapy
A. DAAs have drastically improved the cure rates for chronic HCV
B. Older agents – pegIFN, RBV, TVR, BOC
   i. More difficult regimens requiring every eight hour dosing
   ii. Increased drug interactions and adverse drug reactions
C. Newer agents – SIM, SOF
   i. Better tolerability and simpler dosing schemes
   ii. Improved overall SVR for GT1
      a. Includes treatment experienced, cirrhotic, and HCV/HIV co-infected patients
      b. GT2 and 3 now being considered the more difficult patients to treat
I. Payment Controversy
   A. Medication cost
      i. United States
         a. SIM: $750 per pill; $63,000 per 12-week treatment
         b. SOF: $1,000 per tablet; $84,000 per 12-week treatment
         c. LDV/SOF: $1,250 per tablet; $94,500 per 12-week treatment
      ii. Rest of the world
         a. Gilead in contract with underdeveloped countries
         b. Pricing will be much lower than that in the US - $1 per tablet
         c. Rationale is that the infected population is much higher and that they will be treated for a longer duration of time due to the most prevalent GT

B. AASLD/IDSA/IAS-USA Guidelines
   i. Highest priority
      a. Advanced fibrosis – Metavir F3
      b. Compensated cirrhosis – Metavir F4
      c. Organ transplant
      d. Type 2 or 3 mixed cryoglobulinemia with end-organ manifestations
      e. Proteinuria, nephrotic syndrome, or membranoproliferative glomerulonephritis

   Table 4 - AASLD/IDSA/IAS-USA Treatment Recommendations

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Recommended</th>
<th>Alternative</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>IFN eligible: SOF + pegIFN/RBV x 12 weeks</td>
<td>IFN ineligible: SIM x 12 weeks + pegIFN/RBV x 24 weeks</td>
</tr>
<tr>
<td></td>
<td>IFN ineligible: SOF + SMV +/- RBV x 12 weeks</td>
<td>IFN ineligible: SOF + RBV x 24 weeks</td>
</tr>
<tr>
<td>2</td>
<td>SOF + RBV x 12 weeks</td>
<td>None</td>
</tr>
<tr>
<td>3</td>
<td>SOF + RBV x 24 weeks</td>
<td>SOF + pegIFN/RBV x 12 weeks</td>
</tr>
</tbody>
</table>

   ii. Who is considered pegIFN ineligible
      a. Intolerance or hypersensitivity to IFN
      b. Autoimmune disorder
      c. Decompensated hepatic disease
      d. History of depression
      e. Neutrophils <1500 IU/µL, platelets <90 IU/µL, hemoglobin <10 g/dL
      f. History of preexisting cardiac disease
      g. HCC

C. Third Party Payers
   i. Caremark – Sofosbuvir
      a. Chronic Hepatitis C AND
         1. Genotype 1
         2. Compensated liver disease
         3. Moderate- to- severe cirrhosis (Metavir 3-4)
         4. Absence of significant or unstable cardiac disease
         5. Not had a liver transplant OR treatment naïve post transplant
         6. Viral loads
            i. Drawn at 4 and 6 weeks
            ii. Discontinue if HCV RNA levels declined <2 log10 IU/mL
         7. AND Treatment naïve and not able to receive IFN OR IFN ineligible
ii. VA
   a. Consider treating
      1. Development of decompensated cirrhosis
      2. Dying from liver or liver-related disease
      3. Prolonging graft survival in liver transplant
      4. HCC awaiting transplant
   b. Consider waiting
      1. Mild liver disease (Metavir F0-2)
      2. IFN intolerance

D. Summary
   i. Treatment considerations are made based on the severity of the illness
   ii. Guidelines are constantly being updated
      a. Serve as a guide for third party payers to differentiate who should be treated and who should wait
         Considers the data for regimens and drugs that are not currently available as rationale for awaiting therapy

FUTURE DIRECTIONS

I. What’s on the Horizon
   A. Combination products
      i. Most contain two active agents against HCV
      ii. Co-formulated with pharmacologic inhibitors
   B. SVR response rates are nearing or reaching 100%
   C. Clinicaltrials.gov – over 1500 trials in progress or near completion
   II. Ledipasvir/Sofosbuvir (LDV/SOF)32-35
      A. Product information
         i. FDA approval on October 10, 2014
         ii. LDV: new NS5A inhibitor that has activity against HCV GT1a/1b
         iii. Only available as a co-formulation with SOF
         iv. Once-daily dosing
      B. LDV/SOF Combination
         i. Approval based off of three phase III, randomized, open-label studies

Table 5 - LDV/SOF Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Regimen</th>
<th>SVR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ION-1 n=865</td>
<td>Treatment naive GT1 +/- Cirrhosis</td>
<td>LDV/SOF x12 wks</td>
<td>99</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LDV/SOF + RBV x12/24 wks</td>
<td>97</td>
</tr>
<tr>
<td>ION-2 n=440</td>
<td>Treatment experienced GT1 +/- Cirrhosis</td>
<td>LDV/SOF x12/24 wks</td>
<td>94/99</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LDV/SOF + RBV x12/24 wks</td>
<td>96/99</td>
</tr>
<tr>
<td>ION-3 n=431</td>
<td>Treatment naive GT1 Without Cirrhosis</td>
<td>LDV/SOF x8/12 wks</td>
<td>94/96</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LDV/SOF + RBV x8 wks</td>
<td>93</td>
</tr>
</tbody>
</table>
ii. First study looking at SVR with an 8-week treatment regimen
   a. Relapses
      1. 5% in the 8-week group compared to 1% in the 12-week group
      2. Associated with HCV RNA > 6 million IU/mL – 10% relapse rate when this was the case; otherwise, only 2% relapse rate for either group
   b. FDA approval for 12-week regimen only

III. Upcoming Agents
A. Various agents in clinical trials and some with anticipation of FDA approval in 2015
B. Agents
   i. NS5A inhibitors: daclatasvir, ombitasvir, dasabuvir
   ii. NS3 protease inhibitors: asunaprevir, ABT-450/r

IV. Take-Home Messages
A. HCV is a chronic disease that takes many years to see severe liver disease
B. Treatment has revolutionized over the past decade to improved SVR
C. Novel oral agents: decreased time on therapy, adverse drug reactions, and interactions; improved SVR
D. Current focus: HCV genotype 1 patients, patients progressing to decompensated liver failure
E. Future directions include improving SVR for treatment naïve and GT2 and 3

NOW WHAT?

I. Why is prioritization of treatment even a question?
   A. Drug cost must come into play when making treatment decisions for HCV

Table 6 - Cost for Therapy

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cost for 12-week Course (USD)</th>
</tr>
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<tbody>
<tr>
<td>pegIFN</td>
<td>$9,600</td>
</tr>
<tr>
<td>RBV</td>
<td>$3,900</td>
</tr>
<tr>
<td>SOF</td>
<td>$84,000</td>
</tr>
<tr>
<td><strong>Total:</strong></td>
<td>$97,500</td>
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</tbody>
</table>

i. Newer regimens are estimated to be at a higher cost – LDV/SOF = $95,000 for 12-weeks
ii. Many Medicare patients are required to pay a percentage of their drug costs
   a. Assume that a Medicare patient is expected to 20% of drug cost
   b. $97,500 * 0.2 = $19,500 out-of-pocket cost!

B. Keep in mind, for most patients it will take several decades to see the cost savings for the prevention of progression to liver failure

II. Final Recommendations
A. Treat now – pegIFN/RBV/SOF
   i. Patients who are progressing rapidly to liver decompensation regardless of GT
   ii. Failed previous therapy, non-responders, or relapsers
   iii. Chronic infection with cirrhosis
   iv. HIV/HCV co-infected patients
   v. Consider LDV/SOF for those who are pegIFN ineligible

B. Wait for treatment – newer agents
   i. Treatment naïve patients
   ii. Those with less evidence of fibrosis/cirrhosis or extrahepatic symptoms
   iii. Realize that the payoff for treatment will not be seen for some time
REFERENCES

11. Copegus (ribavirin) [prescribing information]. South San Francisco, CA: Genetech USA, Inc; 2013.
16. Olysio (simeprevir) [prescribing information]. Latina, Italy: Jansen Therapeutics; 2014.


32. Harvoni (ledipasvir/sofosbuvir) [prescribing information]. Foster City, CA; Gilead Sciences, Inc; 2014.


### APPENDIX 1

**Definitions**

**Fibrosis:** first stage of scar tissue development that occurs from liver damage

**Cirrhosis:** development of scar tissue that takes over most of the liver

**Genotype:** various genetic polymorphism that exist within HCV to include subtypes within the genotype

**HCV RNA:** viral burden of circulating HCV; viral load

**Sustained virologic response (SVR):** maintained suppression of virus measured at some time point after completion of therapy

**Metavir scale:** scoring system that is utilized to quantify the degree of fibrosis and inflammation that is present at liver biopsy (F0-F4)

**Fibrosis-4 Score (FIB-4):** scoring system that estimates the amount of liver scarring

**AST-to-Platelet Ratio Index (APRI):** scoring system that aids in the staging of liver cirrhosis

**IL28B:** Interleukin 28B; nucleotide polymorphism that is associated with a level of response to therapy – historically pegylated interferon (pegIFN) ribavirin

**Q80K polymorphism:** genetic polymorphism associated with decreased response to simepravir

**Null response:** patients are treated without virologic suppression

**Partial response:** initial decrease in viral load without complete viral suppression

**Virologic breakthrough:** suppression of viral load with treatment then reactivation of the virus while on therapy

**Relapse:** recurrence of the virus after completion of therapy
<table>
<thead>
<tr>
<th>Boceprevir</th>
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<tbody>
<tr>
<td><strong>SPRINT-2</strong></td>
</tr>
<tr>
<td>- Phase 3, international, randomized, placebo-controlled study</td>
</tr>
<tr>
<td>- Assessed safety and efficacy of two treatment regimens → BOC added after lead-in period with pegIFN/RBV</td>
</tr>
<tr>
<td>- Treatment groups; n=368</td>
</tr>
<tr>
<td>- Inclusion criteria – no previous treatment for HCV, 18 years of age and older, weight 40-125 kg, chronic HCV GT1, HCV RNA &gt;10,000</td>
</tr>
<tr>
<td>- Exclusion criteria – liver disease of other cause, decompensated cirrhosis, renal insufficiency, HIV or HCB infection, pregnancy or current breast feeding, and active cancer</td>
</tr>
<tr>
<td>- Regimen – four-week lead-in period with pegIFN/RBV, followed by response-guided therapy including pegIFN/RBV + BOC for a total of 24 weeks; IF HCV RNA undetectable from week 8-24, treatment was considered complete; otherwise, treatment was continued with pegIFN/RBV + placebo at week 28-48</td>
</tr>
<tr>
<td>- Results – SVR 24</td>
</tr>
<tr>
<td>- Overall SVR: 65%</td>
</tr>
<tr>
<td>- IL28B: CC 81%; CT 68%; TT 57%</td>
</tr>
<tr>
<td>- Metavir: F0-2 67%; F3-4/Cirrhosis 47%</td>
</tr>
<tr>
<td>- Conclusions</td>
</tr>
<tr>
<td>- Significant increase in SVR with the addition of BOC</td>
</tr>
<tr>
<td>- Lead-in strategy used to lower HCV RNA levels, allowed for assessment of the relationship between IFN responsiveness and SVR after the addition of BOC</td>
</tr>
<tr>
<td>- Increased rates of anemia</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>RESPOND-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Phase 3, international, randomized, placebo-controlled study</td>
</tr>
<tr>
<td>- Compare the safety and efficacy of two therapeutic regimens of BOC in combination with pegIFN/RBV versus pegIFN/RBV in previously treated patients in GT1</td>
</tr>
<tr>
<td>- Treatment groups; n=162</td>
</tr>
<tr>
<td>- Inclusion criteria – interferon response (with at least 12 weeks of therapy)</td>
</tr>
<tr>
<td>- Exclusion criteria – HBV/HIV infection, any other cause of clinically-significant liver disease, decompensated liver disease, uncontrolled diabetes mellitus, severe psychiatric disorder and active substance abuse</td>
</tr>
<tr>
<td>- Four-week lead in with pegIFN and RBV; addition of BOC for 44 weeks of treatment</td>
</tr>
<tr>
<td>- Results – SVR 24</td>
</tr>
<tr>
<td>- Overall SVR: 63%</td>
</tr>
<tr>
<td>- Metavir: F0-2 68%; F3-4/Cirrhosis 56%</td>
</tr>
<tr>
<td>- Conclusions</td>
</tr>
<tr>
<td>- High rates of SVR in patients who have previously failed therapy</td>
</tr>
<tr>
<td>- Early response at 4 weeks guides shorter treatment (32 vs 44 weeks of therapy)</td>
</tr>
<tr>
<td>- High rates response among black patients and patients with advanced liver disease</td>
</tr>
<tr>
<td>- Rates of anemia were higher in the BOC group</td>
</tr>
</tbody>
</table>
### Telaprevir

**ADVANCE**

- International, phase 3, randomized, double-blind, placebo-controlled trial
- Evaluate the safety and efficacy of TVR-based therapy
- Treatment groups: n=363
  - Inclusion criteria – age 18-70 years old, HCV GT1 with evidence of chronic hepatitis (liver biopsy within one year), compensated liver disease
  - Exclusion criteria – HBV/HIV positivity, ANC <1500, platelets <90,000, and Hgb <12 or 13 for females, decompensated liver disease, liver disease from other causes, or HCC
  - TVR for 12 weeks in combination with pegIFN and ribavirin for 12 weeks if HCV RNA was undetectable at 4 and 12; otherwise, treatment continued for 36 weeks
- Results
  - Overall SVR: 75%
  - IL28B: CC 90%; CT 71%; TT 73%
  - Metavir: F0-2 78%; F3-4/Cirrhosis 62%
- Conclusions
  - Significant increase in SVR among patients with GT1 → TVR with pegIFN and RBV for 12 or 8 weeks followed by pegIFN/RBV for a total of 24-48 weeks
  - Decreased relapse in those patient with an initial lower viral load and treatment naïve when treated for 24 weeks with an undetectable viral load at weeks 4 and 12
  - Numerically higher SVR when TVR was given for 12 weeks instead of only for 8 weeks

### REALIZE

- Randomized, double-blind, placebo-controlled, phase 3 study
- Assessed the efficacy and safety of the addition of TVR to a regimen of pegIFN/RBV in patients with GT1 who did not have a sustained response to previous treatment
- Treatment groups: n=530
  - Inclusion criteria – GT1 without a sustained response to one previous course of pegIFN/RBV despite receiving at least 80% of the intended dose, detectable HCV RNA, liver biopsy within 18 months, ANC >1200, platelets >90,000, Hgb >12 or 13 for females
  - Exclusion criteria – decompensated liver disease, other causes of significant liver disease, or active cancer
  - TVR for 12 weeks in combination with pegIFN/RBV followed by pegIFN/RBV for 48 weeks
- Results – SVR 24
  - Overall SVR: 65%
  - Metavir: F0-2 71%; F3-4/Cirrhosis 47%
- Conclusions
  - Addition of TVR to pegIFN/RBV significantly increased SVR in HCV GT1 and in whom pegIFN/RBV had previously failed viral eradication
  - High success rates in patients with high viral load, severe liver fibrosis, and cirrhosis
  - Increased incidence of fatigue, GI side effects, rash, and pruritus
### Simeprevir

**QUEST 1 and 2**<sup>17-18</sup>

- Multi-center, randomized, double-blind, parallel-group, placebo-controlled, phase 3 trial
- Assessed efficacy, safety and tolerability of SIM in combo with pegIFN/RBV in treatment naïve
- Treatment groups; n=521
  - Inclusion criteria – 18 years and older, confirmed chronic HCV GT1, HCV RNA >10,000 IU/mL, and no history of prior treatment, cirrhosis if ultrasound in past six months showed no evidence of HCC
  - Exclusion – hepatic decompensation or any non-HCV-related liver disease, HIV or HBV co-infection
  - Control group – placebo plus pegIFN/RBV for 48 weeks
  - Treatment group – SIM plus pegIFN/RBV for 12 weeks followed by pegIFN/RBV for additional 12 or 36 weeks
- **Results** – SVR 12
  - Overall SVR: 80%
  - IL28B: CC 95%; CT 78%; TT 61%
  - Metavir: F0-2 84%; F3-4/Cirrhosis 68%
  - Baseline Q80K: 52-75% vs 85% without polymorphism
- **Conclusions**
  - High SVR when SIM used in combination with pegIFN

### PROMISE<sup>24</sup>

- Randomized, multi-center, double-blind, parallel-group, placebo-controlled, phase 3 trial
- Assessed the efficacy, safety, and tolerability of SIM with pegIFN/RBV for the treatment of GT1 in patients who have relapsed after previous IFN-based therapy
- Treatment groups; n=260
  - Inclusion criteria – at least 18 years old, GT1, HCV RNA > 10,000 IU/mL, relapsed after 24 weeks or more of IFN-based therapy, liver biopsy within 3 years showing consistent HCV (F3/4)
  - Exclusion criteria – hepatic decompensation, non-HCV-related liver disease, co-infection with HBV/HIV, or non-GT1 HCV, defined laboratory abnormalities, any other active disease, or pregnant/planning pregnancy
  - SIM for 12 weeks in combination with pegIFN/RBV for 24 or 48 weeks
- **Results**
  - Overall SVR: 79%
  - IL28B: CC 89%; CT 78%; TT 65%
  - Metavir: F0-2 82%; F3-4/Cirrhosis 73%
  - With Q80K: GT1a: 86%; GT1b: 85%
- **Conclusions**
  - Addition of SIM pegIFN/RBV substantially improved SVR in GT1 treatment-experienced patients irrespective of IL28B status, METAVIR score, or presence of baseline polymorphisms
  - Most patients met criteria for shorter 24-week treatment
  - Generally well tolerated with safety and tolerability similar to pegIFN/RBV alone
Sofosbuvir

**NEUTRINO**
- Single-group, open label study
- Evaluate the safety and efficacy of 12 weeks of therapy with SOF-containing regimens in treatment naïve in GT 1, 4, 5, or 6
- Treatment groups; n=327
  - Inclusion criteria – at least 18 years of age, HCV RNA $\geq$10,000 IU/mL, treatment naïve
  - SOF in combination with pegIFN and ribavirin for 12 weeks
- Results
  - Overall SVR: 90%
  - IL28B: CC 98%; TT 87%
  - Metavir: F0-2 92%; F3-4/Cirrhosis 81%
- Conclusions
  - High rates of response in the cirrhotics and the GT1a and 1b populations
  - High rates of SVR in difficult-to-treat: black patients, high baseline viral load, and IL28B CT/TT
  - Response-guided therapy not required since almost all patients had a response by week 4

**FISSION**
- Randomized, open-label, active-control study
- Evaluate the safety and efficacy of 12 weeks of therapy with SOF-containing regimens in treatment naïve in GT 2 or 3
- Treatment groups; n=256
  - Inclusion criteria – at least 18 years of age, HCV RNA $\geq$10,000 IU/mL, treatment naïve
  - SOF in combination with ribavirin for 12 weeks
- Results
  - Overall SVR: 67%
  - Genotype 2: 95%
    - Cirrhosis: 97%
    - No Cirrhosis: 83%
  - Genotype 3: 56%
    - Cirrhosis: 61%
    - No Cirrhosis: 34%
- Conclusions
  - No difference seen when pegIFN was added to the regimen and treated for 24 weeks
  - Higher SVR rates associated in historically difficult-to-treat: black patients, IL28B CT/TT
  - Decreased ADRs (influenza-like reactions and neuropsychiatric events) in non-pegIFN group
  - May have higher success rates in GT if peg/IFN is added or by extending the duration of therapy

**POSITRON**
- Randomized, multicenter, blinded, placebo-controlled study
- Evaluate the efficacy of SOF/RBV for 12 weeks in HCV GT2 or 3
- Treatment groups; n=207
  - Inclusion criteria: patients who previously discontinued IFN therapy due to unacceptable adverse events, concurrent medical condition precluding therapy
with IFN, or who had decided against therapy with IFN
  - SOF in combination with RBV for 12 weeks

- Results – SVR 12
  - Overall SVR: 78%; GT2: 93%; GT3: 68%
  - Cirrhosis: GT2: 94%; GT3: 21%

- Conclusions
  - High rates of SVR associated with GT2 in patients who are ineligible to receive pegIFN

<table>
<thead>
<tr>
<th>Fusion²⁵</th>
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<tbody>
<tr>
<td><strong>Randomized, multicenter, blinded, active-controlled study</strong></td>
</tr>
<tr>
<td><strong>Evaluate the efficacy of SOF/RBV for 12 or 16 weeks in HCV GT2 or 3 in those who did not have response to an IFN-based regimen</strong></td>
</tr>
<tr>
<td><strong>Treatment groups</strong></td>
</tr>
<tr>
<td>- Inclusion criteria – GT2 or 3</td>
</tr>
<tr>
<td>- Sofosbuvir in combination with RBV for 12 (n=103) or 16 (n=98) weeks</td>
</tr>
<tr>
<td><strong>Results – SVR 12</strong></td>
</tr>
<tr>
<td>- Overall SVR: 50%</td>
</tr>
<tr>
<td>- 12 weeks: GT2: 86%; GT3: 30%</td>
</tr>
<tr>
<td>- 16 weeks: GT2: 94%; GT3: 62%</td>
</tr>
<tr>
<td><strong>Conclusions</strong></td>
</tr>
<tr>
<td>- High response rates observed in patients with GT2</td>
</tr>
<tr>
<td>- Extending the duration to 16 weeks increased the SVR → longer therapy may be required to obtain more substantial viral suppression (reservoirs)</td>
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<thead>
<tr>
<th>Valence²¹</th>
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<tbody>
<tr>
<td><strong>Multicenter, unblinded, phase 3 trial</strong></td>
</tr>
<tr>
<td><strong>Assess the efficacy of 24 weeks of SOF/RBV therapy in patients with GT3</strong></td>
</tr>
<tr>
<td><strong>Confirm the previous findings that treatment with 12 weeks of therapy for GT2 is efficacious</strong></td>
</tr>
<tr>
<td><strong>Treatment groups</strong></td>
</tr>
<tr>
<td>- Inclusion criteria – at least 18 years of age, GT2 or 3, HCV RNA &gt;10,000 IU/mL</td>
</tr>
<tr>
<td>- Exclusion criteria – hepatic decompensation or any non-HCV-related liver disease, HIV/HBV co-infection</td>
</tr>
<tr>
<td>- Sofosbuvir in combination with ribavirin for 12 or 24 weeks</td>
</tr>
<tr>
<td><strong>Results – SVR 12</strong></td>
</tr>
<tr>
<td>- n=267</td>
</tr>
<tr>
<td>- Overall SVR: 78%</td>
</tr>
<tr>
<td>- Genotype 2: 93%; Cirrhosis: 92%; No Cirrhosis: 94%</td>
</tr>
<tr>
<td>- Genotype 3: 61%; Cirrhosis: 68%; No Cirrhosis: 21%</td>
</tr>
<tr>
<td>- n=250; Sofosbuvir in combination with ribavirin for 24 weeks</td>
</tr>
<tr>
<td>- Genotype 3: 85%; Cirrhosis: 93%; No Cirrhosis: 92%</td>
</tr>
<tr>
<td><strong>Conclusions</strong></td>
</tr>
<tr>
<td>- High rates of SVR with oral regimen of SOF/RBV for GT2 when treated for 12 weeks and GT3 when treated for 24 weeks</td>
</tr>
<tr>
<td>- Makes IFN-free regimen available for patients who are IFN ineligible</td>
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