Care of Patients Post SVR Including Those with Cirrhosis

Jennifer Price, MD, PhD
Associate Professor of Medicine
Division of Gastroenterology and Hepatology
University of California, San Francisco
Learning Objectives

Upon completion of this presentation, learners should be better able to:

- Recognize the impact of SVR on the natural history of HCV cirrhosis
- Explain guidelines for HCC surveillance in patients who have achieved SVR
- Identify factors associated with improvement in decompensated cirrhosis post-SVR

Faculty and Planning Committee Disclosures:

Please consult your program book or Conference App.

Off-Label Disclosure:

The following off-label/investigational uses will be discussed in this presentation: None
HCV Care Continues Past Achievement of SVR

- Diagnosis
- Linkage to care
- Treatment
- Cure

Persons at risk for infection:
- Counseling
- Harm reduction (injection and sex practices)
- Surveillance for reinfection

Persons with advanced fibrosis (stage 3/4)
- Counseling
- Harm reduction (alcohol and obesity)
- Surveillance for HCC

Robert S.

- 47 y/o man with HCV genotype 3a, treatment naive
- Compensated cirrhosis

Achieving SVR will reduce Robert’s risk of which of the following?

1. Hepatocellular carcinoma (HCC)
2. Liver-related mortality
3. All-cause mortality
4. All of the above
Natural History of Cirrhosis

Chronic liver disease → Compensated cirrhosis → Decompensated cirrhosis → Death

Clinical symptoms
- Ascites
- Variceal bleed
- Hepatic encephalopathy
- Jaundice

Chronic liver disease → Compensated cirrhosis → Decompensated cirrhosis → Death
Natural History of Cirrhosis

Clinical symptoms
- Ascites
- Variceal bleed
- Hepatic encephalopathy
- Jaundice

Chronic liver disease \(\rightarrow\) Compensated cirrhosis \(\rightarrow\) Decompensated cirrhosis \(\rightarrow\) Death

\(\downarrow\)

Hepatocellular carcinoma (HCC)
Management of Compensated Cirrhosis

1. Treat etiology of liver disease

HCV Cure Decreases Mortality and Liver-Related Complications

Multicenter Study of 530 patients with advanced fibrosis followed for a median 8.4 yrs; SVR 36% (interferon era)

Robert S.

- 47 y/o man with HCV genotype 3a, treatment naive
- Compensated cirrhosis

- Treated with SOF/VEL x 12 weeks and achieved SVR12
What should you do next?

1. Congratulate him on his HCV cure and discharge him from clinic
2. Counsel him regarding HCV reinfection and discharge him from clinic
3. Counsel him regarding HCV reinfection and screen for esophageal varices annually
4. Counsel him regarding HCV reinfection and screen for HCC every 6 months

Management of Compensated Cirrhosis

1. Treat etiology of liver disease ✓
Management of Compensated Cirrhosis

1. Treat etiology of liver disease ✓
2. Screen/Prevent complications of cirrhosis

Natural History of Cirrhosis

Clinical symptoms
- Ascites
- Variceal bleed
- Hepatic encephalopathy
- Jaundice

Chronic liver disease → Compensated cirrhosis → Decompensated cirrhosis → Death

Hepatocellular carcinoma (HCC)
Natural History of Cirrhosis

Clinical symptoms
- Ascites
- Variceal bleed
- Hepatic encephalopathy
- Jaundice

Chronic liver disease → Compensated cirrhosis → Decompensated cirrhosis → Death

Hepatocellular carcinoma (HCC)

SVR after DAAs reduces but does not eliminate HCC risk

Large VA study of 22,500 pts (39% with cirrhosis)

SVR after DAAs reduces but does not eliminate HCC risk

Large VA study of 22,500 pts (39% with cirrhosis)

- DAA-induced SVR associated with 76% reduction in HCC risk
- Absolute risk of HCC persisted despite SVR

SVR after DAAs reduces but does not eliminate HCC risk

Large VA study of 22,500 pts (39% with cirrhosis)

✓ DAA-induced SVR associated with 76% reduction in HCC risk
✓ Absolute risk of HCC persisted despite SVR
✓ Risk of HCC highest in cirrhotics: 1.0-2.2% per year

Post-SVR HCC Surveillance for Patients with Advanced Fibrosis (≥F3)

- Every 6 month abdominal ultrasound +/- AFP
  - Alternative imaging modalities: quad phase abdominal CT, contrast-enhanced MRI
- Early detection increases likelihood of receiving curative treatment
  - Resection
  - Locoregional therapy
  - Liver transplant


John P.

- 61 year old male with HCV genotype 1a s/p SVR
- HCV was treated by another provider
- T bilirubin 0.5, AST 30, ALT 25, INR 1.0, albumin 4.1, platelets 154, AFP 2.6
- Abdominal ultrasound: liver and spleen unremarkable
- No jaundice, GI bleeding, ascites, or encephalopathy
What do you advise John about HCC surveillance?

1. HCC screening is not needed because he has no signs or symptoms of cirrhosis
2. You will request pre-treatment records to determine the need for HCC screening
3. You will get a Fibroscan or calculate FIB-4 to determine the need for HCC screening
4. HCC screening should be started now and continued indefinitely

HCC Surveillance Should be Based on Pre-HCV Treatment Fibrosis Staging

- Accuracy of non-invasive estimates of fibrosis post-SVR is unclear
- Risk of HCC in pts with pre-HCV treatment ≥F3 fibrosis who regress to minimal fibrosis post-treatment is unknown
  - Pts should continue to be monitored for HCC regularly

HCC Surveillance Should be Based on Pre-HCV Treatment Fibrosis Staging

**Serum Markers**

- AST-to-plt ratio index (APRI)
  \[
  \frac{\text{AST/ upper limit of nl}}{\text{Platelet count (10}^9/\text{L})} \times 100
  \]

- FIB-4
  \[
  \frac{\text{Age (years)} \times \text{AST}}{\text{Platelet count (10}^9/\text{L}) \times \sqrt{\text{ALT}}}
  \]

https://www.hepatitisc.uw.edu/
Liver Stiffness Measurements Improve with HCV Treatment

- Nearly 50% of pts with ≥F3 fibrosis on pre-treatment FibroScan® will have post-SVR FibroScan <9.5 kPa
- Early decline is probably due to inflammation resolution
- Decline >1 year may represent fibrosis regression but this has not been validated in post-SVR pts


Estimation of Advanced Fibrosis can be Difficult Post-SVR

- 33 patients with cirrhosis on pre-treatment biopsy had post-SVR biopsy and FibroScan®
  - 13 had cirrhosis on post-SVR biopsy
  - 5 (38%) had post-SVR FibroScan® <12 kPa and would have been misclassified as non-cirrhotic

Estimation of Advanced Fibrosis can be Difficult Post-SVR

• 33 patients with cirrhosis on pre-treatment biopsy had post-SVR biopsy and FibroScan®
  – 13 had cirrhosis on post-SVR biopsy
  – 5 (38%) had post-SVR FibroScan® <12 kPa and would have been misclassified as non-cirrhotic

• UCSF series of 18 patients who underwent post-SVR biopsy and FibroScan®
  – 9 had ≥F3 fibrosis on post-SVR biopsy
  – 6 (67%) had post-SVR FibroScan® <9.5 kPa and would have been misclassified as having <F3 fibrosis
  – 2 developed HCC post-SVR


Esophageal Varices Screening

• Seen in 45-50% of patients with cirrhosis
  – 40% in CPT A, 60% in CPT B, 80% in CPT C

• Active bleed is associated with 20-30% mortality

• Primary prophylaxis: non-selective beta blockers or band ligation

D’Amico G. Portal Hypertension in the 21st Century, 2004
Esophageal Varices Screening

Diagnosis of Cirrhosis

Endoscopy

No Varices

Expert opinion
Diagnosis of Cirrhosis

Endoscopy

No Varices

Follow-up EGD in 2-3 years*

Small Varices

*EGD every year in decompensated cirrhosis

Expert opinion
Diagnosis of Cirrhosis

Endoscopy

No Varices
Small Varices

Follow-up EGD in 2-3 years*
Follow-up EGD in 1-2 years*

*EGD every year in decompensated cirrhosis

Expert opinion
Esophageal Varices Screening

Diagnosis of Cirrhosis

Endoscopy

- No Varices
  - Follow-up EGD in 2-3 years*

- Small Varices
  - Follow-up EGD in 1-2 years*

- Medium/Large Varices
  - Beta-blocker therapy

*EGD every year in decompensated cirrhosis

Expert opinion
Esophageal Varices Screening

Diagnosis of Cirrhosis

- Endoscopy

  - No Varices
  - Small Varices
  - Medium/Large Varices

  - Follow-up EGD in 2-3 years*
  - Follow-up EGD in 1-2 years*

*EGD every year in decompensated cirrhosis

- Beta-blocker therapy

- No Contraindications

- Contraindications or Beta-blocker intolerance

- Endoscopic Variceal Band Ligation

Expert opinion

EGD Can be Safely Avoided in Low Risk Patients with Cirrhosis

- Pts with clinically significant portal hypertension (HVPG ≥10 mmHg) are at risk of bleeding
  - Liver stiffness ≥20 kPa detects clinically significant portal HTN
  - EGD can be safely avoided in compensated pts with:
    - LS<20 kPa AND plts >150,000 mm³ (Baveno VI Criteria)
    - These patients have very low probability (<5%) of having high-risk varices
    - These criteria have been validated in HCV+ patients who achieve SVR

Management of Compensated Cirrhosis

1. Treat etiology of liver disease✓
2. Screen/Prevent complications of cirrhosis✓
   • HCC surveillance every 6 months
   • Varices screening unless liver stiffness <20 kPa and platelets >150

3. Minimize risk of further liver disease progression
Modifiable Risk Factors for Liver Disease Progression Post-SVR

• Viral infection
  – HCV reinfection: counseling, harm reduction
  – Hepatitis A and B vaccination

• Alcohol
  – No amount is “safe” in patients with cirrhosis
Modifiable Risk Factors for Liver Disease Progression Post-SVR

- Viral infection
  - HCV reinfection: counseling, harm reduction
  - Hepatitis A and B vaccination
- Alcohol
  - No amount is “safe” in patients with cirrhosis
- Metabolic factors
  - Aim for normal weight
  - Optimize metabolic syndrome components

- Drug-induced liver injury
  - Avoid drugs that may worsen volume/renal status
  - NSAIDS should be avoided due to risk of renal vasoconstriction and renal failure
  - Acetaminophen can be used if <2000 mg/day
  - Statins are safe and may have beneficial effects on liver
Robin T.

- 65 year old woman with HCV genotype 2
- T bili 2.5, AST 30, ALT 20, INR 1.3, albumin 3.0, platelets 75
- Physical exam: BMI 30, moderate ascites, no encephalopathy
What are the chances that Robin’s decompensated cirrhosis will improve after SVR?

1. <10%
2. 15-35%
3. 55-75%
4. >90%

Child-Turcotte-Pugh (CPT) Score Estimates Cirrhosis Severity

<table>
<thead>
<tr>
<th></th>
<th>Points</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>None</td>
<td>Mild-Moderate (grade 1 or 2)</td>
<td>Severe (grade 3 or 4)</td>
</tr>
<tr>
<td>Ascites</td>
<td>None</td>
<td>Mild-Moderate (diuretic responsive)</td>
<td>Severe (diuretic refractory)</td>
</tr>
<tr>
<td>Bilirubin (mg/dL)</td>
<td>&lt;2</td>
<td>2-3</td>
<td>&gt;3</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>&gt;3.5</td>
<td>2.8-3.5</td>
<td>&lt;2.8</td>
</tr>
<tr>
<td>INR</td>
<td>&lt;1.7</td>
<td>1.7-2.3</td>
<td>&gt;2.3</td>
</tr>
</tbody>
</table>

Child A: 5-6 Points Compensated
Child B: 7-9 Points Decompensated
Child C: 10-15 Points Further Decompensated

https://www.hepatitisc.uw.edu/page/clinical-calculators/ctp
## Child-Turcotte-Pugh (CPT) Score Estimates Cirrhosis Severity

<table>
<thead>
<tr>
<th></th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>None</td>
</tr>
<tr>
<td>Ascites</td>
<td>None</td>
</tr>
<tr>
<td>Bilirubin (mg/dL)</td>
<td>&lt;2</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>&gt;3.5</td>
</tr>
<tr>
<td>INR</td>
<td>&lt;1.7</td>
</tr>
</tbody>
</table>

Child A: 5-6 Points
Compensated

Child B: 7-9 Points
Decompensated

Child C: 10-15 Points
Further Decompensated

https://www.hepatitisc.uw.edu/page/clinical-calculators/ctp

---

### “Recompensation” is Possible After Decompensation

- **Clinical symptoms**
  - Ascites
  - Variceal bleed
  - Hepatic encephalopathy
  - Jaundice

- **Chronic liver disease** → Compensated cirrhosis
- **Decompensated cirrhosis** → Death

- **Recompensation**
- Alcohol abstinence
- HBV anti-viral therapy

Evaluation of Improvement of Decompensation with DAA Therapy

• Retrospective analysis from 4 trials of SOF-based therapy in patients with decompensated cirrhosis
  – 502 CPT B, 120 CPT C
  – Excluded:
    • HBV, HIV, or HCC
    • Prior NS5A exposure
    • Plts <30, liver enzymes ≥10x ULN, t bili >5 or >10, or GFR <30

Ei-Sherif O, Gastroenterology, 2018.

Evaluation of Improvement of Decompensation with DAA Therapy

• Retrospective analysis from 4 trials of SOF-based therapy in patients with decompensated cirrhosis
  – 502 CPT B, 120 CPT C
  – Excluded:
    • HBV, HIV, or HCC
    • Prior NS5A exposure
    • Plts <30, liver enzymes ≥10x ULN, t bili >5 or >10, or GFR <30

• Primary end point: proportion achieving a clinically meaningful treatment benefit
  – Sustained down-staging to CPT A

Ei-Sherif O, Gastroenterology, 2018.
“Recompensation” Can Occur in Patients with Child Pugh B or C Cirrhosis who Achieve SVR

Post-SVR improvement to CPT A: 32% baseline CPT B, 12% CPT C


What if my patient remains decompensated despite SVR?
Indications for Liver Transplant

- Complications of cirrhosis (Child Pugh B or C)
  - Ascites
  - Portal hypertensive bleeding
  - Hepatic encephalopathy
  - Spontaneous bacterial peritonitis (SBP)
  - Synthetic function abnormalities: bilirubin, albumin, INR
- HCC within criteria for transplant
- Waiting list priority is based on liver disease severity (MELD-Na) NOT waiting time
  - Patients with HCC get MELD-Na exception points

Contraindications to Liver Transplant

- Ongoing substance use
  - Alcohol abstinence of 6 months required
    - Consideration in patients with high MELD and <6 month sobriety varies by transplant center
  - Non-marijuana recreational drug use
    - Required duration of abstinence varies by transplant center
    - Prescription narcotics- policies vary by center
    - Cigarette smoking- would not delay transplant evaluation
- Lack of social support
- Severe, irreversible co-morbid medical conditions that adversely impact short-term life expectancy
HIV Organ Policy Equity (HOPE) Act

- HOPE Act November 21, 2013: organs infected with HIV may be transplanted into individuals who are:

  1) HIV-infected before receiving such an organ
  2) Participating in clinical research approved by an IRB until participation in such research is no longer warranted

HOPE consents and transplants

<table>
<thead>
<tr>
<th>Organ</th>
<th>Consent</th>
<th>Transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>KIDNEY</td>
<td>Consented: N = 289</td>
<td>Received: N = 76</td>
</tr>
<tr>
<td></td>
<td>HIV D-/R+ N = 31</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HIV false positive D/R+ N = 23</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HIV D+/R+ N = 22</td>
<td></td>
</tr>
<tr>
<td>LIVER</td>
<td>Consented: N = 57</td>
<td>Received: N = 35</td>
</tr>
<tr>
<td></td>
<td>HIV D+/R+ N = 10</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HIV false positive D/R+ N = 16</td>
<td></td>
</tr>
</tbody>
</table>

Slide credit: Christine Durand
Transplant Centers Participating in HOPE

Columbia/New York-Presbyterian
Cornell Medical Center/NY-Presbyterian
Duke University Hospital
Emory University Hospital
Georgetown University Medical Center
Hahnemann University Hospital
Indiana University Health
Johns Hopkins Hospital
Massachusetts General Hospital
Methodist Dallas Medical Center
Montefiore Medical Center
Mount Sinai Medical Center
Rush University Medical Center
University of Alabama Hospital, Birmingham
University of California, San Francisco
University of Colorado Hospital
University of Maryland Medical System
University of Minnesota
VCU Medical Center
Yale New Haven Hospital

Additional information:
https://optn.transplant.hrsa.gov/learn/professional-education/hope-act/

Slide credit: Christine Durand

Summary

• Pre-HCV treatment fibrosis estimation is essential to determine post-SVR management plan
  – Send the work-up before you treat
• Patients with ≥F3 fibrosis pre-treatment require q6 month HCC surveillance
• Patients with cirrhosis require varices screening unless:
  – Compensated, no history of varices, liver stiffness <20 kPa, AND platelets >150
• Focus on modifiable risk factors for disease progression
  – Counseling and harm reduction for HCV reinfection
  – Vaccinations
  – Alcohol
  – Metabolic factors: obesity, insulin resistance/diabetes
Summary

• With more advanced cirrhosis, the likelihood of clinically meaningful benefit of SVR decreases
  – Underscores importance of diagnosing and treating HCV earlier in the disease stage
  – Important information for pre-treatment counseling and expectation setting for patients with advanced cirrhosis

Questions?
ACTHIV 2019: A State-of-the-Science Conference for Frontline Health Professionals