HCV care after cure

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Speaking and teaching: Merck, Abbvie BMS, Gilead Science
Outline

- Long-term Outcomes After SVR
- Post-SVR Monitoring of HCV RNA
- Post-SVR Monitoring for HCC
- Management of Varices post SVR
- Additional Considerations:
  - Reinfections Risk after SVR
  - Alcohol use
  - Obesity
Long-term Outcomes After SVR
Benefits of Achieving SVR

- **SVR**
  - Decreased transmission
  - Improved clinical outcomes
    - Hepatic
      - ↓ Cirrhosis
      - ↓ Decompensation
      - ↓ HCC
      - ↓ Transplantation
    - Extrahepatic
      - ↓ All-cause mortality
      - ↑ QoL
      - ↓ Malignancy
      - ↓ Diabetes
      - ↓ CVD
      - ↓ Renal
      - ↑ Neurocognitive

SVR and Mortality: IFN Era

- Long-term follow-up study of pts with chronic HCV infection and advanced fibrosis or cirrhosis (N = 530 treated 1990-2003; median follow-up: 8.4 yrs)[1]

Baseline factors significantly associated with all-cause mortality:
- Older age
- Genotype 3 (2-fold increase in mortality and HCC)
- Higher Ishak fibrosis score
- Diabetes
- Severe alcohol use

SVR also reduces all-cause mortality even in absence of cirrhosis[2]

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Prospective cohort analysis of 4668 patients who started DAAs Mar 2015 - Dec 2016 (previous HCC or OLT excluded)

69% with CTP A cirrhosis; 8.8% with CTP B cirrhosis

SVR: 90.7%; no SVR: 5%

Primary endpoint: survival since initiating HCV DAAs

Median follow-up: 72 wks

SVR associated with reduced risk of liver-related mortality across disease stages, but benefit lower in CTP B cirrhosis

Univariate HR for no SVR vs SVR in CTP B: 3.49; \( P = .036 \)

<table>
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<tr>
<th>Multivariate Cox Regression</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
</table>
| Independent predictors of liver-related mortality in CTP A cirrhosis

- No SVR
  - 18.50 (6.75-50.70)
  - < .001
- Albumin < 3.5 g/dL
  - 6.01 (2.30-15.73)
  - < .001

| Independent predictors of cardiovascular mortality in DAA-treated patients

- No SVR
  - 10.56 (3.43-32.46)
  - < .001
- Diabetes
  - 4.11 (1.30-12.98)
  - .011

Scottish National Study: Reduction in Liver Outcomes After Initiation of DAA Therapy

Retrospective study of Scottish HCV Clinical Database, 2000-2017
DAA therapy introduced April 2014
Endpoint: hospital admission with decompensated cirrhosis
Ascites, hepatic encephalopathy, hepatorenal syndrome, bleeding varices
From April 2014-2017, 4800 persons with HCV initiated on HCV therapy in Scotland

<table>
<thead>
<tr>
<th>Characteristics, %</th>
<th>Treated Pts (N = 4800)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GT1</td>
<td>54</td>
</tr>
<tr>
<td>GT3</td>
<td>38</td>
</tr>
<tr>
<td>Other GT</td>
<td>8</td>
</tr>
<tr>
<td>F2/F3</td>
<td>24</td>
</tr>
<tr>
<td>Compensated cirrhosis</td>
<td>27</td>
</tr>
<tr>
<td>Decompensated cirrhosis</td>
<td>5</td>
</tr>
<tr>
<td>Treated with DAAs</td>
<td>83</td>
</tr>
</tbody>
</table>

These data provide the first country-level evidence of the immediate impact that DAAs can have in averting HCV-related DC. Greater emphasis needs to be placed however on addressing comorbidities that pose a continued risk of liver disease progression among those attaining SVR.
Impact of DAAs on Survival in Patients With HCV Infection and Decompensated Cirrhosis

Incidence of observed deaths in DAA-treated patients with decompensation vs expected deaths in untreated patients in modeling study

Observed mortality data derived from SOLAR (LDV/SOF + RBV) and ASTRAL-4 (SOF/VEL ± RBV)

Expected mortality model based on pre-DAA era liver transplant list data

56% reduction in mortality 1 yr after DAA treatment initiation for observed deaths vs expected deaths ($P < .05$)

Post-SVR Monitoring of HCV RNA
Late Relapse Beyond SVR12 With DAA Therapy

- Risk of late relapse very low, *but* can happen
- Analysis of recurrent viremia after SVR12 in 11 SOF ± LDV phase III trials

# Recommendations on HCV RNA Follow-up After SVR

<table>
<thead>
<tr>
<th>Organization</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>AASLD/IDSA</td>
<td>✷ Additional testing can be considered at ≥ 24 wks post treatment for pts with ALT increases to &gt; ULN</td>
</tr>
<tr>
<td>EASL</td>
<td>✷ Noncirrhotics should be tested for ALT and HCV RNA at 48 wks post treatment and discharged if ALT normal and HCV RNA negative</td>
</tr>
</tbody>
</table>
HCV clearance on DAAs and occurrence and recurrence of HCC
Post-SVR Monitoring for HCC

Which Patients Need It
SVR and HCC Risk: IFN Era

Meta-analysis of studies assessing HCC development in HCV pts following SVR through February 2012

<table>
<thead>
<tr>
<th>Outcome</th>
<th>All Pts (n = 25,497)</th>
<th>Pts With Advanced Fibrosis* (n = 2649)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SVR</td>
<td>No SVR</td>
</tr>
<tr>
<td>Developed HCC, %/PY</td>
<td>0.33</td>
<td>1.67</td>
</tr>
<tr>
<td>Adjusted HR (95% CI)</td>
<td>0.24 (0.18-0.31)</td>
<td>0.23 (0.16-0.35)</td>
</tr>
</tbody>
</table>

*METAVIR score of F3/F4 or Ishak score of 4-6.

Sustained virologic response after treatment among HCV-infected persons at any stage of fibrosis is associated with reduced HCC.

The incidence of HCC is reduced in HCV patients after an SVR to DAAs: the VA cohort

Annual incidence rate (per 100 person-yrs) of HCC development after SVR 0.90 vs 3.45 in non-SVR. Higher rate in those with cirrhosis and with alcohol use.

Retrospective cohort study assessing the relationship between SVR and de novo HCC risk in pts with HCV in the VA system receiving antiviral therapy 1999-2015 (N = 62,354)

- Mean follow-up: 6.1 yrs

SVR with DAA regimen associated with 79% decrease in de novo HCC risk

<table>
<thead>
<tr>
<th>Regimen</th>
<th>HCC/100 PY</th>
<th>aHR</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFN only♀ SVR ♠ No SVR</td>
<td>0.28 1.07 0.32</td>
<td></td>
</tr>
<tr>
<td>DAA + IFN ♛ SVR ♠ No SVR</td>
<td>0.6 1.73 0.48</td>
<td></td>
</tr>
<tr>
<td>DAA only ♛ SVR ♠ No SVR</td>
<td>0.92 5.2 0.29</td>
<td></td>
</tr>
</tbody>
</table>

Some Key Questions With SVR and HCC

- Patients with what stage(s) of fibrosis may be at increased risk for HCC following SVR?
- Are patients with < F3 fibrosis at risk?
- Is there a typical time course for when HCC develops among at-risk patients following SVR?
- How long should HCC surveillance continue?
Pretreatment Fibrosis Stage and HCC in Pts Achieving SVR: Retrospective Japanese Study

- Retrospective cohort study of de novo HCC incidence in Japanese pts achieving SVR on IFN therapy Median follow-up: 4.8 yrs

<table>
<thead>
<tr>
<th>Fibrosis Stage</th>
<th>n</th>
<th>HCC, n (%)</th>
<th>Cumulative HCC, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>5 Yrs</td>
</tr>
<tr>
<td>F0</td>
<td>53</td>
<td>0 (0)</td>
<td>0</td>
</tr>
<tr>
<td>F1</td>
<td>187</td>
<td>1 (0.5)</td>
<td>0.7</td>
</tr>
<tr>
<td>F2</td>
<td>193</td>
<td>13 (6.7)</td>
<td>3.5</td>
</tr>
<tr>
<td>F3</td>
<td>78</td>
<td>11 (14.1)</td>
<td>3.7</td>
</tr>
<tr>
<td>F4</td>
<td>51</td>
<td>6 (11.8)</td>
<td>11.7</td>
</tr>
<tr>
<td>All</td>
<td>562</td>
<td>31 (5.5)</td>
<td>3.1</td>
</tr>
</tbody>
</table>

SVR patients must be observed at 6-month intervals, at a minimum, to facilitate diagnosis at an early stage, for as long as possible after completion of therapy even if not at an advanced stage of fibrosis.
How Accurate Is Transient Elastography to Monitor for Regression of Cirrhosis After SVR?

33 pts with HCV and biopsy-proven cirrhosis who achieved SVR after IFN based therapy

FibroScan and biopsy ~ 60 mos post SVR

- Biopsy
  - 20 pts regressed (≤ F3)
  - 13 pts had persistent cirrhosis (F4)

- FibroScan
  - 19 (95%) pts regressed (TE < 12 kPa)
  - 5 (38%) pts regressed (TE < 12 kPa)

Diagnostic accuracy of TE for diagnosing post-SVR cirrhosis: 61% sensitivity, 95% specificity

LB still remains the only reliable approach to stage liver fibrosis following an SVR.

Post HCV SVR Liver Stiffness Measurement (LSM) Not Predictive of HCC

828 patients without previous HCC from 2 French treatment centers May 2008 - Nov 2016; SVR: 94% (799/849)

LSM assessed by FibroScan before HCV therapy and ≥ 1 time during 12-48 wks of follow-up

Post-SVR HCC screening every 6 mos by ultrasound

Median LSM decrease from baseline to follow-up: -3.6 kPa (-6.2 to -1.1; P < .0001)

At median f/u of 6 mos, 2 patients died and 22 (2.8%) developed HCC

Factors assoc. with HCC in multivariate analysis: age, sex, diabetes, and baseline LSM, but NOT change in LSM

<table>
<thead>
<tr>
<th>Factor</th>
<th>HR (95% CI)</th>
<th>P Value</th>
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<tbody>
<tr>
<td>Age (per yr)</td>
<td>1.06 (1.02-1.10)</td>
<td>.005</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.70 (1.12-6.51)</td>
<td>.026</td>
</tr>
<tr>
<td>Baseline LSM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per kPa</td>
<td>1.05 (1.02-1.07)</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Qualitative baseline LSM</td>
<td></td>
<td>.005</td>
</tr>
<tr>
<td>≤ 8-12.5 vs &lt; 8</td>
<td>1.59 (0.14-17.59)</td>
<td></td>
</tr>
<tr>
<td>≥ 12.5 vs &lt; 8</td>
<td>10.44 (1.38-78.63)</td>
<td></td>
</tr>
<tr>
<td>Change in LSM, per kPa</td>
<td>0.99 (0.94-1.04)</td>
<td>.705</td>
</tr>
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# Recommendations for HCC Screening After SVR

<table>
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<tr>
<th>Organization</th>
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<tbody>
<tr>
<td>F0-F2</td>
<td></td>
</tr>
<tr>
<td>AASLD/IDSA</td>
<td>Follow-up same as for those never infected with HCV</td>
</tr>
<tr>
<td></td>
<td>Ultrasound surveillance every 6 mos</td>
</tr>
<tr>
<td>EASL</td>
<td>None</td>
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Surveillance and Management of Varices After SVR
Impact of SVR on Portal Hypertension

- Study of 48 wks of SOF + RBV for cirrhotic pts with portal hypertension (N = 50)
  - SVR12: 72% (n/N = 33/46)

Patients with chronic HCV and compensated or decompensated cirrhosis who achieve SVR can have clinically significant reductions in HVPG at long-term follow-up

HVPG Reduction in Pts With Baseline HVPG ≥ 12 mm Hg Who Achieved SVR12 and Completed 48-Wk Follow-up (n = 9*)

* n = 8 pts with > 20% decrease.

Endoscopic Surveillance for Varices Following SVR

Study of de novo esophageal varices in pts with HCV and compensated cirrhosis (N = 218) In the long term, the achievement of SVR prevents the development of EV in patients with compensated HCV-induced cirrhosis.

HVPG fell to < 10 mm Hg in 4/4 pts with HVPG > 10 mm Hg before treatment

Recommendations for Surveillance and Management of Varices After SVR

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<td>AASLD/IDSA and EASL</td>
<td>Noncirrhotics: No specific recommendations</td>
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Additional Considerations
- Reinfections Risk after SVR
- Alcohol use
- Obesity
## Additional Considerations for Maintaining Liver Wellness After SVR

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✗ Recommendations: for pts with ongoing risk for HCV infection  
  – Counsel and educate on risk reduction  
  – Test HCV RNA annually |
| Alcohol use | ✗ Alcohol use associated with liver fibrosis progression and HCC risk with chronic HCV infection; less evidence in post-SVR setting  
✗ Recommendations:  
  – Counsel avoidance of significant alcohol use in all pts and abstinence for pts with advanced liver fibrosis or cirrhosis |
| Obesity | ✗ Fatty liver disease can cause fibrosis/cirrhosis; diabetes associated with unfavorable liver-related outcomes  
✗ Recommendations:  
  – Counsel lifestyle modifications, glycemic control |
Prospective cohort study of risk factors for HCV reinfection in HIV/HCV-coinfected pts achieving SVR (N = 257)

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| Obesity            | ✤ Fatty liver disease can cause fibrosis/cirrhosis; diabetes associated with unfavorable liver-related outcomes  
                   | ✤ Recommendations:  
                   | ‒ Counsel lifestyle modifications, glycemic control                                                                                                    |
Conclusions

- SVR associated with myriad clinical benefits
- Mandatory to continue HCC surveillance post SVR in pts with F3/F4 fibrosis; ultrasound every 6 mos
  Consider assessing AFP levels as well for these pts
  Less evidence to support continued screening of F0-F2 but remains a theoretical concern
- Indefinite screening for varices not warranted if varices absent at baseline: 1 more exam after SVR?
  Surveillance of small varices if no other liver disease present requires further study but advisable
  Large varices require ongoing management and surveillance
- Routine monitoring for fibrosis regression not the standard of care; further studies may change this
- For pts with ongoing risk for HCV infection after SVR, counsel and test HCV RNA annually