The impact of the treatment of HCV in developing Hepatocellular Carcinoma

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Hepatocellular Carcinoma (HCC)

- Hepatocellular carcinoma is the 4th most common cancer in the world
- Third leading cause of cancer related death
- 80% of HCC is caused by chronic HCV or HBV infection
- HCC rarely seen during the first 4 decades of life, except in populations in which HBV infection is hyperendemic.
- The mean ages of diagnosis with HCC were:
  - 55–59 years in China
  - 63–65 years in Europe and North America
HCC and Hepatitis C

- Risk of HCC increases with fibrosis stage
- Most cases of HCV-related HCC occur among patients with advanced fibrosis/cirrhosis
- Incidence of cirrhosis 25–30 years after HCV infection is 15%–35%,
  - highest among recipients of HCV-contaminated blood products and hemophiliac patients
  - lowest among women who received dose of contaminated anti-D immunoglobulin
- HCC develops at annual rate of 1%–4%
  - rates up to 8% have been reported in Japan.
HCC and Hepatitis C: Other reported risk factors

- Gender
- Co-infection with HBV or HIV
- Diabetes, obesity, steatosis
- Viral genotype (HCV 1b)
- Level of alcohol consumption
- Age
- Thrombocytopenia
- Increased levels of alpha-fetoprotein
Age-standardized incidence rates of liver cancer per 100,000 person-years
Prevalence of HBsAg carrier and chronic HCV status in different geographic regions
Multistep Malignant Transformation to HCC

Potential Therapeutic Targets

<table>
<thead>
<tr>
<th>Potential Therapeutic Targets</th>
<th>HCC&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Epigenetic alterations</th>
<th>Genetic alterations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysplastic nodules&lt;sup&gt;1&lt;/sup&gt;</td>
<td>HCC&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Epigenetic alterations</td>
<td>Genetic alterations</td>
</tr>
<tr>
<td>Liver cirrhosis</td>
<td></td>
<td></td>
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<tr>
<td>Hepatitis C</td>
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<td></td>
<td></td>
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<tr>
<td>Hepatitis B</td>
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<td>Ethanol</td>
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<td>NASH</td>
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<td>Normal liver</td>
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<td></td>
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<tr>
<td>Oxidative stress and inflammation</td>
<td></td>
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<tr>
<td>Viral oncogenes</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Carcinogens</td>
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<td>Growth factors</td>
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<tr>
<td>Telomere shortening</td>
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<td>Cancer stem cells</td>
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<tr>
<td>Loss of cell cycle checkpoints</td>
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<tr>
<td>Anti-apoptosis</td>
<td></td>
<td></td>
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<tr>
<td>Angiogenesis</td>
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</tbody>
</table>

Is Hepatitis C infection carcinogenic?

- Active HCV infection increases the risk of HCC by 18-fold
- 8% of HCC cases in HALT-C study had no cirrhosis
- Hepatitis C elicits inflammatory and fibrotic responses in the host contributing to carcinogenesis
- SVR reduces risk of HCC by 3 fold in cirrhotic patients
Direct vs indirect mechanisms of carcinogenesis in the HCV-infected liver

HCV infection deregulates host cell cycle checkpoints → Immune- and virus-mediated oxidative stress and DNA damage → Infected cells accumulate mutations, eventually resulting in transformation.

Indirect:
- Immune- or virus-mediated apoptosis
- Compensatory proliferation and reinfection
- Uninfected bystander cells accumulate mutations in an environment of inflammation and oxidative stress
- Proliferation of transformed hepatocytes

HCV-infected normal hepatocyte

HCV-infected, transformed hepatocyte

Uninfected normal hepatocyte

Transformed hepatocyte

Lemon et al GASTROENTEROLOGY 2012;142:1274–1278
Cirrhosis regression in patients with and without a sustained viral response in trials in which the follow-up biopsy had a mean or median time of < 36-months.

<table>
<thead>
<tr>
<th>Source</th>
<th>NonSVR</th>
<th>SVR</th>
<th>Weight (%)</th>
<th>Risk Ratio, (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abergel 2004</td>
<td>4/43 (9%)</td>
<td>6/18 (33%)</td>
<td>6.8</td>
<td>3.58 [1.15, 11.20]</td>
</tr>
<tr>
<td>Arif 2003</td>
<td>4/9 (44%)</td>
<td>5/6 (83%)</td>
<td>13.2</td>
<td>1.88 [0.83, 4.23]</td>
</tr>
<tr>
<td>Poynard 2002</td>
<td>50/116 (43%)</td>
<td>25/37 (68%)</td>
<td>80.0</td>
<td>1.57 [1.15, 2.13]</td>
</tr>
</tbody>
</table>

Total (95% CI) | 168 | 61 | 100 | 1.70 [1.26, 2.29]

Test for Heterogeneity: Chi² = 2.07 (P = 0.35), I² = 3%

Test for overall effect: Z = 3.47 (P < 0.01)
Cirrhosis regression in patients with and without a sustained viral response in trials in which the follow-up biopsy had a mean or median time of >36-months.

<table>
<thead>
<tr>
<th>Source</th>
<th>NonSVR</th>
<th>SVR</th>
<th>Weight (%)</th>
<th>Risk Ratio, (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mallet 2008</td>
<td>5/61 (8%)</td>
<td>22/35 (63%)</td>
<td>38.0</td>
<td>7.67 [3.19, 18.44]</td>
</tr>
<tr>
<td>Pol 2004</td>
<td>1/47 (2%)</td>
<td>4/17 (24%)</td>
<td>21.7</td>
<td>11.06 [1.33, 92.13]</td>
</tr>
<tr>
<td>Shiratori 2000</td>
<td>9/30 (30%)</td>
<td>11/24 (46%)</td>
<td>40.3</td>
<td>1.53 [0.76, 3.07]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>138</td>
<td>76</td>
<td>100</td>
<td>4.33 [1.10, 17.04]</td>
</tr>
</tbody>
</table>

Total events: 15

Test for Heterogeneity: Chi² = 9.95 (P < 0.01), I² = 80%

Test for overall effect: Z = 2.10 (P = 0.04)
Antiviral Therapy With SVR Reduces Risk of Hepatocellular Carcinoma in Patients With Hepatitis C Virus–Related Cirrhosis

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>SVR Events</th>
<th>Total</th>
<th>NSVR Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk ratio M-H, random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azzaroli 2004</td>
<td>0</td>
<td>21</td>
<td>2</td>
<td>50</td>
<td>1.0%</td>
<td>0.46 [0.02, 9.27]</td>
</tr>
<tr>
<td>Braks 2007</td>
<td>1</td>
<td>37</td>
<td>24</td>
<td>76</td>
<td>2.3%</td>
<td>0.09 [0.01, 0.61]</td>
</tr>
<tr>
<td>Bruno 2007 (1)</td>
<td>7</td>
<td>124</td>
<td>12</td>
<td>759</td>
<td>16.0%</td>
<td>0.35 [0.17, 0.73]</td>
</tr>
<tr>
<td>Floreani 2008 (2)</td>
<td>0</td>
<td>40</td>
<td>5</td>
<td>38</td>
<td>1.1%</td>
<td>0.09 [0.00, 1.51]</td>
</tr>
<tr>
<td>Hasegawa 2007 (3)</td>
<td>3</td>
<td>48</td>
<td>16</td>
<td>57</td>
<td>6.3%</td>
<td>0.22 [0.07, 0.72]</td>
</tr>
<tr>
<td>Hung 2006</td>
<td>5</td>
<td>73</td>
<td>11</td>
<td>59</td>
<td>8.7%</td>
<td>0.37 [0.14, 1.00]</td>
</tr>
<tr>
<td>Nishiguchi 1995</td>
<td>0</td>
<td>7</td>
<td>2</td>
<td>38</td>
<td>1.0%</td>
<td>0.97 [0.05, 18.43]</td>
</tr>
<tr>
<td>Okanoue 1999</td>
<td>0</td>
<td>2</td>
<td>7</td>
<td>38</td>
<td>1.3%</td>
<td>0.87 [0.06, 11.79]</td>
</tr>
<tr>
<td>Shioda 1999</td>
<td>4</td>
<td>204</td>
<td>18</td>
<td>448</td>
<td>7.6%</td>
<td>0.49 [0.17, 1.42]</td>
</tr>
<tr>
<td>Shiratori 2005</td>
<td>11</td>
<td>64</td>
<td>73</td>
<td>207</td>
<td>26.9%</td>
<td>0.49 [0.28, 0.86]</td>
</tr>
<tr>
<td>Tanaka 1998</td>
<td>0</td>
<td>8</td>
<td>10</td>
<td>47</td>
<td>1.2%</td>
<td>0.25 [0.02, 3.96]</td>
</tr>
<tr>
<td>Veldt 2008</td>
<td>3</td>
<td>142</td>
<td>32</td>
<td>337</td>
<td>6.4%</td>
<td>0.22 [0.07, 0.71]</td>
</tr>
<tr>
<td>Yoshida 1999 (4)</td>
<td>1</td>
<td>53</td>
<td>30</td>
<td>168</td>
<td>2.2%</td>
<td>0.11 [0.01, 0.76]</td>
</tr>
<tr>
<td>Yu 2006</td>
<td>9</td>
<td>85</td>
<td>27</td>
<td>80</td>
<td>18.3%</td>
<td>0.31 [0.16, 0.63]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>908</strong></td>
<td><strong>2402</strong></td>
<td><strong>Risk ratio M-H, random, 95% CI</strong></td>
<td><strong>0.35 [0.26, 0.46]</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 8.67$, df = 13 ($P = .80$)  
Test for overall effect: $Z = 7.06$ ($P < .000001$)

Maintenance interferon did not reduce risk of HCC
SVR reduces HCC risk across all fibrosis stages

<table>
<thead>
<tr>
<th>Study</th>
<th>RR (95% CI)</th>
<th>Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arase 2007 [10]</td>
<td>0.16 (0.04, 0.67)</td>
<td>16.83</td>
</tr>
<tr>
<td>Coverdale 2004 [11]</td>
<td>0.18 (0.03, 1.34)</td>
<td>11.22</td>
</tr>
<tr>
<td>Giannini 2001 [12]</td>
<td>0.46 (0.02, 11.13)</td>
<td>5.42</td>
</tr>
<tr>
<td>Kasahara 2004 [15]</td>
<td>0.04 (0.01, 0.28)</td>
<td>11.33</td>
</tr>
<tr>
<td>Lau 1998 [18]</td>
<td>0.33 (0.01, 8.01)</td>
<td>5.41</td>
</tr>
<tr>
<td>Yoshida 2004 [27]</td>
<td>0.19 (0.09, 0.42)</td>
<td>26.88</td>
</tr>
<tr>
<td>Yu 2006 [28]</td>
<td>0.80 (0.29, 2.19)</td>
<td>22.90</td>
</tr>
<tr>
<td>Overall</td>
<td>0.23 (0.10, 0.52)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

(I-squared = 45.2%, P = .090)
SVR reduces HCC risk in those with cirrhosis.

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**Figure:**

![Graph showing the relationship between SVR and HCC risk.](image)

- **Study:** Braaks 2007 [29]
- **RR (95% CI):** 0.06 (0.00, 0.97)
- **Weight (%):** 16.31

- **Study:** Bruno 2007 [30]
- **RR (95% CI):** 0.15 (0.04, 0.60)
- **Weight (%):** 33.12

- **Study:** Mallet 2008 [31]
- **RR (95% CI):** 0.23 (0.07, 0.78)
- **Weight (%):** 21.92

- **Study:** Veldt 2007 [34]
- **RR (95% CI):** 0.07 (0.01, 0.51)
- **Weight (%):** 28.65

- **Overall**
  - **RR (95% CI):** 0.13 (0.06, 0.29)
  - **Weight (%):** 100.00
  - **I-squared = 0.0%, P = 0.660**
SVR Decreases but Does Not Eliminate Risk for Liver Related Complications in those with hepatitis C

Between 1995 and 2010, 41% of the 126,862 new primary registrants for liver transplants carried a diagnosis of HCV infection. Between 1995 and 2010, 41% of the 126,862 new primary registrants for liver transplants carried a diagnosis of HCV infection.
AASLD Surveillance Guidelines
- Surveillance recommended in at-risk groups
- HCC surveillance should be performed with ultrasound
- Patients should be screened at 6-mo intervals
  - AFP levels not part of surveillance guidelines

APASL Surveillance Guidelines
- Surveillance recommended in at-risk groups
- HCC surveillance should be performed with ultrasound
- Patients should be screened at 6-mo intervals
- AFP levels are part of surveillance guidelines

Evolution of Therapy in HCV GT1

- **1990**: IFN 6m, 2%
- **1999**: IFN 12m, 10%
- **2001**: IFN/RBV 6m, 15%
- **2011**: IFN/RBV 12m, 25%
- **2015**: PEG/RBV 12m, 40%
- **2015**: PEG/R/PI 6-12m, 60%
- **2015**: PEG/R/PI 6-12m, 75%
- **2015**: All oral DAA 12-24 weeks, 100%

Genotype 3 requires additional strategies to achieve success of genotype 1.
TURQUOISE II: 12 vs 24 Wks
OMV/PTV/RTV + DSV + RBV in Cirrhotics

SOLAR: SVR12 in Patients With Advanced Liver Disease

SOLAR - 1
SOLAR - 2

Daclatasvir/Asunaprevir/Beclabuvir, ± Ribavirin for 12 weeks for G1

Naive Cohort

Experience Cohort

SVR12, %

![Graph showing SVR12 percentages for different treatment groups]

Daclatasvir/Trion/Beclabuvir, ± Ribavirin for 12 weeks for G1

Naive Cohort

Experience Cohort

DCV-TRIO

DCV-TRIO

DCV-TRIO

DCV-TRIO

+ RBV

+ RBV


53/57

54/55

39/45

42/45

93

98a

87

93

97.5% confidence intervals.

One patient with HCV RNA <LLOQ/TND at end of therapy and posttreatment Week 4 had missing data at posttreatment Week 12.

Error bars indicate 97.5% confidence intervals.
Groups in Whom the Risk of HCC is Increased, but in Whom Efficacy of Surveillance Has *Not* Been Demonstrated

<table>
<thead>
<tr>
<th>Population Group</th>
<th>Threshold Incidence for Efficacy of Surveillance (%/year)</th>
<th>Incidence of HCC (%/year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis B Carriers &lt;40 (males) or 50 (females)</td>
<td>0.2</td>
<td>&lt;0.2</td>
</tr>
<tr>
<td>Hepatitis C and stage 3 fibrosis</td>
<td>1.5</td>
<td>&lt;1.5</td>
</tr>
<tr>
<td>Noncirrhotic NAFLD</td>
<td>1.5</td>
<td>&lt;1.5</td>
</tr>
</tbody>
</table>
The Impact of HCV Treatments on HCC development

- We have the tools to achieve SVR in the majority of chronically infected hepatitis C patients
- These tools can reduce HCC development worldwide
- High SVR rates in F0-F4 fibrosis
- Those who are cured with cirrhosis must be entered into screening for HCC (US+AFP) if available
- Cirrhosis regression will occur in many who achieve SVR
- HCC risk will fall
  - Long term studies required to assess natural history of cirrhosis patients who achieve SVR on HCC development
The Impact of HCV Treatments on HCC development

Higher efficacy rates alone will not reduce burden

Greater efforts at diagnosing and linking to evaluation and treatment

High priority for developing countries to obtain access to therapies

Incorporate with effective programs to diagnose HCV infection

Journal of Viral Hepatitis, 2015, 22, (Suppl. S1), 1–5