Remaining Issues in Hepatitis C

Mario U. Mondelli

Division of Infectious Diseases II and Immunology,
Department of Medical Sciences and Infectious Diseases,
Fondazione IRCCS Policlinico San Matteo,
Department of Internal Medicine and Therapeutics,
University of Pavia, Pavia, Italy.
SVR as a Major Treatment Endpoint in HCV

- Prevent complications of HCV-related hepatic and extra-hepatic disease, including cirrhosis, liver decompensation, HCC and death

- Improve quality of life and remove stigma

- Prevent onward transmission of HCV
Mortality Reduction Achieved by HCV Cure. The Benefits Extend Beyond the Liver

Survival in ERCHIVES Veterans (N = 13,940*†)[1]

ANRS HEPATHER. All-Cause Mortality (N = 9,295#)[2]

DAA-induced SVR is associated with a 43% reduction in mortality

DAA treatment associated with decreased risk of death vs no treatment

*For 18 mos of follow-up.
†BL cirrhosis: PrOD, 24.9%; LDV/SOF, 29.4%; untreated, 19.4%.
#24 mos F/U

*8482 person-yrs. †10040 person-yrs.

Decline in the Proportion of Pts on LT WL Whose Etiology of Cirrhosis Is HCV Since Introduction of DAAs, in the US (A) and in Europe (B)

Ioannou GN & Feld JJ. *Gastroenterology* 2019;156:446–460
Remaining Problems After Successful DAA Treatment

• Management of advanced cirrhosis
• HCC surveillance
  • Role of comorbidities
  • Can we stop surveillance and in which patients?
• Persistent immunologic abnormalities
• Residual extrahepatic manifestations
• DAA resistance
• Reinfection
Remaining Problems After Successful DAA Treatment

- Management of advanced cirrhosis
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  - Can we stop surveillance and in which patients?
- Persistent immunologic abnormalities
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- DAA resistance
- Reinfection
Global Survival, Survival Free from HCC, and Survival Free From Decompensated Cirrhosis, According to Exposure to DAAs in Cirrhotic Pts

# Competing Risks of Death in Compensated Cirrhosis

## A Multicenter Study in France

### 35 Centers: follow-up 34 months from 2006 to 2012

<table>
<thead>
<tr>
<th></th>
<th>HCV (n=1308)</th>
<th>HBV (n=315)</th>
<th>HCV and HBV (n=31)</th>
<th>Whole cohort (n=1654)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Death</strong></td>
<td>93 (7.1%)</td>
<td>6 (1.9%)</td>
<td>3 (10%)</td>
<td>102 (6.2%)</td>
</tr>
<tr>
<td><strong>HCC-related</strong></td>
<td>17 (19.5%)</td>
<td>1 (16.6%)</td>
<td>0</td>
<td>18 (18.7%)</td>
</tr>
<tr>
<td><strong>Non-HCC liver-related</strong></td>
<td>27 (30.7%)</td>
<td>2 (33.3%)</td>
<td>1 (50%)</td>
<td>30 (31.2%)</td>
</tr>
<tr>
<td><strong>Bacterial infection</strong></td>
<td>13 (14.7%)</td>
<td>0</td>
<td>0</td>
<td>13 (13.5%)</td>
</tr>
<tr>
<td><strong>Extrahepatic cancer</strong></td>
<td>7 (7.9%)</td>
<td>3 (50%)</td>
<td>0</td>
<td>10 (10.4%)</td>
</tr>
<tr>
<td><strong>Cardiovascular disease</strong></td>
<td>5 (5.7%)</td>
<td>0</td>
<td>0</td>
<td>5 (5.2%)</td>
</tr>
<tr>
<td><strong>Other extrahepatic disease</strong></td>
<td>19 (21.5%)</td>
<td>0</td>
<td>1 (50%)</td>
<td>20 (20.8%)</td>
</tr>
<tr>
<td><strong>Missing data</strong></td>
<td>5 (5.4%)</td>
<td>0</td>
<td>1 (33.3%)</td>
<td>6 (5.8%)</td>
</tr>
</tbody>
</table>

*Trinchet et al, Hepatology. 2015;62:737-50*
Independent predictor of HVPG response: Child-Pugh B vs A, HR 0.13, CI 0.002-0.514, p=0.0069

Progression of PHT According To:

• Virological Response and Initial EV Grade
• Baveno VI status at the Time of Viral Suppression

ANRS-CO12 CirVir cohort with compensated cirrhosis

5-Year Mortality According to Baveno VI Status and Viral Suppression

De Franchis R. Gastroenterology 2019;156:864-866
Remaining Problems After Successful DAA Treatment

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- HCC surveillance
  - Role of comorbidities
  - Can we stop surveillance and in which patients?
- Persistent immunologic abnormalities
- Residual extrahepatic manifestations
- DAA resistance
- Reinfection
Chronic HCV Infection Induces Persistent Epigenetic Changes Regulating Expression of Genes Increasing Liver Cancer Risk

Epigenetic alterations affect the expression of genes without changing the nucleotide sequence, via DNA methylation, nucleosome remodeling, and histone modification. Virus-Induced Modifications of Histone Mark H3K27ac Persist in Human Liver After HCV Cure with DAAs, including TNFα signaling, inflammatory response...

Epigenetic alterations are independent on the type of therapy (DAA or interferon)

Lohmann V & Bartenschlager R. Gastroenterology 2019;156:2130–2132
HCC Occurrence and Recurrence After IFN or DAA Based Treatment

A. IFN: HCC occurrence

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>ES (95% CI)</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ogawa</td>
<td>2013</td>
<td>6.37 (1.75, 7.70)</td>
<td>7.34</td>
</tr>
<tr>
<td>D’Ambrosio</td>
<td>2011</td>
<td>0.71 (0.23, 2.20)</td>
<td>4.41</td>
</tr>
<tr>
<td>Bruno</td>
<td>2009</td>
<td>1.74 (0.63, 3.64)</td>
<td>7.34</td>
</tr>
<tr>
<td>Mallet</td>
<td>2008</td>
<td>0.78 (0.25, 2.43)</td>
<td>4.41</td>
</tr>
<tr>
<td>Cardoso</td>
<td>2010</td>
<td>6.66 (0.75, 3.70)</td>
<td>6.78</td>
</tr>
<tr>
<td>Yu</td>
<td>2006</td>
<td>2.04 (1.06, 3.93)</td>
<td>8.25</td>
</tr>
<tr>
<td>Hung</td>
<td>2006</td>
<td>2.22 (0.92, 5.34)</td>
<td>6.12</td>
</tr>
<tr>
<td>Morgan</td>
<td>2010</td>
<td>0.20 (0.05, 0.80)</td>
<td>3.27</td>
</tr>
<tr>
<td>Alemán</td>
<td>2013</td>
<td>1.03 (0.46, 2.29)</td>
<td>6.78</td>
</tr>
<tr>
<td>Cheinquer</td>
<td>2010</td>
<td>0.98 (0.41, 1.36)</td>
<td>1.64</td>
</tr>
<tr>
<td>Moon</td>
<td>2015</td>
<td>1.12 (0.16, 7.94)</td>
<td>1.64</td>
</tr>
<tr>
<td>Fernandez-Rodriguez</td>
<td>2010</td>
<td>0.99 (0.41, 2.37)</td>
<td>6.12</td>
</tr>
<tr>
<td>Janjua</td>
<td>2016</td>
<td>0.74 (0.33, 1.64)</td>
<td>6.78</td>
</tr>
<tr>
<td>Rutter</td>
<td>2015</td>
<td>0.95 (0.48, 1.91)</td>
<td>7.83</td>
</tr>
<tr>
<td>Velosa</td>
<td>2011</td>
<td>0.36 (0.05, 2.56)</td>
<td>1.64</td>
</tr>
<tr>
<td>Nanton</td>
<td>2017</td>
<td>0.88 (0.61, 1.28)</td>
<td>11.70</td>
</tr>
<tr>
<td>Di Marco</td>
<td>2016</td>
<td>0.65 (0.41, 1.78)</td>
<td>7.34</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>1.14 (0.85, 1.52)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

NOTE: Weights are from random effects analysis.

B. DAA: HCC occurrence

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>ES (95% CI)</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardoso</td>
<td>2016</td>
<td>7.41 (2.78, 19.74)</td>
<td>10.77</td>
</tr>
<tr>
<td>Conti</td>
<td>2016</td>
<td>4.51 (2.35, 8.67)</td>
<td>13.73</td>
</tr>
<tr>
<td>Rinaldi</td>
<td>2016</td>
<td>10.29 (4.91, 21.59)</td>
<td>12.92</td>
</tr>
<tr>
<td>Kozbiel</td>
<td>2016</td>
<td>1.80 (0.97, 3.35)</td>
<td>14.04</td>
</tr>
<tr>
<td>Lei-Zeng</td>
<td>2016</td>
<td>0.04 (0.00, 1.30e+07)</td>
<td>0.07</td>
</tr>
<tr>
<td>Plovesen</td>
<td>2016</td>
<td>1.40 (0.90, 2.17)</td>
<td>15.62</td>
</tr>
<tr>
<td>Alfronti</td>
<td>2016</td>
<td>3.33 (1.25, 8.88)</td>
<td>10.77</td>
</tr>
<tr>
<td>Muir</td>
<td>2016</td>
<td>0.12 (0.02, 0.85)</td>
<td>4.98</td>
</tr>
<tr>
<td>Carrau</td>
<td>2016</td>
<td>3.30 (2.67, 4.08)</td>
<td>17.98</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>2.96 (1.76, 4.96)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

NOTE: Weights are from random effects analysis.

C. IFN: HCC recurrence

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>ES (95% CI)</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hagiwara</td>
<td>2011</td>
<td>9.15 (4.58, 18.30)</td>
<td>12.00</td>
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<tr>
<td>Karogawa</td>
<td>2015</td>
<td>6.49 (3.49, 12.05)</td>
<td>16.13</td>
</tr>
<tr>
<td>Kunimoto</td>
<td>2016</td>
<td>7.87 (4.62, 12.94)</td>
<td>25.81</td>
</tr>
<tr>
<td>Saito</td>
<td>2014</td>
<td>12.88 (6.14, 27.01)</td>
<td>11.29</td>
</tr>
<tr>
<td>Sarafuji</td>
<td>2009</td>
<td>13.33 (4.30, 41.34)</td>
<td>4.84</td>
</tr>
<tr>
<td>Minami</td>
<td>2016</td>
<td>8.10 (4.05, 16.19)</td>
<td>12.00</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>9.21 (7.18, 11.81)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

NOTE: Weights are from random effects analysis.

D. DAA: HCC recurrence

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>ES (95% CI)</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conti</td>
<td>2016</td>
<td>45.82 (28.49, 73.71)</td>
<td>14.95</td>
</tr>
<tr>
<td>Pol, CO22</td>
<td>2016</td>
<td>8.11 (5.43, 12.16)</td>
<td>15.14</td>
</tr>
<tr>
<td>Pol, CO12</td>
<td>2016</td>
<td>4.40 (0.62, 21.12)</td>
<td>8.68</td>
</tr>
<tr>
<td>Pol, CO23</td>
<td>2016</td>
<td>2.82 (1.35, 5.92)</td>
<td>14.00</td>
</tr>
<tr>
<td>Reig</td>
<td>2016</td>
<td>55.00 (33.69, 89.78)</td>
<td>14.91</td>
</tr>
<tr>
<td>Rinaldi</td>
<td>2016</td>
<td>26.67 (13.76, 57.42)</td>
<td>8.68</td>
</tr>
<tr>
<td>Minami</td>
<td>2016</td>
<td>20.98 (9.43, 46.70)</td>
<td>13.86</td>
</tr>
<tr>
<td>Torres</td>
<td>2016</td>
<td>0.07 (0.00, 2.22e+07)</td>
<td>0.20</td>
</tr>
<tr>
<td>Zavaglia</td>
<td>2016</td>
<td>1.42 (0.20, 10.07)</td>
<td>8.88</td>
</tr>
<tr>
<td>Lei-Zeng</td>
<td>2016</td>
<td>0.08 (0.00, 2.60e+07)</td>
<td>0.20</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>12.16 (5.00, 29.58)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

NOTE: Weights are from random effects analysis.
Post hoc Image Analysis Retrospectively Identify Lesions Within the Liver on Water-Only DIXON MRI Scans of Pts Who Developed HCC Before Clinical Diagnosis

Pre-Treatment MRI | Post-Treatment MRI | Clinical-Diagnostic MRI

DAA-Induced SVR and HCC Incidence in Large Retrospective VA Cohort

Years after Start of HCV treatment

Probability Free From HCC Diagnosis

- No cirrhosis with SVR
- No cirrhosis with no SVR
- Cirrhosis with SVR
- Cirrhosis with no SVR

Cirrhotic Pts Continue to Have a High Risk for HCC (>2%/year) After SVR

 Patients with cirrhosis must continue surveillance.
 Patients without cirrhosis but with FIB-4 scores ≥3.25 have a high enough risk to merit HCC surveillance, especially if FIB-4 remains ≥3.25 post-SVR.

Patients with Cirrhosis Regression Still Remain at Risk of HCC


© ESCMID eLibrary by author

Courtesy of A. Aghemo
De Novo Incidence of HCC: The NAVIGATORE Database

3917 patients. Follow-up after DAA initiation of 536.2±197.6 days

Metabolic Syndrome and HCC Risk

Incidence of HCC in cirrhotics with metabolic syndrome: 10% at 6 years

Nahon P et al. *Gastroenterology* 2017;152:142-156
Long-Term Follow-Up of HCC

- **F0**: Discharge provided they have no further comorbidities
- **F1**: Ultrasound surveillance and/or alpha-fetoprotein estimation every 6 months
- **F2**: Follow-up as if they were never infected with HCV
- **F3**: Ultrasound surveillance for HCC every 6 months
- **F4+**: Ultrasound surveillance for HCC every 6 months

Remaining Problems After Successful DAA Treatment

- Management of advanced cirrhosis
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  - Role of comorbidities
  - Can we stop surveillance and in which patients?
- Persistent immunologic abnormalities
- Residual extrahepatic manifestations
- DAA resistance
- Reinfection
Lack of full CD8 functional restoration after antiviral treatment for acute and chronic hepatitis C virus infection

Gabriele Missale,1 Massimo Pili,1 Alessandro Zerbini,2 Amalia Penna,1 Lara Ravanetti,1 Valeria Barili,1 Alessandra Orlandini,1 Atim Molinari,1 Massimo Fasano,3 Teresa Santantonio,4 Carlo Ferrari1

Hepatitis C virus-induced NK cell activation causes metzincin-mediated CD16 cleavage and impaired antibody-dependent cytotoxicity

Barbara Oliviero1,1, Stefania Mantovani1,4, Stefania Varchetta1, Dalila Mele1, Giulia Grossi1, Serena Ludovisi1,1, Elisa Nuti1, Armando Rossello3, Mario U. Mondelli1,2,8

Reversion of anergy signatures in clonal CD21\textsubscript{low} B cells of mixed cryoglobulinemia after clearance of HCV viremia

Martina Del Padre, Laura Todi, Milica Mitrevski, Ramona Marrapodi, Stefania Colantuono, Massimo Fiorilli, Milvia Casato, and Marcella Visentini
Department of Clinical Medicine, Sapienza University of Rome Medical School, Rome, Italy

However, B cells maintained features of exhaustion being mostly CD21\textsuperscript{low} IgM+ CD27+ CD11c+ FCRL4+
Memory-Like TCF1+ CD127+ PD1+ HCV-Specific CD8+ T Cells Are Exhausted and Persist Long After DAA-Induced HCV Cure

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HCV Infection Is a Systemic Disease

Age-Adjusted Incidence of EHC Compared to the General French Population Was Higher in Pts Who Achieved SVR

EHC Is A Major Cause of Morbidity and Mortality in DAA-Cured Pts

\[ P = 0.013 \quad \text{SMR 1.57; 95\% CI, 1.08-2.22} \]
Long-Term Outcomes of Pts With HCV Cryoglobulinemic Vasculitis After Cure

48 patients with Cryoglobulinemic Vasculitis followed for 24 (17-41) months after SVR with DAAs

- Baseline
- Follow-up at SVR12
- End of follow-up

Circulating Cryoglobulins:
- 100% (n=48)
- 59% (n=27)
- 22% (n=10)

- Purpura: 63% (n=29), 7% (n=1), 0%
- Kidney disease: 20% (n=9), 7% (n=3), 7% (n=3)
- Neuropathy: 41% (n=19), 15% (n=10), 7% (n=3)

Frequencies and Numbers of Peripheral B-Cell Clones in Pts With Cryoglobulinemic Vasculitis Achieving HCV Cure

MCV clinical response:

Complete 78%
Partial 18%
Null 4%

Cryo detectable in 42%
At 12 mos.

B-cell clones persisted in 40%. Half cleared cryo, 12% relapsed after several mos.
DALYs per 100 000 People for Cardiovascular Disease Attributable to HCV

DALY Higher in LMIC

DAA Cure Improves Carotid Thickness in Pts with Chronic Hepatitis C and Severe Liver Fibrosis

Ultrasonographic assessment of intima-media thickness and carotid thickening in patients with advanced fibrosis/compensated cirrhosis due to HCV infection: Impact of SVR by DAA

- Baseline: 0.94 ± 0.29
- 9-12 mo after DAA: 0.81 ± 0.27

N = 182

Prevalence of IMT ≥ 1 mm (%)

- Baseline: 42.8
- 9-12 mo after DAA: 17

N = 182

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- Reinfection
DAA Treatment Failures

- Treatment with DAAs leads to selection for drug resistant HCV variants.
- Rare HCV subtypes are associated with resistance.
- Pre-existent and DAA-selected NS5A and NS5B S282 RASs frequently detected in subtype 4r$^1$ or 1l$^2$.
- Difficult-to-retreat patients may benefit from SOF/VEL/VOX or alternative treatment combos and/or the addition of RBV and/or longer retreatment duration.

Baseline Resistance-Guided Therapy Does Not Influence Response to DAAs in HCV Infection: A Real Life Prospective Cohort Study

- Prospective observational study in naïve pts.
- 120 treated according to RGT and 512 patients were controls.
- 7.5% in RGT had RASs, all SVR.
- SVR12 rate in RGT population was 97.2% (3 relapses), 98.8% (6 relapses) in the control population (p = 0.382).
- Limitations: non-randomized, previous SOF-containing ± IFN ± RBV regimens allowed, GT effect in some pts treated with grz/elb who had <60% response rate
Remaining Problems After Successful DAA Treatment

- Management of advanced cirrhosis
- HCC surveillance
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- Persistent immunologic abnormalities
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- Reinfection
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

\[ \text{N} = 3,004 \]

\[ \text{SVR12} \]

\[ \text{n} = 2,992 \]

\[ \text{SVR24} \]

\[ \text{n} = 12 \ (<1\%) \]

\[ \text{No SVR24} \]

○ Phylogenetic analyses
  - 5/12 with late relapse
  - 7/12 reinfected

HCV Reinfecion Over 5 Yrs by Study Population

TraP HepC: Outcomes at Vogur Addiction Hospital

- Dramatic reduction in community viral load and HCV incidence in only 2 yrs
- Between 2015 and 2017:
  - 55% reduction in incidence of total new HCV infections
  - 73% reduction in HCV PCR positive (ie, viremic) PWID
- Successful real-world example of treatment as prevention
Conclusions

- HCV cure reduces all cause mortality.
- Hepatic and extrahepatic morbidities are reduced but by no means NOT cancelled following an SVR.
- “Indelibly stamped” epigenetic and immunologic signatures remain long after cure, perhaps for life.
- Patients with advanced fibrosis or cirrhosis with SVR should remain under lifelong surveillance for HCC.
- Resistance is rarely difficult to handle. However, rare African subtypes may spread in at risk populations.
- HCV cure does not protect from reinfection. Treatment as prevention is the greatest remaining challenge for HCV elimination.
Cumulative Incidence of HCC Among 22,500 Veterans Treated With DAAs: Risk Remains High in Cirrhotics

Risk factors for HCC after SVR:
- Advancing age
- Cirrhosis
- Diabetes

DAAs Improve Survival in Pts with History of HCC: A Multicenter North American Cohort Study

![Graph showing survival rates for DAA treated and untreated patients]

- **DAA Treated:** 4.6 deaths per 100 person-years follow-up
- **DAA Untreated:** 19.6 deaths per 100 person-years follow-up

**Multivariable analysis**
- Adjusted for site, age, sex, Child Pugh score, AFP, tumor burden and HCC treatment modality

**DAA therapy associated with lower mortality:**
- HR: 0.54; 95%CI: 0.33 – 0.90

Risk of a Composite Outcome of All-Cause Mortality and HCC as a Function of Steatosis