Is Response to Anti-HCV Treatment Predictive of Mortality in HCV/HIV Co-infected Patients?

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Presenter disclosures

• The presenting author has no conflicts of interest
Background

- Observational studies of HCV mono-infected, a sustained virologic response (SVR) has been associated with reduced all-cause and liver-related mortality.

- In HIV/HCV patients, mixed retrospective-prospective studies from Spain, have shown that, compared with patients who achieved SVR, non-responders to HCV treatment had:
  - an almost nine-fold increased risk of liver-related clinical events
  - reduced risk of HIV progression and non-liver-related death

- Compared with HCV mono-infected patients, the benefit of HCV treatment of HIV/HCV patients could be:
  - greater due to accelerated fibrosis progression in co-infected patients
  - lower due to higher prevalence of competing risk factors (both HIV-related and lifestyle factors) for mortality.

1Berenguer, Hepatology 2009
2Berenguer, CID 2012
Objectives

- To compare the long-term risk of
  - all-cause mortality
  - liver-related death
  - Non-liver-related death

according to HCV treatment response in HIV/HCV co-infected patients in the prospective multi-cohort study COHERE
Methods

• The Collaboration of Observational HIV Epidemiological Research in Europe COHERE is a collaboration of 33 cohorts from across Europe and is part of the EuroCoord network

• Eighteen cohorts provided data for the present analysis.

• Analyses were based on data merged in July 2013
Inclusion criteria

• All HIV/HCV co-infected COHERE patients who had ever started interferon-based (IFN) therapy (baseline) and were followed-up for ≥96 weeks after baseline
Definition of HCV treatment response

- **Follow-up HCV-RNA not available in all**
  - **Non responders**
  - **Responders**
  - **Unknown**

<table>
<thead>
<tr>
<th>Weeks from starting IFN/RBV</th>
<th>IFN/RBV stop</th>
<th>No IFN/RBV stop</th>
<th>No IFN/RBV stop</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>IFN/RBV stop</td>
<td>No IFN/RBV stop</td>
<td>No IFN/RBV stop</td>
</tr>
<tr>
<td>24</td>
<td>or latest HCV RNA positive</td>
<td>and latest HCV RNA negative</td>
<td>and HCV RNA missing</td>
</tr>
<tr>
<td>48</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>72</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>96</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>120</td>
<td></td>
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<td></td>
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<tr>
<td>144</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>168</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Survival?

Follow-up HCV-RNA not available in all.
Statistical methods

- Mortality rates in the three groups were compared using survival analysis.

- Survival times accrued from 96 weeks after baseline up to the date of death or last follow-up.

- Cox regression models were used to compare hazard ratios of death between response groups.
Results

- 3,500 patients had started HCV treatment and were included:
  - 996 (28.5%) responders
  - 1587 (45.3%) non-responders
  - 917 (26.2%) with unknown response
### Patient characteristics at the date of HCV treatment initiation

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Responders N= 996</th>
<th>Non-responders N= 1587</th>
<th>Unknown response N= 917</th>
<th>p-value*</th>
<th>Total N= 3500</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median years (IQR)</td>
<td>42 (37, 46)</td>
<td>42 (37, 46)</td>
<td>41 (37, 46)</td>
<td>0.582</td>
<td>42 (37, 46)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>209 (21.0%)</td>
<td>392 (24.7%)</td>
<td>210 (22.9%)</td>
<td>0.091</td>
<td>811 (23.2%)</td>
</tr>
<tr>
<td>Injection drug use, n (%)</td>
<td>468 (47.0%)</td>
<td>1025 (64.6%)</td>
<td>581 (63.4%)</td>
<td>&lt;.001</td>
<td>2074 (59.3%)</td>
</tr>
<tr>
<td>On ART, n (%)</td>
<td>838 (84.1%)</td>
<td>1387 (87.4%)</td>
<td>787 (85.8%)</td>
<td>0.065</td>
<td>3012 (86.1%)</td>
</tr>
<tr>
<td>CD4 count, median (IQR) cells/mm³</td>
<td>461 (207, 653)</td>
<td>405 (167, 584)</td>
<td>453 (261, 620)</td>
<td>&lt;.001</td>
<td>426 (203, 619)</td>
</tr>
<tr>
<td>HIV-RNA, median (IQR) log₁₀ cp/mL</td>
<td>3.03 (2.00, 4.34)</td>
<td>3.05 (1.74, 4.15)</td>
<td>3.08 (1.94, 4.17)</td>
<td>0.411</td>
<td>3.05 (1.88, 4.17)</td>
</tr>
<tr>
<td>HCV RNA, median (IQR) log₁₀ IU/mL</td>
<td>5.85 (5.11, 6.34)</td>
<td>6.04 (5.56, 6.60)</td>
<td>5.99 (5.60, 6.51)</td>
<td>&lt;.001</td>
<td>5.95 (5.37, 6.51)</td>
</tr>
<tr>
<td>HCV genotype 1, n (%)*</td>
<td>262 (50.2%)</td>
<td>351 (62.2%)</td>
<td>138 (55.0%)</td>
<td>&lt;.001</td>
<td>751 (56.2%)</td>
</tr>
<tr>
<td>HBsAg-positive, n (%)</td>
<td>87 (10.5%)</td>
<td>371 (33.8%)</td>
<td>23 (4.1%)</td>
<td>&lt;.001</td>
<td>481 (19.3%)</td>
</tr>
<tr>
<td>APRI score, median (IQR)</td>
<td>0.9 (0.5, 2.1)</td>
<td>0.8 (0.5, 1.6)</td>
<td>0.8 (0.5, 1.4)</td>
<td>&lt;.001</td>
<td>0.8 (0.5, 1.7)</td>
</tr>
</tbody>
</table>

*N with data: 1337
Incidence rates of all-cause death

- After a median of 3.8 years of follow up, a total of 213 (6.1%) deaths had occurred.
  - The rates (per 1,000 PYFU, 95% CI) of all cause death were
    - 12.31 (10.35 - 14.65) for non-responders
    - 6.79 (4.92 - 9.37) for responders
    - 7.8 (5.86 - 10.26) for unknown responders
Cumulative risk of all-cause mortality

<table>
<thead>
<tr>
<th>Stratum</th>
<th>Obs</th>
<th>Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1587</td>
<td>127</td>
</tr>
<tr>
<td>2</td>
<td>996</td>
<td>37</td>
</tr>
<tr>
<td>3</td>
<td>917</td>
<td>49</td>
</tr>
</tbody>
</table>

Log rank $p = 0.0019$

<table>
<thead>
<tr>
<th>Year from TO (96 weeks after starting treatment)</th>
<th>Non-responders</th>
<th>Responders</th>
<th>Unknown response</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>1587</td>
<td>996</td>
<td>917</td>
</tr>
<tr>
<td>0.5</td>
<td>1428</td>
<td>818</td>
<td>828</td>
</tr>
<tr>
<td>1.0</td>
<td>1222</td>
<td>646</td>
<td>736</td>
</tr>
<tr>
<td>1.5</td>
<td>998</td>
<td>472</td>
<td>632</td>
</tr>
<tr>
<td>2.0</td>
<td>814</td>
<td>342</td>
<td>518</td>
</tr>
<tr>
<td>2.5</td>
<td>626</td>
<td>256</td>
<td>408</td>
</tr>
<tr>
<td>3.0</td>
<td>479</td>
<td>174</td>
<td>308</td>
</tr>
<tr>
<td>3.5</td>
<td>334</td>
<td>114</td>
<td>225</td>
</tr>
<tr>
<td>4.0</td>
<td>201</td>
<td>65</td>
<td>151</td>
</tr>
</tbody>
</table>
Hazard ratio for all-cause death

Adjusted for demographic factors
(age, gender, origin, year of baseline and mode of HIV transmission)

Adjusted for HIV-related factors
(prior AIDS, CD4 count, HIV RNA, HIV treatment use)

Adjusted for hepatitis-related factors
(HBsAg, APRI)

Adjusted for demographic, HIV- and hepatitis related factors

Responders
Non-responders
Unknown response

Adjusted incidence rate ratio (95% CI)
Incidence rates of liver-related death

- Liver-related death accounted for
  - 45/127 (35.4%) of all deaths among non-responders
  - 4/37 (10.8%) among responders
  - 12/49 (24.5%) among patients with unknown response

- Among responders with liver-related death, one out four had evidence of reinfection. None died from hepatocellular carcinoma

- Rates (per 1,000 PYFU, 95% CI) of liver-related death were
  - 4.17 (3.09 - 5.62) for non-responders
  - 0.73 (0.28 - 1.96) for responders
  - 1.9 (1.08 - 3.34) for unknown responders
Cumulative risk of liver-related death

<table>
<thead>
<tr>
<th>Stratum</th>
<th>Obs</th>
<th>Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1587</td>
<td>45</td>
</tr>
<tr>
<td>2</td>
<td>996</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>917</td>
<td>12</td>
</tr>
</tbody>
</table>

Non-responders  
- 1587  
- 1428  
- 1222  
- 998   
- 814   
- 626   
- 479   
- 334   
- 201   

Responders  
- 996   
- 818   
- 646   
- 472   
- 342   
- 256   
- 174   
- 114   
- 65    

Unknown response  
- 917   
- 828   
- 736   
- 632   
- 518   
- 408   
- 308   
- 225   
- 151
Hazard ratio for liver-related death

Adjusted for demographic factors
(age, gender, origin, year of baseline and mode of HIV transmission)

Adjusted for HIV-related factors
(AIDS, CD4 count, HIV RNA, HIV treatment use)

Adjusted for hepatitis-related factors
(HBsAg, APRI)

Adjusted for demographic, HIV- and hepatitis related factors

Responders
Non-responders
Unknown response

Adjusted incidence rate ratio (95% CI)
Non-liver-related mortality according to HCV treatment response

• All liver-related deaths excluded from analysis

• In unadjusted analysis there was no difference (non-responders vs. responders) in relative hazard of non-liver-related death (1.17, 95% CI 0.78 – 1.76).

• In fully adjusted model the relative hazard was 1.16 (95% CI 0.77 – 1.76)
Strengths and limitations

• Large prospective cohort study

• Lack of follow-up HCV-RNA measurements on all patients at least six months after end of therapy
  – some of the patients categorized as responders could have had HCV-RNA relapse
  – some patients categorized as non-responders could have achieved an SVR

• This limitation would only tend to underestimate the survival benefit of HCV therapy
Conclusions

• HIV/HCV co-infected patients with a favourable virological response to HCV treatment had
  – reduced risk of liver-related death and
  – improved overall survival

• There was no differences in risk of non-liver-related death between HCV treatment response groups
**Acknowledgements**

**Project leaders and statistical analysis:**


**Writing group**

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