How to treat HCV-HBV co-infection?

Robert Flisiak

Department of Infectious Diseases and Hepatology
Medical University of Białymstoku

Paris Hepatology Conference, 14-15 January 2019
Conflict of interest

Advisory and grants from:
AbbVie, Gilead, MSD, Roche
Categories of virus–virus interaction

I. Direct interactions
   a. Helper-dependent viruses
   b. Pseudotype viruses
   c. Superinfection exclusion
   d. Genomic recombination
   e. Embedded viruses
   f. Heterologous transactivation

II. Environmental interactions
   a. Indirect transactivation of genes
   b. Breakdown of physical barriers
   c. Altered receptor expression
   d. Heterologous activation of pro-drugs
   e. Modification of the interferon-induced antiviral state

III. Immune effects
   a. Altered immune cell activation
   b. Induction of autoimmunity
   c. Antibody-dependent enhancement of infection
   d. Heterologous immunity
No direct viral interference in HBV/HCV coinfection

In vitro model of Huh-7 cell lines replicating HBV and HCV

HBV inhibition does not affect HCV replication

HCV inhibition does not affect HBV replication

HBV and HCV may replicate within the same cell

Possible superinfection of HBV-inducible cell lines with HCV

Practical issues related to treatment of HBV/HCV coinfected patients

1. Risk of drug to drug interactions between regimens provided to cure HCV and suppress HBV infection.

2. Possible reactivation of HBV during or shortly after therapy with direct acting antivirals (DAA) due to HCV infection.
Tenofovir blood concentration can be increased when administered with sofosbuvir containing regimens, so patients on tenofovir disoproxil, particularly those with kidney diseases should be monitored and if possible an alternative DAA regimen should be selected.

https://www.hep-druginteractions.org/checker
HBV reactivation associated with DAA – FDA report

<table>
<thead>
<tr>
<th>Case Number (Reference)</th>
<th>HCV Genotype</th>
<th>HBV Genotype</th>
<th>HBsAg</th>
<th>HBsAb</th>
<th>HBeAg</th>
<th>HBeAb</th>
<th>HBV DNA Level, copies/mL*</th>
<th>DAA</th>
<th>Country of Report</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Negative Positive</td>
<td>2700 (elevated)</td>
<td>Viekira Pak (AbbVie)/RBV</td>
<td>United States</td>
</tr>
<tr>
<td>2 (42)</td>
<td>1b</td>
<td>Positive</td>
<td>NR</td>
<td>NR</td>
<td>Negative Positive</td>
<td>2.5 log10 (elevated)</td>
<td>DCV/ASV</td>
<td>Japan</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Negative Positive</td>
<td>Undetectable</td>
<td>DCV/ASV</td>
<td>Japan</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1b</td>
<td>Positive</td>
<td>NR</td>
<td>NR</td>
<td>Negative Positive</td>
<td>3.9 log10 (elevated)</td>
<td>DCV/ASV</td>
<td>Japan</td>
<td></td>
</tr>
<tr>
<td>5 (29)</td>
<td>1a</td>
<td>NR</td>
<td>NR</td>
<td>Negative Positive</td>
<td>Undetectable</td>
<td>DCV/ASV</td>
<td>Japan</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 (29)</td>
<td>1a</td>
<td>Negative</td>
<td>Negative</td>
<td>Positive</td>
<td>NR</td>
<td>NR</td>
<td>Undetectable</td>
<td>SIM/SOF</td>
<td>United States</td>
</tr>
<tr>
<td>7 (26)</td>
<td>1</td>
<td>Negative</td>
<td>Negative</td>
<td>Positive</td>
<td>NR</td>
<td>NR</td>
<td>Undetectable</td>
<td>SIM/SOF/RBV</td>
<td>United States</td>
</tr>
<tr>
<td>8</td>
<td>3a</td>
<td>Positive</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Undetectable</td>
<td>244 (elevated)</td>
<td>SOF/RBV</td>
<td>United States</td>
</tr>
<tr>
<td>9 (38)</td>
<td>4</td>
<td>D</td>
<td>Negative</td>
<td>Negative</td>
<td>Positive</td>
<td>Undetectable</td>
<td>244 (elevated)</td>
<td>SOF/RBV</td>
<td>Portugal</td>
</tr>
<tr>
<td>10 (28)</td>
<td>NR</td>
<td>NR</td>
<td>Positive</td>
<td>NR</td>
<td>NR</td>
<td>Undetectable</td>
<td>244 (elevated)</td>
<td>SOF/RBV</td>
<td>France</td>
</tr>
<tr>
<td>11</td>
<td>NR</td>
<td>NR</td>
<td>Positive</td>
<td>NR</td>
<td>NR</td>
<td>Undetectable</td>
<td>244 (elevated)</td>
<td>SOF/RBV</td>
<td>United States</td>
</tr>
<tr>
<td>12 (43)</td>
<td>1</td>
<td>B</td>
<td>Positive</td>
<td>NR</td>
<td>NR</td>
<td>Negative Positive</td>
<td>Undetectable</td>
<td>SIM/PEG/RBV</td>
<td>Japan</td>
</tr>
<tr>
<td>13</td>
<td>1</td>
<td>A</td>
<td>Positive</td>
<td>NR</td>
<td>NR</td>
<td>Negative Positive</td>
<td>Undetectable</td>
<td>SOF/RBV</td>
<td>Japan</td>
</tr>
<tr>
<td>14</td>
<td>NR</td>
<td>NR</td>
<td>Positive</td>
<td>NR</td>
<td>NR</td>
<td>Negative Positive</td>
<td>1.3 log10 (elevated)</td>
<td>LDV/SOF</td>
<td>Japan</td>
</tr>
<tr>
<td>15</td>
<td>1b</td>
<td>B</td>
<td>Positive</td>
<td>NR</td>
<td>NR</td>
<td>Negative Positive</td>
<td>2.7 log10 (elevated)</td>
<td>DCV/ASV</td>
<td>Japan</td>
</tr>
<tr>
<td>16</td>
<td>NR</td>
<td>C</td>
<td>Positive</td>
<td>NR</td>
<td>NR</td>
<td>Undetectable</td>
<td>244 (elevated)</td>
<td>SOF/RBV</td>
<td>Japan</td>
</tr>
<tr>
<td>17</td>
<td>1a</td>
<td>NR</td>
<td>Positive</td>
<td>NR</td>
<td>NR</td>
<td>Negative Negative</td>
<td>Undetectable</td>
<td>DCV/SOF/RBV</td>
<td>Australia</td>
</tr>
<tr>
<td>18</td>
<td>NR</td>
<td>NR</td>
<td>Positive</td>
<td>NR</td>
<td>NR</td>
<td>Negative Positive</td>
<td>3.6 log10 (elevated)</td>
<td>LDV/SOF/RBV</td>
<td>Japan</td>
</tr>
<tr>
<td>19</td>
<td>1b</td>
<td>NR</td>
<td>Negative</td>
<td>Positive</td>
<td>NR</td>
<td>NR</td>
<td>&lt;2.1 log10†</td>
<td>DCV/ASV</td>
<td>Japan</td>
</tr>
<tr>
<td>20</td>
<td>1b</td>
<td>NR</td>
<td>Positive</td>
<td>Undetectable</td>
<td>DCV/ASV</td>
<td>Japan</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>NR</td>
<td>Positive</td>
<td>NR</td>
<td>NR</td>
<td>Undetectable</td>
<td>DCV/ASV</td>
<td>Japan</td>
<td></td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>NR</td>
<td>NR</td>
<td>Negative</td>
<td>Undetectable</td>
<td>DCV/ASV</td>
<td>Japan</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Undetectable</td>
<td>DCV/ASV</td>
<td>Japan</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>NR</td>
<td>C</td>
<td>NR</td>
<td>Undetectable</td>
<td>DCV/ASV</td>
<td>Japan</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>NR</td>
<td>B</td>
<td>Negative</td>
<td>Undetectable</td>
<td>DCV/ASV</td>
<td>Japan</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>26</td>
<td>NR</td>
<td>B</td>
<td>NR</td>
<td>Undetectable</td>
<td>DCV/ASV</td>
<td>Japan</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>27</td>
<td>NR</td>
<td>B</td>
<td>Negative</td>
<td>Undetectable</td>
<td>DCV/ASV</td>
<td>Japan</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>28</td>
<td>NR</td>
<td>NR</td>
<td>Negative</td>
<td>Undetectable</td>
<td>DCV/ASV</td>
<td>Japan</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>29 (44)</td>
<td>1b</td>
<td>NR</td>
<td>Negative</td>
<td>Undetectable</td>
<td>DCV/ASV</td>
<td>Japan</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ASV – asunaprevir; DAA – direct-acting antiviral agent; DCV – daclatasvir; HBCAb – hepatitis B core antibody; HBeAb – hepatitis B e antibody; HBsAg – hepatitis B surface antigen; HBSAb – hepatitis B surface antibody; HCV – hepatitis C virus; LDV – ledipasvir; RBV – ribavirin; SIM – simprevir; SOF – sofosbuvir.

* Values interpreted as undetectable only if specifically stated as such in the U.S. Food and Drug Administration Adverse Event Reporting System report. Values expressed by a numeral, provided without units, and/or not specifically stated as undetectable were interpreted as elevated/detectable.
† Values preceded by “<” were regarded as uninterpretable if not specifically stated as undetectable.
DAA and PegIFN cause similar risk of HBV reactivation

<table>
<thead>
<tr>
<th></th>
<th>N available and Rate per 1000 person-years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N available (Number of events/number available for analysis)</td>
</tr>
<tr>
<td>DAA</td>
<td>9/377 (2.4%)</td>
</tr>
<tr>
<td>PEG/RBV</td>
<td>37/209 (18%)</td>
</tr>
<tr>
<td>P-value. DAA vs PEG/RBV</td>
<td>—</td>
</tr>
</tbody>
</table>
HBV reactivation in 111 HCV coinfected, HBsAg-positive patients treated with LDV/SOF

HBV DNA reactivation through treatment and post-treatment week 12

5 patients with concomitant HBV DNA elevation and ALT>2 ULN through post-treatment week 12

<table>
<thead>
<tr>
<th>Patients, n</th>
<th>During treatment</th>
<th>After treatment</th>
<th>Total</th>
<th>During treatment</th>
<th>After treatment</th>
<th>Total</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 patients with concomitant HBV DNA elevation and ALT&gt;2 ULN through post-treatment week 12</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

There is a potential risk of HBV reactivation during or after HCV clearance, but the risk is unpredictable.

Patients commencing DAA-based treatment for hepatitis C should be tested for HBs antigen, anti-HBc antibodies and anti-HBs antibodies.

- Patients with HBV-HCV coinfection should be treated with the same anti-HCV regimens, following the same rules as HCV monoinfected patients (B1).
- Patients coinfected with HCV and HBV fulfilling the standard criteria for HBV treatment should receive nucleoside/nucleotide analogue treatment according to the EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection (A1).
- Patients who are HBs antigen-positive should receive nucleoside/nucleotide analogue prophylaxis at least until week 12 post anti-HCV therapy and be monitored monthly if HBV treatment is stopped (B1).
- In patients who are HBs antigen-negative but anti-HBc antibody-positive, serum ALT levels should be monitored monthly, HBs antigen and HBV DNA should be tested if ALT levels do not normalise or rise during or after anti-HCV therapy, and nucleoside/nucleotide analogue analogue therapy should be initiated if HBs antigen and/or HBV DNA are present (B1).
Do we really need to follow all HBsAg-negative but anti-HBc positive patients?
Risk of HBV reactivation on DAA in HBsAg-/anti-HBc+

**Studies carried-out in immunocompetent, HCV infected with isolated anti-HBc positivity before start of DAA therapy.**

<table>
<thead>
<tr>
<th>Study</th>
<th>anti-HBc positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yanny BT et al, 2018</td>
<td>127</td>
</tr>
<tr>
<td>Sulkowski MS et al, 2016</td>
<td>103</td>
</tr>
<tr>
<td>Wang C et al, 2017</td>
<td>124</td>
</tr>
<tr>
<td>Loggi E et al, 2017</td>
<td>42</td>
</tr>
<tr>
<td>Mucke VT et al, 2017</td>
<td>263</td>
</tr>
<tr>
<td>Liu et al, 2016</td>
<td>46</td>
</tr>
<tr>
<td>Yeh ML et al, 2017</td>
<td>57</td>
</tr>
<tr>
<td>Jaroszewicz J et al, 2019</td>
<td>742</td>
</tr>
<tr>
<td></td>
<td><strong>1504</strong></td>
</tr>
</tbody>
</table>
Case of HBV reactivation in HBsAg-/ant-HBc+ During DAA treatment in 88 years old patient after kidney transplantation

88-year-old male post kidney transplant
HCV (Genotype: 1b, viral load: 6.0 log/mL)
HBV (viral load; under detection levels, anti-HBs; below 10 IU/mL)

<table>
<thead>
<tr>
<th></th>
<th>HBsAg</th>
<th>Anti-HBs</th>
</tr>
</thead>
<tbody>
<tr>
<td>(IU/mL)</td>
<td>0.001</td>
<td>0.1</td>
</tr>
</tbody>
</table>

21 IU/mL

Tamari A et al. J Viral Hepatitis 2017
Case of HBV reactivation in HBsAg-/ant-HBc+

38 wks after DAA administered due to post OLTx recurrence of HCV

...a case of late HBV reactivation, 38wk after DAA-based treatment (2015) of recurrent hepatitis C in an antibody against hepatitis B core antigen (anti-HBc)-positive LT recipient (2011). Immunosuppressive treatment was unchanged over the last year and consisted of tacrolimus (trough levels 5-6 mg/L) and prednisone 5mg qd.
Transient increase of HBV DNA in patients HBsAg-/anti-HBc+ treated with DAA

HBV DNA, HCV RNA, ALT, HBsAg and anti-HBs measured every 4 wks in 63 patients

- About 6% patients with resolved HBV infection had HBV DNA become detectable during DAA treatment.

- Detectable HBV DNA was a transient phenomenon related to negative or very low-titre anti-HBs, which did not result in hepatic failure.

Conclusions

• All patients scheduled for treatment of HCV infection should be tested for HBsAg.

• At least patients with confirmed or suspected immunodeficiency should be additionally tested for anti-HBc.

• Prophylaxis with potent nucleoside/nucleotide analogue should be administered at least 4 weeks before start of anti-HCV treatment in all HBsAg-positive and immunodeficient HBsAg-negative/anti-HBc-positive patients and continued at least until 12 weeks after HCV treatment termination.

• Immunocompetent HBsAg-negative/anti-HBc-positive patients probably do not need specific monitoring for possible HBV reactivation.