DAA controversies: Do they cause HBV reactivation and HCC?

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Disclosures

• Research Grants: Abbott, Abbvie, Gilead, Janssen, Merck

• Consulting: Abbvie, Contravir, Gilead, Intellia, Janssen, Merck
Outline

• DAAs and HBV reactivation
  – HBsAg +ve
  – HBsAg –ve/anti-HBc +ve

• DAAs and HCC
  – Recurrence
  – De novo HCC
  – Affect of HCC on SVR
Outline

• DAAs and HBV reactivation
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HBV reactivation with DAAs...
Patient 1
HBsAg +ve, HCV G1b, Cirrhosis

Patient 2
HBsAg –ve / cAb + / DNA<20 IU/mL
FDA Drug Safety Communication: FDA warns about the risk of hepatitis B reactivating in some patients treated with direct-acting antivirals for hepatitis C

- Recommendations based on 29 cases of HBVr including 2 deaths and 1 transplant
  - Average 4-8 weeks (53 d) of DAA therapy
  - 10 cases – DAA hepatotoxicity was suspected and DAAs stopped
  - 15 eventually received HBV therapy with ETV/TDF – 7-60 d delay and 26 (90%) meant treatment criteria
  - 4 HBsAg negative, anti-HBc +ve at baseline and 11 had unclear serology – limited data on many patients

- Screen all patients for evidence of current or prior HBV infection before initiating treatment with DAAs by measuring HBsAg and anti-HBc. In patients with serologic evidence of HBV infection, measure baseline HBV DNA prior to DAA treatment.
What’s the risk?

• HBsAg +ve
  – Excluded from all trials

  – Hong Kong
    • 3 of 10 HBsAg +ve with HBV reactivation – 1 liver failure – 4-10 weeks into DAA therapy

  – New Zealand
    • 7 of 8 → HBV DNA rose but <20,000 IU/mL, no hepatitis

  – Japan
    • 25 HBsAg +ve – 3 DNA>2000 IU/mL → ETV and no HBVr
    • 3 of 22 with HBVr → no hepatitis

IFN vs DAA: A meta-analysis

• 36 studies with 1185 patients
• IFN - 29 studies with 1037 patients
• DAA – 7 studies with 148 patients

• Excluding 8 case reports
  – 779 HBsAg +ve
  – 130 anti-HBc +ve
**Reactivation vs Hepatitis Rate**

**HBV Reactivation:** 14.5% IFN  
12.2% DAA

**HBV-associated hepatitis:** 0% (0-1.1) IFN  
12.2% (0.2-33.2) DAA

- **In HBsAg +ve:** Reactivation common, hepatitis less so
- **Based on very few DAA-treated patients...wide CI**
Some other findings

• **Timing**
  – IFN – end of or post-treatment
  – DAA – 4-12 weeks during treatment

• **HBsAg loss**
  – IFN - 9.2% (3.1-17.8)
  – DAA – 0 (only 1 study)

• **Effect on SVR**
  – No effect with IFN or DAA

But still based on small numbers for DAAs...
An adequate trial – HBsAg +ve

HBsAg + with HCV G1 (n=68) or G2 (n=43) SOF/LDV x 12w  →  100% SVR

HBV DNA undetectable at baseline (n=37)
- HBV DNA rise > 1 log – 22/37 (60%)
- ALT > 2 x ULN - 0

HBV DNA > 20 IU/mL at baseline (n=74)
- HBV DNA rise > 1 log – 39/74 (53%)
- ALT > 2 x ULN – 5/39 (13%)

• Most rises in HBV DNA subclinical (no ALT rise) – no liver failure
• Occurred during AND after treatment

Liu Gastro In Press
Patients with HBVr + Hepatitis

- 3 started therapy – 1 at wk 8 and 2 **post-treatment** (F/U 4 & 36) – 1 with jaundice
- Therapy might have been reasonable in 1 or both of the others
- No data on stopping HBV therapy – withdrawal flares...

Liu Gastro *In Press*
Authors’ conclusion

- HBV reactivation in HBsAg +ve individuals is common but rarely of clinical consequence (ie associated with ALT elevation or bilirubin rise)
- More relevant if HBV DNA detectable at baseline
- They recommend:
  - Screen everyone
  - *Monitor during and after treatment with treatment if required as per guidelines…*not entirely sure I agree
What about HBsAg-neg/anti-HBc-pos?

- **HBsAg –ve / HBc +ve**
  - **Hong Kong**: 0 of 124 HBsAg –ve/ HBc +ve
    - 7 hepatitis but none HBV-related
  - **Taiwan/Korea**: 0 of 103 in SOF/LDV trials

**Japan**
- 1 of 765 (0.1%) – no hepatitis & DNA to neg post-DAA
- 3 of 145 DNA (2%) became detectable, no ALT rise

- **Meta-analysis**: 0 cases with IFN, 3 case reports with DAAs

Chen Hepatology 2017
A ‘real-world’ cohort

808 patients – 262 lone anti-HBc +ve, 9 HBsAg +ve incl 6 with DNA +ve

<table>
<thead>
<tr>
<th>HCV GT</th>
<th>Age</th>
<th>Cirrhosis, CPT score</th>
<th>DAA Treatment for HCV</th>
<th>Baseline HBsAg (IU/mL)</th>
<th>Baseline HBV DNA (IU/mL)</th>
<th>Wk 4-8 HBV DNA (IU/mL)</th>
<th>EOT HBV DNA (IU/mL)</th>
<th>FU 12/24 HBV DNA (IU/mL)</th>
<th>HBV Treatment initiated</th>
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<td>9980</td>
<td>TND</td>
<td>&lt;20</td>
<td>29 400</td>
<td>Yes, TDF 36 weeks post-EOT</td>
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<td>No</td>
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<td>LDV/SOF+RBV, 12 weeks</td>
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<td>3a</td>
<td>43</td>
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<td>DCV+SOF+RBV, 24 weeks</td>
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<td>TND</td>
<td>TND</td>
<td>No*</td>
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</table>

- **Anti-HBc**: No events but 7 with detectable HBV DNA → back to <20 IU/mL by SVR12
- **HBsAg +ve**: 4/9 required treatment – 3 of 4 after DAAs – 36-40 weeks post-EOT!
Big Data – the VA steps in...

- 69,920 patients
  - 85% HBsAg testing $\rightarrow$ 0.70% +ve (377/53,784)
  - 64% anti-HBc testing $\rightarrow$ 45.7% +ve (7,295/18,462) $\rightarrow$ it’s common!

- **HBsAg +ve (n=377)**
  - 96 (25%) on HBV therapy
  - 8 (2.1%) with HBV reactivation (>3 log rise in DNA)
    - 6 of 8 with rise in ALT but only 1 significant rise (1,540 with DNA 7 logs), all SVR

- **Anti-HBc +ve (n=7,295)**
  - 0/390 tested became HBsAg +ve
  - DNA tested in 2.4% (n=173) and 4 +ve $\rightarrow$ 1 with rise in HBV DNA to 5.4 log but ALT of 17

- HBV reactivation not affected by HCV genotype, regimen, cirrhosis and no effect on chance of SVR
- Another study…IFN vs DAAs (25.4 vs 30.0 per 100 py p=0.8)
What do the Guidelines say?

- All patients initiating HCV DAA therapy should be assessed for HBV coinfection with HBsAg, anti-HBs, and anti-HBc.  
  Rating: Class IIa, Level B

- For HBsAg+ patients who are not already on HBV suppressive therapy,
  1. If HBV DNA levels meet criteria for treatment → start antiviral therapy
  2. If HBV DNA levels do NOT meet criteria for treatment
     1. Initiate prophylactic antiviral therapy and continue through 12 weeks post-DAA (ie SVR)
     2. Monitor HBV DNA during DAA therapy and start HBV therapy if HBV DNA levels rise by 1 log or to > 1000 IU/mL if undetectable at baseline

- For HBsAg-negative but anti-HBc or anti-HBc/anti-HBs positive
  - Insufficient data to provide clear recommendations on HBV DNA monitoring
  - However the possibility of HBV reactivation should be considered if unexplained rise in ALT during or after DAA therapy
HBV reactivation – my take

• Clearly a risk in HBsAg +ve patients
  – Screen everyone
  – Treat positives to SVR – watch for withdrawal flare

• No clear cases of clinical reactivation reported in HBsAg –ve/anti-HBc +ve without additional therapy (e.g. immunosuppression) to date
  – Screen for anti-HBc
    • If ALT does not normalize or rises – check HBsAg and/or HBV DNA

HBsAg +ve → treatment
Lone Anti-HBc → low risk → follow ALT +/- HBsAg, no treatment
ECHO and Pockros agree
And the mechanism?

Weren’t you listening...
I’m Jake Dickens and I’m an alpha male virus

HCV is the alpha virus dominating that puny B virus
Outline

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• DAAs and HCC
  – Recurrence
  – De novo HCC
  – Affect of HCC on SVR
Unexpected early tumor recurrence in patients with hepatitis C virus-related hepatocellular carcinoma undergoing interferon-free therapy: a note of caution

María Reig\textsuperscript{a}, Zoe Mariño\textsuperscript{a}, Christie Perelló, Mercedes Iñarrairegui, Andrea Ribeiro, Sabela Lens, Alba Díaz, Ramón Vilana, Anna Darnell, María Varela, Bruno Sangro, José Luis Calleja, Xavier Forns\textsuperscript{b}, Jordi Bruix

\textsuperscript{a} These authors contributed equally as first co-authors.
\textsuperscript{b} These authors contributed equally as senior co-authors.
Raising the alarm bells!

- 58 patients with ‘curative’ therapy for HCC treated with DAAs
- Mean 5.7 months F/U
  - 3 died
  - 16 recurrent HCC (27.6%)
    - Tumor growth (3 patients)
    - New lesion (n=10 – 1 lesion (n=5), ≤3 (n=4), Multifocal (n=1)
    - Infiltrative or extra-hepatic mets (n=3)

Reig et al J Hepatology 2016
Similar results

344 consecutive cirrhotic patients tx with DAAs, 59 previous HCC, 90% SVR

Risk factors for HCC post-DAAs
- CP-Class 4.18 (1.2-14.8)
- Prior HCC 12 (4.0-35.7)

81 OLTx for HCV-related HCC, 18 tx with DAAs, 63 no DAAs

Similar results to Spanish study – high rate of early recurrent HCC

Why might this happen?

• Not known
• Theories abound

1. Reduced immune surveillance
   – HCV stimulates immune response
   – HCV-specific T cells produce cytokines (incl IFN) with anti-HCC effects

2. DAAs are pro-neoplastic
   – Promote HCC growth and spread

Llovet & Villanueva Nat Rev Gastro Hep 2016
Not everyone agrees...

- 3 French Cohorts
  - HEPATHER - 267 previous HCC → 189 DAAs vs 78 no treatment
    - Survival-free of HCC recurrence
      - 0.73 vs 0.66/100 pt mos
      - p=ns
  - CirVir – 79 post HCC → 13 DAA vs 66 no DAA → 1.11 vs 1.73/100 pt mos
    - p=NS
  - CUPILT – 314 post OLTx for HCC → all DAAs → 7 recurrent HCC = 2.2 per 100 pt mo

ANRS Coll Study Group J Hep 2016
Not everyone agrees

143 consecutive patients with curative therapy for HCC treated with DAAs

Risk factors for recurrence
- Previous recurrence
- Tumor size

Probability of HCC recurrence

Recurrence rate relatively high – 27% at 1 yr…but not increased post-DAA

Untreated (n=701)
DAA-treated (n=101)
Follow-up time matters...

Risk of HCC recurrence appears highest in those with early DAA treatment

Very likely HCC that is there before treatment

Tsai et al J Hepatology 2017
HCC Recurrence - conclusions

• Somewhat conflicting results
• Early recurrence may be a real issue
  – Very likely at least some incompletely cured HCC
• Long-term recurrence seems less of an issue
• Important to report ‘incidence’ rather than ‘% recurrence’ – *follow-up time is important*
• So what should we do now?
  – Warn patients – *image before HCV treatment*
  – Don’t rush to treat HCV after HCC therapy – wait a bit
  – Close follow-up after DAAs → q 3 mo?
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HCC after IFN-based treatment

Long-term follow-up of 534 patients with F3/F4 post-treatment

SVR reduces but does not eliminate the risk of HCC

Van der Meer JAMA 2012
And with DAAs?

Patients with cirrhosis followed after SOF-based SVR – median f/u 85 wks

- No untreated control group BUT...
- Incidence lower than no trt (3-5%/yr) and IFN-trt – 1%/yr
- Risk MUCH higher with decompensated cirrhosis
Did we discuss anything else?
Putting the data together

Systematic review & meta-regression of studies on HCC occurrence & recurrence post-SVR in IFN & DAA-treated patients

- DAA studies – shorter f/u and older patients with more severe liver disease
- Controlling for f/u time (?) as well as age & liver disease severity \(\rightarrow\) similar HCC risk

Waziry J Hep 2017
Helpful but hard to interpret

Assume both have 100 HCCs in 10 yr period but **point estimate** for incidence
IFN at 10 yr f/u and DAA at 2 yr f/u

“Controlling for follow-up time” will:

- **Constant rate over time**
  - IFN – 100 in 10 yr = **10/yr**
  - DAA – 20 in 2 yr = **10/yr**

- **Most HCCs early**
  - IFN – 90 in 2 yr & 10 in 8 yr = **10/yr**
  - DAA – 90 in 2 yr = **50/yr**

- **HCCs increase with age**
  - IFN – 10 in 2 yr & 90 in 8 yr = **10/yr**
  - DAA – 10 in 2 yr = **5/yr**

Hard to know...only real way to look at this is patient level data or cumulative incidence at **same f/u time** eg. At 2 yrs
## HCC after IFN-based treatment

A study involving 1000 patients with SVR with F3/4 showed 51 HCCs at 8 years, with an incidence of approximately 1% per year. The cumulative HCC incidence is shown in the graph below:

### Cumulative HCC incidence (%)

- **>60 years**
- **45-60 years**
- **<45 years**

### At risk

<table>
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<tr>
<th>Age Group</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
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<td>&gt;60 years</td>
<td>19</td>
<td>18</td>
<td>16</td>
<td>14</td>
<td>13</td>
<td>110</td>
<td>89</td>
<td>59</td>
<td>38</td>
<td>21</td>
<td>14</td>
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<td>5</td>
<td>1</td>
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<td>115</td>
<td>82</td>
<td>51</td>
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<td>&lt;45 years</td>
<td>45</td>
<td>40</td>
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<td>33</td>
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<td>5</td>
<td>0</td>
<td>5</td>
<td>47</td>
<td>36</td>
<td>28</td>
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</table>

### P = .006

Is this real? If so, concerning...

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Van der Meer J. Hepatology 2016

Toronto Centre for Liver Disease
A more direct comparison

HCC risk post-SVR in IFN and DAA-treated patients - Propensity score matched

Fib-4 <3.25

When using the same time scale...risk still looks similar when control for disease severity - reassuring

Fib-4 ≥3.25

Nagaoki PLoS One 2017
Big numbers...back to the VA

22,500 patients treated with DAAs in the VA

- Annual Incidence (per 100 py)
  - No SVR: 3.45 (2.73-4.18)
  - SVR: 0.9 (0.77-1.03)

HCCs incidence markedly lower with SVR...DAAs do not cause cancer

Kanwal Gastro In Press
HCC after SVR with DAAs

• Cirrhosis the key factor
  • Cirrhosis – 1.82/100 py (vs 1.1 to 1.39/100 py with IFN)
  • No cirrhosis – 0.34/100py

• Can we use pre-treatment FIB4?
  • FIB4 > 3.25 – 2.16/100 py
  • FIB4 1.45 – 3.25 - 0.45/100 py
  • FIB4 < 1.45 – 0.30/100 py

Message: Cirrhosis is the key risk factor for HCC post-SVR
  • Can use FIB4 before treatment to determine post-SVR risk
  • Higher rates in DAA patients (vs IFN) related to sicker, older, worse cirrhosis

Kanwal Gastro In Press, Maan, Feld Gastro In Press
More VA data

HCC incidence after treatment with IFN or DAAs in the VA

- Clearly a benefit in those who achieve SVR
- Curves look fairly similar

Ioannou AASLD 2017
Looking at the numbers

<table>
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<th>SVR</th>
<th>Patients</th>
<th>HCC</th>
<th>HCC per 100 patient-years</th>
<th>Crude Hazard Ratio</th>
<th>Adjusted* Hazard Ratio</th>
<th>Risk Reduction %</th>
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<td>2348</td>
<td>1.07</td>
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<td>1</td>
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<td>0.18</td>
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</table>

- More HCCs after DAAs – **sicker pts**
- Benefit of SVR equivalent DAA vs IFN
- Similar results from ERCHIVES cohort

Ioannou AASLD 2017, Li Hepatology 2017
What about in decompensated patients? Do DAAs cause HCC?

• UK Expanded Access Programme
  – Phased in allowing for ‘untreated’ control group
  – Incidence of HCC first 6 months
    • SVR – 4% (17/406)
    • Untreated – 4% (11/261)
  – Incidence of HCC months 6 to 15
    • SVR – 2.4% (10/406)

**Message:** No benefit in early HCC occurrence in decompensated cirrhosis
Benefit likely to accrue with time (eliminate HCCs present pre-treatment)
Not just incidence, but severity

3,075 Italian patients treated with DAAs, 72% cirrhosis

HCC Patterns in Relation to SVR

- SVR markedly reduced risk of HCC compared to non-SVR/untreated
  - HR 0.20 (0.09-0.41) p=0.001
- But – HCC post DAA seemed to be VERY aggressive
  - Multifocal, PV thrombosis, mets
  - Appeared early – 3 m post-treatment

Romano AASLD 2016 Abstract 19
What about surveillance?

- **AASLD/IDSA & EASL Guidelines:**
  - Continued US surveillance after SVR in patients with ‘advanced fibrosis’ ie F3/4

- **Based on Kanwal data**
  - Incidence in cirrhosis post-DAAs: 1.82%/yr
  - Incidence without cirrhosis: 0.30%/yr
  - FIB-4 > 3.25 → 2.16%/yr
  - FIB-4 < 3.25 → 0.40%/yr

- **ICER for surveillance (US q 6m) vs no screening**
  - **Cirrhosis:** $40,803/QALY
  - **No Cirrhosis:** $187,000/QALY
  - **FIB4 > 3.25:** $32,016/QALY
  - **FIB-4 < 3.25:** $133,977/QALY

*Probably should limit surveillance post-SVR to those with cirrhosis or FIB-4 > 3.25*
De novo HCC - conclusions

- HCC incidence post-SVR with DAAs likely higher than post-IFN treatment
  - But lower than without treatment – particularly long-term
  - *Biggest issue is we are treating sicker patients*
- Possibly more severe HCCs
  - Needs confirmation
- *We should definitely still treat patients with cirrhosis but post-SVR surveillance critical!*
  - Likely not cost-effective in those without cirrhosis
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  – HBsAg –ve/anti-HBc +ve

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Should we treat HCV with active HCC?

VA – 17,487 treated DAAs including with HCC & OLTx after HCC

- Similar effect seen other smaller studies
- HCC may affect vasculature – DAA exposure in the liver
- **Bottom line: Treat HCC first (OLTx) then HCV**

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<th>SVR12 (%)</th>
<th>Post OLTx</th>
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<td>Non-HCC</td>
<td>92</td>
<td>15,497/16,863</td>
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<td>HCC</td>
<td>75</td>
<td>349/482</td>
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<tr>
<td>HCC Post OLTx</td>
<td>93</td>
<td>133/142</td>
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Beste J Hep 2017
Could the SVR effect explain these findings?

22,500 patients treated with DAAs in the VA

- Annual Incidence (per 100 py)
  - No SVR: 3.45 (2.73-4.18)
  - SVR: 0.9 (0.77-1.03)

If HCCs pre-exist...lead to non-SVR

If limit to cirrhosis...those with pre-treatment HCC could have lower SVR and make the ‘non-SVR’ appear to develop HCC...

Doubt this is true but need longer follow-up to be sure

Kanwal Gastro *In Press*, Andrea Branch
Andrea’s provocative thought experiment...

- 1000 patients
  - 400 with cirrhosis and 10 with undiagnosed HCC
- SVR – with HCC 80%, with cirrhosis 90%, without cirrhosis 95%
  - Annual HCC incidence unchanged by treatment → 2% cirrhosis, 0 without cirrhosis

- HCC patients – of the 10 → 8 to SVR group and 2 to non-SVR
- Cirrhosis – of the 400 → 360 to SVR group and 40 to non-SVR
- Non-cirrhotic – of the 590 → 560 to SVR and 30 to non-SVR

- After 12 months:
  - SVR group → 8 pre-existing and 360x2% = 7 new HCCs → 15/928 or 1.6%
  - Non-SVR group → 2 pre-existing and 40 x 2% = 1 new HCC → 3/72 or 4.2%

To address this, need longer term F/U and good data showing no HCC pre-treatment

Andrea Branch, personal communication
Conclusion

• HBV reactivation
  – Screen for HBsAg → treat if +ve
  – Screen for anti-HBc → further testing if ALT rises or fails to normalize

• HCC
  – Recurrence rate may be higher with DAA therapy
    • Warn patients – **image before treatment**
    • Don’t treat HCV immediately after HCC - Wait 6 m?
    • Close surveillance
  – De novo HCC is not caused by DAAs but may occur more than with IFN because sicker patients especially decomp
  – Surveillance post-SVR should be limited to those with cirrhosis
  – Wait for HCC treatment (incl OLTx) before treating HCV