Reactivation of Hepatitis B in Clinical Trials with Immunosuppressive Drugs

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HBV Reactivation (HBVr): Overview

- Clinical syndrome characterized by an increase in HBV DNA and ALT/AST with or without symptoms or jaundice
- Occurs in pts with active (HBsAg+) and resolved/occult (HBsAg-, anti-HBc+) HBV infection
- Wide clinical spectrum for HBVr
  - Ranges from silent to liver failure
- Can occur during treatment with many immunosuppressive agents, DAA, HIV, organ transplant
  - May also occur up to 12 months after event or treatment
- Preventable by antiviral prophylaxis

Definitions

• Virologic increase of 1 log IU/ml or de novo appearance of HBV DNA when previously non detectable

Proposed: 2 log increase or de novo or reappearance of HBV DNA to a level of at least 100 IU/mL (AASLD Emerging Trends Conference on HBV Reactivation, March, 2013)

In absence of HBV DNA measurements, reappearance of HBeAg or HBsAg is reasonable evidence

• Increase of 3 fold or greater in ALT levels if BSL levels normal or 2 fold or greater increase over BSL if initially abnormal.
Case: 55-Yr-Old Chinese Woman With Stage II Breast Cancer

- Treated with doxorubicin, paclitaxel, dexamethasone, and cyclophosphamide

![Graph showing serum ALT and total bilirubin levels over time following initiation of chemotherapy. The graph indicates first abnormal ALT, chemotherapy discontinuation, entecavir initiation, and pt dies.](Courtesy of Dr. Perrillo)
HBV may reactivate in anyone who is Anti-HBc+

<table>
<thead>
<tr>
<th>HBsAg</th>
<th>Anti-HBc total</th>
<th>Anti-HBc IgM</th>
<th>Anti-HBs</th>
<th>What it means</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>B</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>C</td>
<td>–</td>
<td>+</td>
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<td>+</td>
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<tr>
<td>D</td>
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<td>E</td>
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<tr>
<td>F</td>
<td>–</td>
<td>+</td>
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</tbody>
</table>
The (non) role of anti-HBs

- Does the presence of anti-HBs in addition to anti-HBc in HBsAg-negative patients confer additional protection against HBVr?
  - Studies have shown pre-treatment anti-HBs titers to be an independent risk factor for reactivation *only* with rituximab (OR 0.003, 95%CI 0-0.3, p = 0.014)
  - No RCTs available that compare a monitoring strategy based on anti-HBs vs. antiviral prophylaxis to be non-inferior

- Recommendation:
  - The AGA suggests against using anti-HBs status to guide antiviral prophylaxis for all risk groups.

**GRADE**: Weak recommendation; Very low-quality evidence
Why Do Patients Reactivate HBV Despite Serological Evidence of Viral Clearance?

- HBV DNA persists within the liver even after resolution of infection
- cccDNA resides in nucleus of hepatocytes
- cccDNA can become transcriptionally active
- Viral replication is suppressed with intact immune function
- Loss of immune surveillance by IST results in active replication
Pre-Chemo HBsAg+ HBV DNA +/- ALT Normal

HBV DNA In nucleus cccDNA

HBV-specific B & T cells Control HBV replication

During-Chemo HBsAg+ HBV DNA +++ ALT Abnormal

HBV DNA In nucleus cccDNA

Loss of HBV-specific B & T cells Uncontrolled HBV replication

Post-Chemo HBsAg+ HBV DNA +++ ALT Flare

HBV DNA In nucleus cccDNA

Immune activation HBV clearance Hepatocyte damage
HBcAg Staining Demonstrates Impact of Immunosuppression on HBV Activity

Immunohistochemistry from HBV patient

Increased HBcAg staining from HBV patient on immunosuppression
HBV Reactivation: Interaction of HBV Status and Immunosuppression

Risk of Reactivation

Degree of Immune Control

Degree of Risk for HBVr

HBsAg

Negative  Positive

Anti-HBc

Positive

HBV DNA

Negative  Low Level  High Level

Resolved Infection  Inactive HBsAg Carrier  Immuneactive Chronic HBV

(ex. Steroids < 5 days)

Example: Rituximab

Adapted from Gonzalez and Perrillo, 2016
Natural History of HBV Reactivation During Chemotherapy

Weeks after Exposure

- ChemoRx and/or Steroids
- Or HCV DAAs
- Or Liver SOT

Recovery of neutropenia or steroid withdrawal

Acute liver failure

Death

Liver Transplant

HBV DNA

ALT

Chronic hepatitis

Cirrhosis

Acute hepatitis

IMMUNE change or SUPPRESSION

IMMUNE REBOUND

RECOVER

 Weeks after Exposure
Immunosuppressive Therapy (IST) Reported to Cause HBV Reactivation

- Anti-TNF
  (Infliximab, adalimumab, etanercept)
- Anti-Metabolite
  (Methotrexate)
- Purine Analogues
  (Azathioprine/6MP)
- Steroids
  (Prednisone, budesonide)
- Other
  (Rituximab, cyclosporine)
HBV lifecycle and targets for Immunosuppressive therapy

Loomba R, Liang JT Gastroenterology 2017:152;1297-09
### High risk for HBVr (>10%)

<table>
<thead>
<tr>
<th>B-cell depleting agents (rituximab, ofatumumab)</th>
<th>HBsAg + core +</th>
<th>HBsAg - core +</th>
<th>Confidence in estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30 – 60%</td>
<td>17%</td>
<td>A</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Anthracycline derivatives (e.g., doxorubicin / epirubicin)</th>
<th>HBsAg + core +</th>
<th>Confidence in estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>15 – 30%</td>
<td>A</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Corticosteroids for &gt; 4 wks (&gt; 10 mg prednisone)</th>
<th>HBsAg + core +</th>
<th>Confidence in estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&gt; 10%</td>
<td>B</td>
</tr>
</tbody>
</table>

**Categories of confidence in the estimate:**
(A) High confidence that the estimate lies within group risk boundaries
(B) Moderate confidence that the estimate lies within group risk boundaries
(C) Little or no confidence that the estimate lies within group risk boundaries
## Moderate risk (1% - 10%)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>HBsAg + core +</th>
<th>HBsAg - core +</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TNF-alpha inhibitors</strong> <em>(etanercept, adalimumab, certolizimab, infliximab)</em></td>
<td>1 – 10% (B)</td>
<td>1% (C)</td>
</tr>
<tr>
<td><strong>Other cytokine &amp; integrin inhib.</strong> <em>(abatacept, ustekinimab, natalizumab, vedolizumab)</em></td>
<td>1 – 10% (C)</td>
<td>1% (C)</td>
</tr>
<tr>
<td><strong>Tyrosine kinase inhibitors</strong> <em>(imatinib, nilotinib)</em></td>
<td>1 – 10% (B)</td>
<td>1% (C)</td>
</tr>
<tr>
<td><strong>Corticosteroids for &gt; 4 weeks</strong> <em>(low dose: &lt;10 mg)</em></td>
<td>1 – 10% (B)</td>
<td>1 – 10% (C)</td>
</tr>
<tr>
<td><strong>Anthracycline derivatives</strong> <em>(e.g., doxorubicin / epirubicin)</em></td>
<td>1% (C)</td>
<td></td>
</tr>
</tbody>
</table>
### Low risk group (<1%)

<table>
<thead>
<tr>
<th>Category</th>
<th>HBsAg +</th>
<th>core +</th>
<th>HBsAg -</th>
<th>core +</th>
</tr>
</thead>
<tbody>
<tr>
<td>Traditional immunsupp. agents</td>
<td>&lt;1% (A)</td>
<td></td>
<td>&lt;&lt;1% (A)</td>
<td></td>
</tr>
<tr>
<td>(azathioprine, 6-mercaptopurin, methotrexate alone)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intra-articular corticosteroid</td>
<td>&lt;1% (A)</td>
<td></td>
<td>&lt;&lt;1% (A)</td>
<td></td>
</tr>
<tr>
<td>Corticosteroids for ≤ 1 week</td>
<td>&lt;1% (B)</td>
<td></td>
<td>&lt;&lt;1% (A)</td>
<td></td>
</tr>
<tr>
<td>Corticosteroids for &gt; 4 weeks</td>
<td></td>
<td></td>
<td>&lt;1% (B)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(low dose: &lt;10 mg)</td>
<td></td>
</tr>
</tbody>
</table>

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(C) Little or no confidence that the estimate lies within group risk boundaries
High Risk of Reactivation with Hematologic Malignancy

100 patients with NHL undergoing CHOP
27 HBsAg +ve

- 48% HBV Reactivation
- 22% Jaundice
- 4% Non-Fatal Liver Failure
- 4% Death

Lok et al, 1991
Rituximab in HBsAg- / Anti-HBc+ Patients with Lymphoma

Yeo et al, 2009

None due to HBV

All due to HBV

Yeo et al, 2009
HBV Reactivation With Rituximab in Pts With Hematologic Malignancies

• Single-center study of HBsAg-negative anti-HBc–positive pts receiving rituximab-containing chemotherapy (N = 62)
  – Baseline HBV DNA undetectable (< 10 IU/mL)
  – No previous HBV treatment
  – No chronic liver disease
• 24.2% of patients experienced HBV reactivation within 9 months
  – Reactivation occurred early (86.7% within 6 months)

• Lower baseline anti-HBs levels associated with subsequent HBV reactivation ($P = .015$)

Rituximab-Associated HBV Reactivation in Lymphoproliferative Disorders

- Meta-analysis and review of FDA safety profiles
  - Case reports (n=27)
  - Case series reports (n=156)
- Onset post last rituximab dose
  - Median: 3 months (range: 0-12 months)
  - >6 months: 29%
- Reactivation in anti-HBc positive patients receiving rituximab versus no rituximab
  - Odds ratio: 5.73 ($P=0.0009$)

Anti-TNF Agents and HBV Reactivation

- TNF-\(\alpha\): proinflammatory cytokine that inhibits HBV replication
- Anti-TNF agents associated with HBV reactivation
  - Utilized in IBD, psoriasis, rheumatoid arthritis

<table>
<thead>
<tr>
<th>Disease Studied</th>
<th>No. Patients</th>
<th>HBsAg + HBcAb +</th>
<th>HBsAg – Anti-HBc +</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple</td>
<td>257</td>
<td>39%</td>
<td>5%</td>
</tr>
<tr>
<td>IBD</td>
<td>88</td>
<td>9/25 (36%)</td>
<td>0%</td>
</tr>
<tr>
<td>Rheumatologic</td>
<td>122</td>
<td>12%</td>
<td>N/A</td>
</tr>
<tr>
<td>Rheumatologic</td>
<td>468</td>
<td>N/A</td>
<td>2%</td>
</tr>
</tbody>
</table>

- Antiviral prophylaxis warranted for all HBsAg+ on TNFi
- Low risk of HBVr in anti-HBc + only
  - Consider monitoring for HBVr
  - Higher risk may be associated with addition of other IST

Perez-Alvarez et al, 2011; Loras et al, 2010; Lee et al, 2013; Lee et al, 2013;
HBV Reactivation and Abatacept

• Abatacept: inhibitor of T-cell activation
  – Anecdotal data suggest it should be treated as a TNF inhibitor regarding HBV reactivation[1]
  – Clinical studies have excluded pts who tested positive for hepatitis during screening[2]

• Package insert[2]
  – Pretreatment screening should be performed per guideline recommendations

HBV Screening Prior to Immunosuppressive Therapy

- All pts should be screened
  - Supported by CDC,[1] EASL,[2] and APASL[3] guidelines

- Screening should include assessment of[1-6]:
  - HBsAg*
  - Anti-HBc #
  - Anti-HBs
  - *Additional: HBV DNA levels[2,3,5,6]
  - #isolated anti-HBc consider HBV DNA quant {7% are DNA+ if anti-HBc+ only}

HBV Prophylaxis for Pts Receiving Immunosuppressive Therapy

• Candidates
  – HBsAg+[1-6]
  – HBsAg-/anti-HBc+ if
    • Receiving therapy associated with high HBV reactivation risk (AGA,[5] ASCO[6]*)
    • Detectable HBV DNA (EASL,[2] APASL[3], AASLD[4])

• Timing of initiation[1-6]
  – At or before onset of immunosuppressive therapy

*ASCO states that these pts may alternatively be monitored and treated with on-demand therapy as needed.

HBV Prophylaxis for Pts Receiving Immunosuppressive Therapy

• Duration
  – Varies among guidelines
  – 6 mos post immunosuppressive therapy if HBV DNA < 2000 IU OR until treatment goals reached if > 2000 IU (AASLD)[1]
  – 6 mos post immunosuppressive therapy OR 12+ mos if B-cell–depleting agent (AGA, ASCO)[2,3]
  – 12 mos post immunosuppressive therapy (EASL, APASL)[4,5]

Randomized, Controlled Trials of HBV Prophylaxis

P = .001

70
60
50
40
30
20
10
0

HBV Reactivation (%)

Lymphoma, HBsAg+ (N = 30)
P = .002

HCC, HBV DNA+ (N = 76)
P < .001

Lymphoma, HBsAg+ (N = 52)
P = .001

Breast Cancer, HBsAg+ (N = 42)
P = .02

Lymphoma, HBsAg-Anti-HBc+ (N = 80)
P = .03

Lymphoma, HBsAg-Anti-HBc+ (N = 30)
P = NS

Lymphoma, HBsAg+ (N = 121)
P = .001

Control
Lamivudine

Control
Entecavir

Control
Tenofovir

Choosing an Antiviral for HBV Prophylaxis

- Drugs with high genetic barrier to resistance (tenofovir, entecavir) preferred[^1]
- Lamivudine associated with resistance[^1]
  - Entecavir prophylaxis associated with a significantly lower incidence of HBV reactivation vs lamivudine in randomized controlled trial[^2]
- Adefovir less potent than tenofovir for treating HBV[^3]
- Lamivudine plus adefovir may be an option[^4]

2015 ACR RA Treatment Guidelines: HBV Recommendations

• Screening
  – No specific recommendations\(^1\)
  – 2008 guidance\(^2\): screen pts receiving methotrexate or leflunomide if high risk for HBV infection exists

• Prophylaxis/treatment\(^1\)
  – Active HBV infection: immunosuppressive therapy can be administered with concomitant HBV treatment
  – HBsAg+: refer for HBV prophylaxis prior to immunosuppressive therapy
  – HBsAg-/anti-HBc+: monitor HBV DNA

## Risk Stratification for HBV Reactivation

<table>
<thead>
<tr>
<th></th>
<th>HBsAg +</th>
<th>HBsAg-/Anti-HBc +</th>
<th>Antiviral Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High risk</strong></td>
<td>• Chemotherapy</td>
<td>• Chemotherapy for heme malignancy</td>
<td><strong>Prophylaxis</strong></td>
</tr>
<tr>
<td></td>
<td>• Anti-CD20 or CD52</td>
<td>• Anti-CD20</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• IST for transplantation</td>
<td>• Anti CD52</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Steroids in combination with other IST</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Moderate risk</strong></td>
<td>• Anti-TNF agents</td>
<td>• Chemotherapy for solid tumors</td>
<td><strong>Prophylaxis or On-Demand</strong></td>
</tr>
<tr>
<td></td>
<td>• Maintenance low dose steroids</td>
<td>• IST for transplantation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Other IST w/o steroids</td>
<td>• Steroids w/IST</td>
<td></td>
</tr>
<tr>
<td><strong>Low risk</strong></td>
<td>Steroids only for a few days</td>
<td>• Anti-TNF agent</td>
<td><strong>No prophylaxis</strong></td>
</tr>
<tr>
<td></td>
<td>• Low dose steroid maintenance</td>
<td>• Low dose steroid maintenance</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Other IST</td>
<td>• Other IST</td>
<td></td>
</tr>
</tbody>
</table>

IST = Immunosuppressive therapy  
Anti-CD20: Rituximab,  
Anti-CD52: Alemtuzumab  
Anti-TNF: Infliximab, Etanercept, Adalimumab, Golimumab

Adapted from Hwang and Lok 2014
AGA Institute Guidelines on Hepatitis B Reactivation (HBVr)
Clinical Decision Support Tool

High Risk (reactivation risk > 10%)

- HBsAg-positive/anti-HBc-positive or HBsAg-negative/anti-HBc-positive
- Patients taking B cell depleting agents (e.g., rituximab, ofatumumab)
- Antiviral prophylaxis for at least 12 months after discontinuation of immunosuppressive therapy

- HBsAg-positive/anti-HBc-positive
- Patients taking anthracycline derivatives (e.g., doxorubicin, epirubicin)
- Antiviral prophylaxis for at least 6 months after discontinuation of immunosuppressive therapy

- Patients taking moderate dose (10-20 mg prednisone daily or equivalent) or high dose (> 20 mg prednisone daily or equivalent) corticosteroids daily for ≥4 weeks

GRADE – Strong Recommendation, moderate quality of evidence.

Moderate Risk (reactivation risk 1-10%)

- Patients taking TNF alpha inhibitors (e.g., etanercept, adalimumab, certolizumab, infliximab)
- Patients taking moderate dose (10-20 mg prednisone daily or equivalent) or high dose (>20 mg prednisone daily or equivalent) corticosteroids daily for ≥4 weeks
- Patients taking anthracycline derivatives (e.g., doxorubicin, epirubicin)
- Patients taking other cytokine or integrin inhibitors (e.g., abatacept, ustekinumab, natalizumab, vedolizumab)
- Patients taking tyrosine kinase inhibitors (e.g., imatinib, nilotinib)
- Patient taking low-dose (<10 mg prednisone daily or equivalent) corticosteroids daily for duration of ≥4 weeks

Suggest antiviral prophylaxis for at least 6 months after discontinuation of immunosuppressive therapy*

GRADE – Weak Recommendation, moderate quality of evidence

* Patients who place a higher value on avoiding the long-term use of antiviral therapy and cost associated with its use and a lower value on avoiding the small risk of reactivation (particularly in those who are HBsAg-negative), may reasonably select no prophylaxis over antiviral prophylaxis
**AGA Institute Guidelines on Hepatitis B Reactivation (HBVr) Clinical Decision Support Tool**

**Low Risk (reactivation risk <1%)**

- HBsAg-positive/anti-HBc-positive or HBsAg-negative/anti-HBc-positive
- Patients taking traditional immunosuppressive agents (e.g., azathioprine, 6-mercaptopurine, methotrexate)
- Patients taking intra-articular corticosteroids
- Patients taking low dose (< 10 mg prednisone or equivalent) corticosteroids for ≥ 4 weeks

Suggest not to use routine antiviral prophylaxis in patients undergoing immunosuppressive drug therapy and are at low risk for HBVr

GRADE – Weak Recommendation
Moderate quality of evidence

FDA Drug Safety Communication: FDA warns about the risk of hepatitis B reactivating in some patients treated with direct-acting antivirals for hepatitis C

Safety Announcement

[10-04-2016] The U.S. Food and Drug Administration (FDA) is warning about the risk of hepatitis B virus (HBV) becoming an active infection again in any patient who has a current or previous infection with HBV and is treated with certain direct-acting antiviral (DAA) medicines for hepatitis C virus. In a few cases, HBV reactivation in patients treated with DAA medicines resulted in serious liver problems or death.
HBV Reactivation in Pts Receiving DAAs: Postmarketing Cases Reported to FDA

- Case reports of HBV reactivation in pts receiving DAAs
  - Reactivation: increase in HBV DNA or seroconversion to HBsAg positive
- 29 confirmed cases in ~ 3 yrs (November 2013 to October 2016)
  - Pts from Japan (n = 19), US (n = 5), other (n = 5)
  - Usually occurred within 4-8 weeks (mean 52 days)
  - 2 deaths, 1 transplant, 6 hospitalizations, 10 DAA discontinuations


![Diagram showing the distribution of HBV reactivation cases.]

- Not reported, uninterpretable, or undetectable HBV DNA w/o HBsAg status
- Detectable HBV DNA
- HBsAg+, undetectable HBV DNA
- HBsAg-, undetectable HBV DNA

- 31% (n = 9)
- 38% (n = 11)
- 21% (n = 6)
- 10% (n = 3)
FDA Recommendations for Monitoring During DAA Therapy

- To decrease the risk of HBV reactivation in patients co-infected with HBV and HCV, health care professionals should:
  - 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.
  - Monitor patients who show evidence of current or prior HBV infection for clinical and laboratory signs (i.e., HBsAg, HBV DNA, serum aminotransferase levels, bilirubin) of hepatitis flare or HBV reactivation during DAA treatment and post-treatment follow-up.
  - Consult a physician with expertise in managing hepatitis B regarding the monitoring and consideration for HBV antiviral treatment in HCV/HBV co-infected patients.
AASLD Guidance on HBV Reactivation in Pts Receiving HCV DAA Therapy

• HBV vaccination recommended for all susceptible individuals (eg, no previous immunization, no evidence of immunization response, anti-HBc (-))

• All pts starting HCV DAA therapy should be assessed for HBV infection (HBsAg, anti-HBs, and anti-HBc testing)
  – If HBsAg+, assess HBV DNA prior to, during, and immediately after HCV DAA therapy
    • For active HBV infection, initiate HBV therapy before or simultaneously with HCV DAA therapy
    • For low or undetectable HBV DNA, monitor for HBV reactivation during HCV DAA therapy
  – Insufficient data to provide recommendations for pts who are HBsAg- and anti-HBc+ or anti-HBs+/anti-HBc+

HBV Reactivation
Conclusions

- Reactivation of HBV is a concern in the context of immunosuppressive therapy; risk variable and dependent on the type of immunosuppressive therapy.
- All patients should be screened for HBV (HBsAg and anti-HBc) prior to initiation of biologics and other immunosuppressive therapy.
- Assess risk for reactivation based on HBV serologies and planned immunosuppressive therapy: Guidelines in place
- More information is needed regarding HBV reactivation associated with DAA therapy for HCV
Acknowledgements

• Robert Perrillo MD
• Mike Fried MD
• Jordan Feld MD