Reactivation of Hepatitis B

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Hepatitis B virus infection
- Brief overview -

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HBV genome and Life cycle

Ganem et al, NEJM 2003
<table>
<thead>
<tr>
<th>Immune tolerant</th>
<th>HBeAg-positive CHB [immune clearance]</th>
<th>Immune control [low or non-replicative]</th>
<th>HBeAg-negative CHB [immune escape]</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBeAg</td>
<td>Positive (2000–5000 PEIU/ml)</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Anti-HBe</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBsAg (log IU/ml)</td>
<td>4.5–5</td>
<td>4.0–4.5</td>
<td>2.9–3.0</td>
</tr>
<tr>
<td>Anti-HBs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBV DNA (IU/ml)</td>
<td>&gt;20,000</td>
<td>&gt;20,000</td>
<td>&lt;2000</td>
</tr>
<tr>
<td>Viral diversity (PC/C ORF)</td>
<td>Persistently normal</td>
<td>Elevated (1–2X) and fluctuating</td>
<td>Normal</td>
</tr>
<tr>
<td>Serum ALT level (U/l)</td>
<td>Persistently normal</td>
<td>Elevated (1–2X) and fluctuating</td>
<td>Normal</td>
</tr>
<tr>
<td>Liver histology</td>
<td>Normal or mild hepatitis</td>
<td>Moderate to severe hepatitis</td>
<td>Normal to mild hepatitis. May have cirrhosis</td>
</tr>
<tr>
<td>Intra-hepatic HBV replicative, intermediates</td>
<td>rcDNA/cccDNA (100–1000) &gt;1 cccDNA/cell</td>
<td>rcDNA/cccDNA (10–100) 1 cccDNA/cell (0.1–10/cell)</td>
<td>rcDNA/cccDNA (100–1000) 1 cccDNA/cell (0.1–10/cell)</td>
</tr>
</tbody>
</table>
HBV: An immunologic disease

- The viral infection itself is non-cytopathic
- It is the immune response to HBV that controls viral clearance versus chronic infection.
- It is the immune response to HBV that leads to the necroinflammatory process involved in chronic hepatitis, cirrhosis, and HCC
## Natural HBsAg loss rate

<table>
<thead>
<tr>
<th>Geographic Region</th>
<th>Characteristic</th>
<th>n</th>
<th>Patients with HBeAg %</th>
<th>Follow up Duration</th>
<th>HBsAg seroclearance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>n(%)</td>
</tr>
<tr>
<td>Taiwan</td>
<td>CHB±Cirrhosis</td>
<td>323</td>
<td>NA</td>
<td>2.5</td>
<td>0.3%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Annual rate (%)</td>
</tr>
<tr>
<td>Taiwan</td>
<td>CHB±Cirrhosis</td>
<td>984</td>
<td>69%</td>
<td>4.0</td>
<td>1.9%</td>
</tr>
<tr>
<td>Spain</td>
<td>CHB±Cirrhosis</td>
<td>258</td>
<td>64%</td>
<td>7.8</td>
<td>11.2%</td>
</tr>
<tr>
<td>Europe</td>
<td>Compensated Cirrhosis</td>
<td>196</td>
<td>NA</td>
<td>6.0</td>
<td>8%</td>
</tr>
</tbody>
</table>

Liaw YF et al., AVT 2010
Category of Hepatitis B

- Chronic hepatitis B
  - HBsAg +, HBV DNA (+)

- Inactive HBsAg carrier state
  - HBsAg +, HBV DNA (-), HBeAg (-), HBeAb (+), normal ALT

- Resolved hepatitis B
  - HBsAg (-), HBV DNA (-), Anti-HBc (+) ± Anti-HBs,
  - (rarely, when HBV DNA +, occult HBV infection)
Hepatitis B reactivation
- definitions -

Dong Hyun Sinn M.D., Ph.D

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HBV reactivation: concept

- Immune cells and molecules that reside in the liver life-long keep the virus quiescent.
- Perturbation of these immune mechanisms can lead to HBV reactivation.
- A significant increase of HBV replication in a person with previously stable, low or undetectable levels.

cccDNA = covalently closed circular DNA

Pawlotsky JM. J Hepatol 2006;44:S10-S13
Definition

- Abrupt reappearance or rise in HBV DNA [$>2 \log_{10} \text{IU/ml}$] in a patient with previously inactive or resolved hepatitis B
  - Often accompanied by flare in disease activity
  - Can be severe: high fatality rate
  - Defined by rise or appearance of serum HBV DNA or reappearance of HBsAg in resolved hepatitis B

- Occurs in several categories of patients
- Varies in severity and outcome
HBV reactivation: Occurs in three types of patients

- Chronic hepatitis B
  - Reactivation \(\Rightarrow\) Exacerbation
  - Exacerbation caused by immunosuppressive or chemotherapeutic agents

- Inactive HBsAg carrier state (reactivation)
  - Typical reactivation of CHB

- Resolved hepatitis B (reactivation)
  - Reappearance of HBsAg and HBV DNA: “reverse seroconversion”
Reactivation: different severity and outcome

- Significant rise in HBV DNA levels and
- Silent (1+): no change in ALT or jaundice
- Mild (2+): rise in ALT without jaundice
- Moderate (3+): rise in ALT and bilirubin
- Severe (4+): rise in ALT, bilirubin, INR, signs of hepatic failure
- Fatal (5+): death or liver transplantation

Hoynagle 2013 AASLD STC
Viral replication precedes overt hepatitis

Yoe et al., J Med Virol 2003
Hepatitis B reactivation
- Cancer chemotherapy and other immunosuppressive drug-

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Reactivation of Hepatitis B Virus Replication in Patients Receiving Cytotoxic Therapy
Report of a Prospective Study

ANNA S. F. LOK, RAYMOND H. S. LIANG, EDMOND K. W. CHIU, KEE–LAM WONG, TAI–KWONG CHAN, and DAVID TODD
Department of Medicine, University of Hong Kong, Queen Mary Hospital, Hong Kong

- 100 patients with malignant lymphoma
  - 27 patients with HBsAg +
    - 22.3% (icteric hepatitis)
    - 3.7% (liver failure)
    - 3.7% (death)
Rituximab

- Anti-CD 20+ humanized chimeric monoclonal antibody
- Induces killing of CD 20+ cells
- Profound and induce durable B and T cell depletion

Bezombes et al., Mol Cancer Res 2011; Yoe et al., Hepatology 2006
Rituximab and Reactivation of Hepatitis B

Pei et al., Ann Hematol 2010

Patients with CD20+ lymphoma treated with rituximab-based therapy (N=110)

HBsAg positive (n=15, 13.6%)
- LAM prophylaxis (n=5)
  - HBV-related hepatitis (n=4, including one death)
- No prophylaxis (n=10)
  - HBV-related hepatitis (n=8, including one death)

HBsAg negative (n=95, 86.4%)
- Hepatitis with HBsAg seroreversion (n=4, including 2 death)
- Hepatitis without HBsAg seroreversion (n=11)
- No hepatitis (n=80)
Later onset of HBV reactivation after Rituximab

Pei et al., Ann Hematol 2010
Rituximab and reactivation

HBsAg negative patients with CD20+ DLBCL (n = 80)

Anti-HBc* positive (n = 46)
- Treated with R-CHOP (n = 21)
  - Hepatitis (n = 5)
    - Had reverse seroconversion and elevated HBVDNA (n = 5, 23.8%)
- Treated with CHOP (n = 25)
  - Hepatitis (n = 4)
    - Had reverse seroconversion or elevated HBVDNA (n = 0)

Anti-HBc negative (n = 34)
- Treated with R-CHOP (n = 16)
  - Hepatitis (n = 4)
- Treated with CHOP (n = 18)
  - Hepatitis (n = 4)

* Yoe et al., J Clin Oncol 2009
Reactivation in Breast cancer

- Reactivation in colon cancer: 14-21%
- Reactivation in breast cancer: 41-70%
  - High dose of chemotherapy agent
  - Anthracycline
  - Use of steroid

Table 2. Baseline patient characteristics, viral status and outcome

<table>
<thead>
<tr>
<th></th>
<th>Non-preemptive</th>
<th>Preemptive</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>9</td>
<td>11</td>
<td>0.98</td>
</tr>
<tr>
<td>Median age (range) (years)</td>
<td>43 (27–55)</td>
<td>47 (36–58)</td>
<td>0.99</td>
</tr>
<tr>
<td>Staging 1/2/3/4</td>
<td>0, 5, 3, 1</td>
<td>5, 4, 1, 1</td>
<td>1.00</td>
</tr>
<tr>
<td>Duration of chemotherapy (range) (months)</td>
<td>6 (3–18)</td>
<td>4.5 (3.5–16)</td>
<td>1.00</td>
</tr>
<tr>
<td>Length of follow-up (range) (months)</td>
<td>10 (3–18)</td>
<td>19 (11–25)</td>
<td>1.00</td>
</tr>
<tr>
<td>Baseline ALT</td>
<td>15 (6–54)</td>
<td>14 (12–31)</td>
<td>1.00</td>
</tr>
<tr>
<td>Baseline viral status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBeAg (+)</td>
<td>1/9 (11.1%)</td>
<td>2/11 (18.2%)</td>
<td>0.99</td>
</tr>
<tr>
<td>Anti-HBe Ab (+)</td>
<td>8/9 (88.9%)</td>
<td>9/11 (81.8%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Mean HBV DNA (log copies/ml)</td>
<td>2.57 ± 0.87</td>
<td>3.11 ± 0.36</td>
<td>0.046</td>
</tr>
<tr>
<td>Rate of HBV reactivation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of HBV reactivations</td>
<td>5 (55.6%)</td>
<td>0</td>
<td>0.476</td>
</tr>
<tr>
<td>Mortality due to HBV reactivation</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Anti-HBe, antibody to HBeAg; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; ALT, alanine aminotransferase. *Pearson’s χ² test. Others, Fisher’s exact test.

Yeo W et al., J Med Virol 2003
Steroid and molecular mechanism

- Glucocorticoids regulate gene expression in several human and animal systems.

- HBV genome contains a glucocorticoid responsive element (GRE) that binds steroid and activates transcriptional enhancer.

- Mutations in the GRE may either reduce or increase HBV transcription after exposure to corticosteroids.

Kaspa et al., Proc Nat Acad Sci 2986;83:1627, Suzuki et al., Kurume Medical Journal 1998;45:171
Omission of steroid

50 NHL patients HBsAg +

25 PACE
- Prednisolone
- Epirubicin
- Cyclophosphamide
- Etoposide

25 ACE
- Prednisolone
- Epirubicin
- Cyclophosphamide
- Etoposide

Cheng et al., Hepatology 2003
Omission of steroid

Lower HBV reactivation

Reduced survival

Cheng et al., Hepatology 2003
Reports of steroid-induced HBV reactivation in other settings

- Case reports, but...not frequent
  - Bronchial asthma
  - Inflammatory bowel disease
  - Rheumatic disease
  - Pemphigus (20 – 75mg X 4 – 17 months)
  - Dermatomyositis
Hepatitis B reactivation - Immunotherapy in other specific situation (IBD, Rheumatic Dz)
Anti-TNF inhibitors

Tracey et al., Pharmacol Ther 2008;117:244
Hepatitis B Virus (HBV) Reactivation in Patients Receiving Tumor Necrosis Factor (TNF)-Targeted Therapy

Analysis of 257 Cases

Roberto Pérez-Alvarez, MD, Cándido Díaz-Lagares, MD, Francisco García-Hernández, MD, Leopoldo Lopez-Roses, MD, PhD, Pilar Brito-Zerón, MD, PhD, Marta Pérez-de-Lis, MD, PhD, Soledad Retamozo, MD, Albert Bové, MD, PhD, Xavier Bosch, MD, PhD, Jose-Maria Sanchez-Tupias, MD, PhD, Xavier Forns, MD, PhD, Manuel Ramos-Casals, MD, PhD, and the BIOGEAS Study Group*

- 89 HBsAg+
  - 39% (35/89) had reactivation
    - ALT elevation: 42%, signs and symptoms 16%, death 5%
    - Higher in patients previously treated with immunosuppressives (96% vs 70%)
    - Lower in those receiving prophylaxis (23% vs. 62%)
    - Acute liver failure in 5/89 (6%), 4 fatal cases
    - Infliximab highest risk
Hepatitis B Virus (HBV) Reactivation in Patients Receiving Tumor Necrosis Factor (TNF)-Targeted Therapy

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- 168 HBcIgG+
  - 5% (9/168 cases)
    - 6 RA, 2 IBD, 1 AS
    - Mean time to reactivation 11 months
    - 6 ETN, 3 IFN
    - None received anti-viral prophylaxis
    - 1 Fatal
Reactivation in Inflammatory bowel disease

- HBsAg+: 25 patients
  - 9 patients (36%) showed ALT flare, 6 developed failure.

- HBsAg-, antiHBc+: 65 patients
  - No case of “reverse seroconversion”

- Use of multiple immunosuppressants was risk factor for reactivation

Loras et al., Gut 2010;59:1340
Reativation of TNF-apha agent

- Reactivation in 39% of HBsAg(+), 5% of anti-HBc Ab (+)
- Reactivation rate after preemptive antiviral agent (23% vs. 62%, p=0.003)

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**TABLE 7. Baseline Characteristics of Patients With Chronic HBV Infection Before Starting Anti-TNF Therapy, According to the Development of HBV Reactivation During Anti-TNF Therapy**

<table>
<thead>
<tr>
<th>Baseline Characteristic</th>
<th>No HBV Reactivation (n = 33)</th>
<th>HBV Reactivation (n = 29)</th>
<th>P (2-Sided)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%)</td>
<td>No. (%)</td>
<td></td>
</tr>
<tr>
<td>Age, mean ± SEM, yr</td>
<td>43.54 ± 2.54</td>
<td>46.83 ± 2.84</td>
<td>0.390</td>
</tr>
<tr>
<td>Sex (female)</td>
<td>13/28 (54)</td>
<td>11/24 (46)</td>
<td>1.000</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>10/32 (31)</td>
<td>12/29 (41)</td>
<td>0.437</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td>6/32 (19)</td>
<td>10/29 (34)</td>
<td>0.244</td>
</tr>
<tr>
<td>Disease duration &gt;10 yr</td>
<td>10/18 (56)</td>
<td>7/19 (37)</td>
<td>0.330</td>
</tr>
<tr>
<td>Known HBV infection</td>
<td>16/19 (84)</td>
<td>13/18 (72)</td>
<td>0.447</td>
</tr>
<tr>
<td>Previous treatment with methotrexate</td>
<td>9/20 (45)</td>
<td>13/24 (54)</td>
<td>0.763</td>
</tr>
<tr>
<td>Previous treatment with immunosuppressive agents</td>
<td>14/20 (70)</td>
<td>23/24 (96)</td>
<td><strong>0.035</strong></td>
</tr>
<tr>
<td>Previous treatment with &gt;2 immunosuppressive agents</td>
<td>5/21 (24)</td>
<td>5/24 (21)</td>
<td>1.000</td>
</tr>
<tr>
<td>Raised transaminase levels</td>
<td>3/25 (12)</td>
<td>7/23 (30)</td>
<td>0.162</td>
</tr>
<tr>
<td>Positive HBeAg</td>
<td>2/31 (6)</td>
<td>5/24 (21)</td>
<td>0.220</td>
</tr>
<tr>
<td>Raised serum HBV-DNA</td>
<td>5/29 (17)</td>
<td>8/18 (44)</td>
<td><strong>0.054</strong></td>
</tr>
<tr>
<td>Infliximab</td>
<td>14/33 (42)</td>
<td>17/29 (59)</td>
<td>0.309</td>
</tr>
<tr>
<td>Etanercept</td>
<td>13/33 (39)</td>
<td>9/29 (31)</td>
<td>0.598</td>
</tr>
<tr>
<td>Antiviral prophylaxis</td>
<td>20/32 (62)</td>
<td>7/28 (25)</td>
<td><strong>0.005</strong></td>
</tr>
</tbody>
</table>

*Perez-Alvarez Ret al. Medicine. 2011,*
Hepatitis B reactivation - Settings of transplantation
Type of HSCT and HBV

- **Autologous (auto) HSCT**
  - A way to deliver potentially myeloablative chemotherapy to eradicate malignancy without eradicating host hematopoiesis and immunity
  - HBV reactivation after auto HSCT is immunologically similar to reactivation after intensive chemotherapy

- **Allogenic (allo) HSCT**
  - A way to deliver potentially myeloablative chemotherapy to eradicate malignancy, but, host hematopoiesis and immune system are replaced by that of donor
  - Risk for HBV reactivation (or spontaneous clearance) after transplant are impacted by donor HBV status
Changes in Serologic Markers of Hepatitis B Following Autologous Hematopoietic Stem Cell Transplantation

Ji Eun Uhm, Kibyun Kim, Tae Kyu Lim, Byeong-Bae Park, Sarah Park, Yong Sang Hong, Sang Cheol Lee, In Gyu Hwang, Kwang Cheol Koh, Mark H. Lee, Jin Seok Ahn, Won Seog Kim, Chul Won Jung, Won Ki Kang

Uhm J., Biol Blood Marrow Transplant 2007;13:463
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  - Risk for HBV reactivation (or spontaneous clearance) after transplant are impacted by donor HBV status
Adoptive transfer of immunity

- Transfer of immunity from HBV-immune donor to HBV-infected allo HSCT recipient
  - Though to be due to transfer of core antigen reactive T cells
- Incidence of spontaneous clearance of sAg
  - 3/5 (sAb+ donor) vs. 0/16 (sAb- donor)
    - Significant flare in ALT around time of clearance
  - 24/31 (sAb+ donor) vs. 0/51 (sAb- donor)
    - Prophylactic LAM independently associated with clearance

Lau et al., Gastroenterology 2002;122:614
Hui et al., Blood 2005;106:464
Progressive disappearance of anti-HBs and RS

14 HBsAg-, anti-HBs+ patients (13 anti-HBc+)
7 donors anti-HBs+

Onozawa M, Transplantation 2005;79:616
Progressive disappearance of anti-HBs and RS

- Estimated risk of anti-HBs disappearance 100% at 5 years
- Reverse seroconversion 70% at 7 years

Onozawa M, Transplantation 2005;79:616
## Incidence of reverse seroconversion (RS)

<table>
<thead>
<tr>
<th>Author/year</th>
<th>Country</th>
<th>No. of patients</th>
<th>No.(%) with RS</th>
<th>Median follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seth/2002</td>
<td>Saudi Arabia</td>
<td>42</td>
<td>6 (14%)</td>
<td>16</td>
</tr>
<tr>
<td>Knoll/2007</td>
<td>Germany</td>
<td>7</td>
<td>6 (86%)</td>
<td>53</td>
</tr>
<tr>
<td>Hammond/2009</td>
<td>USA</td>
<td>61</td>
<td>12 (20%)</td>
<td>17</td>
</tr>
<tr>
<td>Ramos/2010</td>
<td>USA</td>
<td>73</td>
<td>8 (10%)</td>
<td>47</td>
</tr>
<tr>
<td>Vigano/2011</td>
<td>Italy</td>
<td>50</td>
<td>6 (12%)</td>
<td>17</td>
</tr>
<tr>
<td>Park/2011</td>
<td>Korea</td>
<td>114</td>
<td>3 (3%)</td>
<td>78</td>
</tr>
</tbody>
</table>

Seth et al, Bone Marrow Transplant 2002;30:189
Knoll A, J viral Hepat 2007;14:478
Ramos C, Biol Blood Marrow Transplant 2010;16:686
Vigano M, Bone Marrow Transplant 2011;46:125
Park S, Biol Blood Marrow Transplant 2011;17:1630
Changes of Hepatitis B Virus Serologic Status after Allogeneic Hematopoietic Stem Cell Transplantation and Impact of Donor Immunity on Hepatitis B Virus

Silvia Park,¹ Kihyun Kim,¹ Dong Hwan Kim,¹ Jun Ho Jang,¹ Seok Jin Kim,¹ Won Seog Kim,¹ Chul Won Jung,¹ Kwang Cheol Koh²

- 181 Korean patients, HBsAg-, anti-HBs+, pre-HSCT
  - 56 (31%) became anti-HBs-, median 76 (21-168) months after HSCT

Table 3. Characteristics of 3 Recipients with HBV RS

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Pre-HSCT Anti-HBc</th>
<th>Pre-HSCT Anti-HBs</th>
<th>Timing of RS (Month after HSCT)</th>
<th>Anti-HBs Status at the Time of RS</th>
<th>HBeAg Status at HBV Diagnosis</th>
<th>Anti-HBe Status at HBV Diagnosis</th>
<th>PCR Titer at HBV Diagnosis (pg/mL)</th>
<th>Pre-HSCT HBsAg</th>
<th>Pre-HSCT Anti-HBc</th>
<th>Pre-HSCT Anti-HBs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(+)</td>
<td>(+)</td>
<td>20.8</td>
<td>(−)</td>
<td>(+)</td>
<td>(−)</td>
<td>1592</td>
<td>(−)</td>
<td>unknown</td>
<td>unknown</td>
</tr>
<tr>
<td>2</td>
<td>(+)</td>
<td>(+)</td>
<td>72.8</td>
<td>(−)</td>
<td>unknown</td>
<td>unknown</td>
<td>unknown</td>
<td>(−)</td>
<td>(+)</td>
<td>(−)</td>
</tr>
<tr>
<td>3</td>
<td>(+)</td>
<td>(+)</td>
<td>27.9</td>
<td>(−)</td>
<td>(−)</td>
<td>(+)</td>
<td>&gt;2266.0</td>
<td>(−)</td>
<td>(−)</td>
<td>(−)</td>
</tr>
</tbody>
</table>

HSCT indicates hematopoietic stem cell transplantation; HPV RS, hepatitis B reverse seroconversion.

Park et al., Biol Blood Marrow Transplant 2011;17:1630
Factors associated with loss of anti-HBs after HSCT

<table>
<thead>
<tr>
<th></th>
<th>Multivariate Hazard ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Park et al</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extensive cGVHD</td>
<td>2.99 (1.40 – 6.39)</td>
<td>0.004</td>
</tr>
<tr>
<td>Donor HBV anti-HBs+</td>
<td>0.38 (0.18 – 0.80)</td>
<td>0.011</td>
</tr>
<tr>
<td>Hammond et al</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-transplant anti-HBs ≥ 10 mIU/ml</td>
<td>4.59 (1.23 – 16.92)</td>
<td>0.023</td>
</tr>
<tr>
<td>Extensive cGVHD</td>
<td>7.21 (1.25 – 41.53)</td>
<td>0.027</td>
</tr>
</tbody>
</table>

Park S, Biol Blood Marrow Transplant 2011;17:1630
<table>
<thead>
<tr>
<th>Author/year</th>
<th>Country</th>
<th>No. of patients</th>
<th>% anti-HBc+</th>
<th>% anti-HBs+</th>
<th>% anti-HBs+</th>
<th>Incidence of RS</th>
<th>Cumulative probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Park/2011</td>
<td>Korea</td>
<td>114</td>
<td>100</td>
<td>99</td>
<td>57</td>
<td>3 (3%)</td>
<td>4.8% at yr 6</td>
</tr>
<tr>
<td>Vigano/2011</td>
<td>Italy</td>
<td>50</td>
<td>100</td>
<td>Unknown</td>
<td>32</td>
<td>6 (12%)</td>
<td>22% at yr 5</td>
</tr>
<tr>
<td>Ramos/2010</td>
<td>USA</td>
<td>73</td>
<td>100</td>
<td>Unknown</td>
<td>Unknown</td>
<td>8 (10%)</td>
<td>11.6% at yr 3</td>
</tr>
<tr>
<td>Hammond/2009</td>
<td>USA</td>
<td>61</td>
<td>100</td>
<td>88</td>
<td>Unknown</td>
<td>12 (20%)</td>
<td>42.9% at yr 4</td>
</tr>
</tbody>
</table>

Ramos C, Biol Blood Marrow Transplant 2010;16:686
Vigano M, Bone Marrow Transplant 2011;46:125
Park S, Biol Blood Marrow Transplant 2011;17:1630
Complex scenario

- HBsAg+
- HBcIgG+
- HBsAg- HBcIgG-

- HBsAb- donor
- HBsAb+ donor
Complex scenario

- **HBsAg+**
  - HBsAb- donor
    - Risk of reactivation (exacerbation)
  - HBsAb+ donor
    - Chance of spontaneous HBsAg seroclerance
    - Risk of reactivation (exacerbation)
Complex scenario

Risk of reactivation

Risk of reactivation (Reduced?)

HBsAb+ donor

HBsAb- donor

HBcIgG+
Complex scenario

- HBcIgG+ HBsAb+ donor
- Risk of reactivation?

- HBcIgG- HBsAb- donor
- No risk of reactivation

- HBsAg- HBcIgG-

- HBcIgG- HBsAb+ donor
- No risk of reactivation?
Impact of prophylaxis

20 allo HSCT compared to matched historical control

Lau et al., Hepatology 2002;35:702
HB Vaccination in the Prevention of Viral Reactivation in Allogeneic Hematopoietic Stem Cell Transplantation Recipients with Previous HBV Infection

Masahiro Onozawa, Satoshi Hashino, Stephanie Darmanin, Kohei Okada, Rena Morita, Mutsumi Takahata, Akio Shigematsu, Kaoru Kahata, Takeshi Kondo, Junji Tanaka, Masahiro Imamura, Masahiro Asaka

A

B

Onozawa et al., Biol Bone Marrow Transplant 2008;14:1226
Patterns of reactivation in organ transplantation

<table>
<thead>
<tr>
<th>Donor</th>
<th>Recipient</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Transmission of Hepatitis B</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBsAg +</td>
<td>Non immune</td>
<td>Transmission, common</td>
</tr>
<tr>
<td>Anti-HBc +</td>
<td>Non immune</td>
<td>Transmission, less frequent</td>
</tr>
<tr>
<td>** Reactivation of Hepatitis B**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non infected</td>
<td>HBsAg +</td>
<td>Reactivation, typical</td>
</tr>
<tr>
<td>Non infected</td>
<td>Anti-HBc +</td>
<td>Reverse seroconversion</td>
</tr>
</tbody>
</table>
## Liver transplantation

<table>
<thead>
<tr>
<th>Donor</th>
<th>Recipient</th>
<th>Recipient</th>
<th>Recipient</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg+</td>
<td>HBsAg+</td>
<td>HBsAg-/HBcIgG+</td>
<td>HBsAG-/HBcIgG-</td>
</tr>
<tr>
<td>HBsAg-/HBcIgG+</td>
<td>NA ± HBIG</td>
<td>NA ± HBIG</td>
<td>NA ± HBIG</td>
</tr>
<tr>
<td>HBsAG-/HBcIgG-</td>
<td>NA ± HBIG</td>
<td>NA or HBIG</td>
<td>NA or HBIG</td>
</tr>
<tr>
<td></td>
<td>Monitoring</td>
<td>Monitoring</td>
<td>Monitoring</td>
</tr>
</tbody>
</table>
Complex situation in non-liver solid organ

<table>
<thead>
<tr>
<th>Donor</th>
<th>Recipient</th>
<th>Transmission risk</th>
<th>Reactivation risk</th>
<th>Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg+</td>
<td>NA</td>
<td>Transmission risk (+)</td>
<td>Reactivation risk (+)</td>
<td>Monitoring or NA for early period*</td>
</tr>
<tr>
<td>HBsAg-/HBcIgG+</td>
<td>NA</td>
<td>Transmission risk (?)</td>
<td>Reactivation risk (+)</td>
<td>Monitoring</td>
</tr>
<tr>
<td>HBsAG-/HBcIgG-</td>
<td>NA</td>
<td>Reactivation risk (+)</td>
<td>Monitoring</td>
<td>Monitoring</td>
</tr>
</tbody>
</table>
Non-Liver solid organ transplantation

- Reactivation frequent among HBsAg positive renal, heart or lung transplant recipient
- Reverse seroconversion has been reported but uncommon
- Timing of reactivation may be delayed and long-term consequences are not clearly defined
Hepatitis B reactivation- Novel agents
Targets agents in cancer therapy

- Case reports
  - Atni-CD52% Tcell Ab: alemtuzumab in CLL
  - Proteasome inhibitor: Bortezomib for myeloma
  - mTOR inhibitor: Everolimus in RCC
  - BCR-abl tyrosine kinase inhibitor: Imatinib mesylate
  - Immune check point inhibitor : Anti PD-1 (nivolumab), Anti CTLa4 (ipilmumab)
- After introduction of prevention of hepatitis B reactivation, limited data are available.
Reactivation

- *Isolated anti-HBc (+) 51.7%*
- *Anti-HBc (+)/Anti-HBs (+) 6.9%*
- *Isolated anti-HBs (+) 6.9%*
- HBsAg (+): 33.4%

76% of patients with HBV carried an HBsAg with mutations.
## Risk factors of reactivation

<table>
<thead>
<tr>
<th><strong>Virus factor</strong></th>
<th><strong>Host factor</strong></th>
<th><strong>Drug factor</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV DNA level before treatment</td>
<td>Category of cancer</td>
<td>Category of chemotherapy or immunosuppressive agent</td>
</tr>
<tr>
<td>cccDNA in liver</td>
<td>Male</td>
<td>Intensity of chemotherapy</td>
</tr>
<tr>
<td>Alternation in PC/BCP</td>
<td>Old age</td>
<td>PBSCT</td>
</tr>
<tr>
<td></td>
<td>High age</td>
<td>Transplantation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

KASL guideline_CHB_2018_Under preparation
## Risk of Hepatitis B Reactivation Associated With Immunosuppressive

<table>
<thead>
<tr>
<th>HBsAg-positive</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High risk (≥10%)</strong></td>
<td></td>
</tr>
<tr>
<td>Rituximab</td>
<td></td>
</tr>
<tr>
<td>High-dose corticosteroids (≥20mg/day, ≥4-week)</td>
<td></td>
</tr>
<tr>
<td>Anthracyclines (doxorubicin and epirubicin)</td>
<td></td>
</tr>
<tr>
<td>TNFα inhibitors (infliximab, etanercept, and adalimumab)</td>
<td></td>
</tr>
<tr>
<td>Local therapy for HCC (transcatheter arterial chemoembolization)</td>
<td></td>
</tr>
<tr>
<td><strong>Moderate risk (1-10%)</strong></td>
<td></td>
</tr>
<tr>
<td>Systemic chemotherapy</td>
<td></td>
</tr>
<tr>
<td>Moderate-dose corticosteroids (10-20mg/day, ≥ 4-week)</td>
<td></td>
</tr>
<tr>
<td>Immunophilin inhibitors (cyclosporine)</td>
<td></td>
</tr>
<tr>
<td>Tyrosine-kinase inhibitors (imatinib and nilotinib)</td>
<td></td>
</tr>
<tr>
<td><strong>Low risk (&lt;1%)</strong></td>
<td></td>
</tr>
<tr>
<td>azathioprine, 6-mercaptopurine, methotrexate</td>
<td></td>
</tr>
<tr>
<td>Short term low-dose corticosteroids (&lt;10mg/day)</td>
<td></td>
</tr>
<tr>
<td>Intra-ocular steroid injection (extremely low risk)</td>
<td></td>
</tr>
</tbody>
</table>

*KASL guideline_CHB_2018_Under preparation*
Risk of Hepatitis B Reactivation Associated With Immunosuppressive

<table>
<thead>
<tr>
<th>HBsAg-negative/anti-HBc positive</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk (≥10%)</td>
<td>Rituximab</td>
</tr>
<tr>
<td>Moderate risk (1-10%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>High-dose corticosteroids (≥20mg/day, ≥4-week)</td>
</tr>
<tr>
<td></td>
<td>Anthracyclines (doxorubicin and epirubicin)</td>
</tr>
<tr>
<td></td>
<td>TNFα inhibitors (infliximab, etanercept, and adalimumab)</td>
</tr>
<tr>
<td></td>
<td>Systemic chemotherapy</td>
</tr>
<tr>
<td></td>
<td>Immunophilin inhibitors (cyclosporine)</td>
</tr>
<tr>
<td></td>
<td>Tyrosine-kinase inhibitors (imatinib, nilotinib)</td>
</tr>
<tr>
<td>Low risk (&lt;1%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Moderate-dose (10-20mg/day) &amp; Low-dose (&lt;10mg/day) corticosteroids</td>
</tr>
<tr>
<td></td>
<td>azathioprine, 6-mercaptopurine, methotrexate</td>
</tr>
</tbody>
</table>
Hepatitis B reactivation
- Prevention and management -

Dong Hyun Sinn M.D., Ph.D

Department of Medicine
Samsung Medical Center, Seoul, Korea
History of CHB treatment

Year of first marketing approval

- Interferons approved for CHB treatment\(^1\)
- Adefovir\(^3\)
- Entecavir\(^6\), PegIFN\(^5\)
- Telbivudine\(^9\)
- Lamivudine\(^2\)
- Landmark study: antiviral therapy slows disease progression in CHB\(^4\)
- REVEAL data associates viral load with cirrhosis/HCC\(^7,8\)
- Tenofovir\(^10\)

References:
Three options become available

- **Prophylaxis**
- **Pre-emptive**
- **On-demand**
Prophylactic vs. Therapeutic

30 HBsAg + patients

Therapeutic group: HBV DNA q 2 weeks
LAM was given for 6 months after completion of chemotherapy

Lau GK et al., Gastroenterology 2003;125:1742
### Meta-analysis: Prophylactic LAM is better for HBsAg positive patients

<table>
<thead>
<tr>
<th></th>
<th>Without Prophylaxis</th>
<th>Lamivudine Prophylaxis</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV reactivation</td>
<td>29 – 56%</td>
<td>0 – 24%</td>
<td>0.0001</td>
</tr>
<tr>
<td>HBV reactivation related hepatitis</td>
<td>33 – 67%</td>
<td>0 – 20%</td>
<td>0.0001</td>
</tr>
<tr>
<td>Liver-related mortality</td>
<td>0 – 50%</td>
<td>0%</td>
<td>0.0001</td>
</tr>
<tr>
<td>Chemotherapy withdrawal</td>
<td>11 – 20%</td>
<td>2 – 6%</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

*Kohrt et al., Alminet Pharmacol Ther 2006*
Lamivudine vs Entecavir

Huang H et al., JAMA, 2014

R-CHOP-14 indicates 2-week chemotherapy regimen containing rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CHOP-21, 3-week R-CHOP chemotherapy regimen.
### Lamivudine vs Entecavir

<table>
<thead>
<tr>
<th>Type of Analysis</th>
<th>Bivariable</th>
<th>Multivariable</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antiviral prophylaxis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lamivudine</td>
<td>60</td>
<td>18</td>
</tr>
<tr>
<td>Entecavir</td>
<td>61</td>
<td>4</td>
</tr>
</tbody>
</table>

- **Sex**
  - Male | 68 | 16 | 2.41 (0.87-6.67) | .08 | 2.62 (0.80-8.55) | .11 |
  - Female | 53 | 6 | | | |

- **Age, y**
  - ≤40 | 54 | 8 | 0.66 (0.25-1.71) | .39 | |
  - >40 | 67 | 14 | | | |

- **Ann Arbor stage**
  - I-II | 47 | 4 | 3.46 (1.09-10.96) | .03 | 3.59 (1.01-12.77) | .049 |
  - III-IV | 74 | 18 | | | |

- **International Prognostic Index**
  - 0-2 | 105 | 18 | 1.61 (0.47-5.57) | .68 | |
  - 3-5 | 16 | 4 | | | |

- **Hepatitis B e antigen status**
  - Seropositive | 34 | 7 | 1.24 (0.46-3.38) | .67 | |
  - Seronegative | 87 | 15 | | | |

- **Hepatic cirrhosis**
  - Yes | 3 | 2 | 9.80 (0.85-113.36) | .09 | 17.32 (0.75-400.83) | .08 |
  - No | 118 | 20 | | | |

- **Liver involvement**
  - Yes | 7 | 1 | 0.74 (0.08-6.46) | .78 | |
  - No | 114 | 21 | | | |

- **Cycles of R-CHOP chemotherapy**
  - ≤6 | 87 | 12 | 2.60 (1.00-6.78) | .05 | 2.23 (0.75-6.59) | .15 |
  - >6 | 34 | 10 | | | |

- **Chemotherapy interval**
  - 2 wk (R-CHOP-14) | 58 | 10 | 0.89 (0.35-2.24) | .80 | |
  - 3 wk (R-CHOP-21) | 63 | 12 | | | |

- **Huang H et al., JAMA, 2014**

- **Entecavir vs Lamivudine**
- **Reactivation rate** (4% vs. 18%, p=0.001)
- **Discontinuation of chemotherapy cause of HBV reactivation** (1% vs. 11%, p=0.002)
When to start anti viral agent?

- (A) Survival free from hepatitis B virological reactivation, (B) survival free from hepatitis due to hepatitis B virological reactivation in HBsAg (+) lymphoma patients

- Early (group 1, - – -) and Deferred (group 2, - ○ - ○-) preemptive lamivudine therapy

- Early is superior to deferred preemptive lamivudine therapy for hepatitis B patients undergoing chemotherapy

Lau GK et al., Gastroenterology 2003
When to stop antivirals after cessation of cancer chemotherapy?

- 46 HBsAg+ patients with a median of 9.2 months of pre-emptive LAM
- A median of 3 months between end of chemotherapy and withdrawal of LAM
- HBV reactivation: none during LAM, 11 (23.9%) after withdrawal of LAM

Hui et al., Gut 2005;54:597
Delayed reactivation

- Prophylactic therapy, may should not be immediately stopped (agreed)
- But how long?
Antiviral Tx after finish chemotherapy

- 6 Month after finish chemotherapy
- 12 Month after finish rituximab contain chemotherapy
- Close monitoring after finish antiviral therapy

Time from the cessation of prophylactic anti-viral drug to HBV delayed reactivation.

Lu WP et al., Leukemia & lymphoma  2016
Stopping Preemptive Antiviral Therapy for Hepatitis B Virus Can Be Considered for Patients with Favorable Predictors

Hyo Jin Kim¹ · Dong Hyun Sinn¹ · Nam Jun Kim¹ · Jung Hee Kim¹ · Eun Kim¹ · Geum-Youn Gwak¹ · Yong-Han Paik¹ · Moon Seok Choi¹ · Joon Hyeok Lee¹ · Kwang Cheol Koh¹ · Seung Woon Paik¹ · Byung Chul Yoo¹

Fig. 1 Sustained off-therapy virological response rate according to baseline hepatitis B virus DNA levels. The sustained off-therapy virological response rate was 81.3, 68.9, 50.0, and 5.0 % for those with undetectable HBV DNA levels (≤12 IU/ml), 13–1999 IU/ml, 2000–19,999 IU/ml, and ≥20,000 IU/ml, respectively (p < 0.001).

Fig. 3 Sustained off-therapy virological response rate of patients with elevated base DNA levels (≥2000 IU/mL). There was significant sustained off-therapy virological response in those with ≥20,000 IU/mL.
Stopping Preemptive Antiviral Therapy for Hepatitis B Virus Can Be Considered for Patients with Favorable Predictors

Hyo Jin Kim¹ · Dong Hyun Sinn¹ · Nam Jun Kim¹ · Jung Hee Kim¹ · Eun Kim¹ · Geum-Youn Gwak¹ · Yong-Han Paik¹ · Moon Seok Choi¹ · Joon Hyeok Lee¹ · Kwang Cheol Koh¹ · Seung Woon Paik¹ · Byung Chul Yoo¹

Fig. 2 Sustained off-therapy virological response rate according to the duration of consolidation treatment in patients with low HBV DNA levels (<2000 IU/mL) at baseline. Although it was not statistically significant, there was linear trend for increased sustained off-therapy virological response along with increase in consolidation treatment
On-going clinical trial

- **Aim**
  - To test duration of antiviral treatment after HBV prophylaxis

- **Indication**
  - HBsAg+ patients receiving Adjuvant chemotherapy
  - HBcIgG+ lymphoma receiving Rituximab based therapy
Reactivation of Hepatitis B
- How to handle it -

2015. Apr. 27
What we all know

- HBV reactivation can occur in HBsAg + patients who receive cytotoxic chemotherapy, and can be fatal.
  - Patients should be screened for HBsAg, and preemptive AVT should be commenced.
Prevention by alert system

- Kaoshing Veterans General Hospital
- Order entry-based alert system (e-REMINDER)
- Order entry-based therapeutic control system (e-CONTROL)

Hsu et al., Hepatology, 2015 Accepted article
Prevention by alert/control system

![Flowchart showing the process of prevention for newly diagnosed cancer patients who received chemotherapy.]

- **Newly diagnosed cancer patients who received chemotherapy** (n = 2611)
  - **Educational stage** (n = 1207)
    - Exclusion: Intracavity chemotherapy (n = 28), Target therapy or hormone therapy alone (n = 22)
  - **Screening reminder stage** (n = 673)
    - Exclusion: Intracavity chemotherapy (n = 13), Target therapy or hormone therapy alone (n = 10)
  - **Therapeutic control stage** (n = 731)
    - Exclusion: Intracavity chemotherapy (n = 15), Target therapy or hormone therapy alone (n = 11)

**Included subjects**
- **Educational stage** (n = 1157)
- **Screening reminder stage** (n = 650)
- **Therapeutic control stage** (n = 705)

---

**Table 4. Acute liver injury in chemotherapy patients among the education, order entry-based screening reminder and order entry-based therapeutic control stages**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Education stage (n = 1157)</th>
<th>Screening reminder stage (n = 650)</th>
<th>Therapeutic control stage (n = 705)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe acute exacerbation in HBsAg-positive patients</td>
<td>14/1157 (1.2%)</td>
<td>8/650 (1.2%)</td>
<td>0/705*† (0.0%)</td>
</tr>
<tr>
<td>Liver decompensation related to severe acute exacerbation of HBV infection</td>
<td>12/1157 (1.0%)</td>
<td>8/650 (1.2%)</td>
<td>0/705*† (0.0%)</td>
</tr>
</tbody>
</table>

* P < 0.01 compared with education stage  
† P < 0.01 compared with screening reminder stage
Prevention by alert system

Cancer patients receiving chemotherapy

Screening HBsAg data within past 2 years

- No data
- Available data

* Alarming message:
  Checking HBsAg & anti-HBc is indicated.

- HBsAg-positive
- HBsAg-negative

* Alarming message:
  Antiviral prophylaxis is indicated.

Pass for chemotherapy

Hsu et al., Hepatology, 2015 Accepted article
Question

- Do we need same system in our center?