Occult Hepatitis B Infection: why, who and what to do?

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Who?

Different patients according to HBV history

Patient groups

1) Acute hepatitis B
2) No history of hepatitis B
3) Chronic hepatitis B (HBsAg seroclearance)
Who?
Different patients according to HBV serology

- **No exposure, no vaccination**
  - Anti-HBc -ve
  - Anti-HBs -ve

- **Vaccination with no exposure**
  - Anti-HBc -ve
  - Anti-HBs +/-

- **Exposure (Acute HBV)**
  - Anti-HBc +ve
  - Anti-HBs +/-

- **Chronic hepatitis B with HBsAg Seroclearance**
  - Anti-HBc +ve
  - Anti-HBs +/-
Contrary to current opinion, the disappearance of hepatitis B surface antigen (HBsAg) from the serum, the development of anti–HBs antibodies, and normalization of liver function may not reflect complete virological recovery from acute hepatitis B virus (HBV) infection. By using the polymerase chain reaction (PCR), in the current study we demonstrate long-term persistence of HBV DNA in the serum and peripheral blood mononuclear cells (PBMC) of four patients for up to 70 mo after complete clinical, biochemical, and serological recovery from acute viral hepatitis. Serum HBV DNA reactivity co-sedimented with HBsAg in sucrose gradients, and it displayed the size and density characteristics of naked core particles and intact HBV virions, presumably contained within circulating immune complexes in these anti–HBs antibody-positive sera. HBV DNA was also present in PBMC in late convalescent samples from all four patients, and HBV RNA was detected in late convalescent phase PBMC in two of these patients. These results suggest that HBV DNA, and possibly HBV virions, can be present in the serum, and that the viral genome can persist in a transcriptionally active form in PBMC for > 5 yr after complete clinical and serological recovery from acute viral hepatitis. (J. Clin. Invest. 1994. 93:230–239.) Key words: hepatitis B • hepato-

Michalak TI et al., J Clin Invest 1994;93:230-9
Patients with “definite” acute hepatitis B: OBI

- 16 patients with acute self-limited HBV 30 years ago
  - all HBsAg neg, anti-HBc +, 11 anti-HBs +
  - all negative for HBV DNA in serum and PBMC
  - 4 patients had liver biopsies
    - 2 minor inflammation and HBV DNA +
    - no mutations in HBV genome to explain latency of infection

Patients with no history of hepatitis B: OBI

  - initial individual screening by NAT
  - NAT+ve specimens tested for HBsAg
  - NAT+ve HBsAg-ve specimens tested for HBV DNA
  - OBI incidence

  11 out of 9,967 i.e. **0.11%**
  - 10 positive for anti-HBc
  - 7 positive for anti-HBs

Yuen MF et al., Gut 2010
Patients with known chronic hepatitis B infection: OBI

**Immune tolerance** | **Immune clearance** | **Immune control**

HBsAg+  
HBeAg  
HBeAg or anti-HBe  
Anti-HBe

HBV DNA (log\(_{10}\) IU/mL)  
IgM anti-HBc (PEI Units)  
ALT (U/L)

**Patients with CHB**  
HBeAg immune tolerant carriers  
HBeAg positive or negative  
Inactive carriers  
Occult hepatitis B carriers

Adapted from Chen CJ and Yang HI. J Gastroenterol Hepatol. 2011;26:628–38
Who will have a higher chance of HBsAg seroclearance/becoming OBI?

3 main factors

HBsAg level

Viral genomic difference

Host genomic difference
A Large Case-Control Study on the Predictability of Hepatitis B Surface Antigen Levels Three Years Before Hepatitis B Surface Antigen Seroclearance

Wai-Kay Seto,1 Danny Ka-Ho Wong,1 James Fung,1 Ivan Fan-Ngai Hung,1 Daniel Yee-Tak Fong,2 John Chi-Hang Yuen,1 Teresa Tong,1 Ching-Lung Lai,1,3 and Man-Fung Yuen1,3

203 CHB achieving HBsAg seroclearance

203 age- and sex-matched HBeAg-negative controls

No treatment

3 Years FU

Seto WK … Yuen MF. Hepatology 2012
HBsAg levels over 3-year study period

- **HBsAg levels (IU/mL)**
  - 36M
  - 24M
  - 12M
  - 6M
  - HBsAg loss

- **HBsAg seroclearance (n=203)**
- **Age- and sex-matched controls (n=203)**

[Seto WK ... Yuen MF. Hepatology 2012]
## Predictors of HBsAg seroclearance

<table>
<thead>
<tr>
<th>Predictor</th>
<th>AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg</td>
<td>0.833</td>
</tr>
<tr>
<td>HBsAg log reduction</td>
<td>0.802</td>
</tr>
<tr>
<td>HBV DNA</td>
<td>0.743</td>
</tr>
<tr>
<td>HBsAg / HBV DNA ratio</td>
<td>0.685</td>
</tr>
<tr>
<td>HBV DNA reduction</td>
<td>0.648</td>
</tr>
</tbody>
</table>

### Optimal cut-off HBsAg level: <200 IU/mL

### Optimal HBsAg log reduction: 0.5 log

<table>
<thead>
<tr>
<th>HBsAg log reduction</th>
<th>AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;200 IU/mL</td>
<td>0.867</td>
</tr>
<tr>
<td>≤200 IU/mL</td>
<td>0.796</td>
</tr>
</tbody>
</table>

Seto WK … Yuen MF. Hepatology 2012
Full length HBV genomes analyses
22 HBsAg negative subjects vs. 11 CHB (control group)

Findings
Genotype C is dominant (77.3%; 81.8%)

Nucleotide diversity over full genome significantly greater in HBsAg –ve group
(d = 0.04 vs. 0.026, p=0.008)

Nucleotide diversity over specific ORFs significantly greater in HBsAg –ve group
pre-S1 (p=0.045)
pre-C (p=0.047)
P (p=0.032)

Huang FY et al., PLoS One 2014;9(6):e99028
Mutational analysis on the pre-S/ S region

Total amino acid variability significantly higher in HBsAg -ve group
  22.2% vs. 8.25%, p < 0.0001
  Pre S1  17.6% vs. 2.5 %, p < 0.0001
  Pre S2  36.4% vs. 12.7% p < 0.001
  S 21.2% vs. 12.8% p < 0.001

Clinically important amino acid substitutions were mainly located in the major hydrophilic region (residues 103-173)
e.g. I126S, T126N, Q129N, T131N, M133T, G145A in “a” determinant region of HBsAg

Huang FY et al., PLoS One 2014;9(6):e99028
Host Genome and HBsAg Seroclearance

203 CHB achieving HBsAg seroclearance

203 age- and sex-matched HBeAg-negative controls

<table>
<thead>
<tr>
<th>SNP</th>
<th>Loci</th>
<th>Major allele</th>
<th>Minor allele</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>rs3077</td>
<td>HLA-DP</td>
<td>G</td>
</tr>
<tr>
<td>2</td>
<td>rs9277378</td>
<td>HLA-DP</td>
<td>G</td>
</tr>
<tr>
<td>3</td>
<td>rs3128917</td>
<td>HLA-DP</td>
<td>G</td>
</tr>
<tr>
<td>4</td>
<td>rs8099917</td>
<td>IL28B</td>
<td>T</td>
</tr>
<tr>
<td>5</td>
<td>rs12979860</td>
<td>IL28B</td>
<td>C</td>
</tr>
</tbody>
</table>

Seto WK ... Yuen MF. Clin Infect Dis 2012
rs3077 (HLA-DP)

<table>
<thead>
<tr>
<th></th>
<th>p value</th>
<th>Odds ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allelic (G vs A)</td>
<td>0.035</td>
<td>1.43</td>
<td>1.02 – 2.0</td>
</tr>
<tr>
<td>Genotypic (GG vs GA+AA)</td>
<td>0.013</td>
<td>1.89</td>
<td>1.13 – 3.17</td>
</tr>
</tbody>
</table>

Patients achieving HBsAg seroclearance

Controls

HLA-DP: rs3077/rs9277378/rs3128917

<table>
<thead>
<tr>
<th>Haplotype</th>
<th>p</th>
<th>Odds ratio</th>
<th>p controlled for rs3077</th>
</tr>
</thead>
<tbody>
<tr>
<td>GAT</td>
<td>0.034</td>
<td>2.17</td>
<td>0.06</td>
</tr>
</tbody>
</table>
Summary for who and why will become OBI

Low baseline HBsAg levels (<200 IU/mL) and significant HBsAg reduction predict HBsAg seroclearance

Specific host HLA-DP locus (using SNP rs3077)
Adding other SNPs increases the predictability of HBsAg seroclearance

HBV with OBI had a higher genetic diversity and higher amino acid mutation frequency than controls

Accumulation of multiple mutations constraining viral transcriptional activities contribute to HBsAg-negativity in HBV infection
What to do?

Clinical Implication?
Chimeric mice study

- 4 chimeric immunodeficiency mice, with livers repopulated with human hepatocytes, inoculated with sera from 2 OBI donors after 10-fold concentration (HBV DNA $\sim 10^2$ copies/mL)
- Serum HBV DNA and ccc DNA detected in 1 out of 4 mice after 9 weeks

Clinical implication: HBV transmissibility from OBI donors
Clinical implication: HBV transmissibility from OBI donors

Hong Kong Red Cross Study 2007-2009

- 67 OBI subjects among 217,595 donors (0.031%)
  - 44 traced (97.7% anti-HBs+; 95.5% anti-HBc+)
  - 31 PCR +
  - 272 recipients
  - 49 traced

Yuen MF et al, Clin Infect Dis 2011
Viral sequence phylogenetic study
Summary

OBI donor blood was shown to be potentially infectious in our animal and human studies.

However, the risk of chronic hepatitis B transmission through transfusion of blood donated by OBI donors in human remained low.

Yuen MF et al, Clin Infect Dis 2011
Clinical profile: HBsAg seroclearance – Intrahepatic viral status
serum HBV DNA, liver biochemistry

298 patients with HBsAg seroclearance
  Median age of HBsAg seroclearance: 49.6 years

29 patients with liver biopsy: 100% had detectable HBV DNA, 79.3% had detectable cccDNA

Serum HBV DNA detectability with time after HBsAg seroclearance
  × 1 yr: 13.4%
  × 5 – 10 yrs: 6.1%
  × >10 yrs: 3.7%

82% had normal ALT levels

Yuen MF et al., Gastroenterology 2008
Clinical profile: HBsAg seroclearance – Liver histology

- 92 Chinese CHB patients with HBsAg seroclearance
  - median follow-up 126 months

<table>
<thead>
<tr>
<th>Patients</th>
<th>Age of HBsAg Seroclearance, y</th>
<th>Interval Between Liver Biopsy and HBsAg Seroclearance, mo</th>
<th>Periportal Bridging Necrosis</th>
<th>Interlobular Degeneration and Focal Necrosis</th>
<th>Portal Inflammation</th>
<th>Fibrosis</th>
<th>Total Score</th>
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<tbody>
<tr>
<td>1</td>
<td>31.31</td>
<td>41.43</td>
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<td>1</td>
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<tr>
<td>2</td>
<td>31.35</td>
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<td>3</td>
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<td>4†</td>
<td>36.61</td>
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<td>5</td>
<td>36.95</td>
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</tr>
<tr>
<td>6</td>
<td>38.72</td>
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<td>0</td>
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<td>7</td>
<td>39.17</td>
<td>47.8</td>
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<td>10</td>
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<td>56.37</td>
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<td>1</td>
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<tr>
<td>11</td>
<td>51.64</td>
<td>29.6</td>
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<td>12</td>
<td>51.88</td>
<td>49.5</td>
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<td>1</td>
<td>0</td>
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<td>13</td>
<td>51.92</td>
<td>65.57</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>14</td>
<td>57.94</td>
<td>43.73</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

*Histological activity index score: 0–10 for periportal bridging necrosis and 0–4 for interlobular degeneration and focal necrosis, portal inflammation, and fibrosis.
†Patient was positive for HBsAg by immunoperoxidase staining HBeAg immunoperoxidase staining was negative in all other patients.

Clinical profile: HBsAg seroclearance – HCC

HCC development

- 5.4% (vs 8.7% in controls; p=NS)
- Mean age of HBsAg seroclearance
  - patients with HCC (63.2 years)
  - patients without HCC (47.9 years)
    \[ p=0.016 \]
- 4 out of 5 had cirrhosis at the time of HBsAg seroclearance

HBsAg Seroclearance – HCC

HBeAg +ve → Anti-HBe +ve → HBsAg -ve

Patient 1
Patient 2
Patient 3
Patient 4
Patient 5
Patient 6

esophageal varice
ascites

HCC (9 mths)
HCC (20 mths)
HCC (21 mths)
HCC (48 mths)
HCC (65 mths)

Clinical profile: HBsAg seroclearance – HCC

Follow-up (month)

Cumulative risk of HCC (%)

HBsAg seroclearance at age ≥ 50

p=0.004

HBsAg seroclearance at age < 50

Yuen MF et al., Gastroenterology 2008
Clinical Profile: OBI patients with unknown history of hepatitis B

1) Serology, genotype, liver biochemistry, histology and intrahepatic viral status

2) Role in HCC

3) HBV reactivation in immunosuppressive therapy & HSCT
## Serology and genotype

<table>
<thead>
<tr>
<th>No. of subjects with:</th>
<th>n = 40</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive anti-HBc (%)</td>
<td>39 (97.5%)</td>
</tr>
<tr>
<td>Positive anti-HBs (%)</td>
<td>36 (90%)</td>
</tr>
<tr>
<td>Negative for anti-HBc and anti-HBs (sero-negative)</td>
<td>0</td>
</tr>
<tr>
<td>HBsAg G145R escape mutant</td>
<td>0</td>
</tr>
<tr>
<td>Genotype B: C</td>
<td>21:19</td>
</tr>
</tbody>
</table>

*Wong DK, Yuen MF. Hepatol Int. 2014;8:S149*
Liver histology and liver biochemistry

<table>
<thead>
<tr>
<th>OBI blood donor with liver biopsy</th>
<th>n = 40</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (M : F)</td>
<td>29 : 11</td>
</tr>
<tr>
<td>Age at biopsy, yrs</td>
<td>49 (21 – 62)</td>
</tr>
<tr>
<td>Knodell HAI score</td>
<td>1 (0 – 4)</td>
</tr>
<tr>
<td>Ishak fibrosis score</td>
<td>0 (0 – 1)</td>
</tr>
<tr>
<td>ALT, IU/L</td>
<td>21.5 (8 – 48)</td>
</tr>
<tr>
<td>AST, IU/L</td>
<td>26 (17 – 40)</td>
</tr>
<tr>
<td>Albumin, g/L</td>
<td>44.5 (41 – 52)</td>
</tr>
<tr>
<td>Bilirubin, µmol/L</td>
<td>8 (4 – 13)</td>
</tr>
</tbody>
</table>

Median values (range)

Wong DK, Yuen MF. Hepatol Int. 2014;8:S149
Intrahepatic HBV DNA and pregenomic RNA quantification

No. of subjects with quantifiable:

Intrahepatic HBV DNA – 30/39 (77%)
Median: 0.22 copies/cell (<0.001 – 18.0)

cccDNA – 1/39 (3%)
0.005 copies/cell

Pregenomic RNA – 5/39 (13%)
Range: <0.0004 – 0.06 copies/cell

Serum HBV DNA – 18 (45%)
Range: <1.1 – 14 IU/mL

Lower limit of detection
Intrahepatic HBV DNA 0.001 copies/mL
cccDNA 0.005 copies/mL
Pregenomic RNA <0.0004 copies/mL

Wong DK, Yuen MF. Hepatol Int. 2014;8:S149
Clinical Profile: OBI patients with unknown history of hepatitis B

Role in HCC
A recent cohort study of HCC

61 HCC patients

- 13 CHB
- 33 cryptogenic
- 6 HCV
- 9 Alc

Nested PCR detection of HBV DNA

- No. of patients with +ve PCR in ≥ 2 regions:
  - 13 (100%)
  - 24 (73%)
  - 1 (17%)
  - 5 (56%)

Wong DKH … Yuen MF. Hepatology 2011
HBV DNA detection by nested PCR

Patient 1  2  3

bp  700  600  500  400  300  250  500  400  300  200  150  100

S  Core  Pol  X

NT  T  NT  T  NT  T  +  -

Wong DKH … Yuen MF. Hepatology 2011
Comparison between different genomic regions

More samples with detectable HBV DNA in the X region than the S, Core, and Pol regions

<table>
<thead>
<tr>
<th>No. of samples with detectable PCR</th>
<th>NT (n = 29)</th>
<th>P*</th>
<th>T (n = 30)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>27 (93%)</td>
<td></td>
<td>22 (73%)</td>
<td></td>
</tr>
<tr>
<td>S</td>
<td>18 (62%)</td>
<td>0.013</td>
<td>10 (33%)</td>
<td>0.006</td>
</tr>
<tr>
<td>Core</td>
<td>13 (45%)</td>
<td>&lt;0.001</td>
<td>14 (47%)</td>
<td>0.020</td>
</tr>
<tr>
<td>Pol</td>
<td>19 (66%)</td>
<td>0.026</td>
<td>11 (37%)</td>
<td>0.011</td>
</tr>
</tbody>
</table>

* Compared to X region

Wong DKH … Yuen MF. Hepatology 2011
HBV DNA/ pgRNA quantification

61 HCC patients

- 13 CHB
- 33 cryptogenic
- 6 HCV
- 9 Alc

Nested PCR detection of HBV DNA

- 13 (100%)
- 24 (73%)
- 1 (17%)
- 5 (56%)

Real-time quantification of HBV DNA/RNA

- serum HBV DNA
  - 12 (92%)
  - 0
  - 0
  - 0

- intrahepatic total HBV DNA
  - 13 (100%)
  - 22 (96%)
  - 1
  - 5 (100%)

- cccDNA
  - 12 (92%)
  - 6 (26%)
  - 0
  - 0

- pgRNA
  - 12 (92%)
  - 12 (52%)
  - 0
  - 3 (60%)
Clinical Profile: OBI patients with unknown history of hepatitis B

HBV reactivation in OBI patients receiving immunosuppressive therapy and HSCT
Hepatitis B reactivation
Different scenarios in HBV reactivation

- **HBsAg +ve/anti-HBc +ve/ HBV DNA detectable**
  - Increase in HBV DNA level

- **HBsAg +ve/anti-HBc +ve/ HBV DNA undetectable**
  - HBV DNA detectable

- **HBsAg –ve/anti-HBc +ve**
  - HBV DNA detectable but HBsAg -ve
  - **Reverse seroconversion**: HBsAg +ve (HBV DNA detectable)
Rituximab: ever expanding indications

Diffuse large B cell lymphoma
Follicular lymphoma
MALToma
Burkitt’s lymphoma
Chronic lymphocytic leukemia
Marginal zone lymphoma
Waldenstrom’s macroglobulinemia
Post-transplant lymphoproliferative disorder

Autoimmune hemolytic anemia
Chronic immune thrombocytopenia
Thrombotic thrombocytopenic purpura
Graft-versus-host disease

Rheumatoid arthritis
Wegener’s granulomatosis
Microscopic polyangiitis

Pemphigus vulgaris

Sarcoidosis
Interstitial lung disease

Graves’ orbitopathy

Autoimmune hepatitis
IgG4 cholangiopathy

Lupus nephritis
Membranous nephropathy

Neuromyelitis optica
Multiple sclerosis
Lambert-Eaton Syndrome
Chronic fatigue syndrome
# Anti-HBc and rituximab: previous studies

<table>
<thead>
<tr>
<th>Study region</th>
<th>Study nature</th>
<th>Anti-HBc patients number</th>
<th>Patients with HBV reactivation</th>
<th>Definition of HBV reactivation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hong Kong¹</td>
<td>Retrospective</td>
<td>23</td>
<td>5 (23.8%)</td>
<td>HBsAg seroreversion</td>
</tr>
<tr>
<td>Japan²</td>
<td>Retrospective</td>
<td>56</td>
<td>5 (8.9%)</td>
<td>HBsAg seroreversion</td>
</tr>
<tr>
<td>Asia-Pacific³</td>
<td>Retrospective</td>
<td>178</td>
<td>17 (9.6%)</td>
<td>HBsAg seroreversion</td>
</tr>
<tr>
<td>Taiwan⁴</td>
<td>Prospective</td>
<td>150</td>
<td>17 (11.3%)</td>
<td>Multiple virologic endpoints</td>
</tr>
</tbody>
</table>

HBV DNA monitoring:
1) No regular interval
2) Insensitive assay

Discrepancy in study endpoints

¹Yeo et al. J Clin Oncol 2009
²Matsue et al. Cancer 2010
³Kim et al. Eu J Cancer 2013
⁴Hsu et al Hepatology 2014
HBV reactivation in HBsAg(-) and anti-HBc(+) lymphoma patients treated with R-CHOP

346 non-Hodgkin’s Lymphoma Patients Screened-2009-2011

150 Enrolled

HBV DNA Check before every course of rituximab-CHOP and then every 4 weeks for 1 year

HBV Reactivation (-) 133 patients

HBV Reactivation (+) 17 patients

ETV 0.5 mg daily for 48 weeks

12 alive

5 Deceased due to tumor progression/adverse events

Anti-HBc and rituximab – a prospective study

- Recruited HBsAg -ve anti-HBc +ve lymphoma patients started on rituximab in QMH
- Clinical monitoring every 4 weeks up to 2 years
- All baseline HBV DNA negative
- HBV reactivation = HBV DNA detectable via realtime PCR
- Entecavir started at HBV reactivation
- No prior antiviral therapy

Anti-HBc and rituximab – a prospective study

260 patients started on rituximab-containing chemotherapy between September 2011 and September 2013

31 (11.9%) HBsAg +ve
229 (88.1%) HBsAg -ve

69 (30.1%) HBsAg-ve anti-HBc+ve
160 (69.9%) HBsAg -ve Anti-HBc -ve

Excluded:
2 with detectable baseline HBV DNA (26 and 28 IU/mL respectively)
3 already on entecavir
1 anti-HCV-positive

63 patients recruited for study

HBV reactivation rate in HBsAg –ve anti-HBc +ve patients receiving rituximab

Cumulative 40.5% in 2 years

19 patients with HBV reactivation

Baseline Anti-HBs – an important factor

Outcome of patients with HBV reactivation

All patients with HBV DNA becoming undetectable after starting of entecavir

1 out of 19 patients with HBV reactivation revert to HBsAg +ve and become –ve after 3 months of entecavir

No patients developed hepatitis flare

No liver related mortality

HBV reactivation in HSCT
HBV reactivation study in anti-HBc +ve patients with HSCT

All HBsAg -ve, anti-HBc +ve patients with hematological malignancies BMT in Queen Mary Hospital, Hong Kong.

All patients baseline HBV DNA undetectable (<10 IU/mL)

Patients monitored prospectively every 4 weeks since start of chemotherapy for at least 2 years

- 296 with HSCT performed

- 89 (30%) HBsAg-negative Anti-HBc positive

Excluded:
- Antiviral started before HSCT by referring centers (n=11)
- HBsAg-positive donor (n=6)*
- Baseline detectable HBV DNA (n=3)*
- Anti-HCV positive (n=1)

- 67 (75.5%) recruited

*Antiviral therapy started before HSCT
HSCT: cumulative rate of HBV reactivation

- 104-week cumulative reactivation: 36.8%
- 52-week cumulative reactivation: 17.2%
- 13 cases of HBV reactivation
- 11 HBsAg-negative at reactivation
GVHD is associated with HBV reactivation

Graph showing the probability of HBV reactivation over time for GVHD and No GVHD conditions.
Outcome of HSCT patients with HBV reactivation

All patients with HBV DNA becoming undetectable after starting of entecavir

No patients developed hepatitis flare

No liver related mortality
Conclusions

- Virological factors and host factors are associated with HBsAg seroclearance leading to OBI status
- HBsAg level is predictive for HBsAg seroclearance
- HBV transmissibility from OBI subjects is possible but the risk is low especially from anti-HBs +ve donor
- OBI may account for the majority of cases of “cryptogenic” HCC
- OBI subjects have a considerable high chance of HBV reactivation during and after rituximab therapy and HSCT
Conclusions

Patients with HBsAg seroclearance

Normal LFT, normal / minimal histology changes/ low serum HBV DNA (detectability decreases with time)/ intrahepatic HBV DNA detectable in nearly all cases

Same risk of HCC if the age of seroclearance > 50 yrs, especially if cirrhosis has developed

Continuous monitoring especially screening for HCC and long-term complications

Patients with cryptogenic HCC

Search for HBV DNA in the liver

Patients with anti-HBc positive undergoing immunosuppressive therapy and BMT

Close monitoring of HBV DNA

Prompt treatment with antiviral when HBV reactivation occurs
Thank you