HBsAg seroclearance in NA-treated patients

Dr Grace Lai-Hung Wong
MBChB (Hons, CUHK), MD (CUHK), MRCP, FHKCP, FHKAM (Medicine)

Professor, Institute of Digestive Disease
The Chinese University of Hong Kong
Disclosures

• Advisory committee member: Gilead

• Speaker: AbbVie, Bristol-Myers Squibb, Echosens & Furui, Gilead, Janssen, Roche
CAN CHRONIC HEPATITIS B BE CURED?
Cure of chronic hepatitis B

- Functional cure
  - HBsAg seroclearance +/- seroconversion

- Absolute or complete cure
  - Absence of cccDNA

<table>
<thead>
<tr>
<th>Parameter measured</th>
<th>Absolute cure</th>
<th>Functional cure</th>
<th>Apparent virological cure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk of death from liver disease</td>
<td>Same as a person who was never infected</td>
<td>Same as a person with naturally resolved infection</td>
<td>To be determined</td>
</tr>
<tr>
<td>Viral load</td>
<td>Undetectable</td>
<td>Undetectable</td>
<td>Undetectable</td>
</tr>
<tr>
<td>HBsAg</td>
<td>Undetectable</td>
<td>Undetectable</td>
<td>Undetectable</td>
</tr>
<tr>
<td>cccDNA</td>
<td>Undetectable</td>
<td>Undetectable</td>
<td>Undetectable or repressed</td>
</tr>
<tr>
<td>HBsAb</td>
<td>Present</td>
<td>Variable</td>
<td>Present or absent</td>
</tr>
<tr>
<td>Treatment status</td>
<td>Off-drug</td>
<td>Off-drug</td>
<td>Off-drug</td>
</tr>
</tbody>
</table>

HBV DNA vs. HBsAg

- **HBV-DNA** (virions)
  - HBV replication
  - Serum HBV DNA: a marker of HBV replication

- **qHBsAg**
  - virions + defective particles
  - Serum HBsAg: a marker of transcriptionally active cccDNA*

- **cccDNA transcription/mRNA translation**
  - HBV replication

HBsAg seroclearance
Treatment goal of chronic hepatitis B

Cumulative risk of HCC (%)

Follow-up (month)

Age of HBsAg seroclearance

No. of patients at risk

< 50 151 124 102 87 71 56 47 37 21 15 10

≥ 50 147 120 86 63 51 46 38 31 24 18 12

APASL 2016, EASL 2017, AASLD 2016
Benefits of HBsAg seroclearance

- ↓ Hepatic decompensation
- ↓ HCC
- ↑ Survival
- ↓ Levels of cccDNA
- As close to cure as we can expect to achieve in chronic hepatitis B
HBsAg seroclearance – what’s new

1. Durability of HBsAg seroclearance

2. Risk factors of HCC after HBsAg seroclearance

3. Management of CHB patients with HBsAg seroclearance
DURABILITY OF HBSAG SEROCLEARANCE
Durability of HBsAg seroclearance in untreated and NA-treated patients

Both spontaneous and NA-induced HBsAg seroclearance are durable

5-year cumulative rate of HBsAg seroclearance:
- Spontaneous: 88.1%
- NA-induced: 92.2%

Log-rank test, \( P = 0.964 \)

Presence of anti-HBs increases durability of spontaneous HBsAg seroclearance, but not NA-induced one

None of patients who had received consolidation therapy for 12 months or more developed HBsAg seroreversion

Summary

- NA-induced HBsAg seroclearance is as durable as that occurs spontaneously.
- HBsAg seroconversion, i.e. the presence of anti-HBs is not essential for maintaining HBsAg seroclearance after NA treatment.
- Consolidation therapy for 12 months or more may minimize the risk of HBsAg seroreversion.
RISK FACTORS OF HCC AFTER HBSAG SEROCLEARANCE
HK data – 1,680 patients in ETV/TDF

Baseline HBsAg level and HCC

<table>
<thead>
<tr>
<th>Cirrhosis</th>
<th>No Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 415</td>
<td>N = 1,265</td>
</tr>
<tr>
<td>( P = 0.933 )</td>
<td>( P = 0.08 )</td>
</tr>
</tbody>
</table>

The were a trend that baseline HBsAg level predicts HCC in non-cirrhotic patients.

Table 4. The HBV Viral Load-Free Risk Prediction Model (REACH-B IIb) and Corresponding Risk Scores for Various Risk Predictors

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Regression coefficient</th>
<th>Hazard ratio (95% CI)</th>
<th>P value</th>
<th>Risk score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>Referent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>0.91297</td>
<td>2.49 (1.77–3.51)</td>
<td>&lt;.0001</td>
<td>2</td>
</tr>
<tr>
<td>Age, 5-year increment</td>
<td>0.47830</td>
<td>1.61 (1.49–1.74)</td>
<td>&lt;.0001</td>
<td>1</td>
</tr>
<tr>
<td>ALT level, U/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;15</td>
<td>Referent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15–44</td>
<td>0.55670</td>
<td>1.75 (1.28–2.38)</td>
<td>.0004</td>
<td>1</td>
</tr>
<tr>
<td>≥45</td>
<td>1.12898</td>
<td>3.09 (2.02–4.74)</td>
<td>&lt;.0001</td>
<td>2</td>
</tr>
<tr>
<td>HBeAg/HBsAg level, IU/mL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative/≤100</td>
<td>Referent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative/100–999</td>
<td>0.33663</td>
<td>1.40 (0.86–2.29)</td>
<td>.1796</td>
<td>1</td>
</tr>
<tr>
<td>Negative/≥1000</td>
<td>0.85832</td>
<td>2.36 (1.51–3.69)</td>
<td>.0002</td>
<td>2</td>
</tr>
<tr>
<td>Positive/any</td>
<td>2.23016</td>
<td>9.30 (6.01–14.40)</td>
<td>&lt;.0001</td>
<td>5</td>
</tr>
</tbody>
</table>

HBsAg seroclearance in patients on NAs

Original cohort: 110 HBsAg seroclearance; 5299 controls
Propensity score matching: 93 HBsAg seroclearance; 372 controls

Kim et al. Gut 2014;63:1325
Wong VW et al. Gastroenterology 2014;147:1435
Impact of age and gender on risk of hepatocellular carcinoma after hepatitis B surface antigen seroclearance

Terry Cheuk-Fung Yip\textsuperscript{1,2}, Henry Lik-Yuen Chan\textsuperscript{1,2,3}, Vincent Wai-Sun Wong\textsuperscript{1,2,3}, Yee-Kit Tse\textsuperscript{1,2}, Kelvin Long-Yan Lam\textsuperscript{1,2}, Grace Lai-Hung Wong\textsuperscript{1,2,3,*}

\textsuperscript{1}Institute of Digestive Disease, The Chinese University of Hong Kong, Hong Kong, China; \textsuperscript{2}Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong, China; \textsuperscript{3}State Key Laboratory of Digestive Disease, The Chinese University of Hong Kong, Hong Kong, China

Background and Aims: Previous studies suggested spontaneous seroclearance of hepatitis B surface antigen (HBsAg) was still associated with an increased risk of hepatocellular carcinoma (HCC), in patients $\geq 50$ years of age. This study aimed to evaluate the risk of HCC after HBsAg seroclearance and the impact of gender on HCC.

Methods: All chronic hepatitis B patients under medical care in Hospital Authority, Hong Kong who had cleared HBsAg between January 2000 and August 2016 were identified. The age of the patient at HBsAg seroclearance, gender, and subsequent development of HCC were analyzed.

Results: A total of 1,509 patients with HBsAg seroclearance were (HCC) after HBsAg seroclearance, whereas female patients aged above 50 years and all male patients are still at risk of HCC.

Introduction

Chronic hepatitis B (CHB) is the leading cause of hepatocellular carcinoma (HCC) worldwide.\textsuperscript{1} Hepatitis B surface antigen (HBsAg) seroclearance is a surrogate of ultimate immune control of hepatitis B virus (HBV). The annual incidence of spontaneous HBsAg sero-
All HBsAg-positive subjects with >1 HBsAg result
N=73,493

68,925 subjects excluded

CHB patients with HBsAg seroclearance
N=4,568

64,373 Subjects remained HBsAg-positive
1,281 Incomplete demographic data
1,963 Acute hepatitis B
786 Co-infected with HCV
37 Co-infected with HDV
262 Liver transplanted before HBsAg seroclearance
27 Younger than 18 years old at HBsAg seroclearance
196 HCC before HBsAg seroclearance

Age ≤50
N=1,314

Female
N=545
HCC
N=0

Male
N=769
HCC
N=5

Age >50
N=3,254

Female
N=1,149
HCC
N=10

Male
N=2,105
HCC
N=39
Age and gender on HCC development

Log-rank test, $P<0.001$

Log-rank test, $P=0.005$

### Cox proportional hazard model

<table>
<thead>
<tr>
<th>Model</th>
<th>Variable</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>HR</td>
<td>95% CI</td>
</tr>
<tr>
<td>1</td>
<td>Age&gt;50</td>
<td>4.49</td>
<td>1.79-11.27</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>2.59</td>
<td>1.30-2.15</td>
</tr>
<tr>
<td>2</td>
<td>Age (per yr)</td>
<td>1.04</td>
<td>1.02-1.07</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>2.59</td>
<td>1.30-2.15</td>
</tr>
</tbody>
</table>

3 risk levels of HCC after HBsAg seroclearance

- **Highest risk**
  - Male > 50

- **Intermediate risk**
  - Male ≤50
  - Female > 50

- **Lowest (no) risk**
  - Female ≤50

Summary – age and gender on HCC risk after HBsAg seroclearance

- Cumulative risk of HCC development after HBsAg seroclearance = 1.5% in 5 years
- Age >50 years and male gender are independent risk factors for HCC
- Male patients who clear HBsAg at age >50 years have significant risk of HCC (2.5% in 5 years)
- Female patients who clear HBsAg before age of 50 have very low risk of HCC (0% in 5 years)

DM on HCC risk after HBsAg seroclearance

DM increases HCC risks  Good glycemic control reduces HCC risk

Yip TC,……Wong GL. APDW 2017
MANAGEMENT OF PATIENTS WITH HBSAG SEROCLEARANCE
Monitoring of patients with HBsAg seroclearance

- In general, no need further evaluation
- In case of suspicion of liver disease (e.g. elevated ALT level or suspicion of liver cirrhosis)
  - Check anti-HBc ± HBV DNA
  - Exclude other liver diseases (e.g. co-infection with HCV, alcohol, NAFLD)
- If detectable HBV DNA (usually low titre)
  - Yearly LFT and HBV DNA
  - Fibroscan to exclude cirrhosis (esp. if age >50)
  - Antiviral if HBV DNA +ve AND cirrhosis
  - HCC screening not essential unless the patient is cirrhotic or had HBsAg seroclearance in males after the age of 50
HBsAg seroclearance – can it be occult HBV infection?

- HBsAg negative
- Detection of HBV DNA in the serum or the liver
- Anti-HBs and anti-HBc may be positive or negative
- In real life, anti-HBc is often the marker for possible occult HBV infection

Raimondo et al. J Hepatol 2008;49:652
# Immunosuppressants and risk of reactivation of occult HBV infection

<table>
<thead>
<tr>
<th>Agent</th>
<th>Risk (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B cell-depleting agents (e.g. rituximab)</td>
<td>&gt;10</td>
</tr>
<tr>
<td>TNF-α inhibitors (e.g. infliximab)</td>
<td>1</td>
</tr>
<tr>
<td>Tyrosine kinase inhibitors (e.g. imatinib)</td>
<td>1</td>
</tr>
<tr>
<td>Doxorubicin and epirubicin</td>
<td>1-10</td>
</tr>
<tr>
<td>Azathioprine, 6-MP, methotrexate</td>
<td>&lt;&lt;1</td>
</tr>
<tr>
<td>Systemic corticosteroids</td>
<td></td>
</tr>
<tr>
<td>Moderate to high dose &gt;4 weeks</td>
<td>1-10</td>
</tr>
<tr>
<td>Moderate to high dose &lt;1 week</td>
<td>&lt;&lt;1</td>
</tr>
<tr>
<td>Low dose &gt;4 weeks</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

Perrillo et al. Gastroenterology 2015;148:221
Conclusions

• HBsAg seroclearance is as durable
  – ~90% in 5 years
  – NA-induced ~ spontaneous

• In NA-induced HBsAg seroclearance, presence of anti-HBs does not affect durability.

• Females of age <50 would be of minimal risk of HCC after HBsAg seroclearance.

• Good glycemic control in DM patients reduces HCC risk after HBsAg seroclearance.
Thank you for your attention!

Database team, Institute of Digestive Disease, CUHK

Grace Lai-Hung Wong
Institute of Digestive Disease
The Chinese University of Hong Kong
E-mail: wonglaihung@cuhk.edu.hk