Practical evaluation and monitoring of patients with chronic hepatitis B

Kwang-Hyub Han, MD
Department of Internal Medicine, Institute of Gastroenterology, Yonsei University College of Medicine, Seoul, Korea
Discovery of HBV

Barush S Blumberg, M.D., Ph.D.
The Nobel Prize in Physiology and Medicine 1976

1960  NIH: Double diffusion in agar gel (Ouchterlony) method to detect antibodies in multiply transfused patients

1963  Au-antigen from hemophiliacs (Mt. Sinai Hospital in New York)

“Why did precipitin band has developed between the serum of hemophilia patients in NY and that of an aborigine from Australia?”


Subsequent study found the Australian Antigen to be the HBs antigen.
Overview

• Introduction

• Surrogate markers for monitoring CHB
  ▪ Why monitoring important in nucleot(s)ide analogues?
  ▪ On-treatment HBV DNA monitoring: Roadmap Concept
  ▪ On-treatment qHBsAg monitoring

• Assessment of liver fibrosis
Treatment intervention in CHB

Active disease *
- HBV DNA ↑
  - ALT ↑
    - Necroinflammation
    - Fibrosis
    - Cirrhosis
    - Decompensation
  - Death

Chronic hepatitis B
- Long term disease control
  - HBV DNA -ve by PCR or HBeAg seroconversion
    - ALT normal
    - Reversal of liver damage
    - Reduced disease progression

Cure
- HBsAg seroconversion
- Loss of ccc HBV DNA
- Healthy liver

* HBeAg+ve or HBeAg-ve CHB
Indications for treatment initiation are currently based on three criteria.

Patients with **high ALT** and **low HBV DNA level** usually experience:

1) **significant histological changes**
2) **high HBeAg seroconversion rate to IFN or oral antiviral therapy**
Treatment Criteria for Chronic Hepatitis B: Comparison of Liver Society Guidelines

- **Recommended HBV DNA and ALT levels outlined in the following table**

<table>
<thead>
<tr>
<th>Liver Society Guidelines*</th>
<th>HBeAg Positive</th>
<th>HBeAg Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HBV DNA, IU/mL</td>
<td>ALT</td>
</tr>
<tr>
<td>APASL 2008[2]</td>
<td>≥ 20,000</td>
<td>&gt; 2 x ULN‡</td>
</tr>
<tr>
<td>AASLD 2009[3]</td>
<td>&gt; 20,000</td>
<td>&gt; 2 x ULN or positive biopsy</td>
</tr>
</tbody>
</table>

*Although ALT and HBV DNA are primary tests used to determine treatment candidacy, the levels of elevation that warrant consideration of treatment are not universally agreed upon.
†Some experts recommend in patients older than 40 yrs of age, 2000 IU/mL should be considered as a cutoff for treatment.
‡Laboratory normal.
§30 U/L for men and 19 U/L for women.

Asian-Pacific consensus statement on the management of chronic hepatitis B: a 2012 update

Yun-Fan Liaw · Jia-Horng Kao · Teerha Piratvisuth · Henry Lik Yuen Chan · Rong-Nan Chien · Chun-Jen Liu · Ed Gane · Stephen Locarnini · Seng-Gee Lim · Kwang-Hyub Han · Deepak Amarapurkar · Graham Cooksley · Wasim Jafri · Rosmawati Mohamed · Jin-Lin Hou · Wan-Long Chuang · Laurentius A. Lesmana · Jose D. Sollano · Dong-Jin Suh · Masao Omata

![Algorithm for the management of hepatitis B e antigen (HBeAg)-positive patients with chronic hepatitis B](image-url)
## Treatment Recommendations for CHB Patients with cirrhosis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>AASLD&lt;sup&gt;1&lt;/sup&gt;</th>
<th>APSAL&lt;sup&gt;2&lt;/sup&gt;</th>
<th>EASL&lt;sup&gt;3&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Compensated cirrhosis</strong></td>
<td>Treatment - HBV DNA&gt;2,000 IU/ml, HBV DNA&lt;2,000 IU/ml and elevated ALT</td>
<td>Treatment - HBV DNA&gt;2,000 IU/mL</td>
<td>Treatment - Detectable HBV DNA even if ALT levels are normal and/or HBV DNA &lt; 2000 IU/ml</td>
</tr>
<tr>
<td><strong>Decompensated cirrhosis</strong></td>
<td>Treatment - antiviral therapy, and consider transplant</td>
<td>Treatment - antiviral therapy, and consider transplant</td>
<td>Treatment - required urgent antiviral agents and consider transplant</td>
</tr>
</tbody>
</table>

1. American Association for the study of the Liver, 2009
2. Asia-Pacific Association for the study of the Liver, 2008
3. Europe Association for the study of the Liver, 2009
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  ▪ Why monitoring important in nucleos(t)ide analogues?
  ▪ On-treatment qHBsAg monitoring

• Assessment of liver fibrosis
CHB treatment goals:
HBsAg clearance is the “Ideal endpoint”

Short-Term
- HBeAg(+) patients
  - HBeAg loss
  - Anti-HBe seroconversion
- HBeAg(-) patients

Long-Term
- HBeAg(+) and (-) patients
  - HBsAg loss
  - Anti-HBs seroconversion

POTENTIAL TO STOP THERAPY
- HBeAg seroconversion

ALT normalization
- HBV DNA undetectable
- Histologic improvement

Treatment initiation

On-treatment Monitoring and Modifying Treatment: NA, Peg-interferon

Patient Profile

Pre Treatment Predictors of Response
- HBV DNA level
- ALT level
- HBeAg status
- HBV genotype
- Age/Gender
- Liver histology

Treatment Strategy

On Treatment Predictors of Response
- HBV DNA kinetics
- qHBeAg levels
- qHBsAg levels

Patient Outcomes

- Sustained viral suppression
- HBeAg seroconversion
- Improve histology
- Prevent cirrhosis and HCC
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  - Why monitoring is important in nucleot(s)ide analogues?
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Antiviral resistance is a major challenge in the management of CHB

1. Sub-optimal Treatment or No Treatment

Elevated Viral Load\(^1\)
Low Genetic Barrier\(^4,7-9\)
Antiviral Resistance\(^2\)

Ongoing Liver Inflammation and Damage\(^1\)

Fibrosis/Cirrhosis\(^8\), Liver Failure\(^1\), Liver Cancer\(^9\), Death\(^1\)

Antiviral Resistance

Once Resistance Occurs, it Stays\(^7\)

Sequence of Events in the Development of Resistance to Antiviral Therapy

<table>
<thead>
<tr>
<th>Time</th>
<th>Antiviral drug</th>
<th>HBV DNA (log_{10} IU/mL)</th>
<th>ALT (IU/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>6</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>1 log_{10}</td>
<td>0</td>
<td>Nadir</td>
<td>1 ULN</td>
</tr>
<tr>
<td>Virologic Breakthrough</td>
<td>Detection of Genotypic Resistance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biochemical Breakthrough</td>
<td></td>
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</tbody>
</table>

BMS Resistance Roundtable, Boston, November 7th 2007

BMS CONFIDENTIAL FOR INTERNAL USE ONLY
When and How to Manage Suboptimal Responders

Early treatment more effective !!!
(before compensatory mutations selected)

Level of Evidence
HBeAg + HBV DNA $\geq$ 60 IU/mL by PCR

RGT

N=72

LVD 100 mg,
For at least 6 months

Screening

Randomization

ETV 1.0 mg,
Once daily for 96 weeks

N=36

LVD 100 mg,
Once daily for 96 Week

N=36

HBV DNA leverage, Drug-resistant mutations, HBeAg status, Liver biochemistry

4w 12w 24w 36w 48w 60w 72w 84w 96w

Yonsei University College of Medicine
Pusan National University School of Medicine
Yeungnam University College of Medicine
Kyungpook National University College of Medicine
Korea University College of Medicine

A prompt switching from LAM to ETV resulted in increased virologic efficacy.
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  ▪ On-treatment qHBsAg monitoring

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HBsAg quantification and HBV DNA quantification provide complementary information.

HBsAg quantification is an additional information to HBV DNA quantification!

ORAL ANTI-VIRAL AGENTS (NAs)

HBV DNA = marker of Virus replication

HBsAg = marker of Immunological response

Peg-interferon
Two concepts for response-guided therapy approach based on HBsAg levels

- **Identify responders (PPV)**
  - Continue therapy
  - Motivate the patient
  - Track success

- **Identify non-responders (NPV)**
  - Change strategy
  - Stop PEG-IFN (or add on an NA?)
  - The earlier the better
HBsAg reduction at week 24 can predict future HBsAg clearance

Among HBeAg-negative patients who achieved HBsAg decline ≥10% from baseline at Week 24 of treatment*

- 43% achieved HBV DNA ≤ 10,000 copies/mL at 1 year post-treatment (N=29/67)
- 45% of those achieved HBsAg clearance at 5 years post-treatment (N=13/29)

*56% of patients achieved HBsAg decline ≥10% at week 24

Marcellin et al. APASL 2010
On-treatment HBsAg decline can distinguish between relapsers and responders

In HBeAg-negative patients

Sustained responders* (N=12)  Non-Responders (N=18)  Relapsers (N=18)

*HBV DNA undetectable by PCR 1 year post-treatment

Moucari et al. Hepatology 2009
Quantitative qHBsAg and qHBeAg level can predict treatment response to Entecavir

**VR**
baseline log qHBsAg level : 3.98 IU/mL

**SR**
the reduction of log qHBeAg : 1.00 PE IU/mL at 6 months
Benefits of HBsAg monitoring

• Quantitative HBsAg can reflect natural history of CHB.

• On-treatment monitoring with qHBsAg level may be beneficial in allowing individualized treatments strategies.

• It can distinguish suboptimal responders where treatment modifications should be considered to enhance antiviral efficacy and improve long-term outcomes.

• However, conclusive guidelines are now lacking, thus further studies based upon clinical trials should be required.
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Lamivudine Maintenance Beyond One Year After HBeAg Seroconversion Is a Major Factor for Sustained Virologic Response in HBeAg-Positive Chronic Hepatitis B

Hyun Woong Lee,1-3 Heon Ju Lee,3,4 Jae Seok Hwang,3,5 Joo Hyun Sohn,3,6 Jae Young Jang,7 Ki Jun Han,8 Jun Yong Park,1,3,9 Do Young Kim,1,3,9 Sang Hoon Ahn,1,3,9 Yong Han Paik,1,3,9 Chun Kyon Lee,3,10 Kwan Sik Lee,1,3,9 Chae Yoon Chun,1,3,9 and Kwang-Hyub Han1,3,9

HBeAg positive (N = 748) Followed up for up to 8 years

Normal ALT, HBV DNA (-) and HBeAg loss

Complete responders (N = 287, 38.4 %)

Discontinued lamivudine (N = 178, 23.8 %)

Sustained responders (N = 138, 18.5 %)

Continued lamivudine (N = 109, 14.6 %)

Relapsers (N = 40, 5.3 %)

Non-complete responders (N = 461, 61.6%)

Virologic responders (N=59, 7.9%)

Virologic breakthrough (N = 280, 37.4%)

Poor compliance and Primary non-responders (N=122, 16.3%)

Cost-effectiveness: The lamivudine-induced virologic response was durable in patients < 40 yrs and those receiving LAM > 12 months after HBeAg seroconversion.
To Treat or Not to Treat
Whom to treat among patients with CHB

- Despite normal or mildly elevated ALT levels, persistent active HBV viremia results in progressive liver damage.

- Liver biopsy is recommended among patients with normal or mild elevated (< 2 times UNL) ALT levels if they are older than 40 years old with elevated HBV DNA levels.

- Antiviral therapy should be started if significant hepatic necroinflammation and/or fibrosis are detected on liver biopsy regardless of the ALT levels.

→ Accurate histologic assessment became increasingly important

Role of non-invasive examinations in evaluating severity of hepatic fibrosis

In the management of patients with chronic hepatitis B, assessment of hepatic fibrosis is of paramount importance. The severity of liver fibrosis is a strong prognostic factor by itself, and it helps to identify patients who will benefit from antiviral therapy, assess response to antiviral therapy, determine the optimal time to start surveillance, and stratify the risk of HCC and hepatic decompensation [1, 55]. To date, liver biopsy is the best standard for assessing liver fibrosis. Although it is generally accepted to be a safe procedure, it can cause discomfort and carries an occasional risk of serious complications. Furthermore, liver biopsy is subject to sampling error and interobserver variability. In addition, it is not practical to use liver biopsy repeatedly in monitoring patients undergoing antiviral therapy because of its limitations and invasive nature.
Diagnosis tools for cirrhosis

• **Histologic**
  ✓ Liver biopsy (LB): current “gold standard”

• **Radiologic**
  ✓ Ultrasound
  ✓ Diffusion-weighted MRI, MR elastography
  ✓ Hepatic venous pressure gradient
  ✓ FibroScan®

• **Serologic**
  ✓ Direct marker
  ✓ Indirect marker

• **Formulae** (APRI, ASPRI…)

Intraoperatively
Evaluation of hepatic fibrosis by probe

Healthy

Moderate F

Cirrhosis

E ~ 3 kPa

E ~ 9 kPa

E ~ 40 kPa

F0

F1

F2

F3

F4

Few fibrosis

Significant

Extensive

Cirrhosis

10mm
Enhancing the performance to predict cirrhosis by using different cut-off values

In this way, liver biopsy can be avoided in approximately 62% of patients with normal ALT and 58% of patients with elevated ALT

*Chan et al. J Viral Hepat 2008*
Usefulness of FibroScan for Detection of Early Compensated Liver Cirrhosis in Chronic Hepatitis B

Table 2  Distribution of fibrosis stage and LSM value

<table>
<thead>
<tr>
<th></th>
<th>All patients (n = 91)</th>
<th>F4 (group A) (n = 39)</th>
<th>F1–3 (group B) (n = 52)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrosis stage on liver biopsy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1</td>
<td>9 (9.9)</td>
<td>–</td>
<td>9 (17.3)</td>
</tr>
<tr>
<td>F2</td>
<td>33 (36.3)</td>
<td>–</td>
<td>33 (63.5)</td>
</tr>
<tr>
<td>F3</td>
<td>10 (11.0)</td>
<td>–</td>
<td>10 (19.2)</td>
</tr>
<tr>
<td>F4</td>
<td>39 (42.9)</td>
<td>39 (100)</td>
<td>–</td>
</tr>
<tr>
<td>LSM value (kPa)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;7.0 (F1)</td>
<td>4 (10.3)</td>
<td>20 (38.5)</td>
<td></td>
</tr>
<tr>
<td>≥7.0 and &lt;9.5 (F2)</td>
<td>5 (12.8)</td>
<td>15 (28.8)</td>
<td></td>
</tr>
<tr>
<td>≥9.5 and &lt;10.3 (F3)</td>
<td>5 (12.8)</td>
<td>4 (7.7)</td>
<td></td>
</tr>
<tr>
<td>≥10.3 (F4)</td>
<td>25 (64.1)</td>
<td>13 (25.0)</td>
<td></td>
</tr>
</tbody>
</table>

Values are expressed as n (%). Cutoff LSM values were set according to previous studies [7]

Fig. 1 Scatter plot of liver stiffness measurement (LSM) values in patients with liver cirrhosis (F4) or chronic hepatitis B (F1–3)

Risk Assessment of Hepatitis B Virus–Related Hepatocellular Carcinoma Development Using Liver Stiffness Measurement (FibroScan)

- N=1,130 (767 men and 363 women)
- Median follow-up: 30.7 months (range, 24-51, 2,885 person-year)
- HCC developed in 57 patients (2.0% per 1 person-year)
HBV-related HCC

Incidence rate of HCC (% (person-year))

- Group 1 (n=598): Initial LSM ≤ 13 kPa, Follow up LSM ≤ 13 kPa, 0.44%
- Group 2 (n=71): Initial LSM > 13 kPa, Follow up LSM ≤ 13 kPa, 1.96%
- Group 3 (n=34): Initial LSM ≤ 13 kPa, Follow up LSM > 13 kPa, 2.05%
- Group 4 (n=119): Initial LSM > 13 kPa, Follow up LSM > 13 kPa, 4.31%

P < 0.001
Summary (I)

How to monitor?

To achieve the most cost-effective treatment, adequate monitoring during and after treatment is crucial. HBV DNA should be measured using assays standardized/validated to report against the WHO IU/mL reference standard. If affordable, drug-resistance testing should also be considered.
Recommendation 6  During therapy, ALT, HBeAg, and/or HBV-DNA should be monitored at least every 3 months (IA). Renal function should be monitored if TDF or ADV is used (IA). Muscle weakness should be monitored, especially if LdT is used (IIIA). During IFN-based therapy, monitoring of blood cell counts and other adverse effects are mandatory (IA).

Recommendation 7  After the end of therapy, levels of ALT and HBV DNA should be monitored monthly for the first 3 months to detect early relapse, and then every 3 months in the first year after therapy. If uneventful, monitor every 3 months (for cirrhotic patients) to 6 months (for responders) thereafter (IIA). For non-responders, further monitoring of HBV markers is required to both recognize a delayed response or to plan retreatment when indicated (IIA).
Thank you for your attention!