UPDATE ON CHRONIC HEPATITIS B MANAGEMENT

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HBV is a global problem

- Up to 5% of population chronically infected

- ~33% of population infected at some time in their life

- ~40% of untreated individuals will die of CHB

- >1 million deaths annually
Geographic differences in HBV genotype
Prevalence of HBV and Incidence of Hepatocellular Carcinoma (HCC)

World prevalence of HBV carriers

- HBsAg carriers – prevalence:
  - <2%
  - 2–7%
  - >8%
  - Poorly documented

Annual incidence of primary HCC

- Cases/100,000 population:
  - 1–3
  - 3–10
  - 10–150
  - Poorly documented

WHO 1999
Natural History of Hepatitis B Virus Infection

- >90% of infected children progress to chronic disease
- <5% of infected immunocompetent adults progress to chronic disease

EASL 2012 Clinical Practice Guidelines: What is long-term treatment success in CHB and how do we achieve it?

"...to improve quality of life and survival by preventing progression of the disease to cirrhosis, decompensated cirrhosis, end-stage liver disease, hepatocellular carcinoma (HCC) and death"

“This goal can be achieved if HBV replication can be suppressed in a sustained manner. Then, the accompanying reduction in histological activity of CHB lessens the risk of cirrhosis and decreases the risk of HCC, particularly in non-cirrhotic patients”
# HBV Genotypes

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Areas of prominence</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>NW Europe, USA, Central Africa</td>
</tr>
<tr>
<td>B</td>
<td>Taiwan, Japan, Indonesia, China, Vietnam</td>
</tr>
<tr>
<td>C</td>
<td>E Asia, Taiwan, Korea, China, Japan, Vietnam</td>
</tr>
<tr>
<td>D</td>
<td>Mediterranean area, India</td>
</tr>
<tr>
<td>E</td>
<td>W Africa</td>
</tr>
<tr>
<td>F</td>
<td>Central and S America</td>
</tr>
<tr>
<td>G</td>
<td>France, USA</td>
</tr>
</tbody>
</table>

Kao et al. *J Gastroent Hepatol* 2002
What is the Relevance of HBV Genotype?

• HBV genotype is associated with:
  – clinical outcome (progression to cirrhosis and HCC)
  – frequency of precore/core promoter mutations
  – response to interferon-based therapy
Progression of liver disease

- Serious consequences associated with CHB
  - Cirrhosis
  - Hepatic decompensation
  - Hepatocellular carcinoma (HCC)
The discovery of HBV – An historical perspective

- HBsAg or ‘Australia antigen’ first isolated from the blood of an Australian aborigine in the 1960s
- Led to identification of HBV by Baruch Blumberg
- Awarded Nobel Prize for Medicine in 1976
HBV structure

The hepatitis B virus
HBsAg and HBV DNA are key to diagnosis and monitoring of CHB

HBsAg and HBV DNA provide different but complementary information

Presence of HBsAg in serum for >6 months defines CHB

Brunetto Editorial. J Hepatol 2010
Clinical significance of HBsAg

• Reflects the balance between the virus and the host immune response, not just viral replication
• Quantitative HBsAg represents a new diagnostic tool in CHB

Brunetto et al. J Hepatol 2010
Where are the Africans with silent chronic HBV infections?

Late presentation with advanced liver cancer and complications of advanced liver cirrhosis is unacceptably common.
Diagnostic Criteria for Chronic Hepatitis B (CHB)

- HBsAg-positive > 6 months positive anti-HBc and negative anti-HBs

- Serum HBV DNA > 20,000 IU/mL ($10^5$ copies/mL); however, lower values of 2,000 – 20,000 IU/mL ($10^4$ – $10^5$ copies/mL) may be seen in HBeAg-negative CHB

- Persistent or intermittent elevation in ALT levels

- Liver biopsy showing chronic hepatitis with moderate or severe necroinflammation

Phases of Chronic HBV Infection

1. Immune-tolerant phase
   - Infection acquired perinatally or early in life
   - HBeAg +ve - HBV DNA +ve (>20,000 IU/ml or >10^5 copies/ml)
   - Normal ALT
   - No necroinflammation & scarring
   - Persons in this phase are highly infectious

2. Immune-reactive phase
   - ▲ ALT levels
   - Suppressed HBV DNA levels
   - Moderate to severe necroinflammation present
   - Accelerated clearance of HBeAg (may be positive or negative)
   - Mutation may develop at this phase
   - The longer the duration, the greater the risk of progressive liver disease
Phases of Chronic HBV Infection (Contd.)

3. Non-replicative (or Inactive) phase
   - HBeAg –ve
   - Anti-HBe +ve
   - ↓ HBV DNA (<2,000 IU/ml or < 10⁴ copies/ml)
   - Normal ALT
   - Minimal necroinflammation

4. Reactivation phase (HBeAg –ve CHB)
   - Reappearance of ↑ serum HBV DNA due to spontaneous mutation in the core or core promoter region of the HBV genome
   - HBeAg –ve
   - Anti-HBe +ve
   - Fluctuating ALT levels
Natural History of Chronic HBV Infection

HBeAg(+) CHB<br>Low-replicative phase<br>Replicative/reactivating phase*

HBeAg(-)/anti-HBe(+) CHB

Replicative/Immune tolerant phase<br>HBeAg clearance phase*

Serum HBV DNA

ALT

Normal liver/Mild CH<br>Normal liver/Mild CH, Inactive CI

Moderate/Severe CH Cirrhosis

*Immune reactive phases

Hadziyannis & Papatheodoridis. Semin Liver Dis 2006; 26: 130-41
# Phases Of Chronic Hepatitis B

## TABLE

<table>
<thead>
<tr>
<th>Phases of Chronic Hepatitis B Infection</th>
<th>Phase</th>
<th>HBeAg</th>
<th>HBV DNA</th>
<th>ALT</th>
<th>Liver Histology</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Immune Tolerant</td>
<td>Positive</td>
<td>Very high &gt;200,000 IU/ml</td>
<td>Normal</td>
<td>Normal or mild inflammation &amp; scant fibrosis</td>
<td>Not Indicated</td>
</tr>
<tr>
<td></td>
<td>Immune Active</td>
<td>Positive or Negative</td>
<td>&gt;2,000 IU/ml Usually &gt;20,000 IU/ml</td>
<td>Elevated</td>
<td>Inflammation and fibrosis; Degree Varies</td>
<td>Treatment Candidate</td>
</tr>
<tr>
<td></td>
<td>Inactive</td>
<td>Negative</td>
<td>&lt;2,000 IU/ml</td>
<td>Normal</td>
<td>Normal or mild inflammation</td>
<td>Not Indicated</td>
</tr>
</tbody>
</table>
Natural History of Chronic HBV Infection

- Replicative/Immune tolerant phase
- HBeAg clearance phase*
- Low-replicative phase
- Replicating/reactivating phase*

HBeAg(+) CHB
- HBeAg(-) CHB

*Immune reactive phases

Serum HBV DNA

ALT

Normal liver/Mild CH

Moderate/Severe CH

Cirrhosis

HBeAg(+) CHB

Inactive carrier state

Inactive CHB

Normal liver/Mild CH, Inactive CH

Moderate/Severe CH Cirrhosis

Hadziyannis & Papatheodoridis. Semin Liver Dis 2006; 26: 130-41
Characteristics of Inactive Chronic Hepatitis B

1. HBsAg positive
2. HBeAg negative
3. Anti-HBe positive
4. Normal serum alanine aminotransferase (ALT)
5. Low HBV DNA (< 2,000 IU/mL or < $10^4$ copies/mL)
6. Minimal or no hepatic necroinflammation and no fibrosis
Characteristics of Inactive Chronic Hepatitis B

• The defining characteristics must be persistent; if fluctuations of HBV DNA or ALT occur, CHB is no longer inactive

• The diagnosis of inactive carrier of HBV requires serial testing of ALT & HBV DNA for one year. Serum ALT must remain persistently normal & HBV DNA ≤ 2,000 IU/mL for one year.

• If HBV DNA becomes elevated > 2,000 IU/mL or ALT rises above normal before the end of one year, the diagnosis of active carrier is made
Is Inactive CHB Really Innocuous?

- About 300 million people are inactive carriers worldwide.
- Approximately 20-30% of inactive CHB may undergo spontaneous reactivation of the disease during follow-up. The male sex is a risk factor for this.
- The risk of hepatocellular carcinoma is not completely eliminated in inactive carriers; the risk is directly related to older age, alcohol consumption and higher baseline serum ALT levels.
Serum HBsAg Quantification & Diagnosis of Inactive CHB

- HBsAg quantification provides additional information for the characterization of CHB phases compared to HBV DNA & ALT only
- Single point quantitative assay of HBsAg gave a specificity of 90.2% and *PPV of 75.4% for distinguishing inactive from active carrier (85% & 70.9% for HBV DNA respectively)
- One time combined quantification of HBV DNA (≤ 2,000 IU/mL) & HBsAg (< 1,000 IU/mL) diagnoses the true inactive carrier with 94.3% accuracy obviating the need to do a one-year monthly monitoring (HBV genotype D)

*PPV = Positive Predictive Value
Brunetto MR et al, Gastroenterol 2010; 139: 483-490
Current Recommendations for Management of Stable Inactive HBV Carriers

1. No treatment is indicated but they should be followed-up for life
2. Family members to be screened with HBsAg & anti-HBs; if negative vaccinate them and confirm vaccination success with anti-HBs testing
3. Safe sex is advised until partner develops protective antibodies
4. Alcohol should be avoided
5. Patients should be informed about the possibility of reactivation or super infection by other viruses and advised to consult their doctor should jaundice occur
Current Recommendations for Management of Stable Inactive HBV Carriers

6. Regular follow up every 6-12 months with serum ALT; if ALT rises, check HBV DNA
7. Serial AFP & Abdominal USS (every 6-12 months) should be done if patient is > 50 years of age or has family history of HCC
8. They should not be denied employment or hospital treatment
9. If the carrier is a health worker, change of duty may not be necessary but should observe universal precautions
10. They should not be allowed to donate blood or organ or tissue or semen
11. Vaccinate the newborn of a carrier with active & passive immunization within 12 hours of birth
12. Monitor closely if undergoing chemotherapy or immunosuppression. Prophylactic therapy with lamivudine is recommended during cancer chemotherapy up till 6 months after completion of therapy
Even though the characteristic features of inactive CHB are defined, these features are by no means static. A subset of inactive carriers of HBV may manifest features of active disease on follow-up. HBV DNA must remain <2,000 IU/mL & ALT persistently normal after 1 year of monthly monitoring before a definitive diagnosis of inactive CHB can be made. Quantification of HBsAg in the serum can help to diagnose the inactive carrier and identify those likely to eventually lose HBsAg.
Combination of serum HBV DNA (≤ 2,000 IU/mL) and HBsAg (< 1,000 IU/mL) may serve as a single diagnostic test for inactive CHB. The need to wait for 1 year before the diagnosis can be made may no longer be necessary. Even though most inactive carriers have good long-term prognosis, subsequent development of HCC cannot be completely ruled out. Disease flare may occur with immunosuppression. Therefore life-long follow-up is recommended.
Serum markers in CHB

HBV DNA

- Virions
  - replication

HBsAg

- Virions + defective particles (exceeding virions by a factor of $10^2$–$10^5$)
- replication
- cccDNA transcription/mRNA translation

Brunetto et al. J Hepatol 2010
Clinical relevance of HBsAg clearance

• HBsAg clearance is an indicator of clinical and serologic recovery from CHB
• HBsAg clearance and eventual seroconversion represents the best possible outcome = CURE from the infection
• HBsAg clearance is usually associated with an excellent prognosis

HBsAg clearance improves survival rates

Retrospective study of 309 cirrhotics, mean follow-up of 5.7 years

According to guidelines, HBsAg clearance is the ‘ideal’ outcome for CHB – closest to cure

HBV DNA monitoring in the management of CHB

- Used for: ¹-³
  - Assessing viral replication status
  - Identifying primary non-response to therapy

- Established link between quantitative serum HBV DNA and risk of disease progression to cirrhosis and HCC⁴,⁵

Monitoring of HBV DNA during antiviral therapy

- Monitoring of viral replication during antiviral therapy
- Most important during NA therapy
- Less able to predict off-treatment response to PEG-IFN (relapsers vs sustained responders)

**Major roles**

- To modify treatment regime according to HBV DNA suppression to reduce the problem of drug resistance
- To detect drug resistance for early and effective salvage treatment
HBV DNA and HBsAg: Complementary markers for monitoring CHB patients

Inhibit Viral Replication

Establish Immune Control

Quantitative HBV DNA

Quantitative HBsAg

Optimize HBV Treatment and Improve Patient Outcomes
Identification of inactive infection using HBsAg and HBV DNA levels

HBV genotype D patients

<table>
<thead>
<tr>
<th>Prediction of:</th>
<th>Inactive infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg levels</td>
<td>&lt;1000 IU/mL plus &lt;2000 IU/mL</td>
</tr>
<tr>
<td>HBV DNA levels</td>
<td></td>
</tr>
<tr>
<td>Population</td>
<td>209</td>
</tr>
<tr>
<td>Sensitivity (%)</td>
<td>91.1</td>
</tr>
<tr>
<td>Specificity (%)</td>
<td>95.4</td>
</tr>
<tr>
<td>PPV (%)</td>
<td>87.9</td>
</tr>
<tr>
<td>NPV (%)</td>
<td>96.7</td>
</tr>
<tr>
<td>Diagnostic accuracy (%)</td>
<td>94.5</td>
</tr>
</tbody>
</table>

This provides comparable information to 1-year of monthly monitoring

Brunetto et al. Gastroenterology 2010
HBV-RELATED CHRONIC LIVER DISEASE
APPROVED DRUGS IN 2013

2000

TENOFOVIR (TDF) (Viread)
TELBIVUDINE (TBV) (Sebivo)
ENTECAVIR (ETV) (Baraclude)
PEG-IFNα-2a (Pegasys)
ADEFOVIR (ADV) (Hepsera)

1990

LAMIVUDINE (LAM) (Zeffix)

IFNα (Intron, Roferon)
CHRONIC HEPATITIS B
GROUPS OF THERAPEUTIC OPTIONS

• (PEG)-IFNα
  (antiviral+immunomodulatory)

• PURE ANTIVIRAL AGENTS
  • Nucleoside analogues (LAM, ETV, TBV)
  • Nucleotide analogues (ADV, TDF)

• COMBINATIONS (no advantage so far)
Treatment strategies for CHB

Sustained response (immune control)
- **PEG-IFN**
  - HBeAg seroconversion
  - HBV DNA <10,000 copies/mL
  - Normal ALT

Maintained response
- **Nucleos(t)ide analog**
  - Undetectable HBV DNA by PCR assay
  - Normal ALT

- HBV DNA suppression
- HBsAg clearance
- Relapse likely when stopped

- HBeAg seroconversion
- HBsAg clearance (HBeAg+)
Two treatment strategies available

<table>
<thead>
<tr>
<th>INTERFERON</th>
<th>NAs</th>
</tr>
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<tbody>
<tr>
<td>Aim for OFF-TREATMENT immune control and HBsAg clearance</td>
<td>Aim for ON-TREATMENT viral suppression</td>
</tr>
<tr>
<td>DURABLE RESPONSE through dual MoA: Immunomodulatory and antiviral</td>
<td>MAINTAINED suppression through continued therapy</td>
</tr>
<tr>
<td>FINITE therapy</td>
<td>LONG-TERM therapy (potentially life-long for some)</td>
</tr>
</tbody>
</table>
Choice of NA VS Interferon

This will have to be highly Individualized
- Affordability
- Accessibility to continuing treatment.
- Accessibility to monitoring
- Age of the patient
- Compensated VS Uncompensated liver disease
- HBEag positive VS Hep Beg negative patients
- The genotype of Hepatitis B
- Concomitant HIV, HCV, and other immunocompromised states
Incidence of Resistance in NUC-naïve Patients

*Collation of currently available data – not from head-to-head studies

adapted from EASL HBV Guidelines, J Hepatol 2012
Baseline Predictors of Response to PEG - IFN

- Low Baseline HBV DNA
- High ALT levels
- Younger age
- Female gender
- HBV Genotype A>B>C>D
- HBeAg Neg CHB carriers of L 28 B Genotype
Efficacy of Therapies of Finite Duration in HBeAg(+) CHB: Sustained off-therapy responses

HBeAg loss
HBeAg seroconversion to anti-HBe

Pts, %

0 20 40 60 80 100

IFNa Peg-IFNa LAM ADV ETV TBV TDF

5-10MU d/tiw 180 μg/wk 100 mg/d 10 mg/d 0.5 mg/d 600 mg/d 300 mg/d

3x4-6 mos x12 mos x12 mos x12 mos x12 mos x12 mos 4x4 mos

Peg-IFN α-2a (40 KD) provides sustained immune control that increases post-therapy

Increase in HBeAg seroconversion 1 year post-treatment among 271 patients with HBeAg+ve CHB treated with Peg-IFN α-2a (40 KD)

Patients with HBeAg seroconversion (%)

- EOT: 27% (72/271)
- Post-treatment (6 months): 32% (87/271)
- Post-treatment (1 year): 42% (73/172*)

* Results from an observational follow-up study

EFFICACY OF 12-MONTH COURSES IN HBeAg(-) CHB: Sustained off-therapy responses

Biochemical & virological responses (different definitions among studies)

End of therapy vs Sustained

Patients, %

- IFNa: 54% (22%) 0.5 MU tiw, 300 mg/d x12 mos
- Peg-IFNa: 36% (25%) 180 μg/wk, 100 mg/d x12 mos
- LAM: 70% (<11%) 10 mg/d x12 mos
- ADV: 74% (8%) 600 mg/d x12 mos
- ETV: 78% (2%) 0.5 mg/d x12 mos
- TBV: 74% (2%) 600 mg/d x12 mos
- TDF: 77% (2%) 600 mg/d x12 mos

Studies:
- Manesis 2001
- Marcellin 2007
- Tassopoulos 1999
- Hadziyannis 2005
- Shouval 2004/2006
- Lai 2005
EFFICACY OF THERAPIES OF FINITE DURATION IN CHB: Sustained off-therapy responses

• 12-month courses of Peg-IFNa better than 12-month courses of NUC(s)

• Sustained off-therapy response rates with Peg-IFNa:
  30-32% in HBeAg(+) & 20-25% in HBeAg(-) CHB.
CHB: Long-term therapy with NUC(s) & HBV resistance

**Consequences of HBV resistance**

- Virological breakthroughs
- Biochemical breakthroughs
- Worsening liver histology
- Hepatic failure in patients with cirrhosis
- Limitation of future treatment options
- Transmission of drug-resistant HBV
- HBV envelope changes: perhaps failure of HBV vaccines
HBV DNA and HBsAg decline: HBeAg-positive patients

HBV DNA decline
Greater with NAs

PEG-IFN (N=61)
ETV (N=33)

Week
0 12 24 36 48
Mean change in HBV DNA (log IU/mL)
-4.5 -4.0 -3.5 -3.0 -2.5 -2.0 -1.5 -1.0 -0.5 0

HBsAg decline
Greater with PEG-IFN

PEG-IFN (N=61)
ETV (N=33)

Week
0 12 24 36 48
Mean change in HBsAg (log IU/mL)
-2.2 -1.7 -1.2 -0.7 -0.2 0

Reijnders et al. J Hepatolol 2010
Benefits of quantifying HBsAg during PEG-IFN therapy

• Monitoring HBsAg levels during PEG-IFN therapy can help identify patients with:
  • A high chance of achieving sustained response
  • A low chance of achieving sustained response
Value of HBsAg monitoring confirmed in several independent studies of PEG-IFN

- Value of HBsAg monitoring has been confirmed in several independent studies of PEG-IFN in HBeAg-positive patients
- On-treatment HBsAg decline/levels are associated with immune control (sustained response)
- On-treatment HBsAg decline is a good sign!

Piratvisuth et al. APASL 2010; Sonneveld et al. Hepatology 2010
HBsAg reduction at week 12 is an early sign of future HBsAg clearance.

HBeAg-positive patients treated with PEG-IFNα-2a +/- lamivudine for 48 weeks:

- 18% of those achieved HBsAg clearance at 6 months post-treatment (N=9/51)
- 57% achieved HBeAg seroconversion 6 months post-treatment (N=51/90)
- Among patients who achieved HBsAg <1500 IU/mL at week 12 of treatment*

*23% of patients (N=90/399) achieved HBsAg <1500 IU/mL at week 12

Piratvisuth et al. APASL 2010
Value of prediction validated by the NEPTUNE study

HBeAg-positive patients treated with PEGASYS for 48 weeks

Week 12

- Low (HBeAg <1500 IU/mL): 58% seroconversion, 18/31 patients
- Medium (1500–20,000 IU/mL): 42% seroconversion, 26/62 patients
- High (>20,000 IU/mL): 0% seroconversion, 0/21 patients

Week 24

- Low (HBeAg <1500 IU/mL): 57% seroconversion, 26/46 patients
- Medium (1500–20,000 IU/mL): 35% seroconversion, 18/52 patients
- High (>20,000 IU/mL): 0% seroconversion, 0/16 patients

Potential early stopping rule with high NPV

Gane et al. EASL 2011
Summary

• HBsAg level or decline at week 12 or 24 is a good indicator of sustained immune control
  • High PPV for <1500 IU/mL

• HBsAg quantification can help motivate patients to complete their finite course of PEG-IFN

• HBsAg levels >20,000 IU/mL at week 12 are associated with a low chance of response
  • High NPV for a potential early stopping rule
Combining HBsAg and HBV DNA decline for early identification of non-response

Validation of proposed rule using combined data from 2 independent studies (N=91 genotype D)

WEEK 12

ANY HBsAg decline

HBV DNA decline (copies/mL)

<2 log
N=17

≥2 log
N=43

Chance of sustained response*

0/17 (0%)

12/43 (28%)

6/14 (43%)

7/17 (41%)

*HBV DNA <10,000 copies/mL and ALT normal 6 months post-treatment

Rijckborst & Lampertico. AASLD 2010
On-treatment HBsAg levels and long-term clearance of HBsAg

Patients who clear HBsAg may be able to stop therapy

Rapid decline in HBsAg levels is associated with HBsAg clearance

<table>
<thead>
<tr>
<th>HBsAg decline patterns during treatment with telbivudine</th>
<th>Rapid decline in HBsAg levels is associated with HBsAg clearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid</td>
<td>Patients N=162</td>
</tr>
<tr>
<td>Slow</td>
<td></td>
</tr>
<tr>
<td>Steady</td>
<td></td>
</tr>
<tr>
<td>Rapid &gt;1 log</td>
<td>20% (32)</td>
</tr>
<tr>
<td>Slow &lt;1 log</td>
<td>46% (74)</td>
</tr>
<tr>
<td>Steady</td>
<td>35% (56)</td>
</tr>
</tbody>
</table>

Wursthorn et al. Hepatology 2010
Summary

• HBeAg seroconversion may not be an appropriate indication for stopping NA therapy
  • High rate of relapse
• HBsAg clearance is infrequent with NAs, however HBsAg decline could potentially be used as an indicator of ultimate HBsAg clearance in a subgroup of patients
  • Requires further confirmation
Summary

• HBsAg decline at week 12 or 24 is good indicator of sustained immune control with PEG-IFN

• Lack of HBsAg and HBV DNA decline at week 12:
  • Identifies a subset of patients who will not achieve sustained response to 48 weeks of PEG-IFN
  • High NPV for an early stopping rule
  • Confirmed in 2 independent studies
  • Allows a potential response-guided approach to therapy

Rijckborst et al. Am J Gastroenterol 2010
Section summary
HBsAg levels during therapy

- PEG-IFN has a greater overall effect on HBsAg levels than NAs
- HBsAg level/declineduring PEG-IFN is significantly associated with sustained immune control
  - Can lead to a response-guided therapy approach
  - Week 12 – potential early stopping rule (high NPV)
  - Week 24 – patient motivation (high PPV)
- Small proportion of HBeAg-positive patients treated with NAs show rapid HBsAg decline and could potentially stop therapy
Thanks for listening