Recent Management of Chronic Hepatitis B

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Hepatitis B Virus

- Nucleocapsid
- DNA polymerase
- Envelope
- Large surface antigen
- Genomic DNA
- Small surface antigen
- Middle surface antigen
- RNA primer
Acute HBV Infection with Recovery
Typical Serologic Course

Table:

<table>
<thead>
<tr>
<th>Symptoms (Weeks of Exposure)</th>
<th>HBeAg</th>
<th>anti-HBe</th>
<th>Total anti-HBc</th>
<th>IgM anti-HBc</th>
<th>anti-HBs</th>
</tr>
</thead>
<tbody>
<tr>
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</tbody>
</table>
| Source: US CDC and Prevention
Progression to Chronic HBV Infection
Typical Serologic Course

Acute (6 months)

<table>
<thead>
<tr>
<th>Weeks of Exposure</th>
<th>Titer</th>
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<tbody>
<tr>
<td>0</td>
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<tr>
<td>4</td>
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<td>8</td>
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<td>44</td>
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<tr>
<td>48</td>
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<tr>
<td>52</td>
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</table>

Chronic (Years)

<table>
<thead>
<tr>
<th>Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
</tr>
<tr>
<td>4</td>
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<tr>
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<td>44</td>
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<tr>
<td>48</td>
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<tr>
<td>52</td>
</tr>
</tbody>
</table>

Source: US CDC and Prevention
# Interpretation of Diagnostic Tests for Hepatitis B

<table>
<thead>
<tr>
<th>Test</th>
<th>Acute Hepatitis B</th>
<th>Past Exposures (Immunity)</th>
<th>Previous Immunization</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>anti-HBs</td>
<td>–</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>HBeAg</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>anti-HBe</td>
<td>–</td>
<td>+/-</td>
<td>–</td>
</tr>
<tr>
<td>anti-HBc</td>
<td>+</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>IgM anti-HBc</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>HBV DNA*</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

* viremia may be detected by other more sensitive tests such as PCR.

ALT Elevated Normal Normal

# Interpretation of Diagnostic Tests for Hepatitis B (cont.)

<table>
<thead>
<tr>
<th>Test</th>
<th>Chronic Hepatitis B</th>
<th>Chronic Pre-core</th>
<th>Chronic Inacti</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>anti-HBs</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>HBeAg</td>
<td>+</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>anti-HBe</td>
<td>−</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>anti-HBc</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>IgM anti-HBc</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>HBV DNA*</td>
<td>+/-</td>
<td>+/-</td>
<td>−</td>
</tr>
</tbody>
</table>

*By conventional assay. A lower level of viremia may be detected by other more sensitive tests such as PCR.

ALT | Elevated | Elevated | Normal
---|----------|----------|--------
Evaluation of Liver Disease in HBV Infection

Indicator
- Alanine aminotransferase (ALT)
- Aspartate aminotransferase (AST)
- Bilirubin
- Prothrombin time (PT)
- Albumin
- Liver histology
- Ultrasound

Interpretation*
- ↑ suggests hepatocyte damage
- ↑ suggests hepatocyte damage
- ↑ suggests hepatic dysfunction
- ↑ suggests hepatic dysfunction
- ↓ suggests hepatic insufficiency
- Indicator of disease stage & grade
- Identifies tumors/cirrhosis
## Knodell Scoring System for Liver Biopsies

<table>
<thead>
<tr>
<th>Category</th>
<th>Components Evaluated</th>
<th>Range of Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade*</td>
<td>1. Periportal necrosis with or without bridging necrosis</td>
<td>0-10</td>
</tr>
<tr>
<td></td>
<td>2. Intralobular degeneration and focal necrosis</td>
<td>0-4</td>
</tr>
<tr>
<td></td>
<td>3. Portal inflammation</td>
<td>0-4</td>
</tr>
<tr>
<td>Stage†</td>
<td>4. Fibrosis</td>
<td>0-4</td>
</tr>
</tbody>
</table>

*The Grade score reflects severity of necrosis and inflammation.  
†The Stage score indicates scarring, or potentially irreversible disease progression.

How Can We Assess Disease Activity in CHB?

- Clinical signs and symptoms
- Blood biochemistry and virology
- Liver histology
- Radiologic imaging
Assessment of Disease Progression or Effect of Therapy

- Grade inflammation & stage fibrosis
- Semi-quantitative Scoring Systems
  - HAI (Knodell)
  - Modified HAI (Ishak)
- Ranked Assessment
  - Rank biopsies, blinded for sequence
  - Simple, powerful
Management of Chronic Hepatitis B

I- Prophylaxis:

II- Diagnosis & Disease Assessment:

III- Treatment:

1. Immune Modulators
2. Antiviral Therapy
3. Adjuvant Therapy
4. Liver Support & Traditional Therapy
5. Treatment of Complications
Aims of therapy for CHB

- Achieve sustained loss of viral replication
  - Hbeag seroconversion (loss of hbeag, gain of hbeab)
  - Loss of HBV DNA

- Limit liver damage due to immune-mediated inflammation and fibrosis
  - Normalisation of ALT
  - Improvement in liver histology

- Eradicate HBV infection
  - Eradicate covalently closed circular DNA
  - Avoid anti-viral drug resistance

- Improve survival
  - Prevent cirrhosis, liver failure and hepatocellular cancer
Alpha interferon in CHB

- 35% response rate in selected patients
- Contra-indicated in advanced cirrhosis
- Not effective in HBeAg -ve HBV (Pre-Core Mutant)
- More favourable outcome in
  - high baseline ALT
  - low baseline HBV DNA.
Previously, interferon-α was the only therapy approved for treatment of chronic hepatitis B

**Predictors of response:**
- Adult-acquired HBV infection
- Female gender
- High baseline ALT
- Low baseline HBV DNA
- Absence of cirrhosis
Interferon-α

Interferon-α is poorly tolerated
- Frequent severe side-effects
- Hepatic decompensation
- Immuno-compromise

Interferon-α is poorly accepted
- Expensive
- Injected
Interferon for Hepatitis B

Advantages

- **Best predictors:** ALT > 150 U/L, HBV DNA < 200 pg/mL, short duration infection

- **40%** HBeAg seroconversion; relative response rate is x2 control

- **33%** of responders lose HBsAg

- **Alters outcome of chronic liver disease**

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e.g. N Engl J Med 334;1470,1996
Interferon for Hepatitis B
Disadvantages

* Unsuitable for majority (>90%) of cases
  - low ALT, prolonged infection
* 60% of optimal cases fail to respond
* Precore mutant doesn’t respond well
* HBeAg seroconversion flare: dangerous in severe liver disease (cirrhosis, low albumin)
* Parenteral, unpleasant to take, many adverse effects
Chronic Hepatitis B
Unmet Therapeutic Needs

- Liver disease with normal ALT
- High circulating HBV DNA
- Cirrhosis
- Decompensated liver disease
- Immuno-compromised patients, including organ Tx recipients
- Patients who previously failed IFN
- Perinatally acquired HBV
- Oral therapy + Less costly therapy
Antiviral Therapy
1-Lamivudine
(Zeffix)
Lamivudine 100 mg (Zeffix)

- A nucleoside analogue with potent antiviral activity against HBV
- Rapidly suppresses HBV replication through inhibition of HBV DNA synthesis

*Lamivudine is a potent inhibitor of HBV replication*
Viral Suppression by Lamivudine

Infectious HBV virion

Partially double-stranded DNA

cccDNA

DNA pol

(-)-DNA

RT

Encapsidated pregenomic mRNA

mRNA

A(n)

HBsAg envelopes
Efficacy of Lamivudine 100 mg

- Suppresses HBV in all patients
- Normalizes ALT
- Significantly increases HBeAg seroconversion
- Improves liver disease in 2/3 of patients and prevents progression in most others
- Decreases progression to cirrhosis
- Effective in pre-core mutant chronic hepatitis B
- Effective in IFN-α naïve patients and IFN-α failures
- Suppresses HBV in patients with decompensated CHB and in liver transplant recipients
Median HBV DNA and ALT during 3 Years Lamivudine in Asian Study

(n=58)

Median HBV DNA (pg/mL)

Median ALT (xULN)
HBeAg seroconversion (HBeAg-ve, HBeAb+ve) increases with duration of lamivudine therapy (n=58)
Durability of Post-Treatment Response

 Patients (%)

<table>
<thead>
<tr>
<th>HBeAg loss</th>
<th>Asian</th>
<th>Caucasian</th>
<th>Interferon</th>
<th>Spontaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Follow-up = &gt;12 months</td>
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</tr>
</tbody>
</table>

73/11/15
83/35/42
87/20/23
68/21/31

Schiff et al. 1998
Korenman et al. 1991
Lok et al. 1987
Lamivudine Responses are Durable
Median 12 Months Follow-up

Patients Sustaining Responses (%)

HBeAg Seroconversion: 36/42
Normal Serum ALT: 23/29

Integrated Phase III Data
Zeffix Reduces Progression of Fibrosis

- Ranked assessment of changes in liver fibrosis
- ITT\textsubscript{m} population: patients lacking either biopsy excluded
- All treatment arms for 52 weeks

### Patients (%)

<table>
<thead>
<tr>
<th>Improved</th>
<th>Lamivudine 100mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>2</td>
<td>17</td>
</tr>
<tr>
<td>47</td>
<td>6</td>
<td>39</td>
</tr>
<tr>
<td>39</td>
<td>4</td>
<td>34</td>
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<tr>
<td>34</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

*\textit{p}<0.01 compared to placebo

**Legend:**
- Yellow: Tassopoulos
- Blue: Schalm
- Pink: Dienstag
- Orange: Schiff
- Green: Lai
Progression to Cirrhosis During One Year of Therapy


Patients Developing Cirrhosis (%)

Lamivudine: 1.8
Placebo: 7.1
IFN: 9.5

p=0.04

Goodman et al., J Hepatology 1999 (Abstr.)
Lamivudine 100 mg in PCM

HBV

Administration of 100mg/daily over the long-term to keep HBV suppressed

Prolonged suppression of HBV results in:

- control of inflammation
- prevention of rises in serum ALT
- improvement of liver function
Safety of Lamivudine 100 mg

Unlike other nucleoside analogues

- little activity against mammalian DNA polymerase γ (enzyme for mitochondrial DNA replication)
- not incorporated into mitochondrial DNA
- less likely to have effects on bone marrow, hepatocytes, nerves and muscles
## Adverse Events: Lamivudine vs Placebo

Percent of Patients with Event in Phase III Studies

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Placebo (n=200)</th>
<th>Lamivudine (n=416)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malaise and fatigue</td>
<td>28</td>
<td>26</td>
</tr>
<tr>
<td>Headache</td>
<td>21</td>
<td>22</td>
</tr>
<tr>
<td>Viral respiratory infection</td>
<td>17</td>
<td>19</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>17</td>
<td>16</td>
</tr>
<tr>
<td>Abdominal discomfort/pain</td>
<td>17</td>
<td>15</td>
</tr>
<tr>
<td>ENT infections</td>
<td>12</td>
<td>14</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>12</td>
<td>14</td>
</tr>
<tr>
<td>Viral ENT infections</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Throat and tonsil discomfort/pain</td>
<td>8</td>
<td>11</td>
</tr>
<tr>
<td>Cough</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>10</td>
<td>8</td>
</tr>
</tbody>
</table>

Integrated Phase III Data
Lamivudine 100 mg
(Zeffix)

ZEFFIX is a potent once a day oral antiviral therapy which is safe and efficacious

- Suppresses serum HBV DNA
- Enhances HBeAg seroconversion
- Normalises aminotransferases
- Reduces progression to cirrhosis
- Zeffix can be used with Pegelated INF. To maximise its benifits
Patients with HBeAg-negative CHB were randomised using a 1:1:1 ratio (n=537).

- **180 μg PEG IFNα-2a qw + oral placebo qd**
- **180 μg PEG IFNα-2a qw + 100 mg lamivudine qd**
- **100 mg lamivudine qd**

**Study weeks**
- 0
- 24
- 48
- 72

**Follow-up**
- 24 week follow-up
- EOF 72 weeks
- EOT 48 weeks

*Marcellin et al, AASLD 2003*
**Peg-IFN-α2a + Lamivudine**

*Naive, HBeAg- patients*

Mean HBV DNA (log_{10} cp/mL)

- **PEG IFN-2a + placebo**
- **PEG IFN-2a + lamivudine**
- **lamivudine**

Study week: 0 6 12 18 24 30 36 42 48 54 60 66 72

Marcellin *et al*. *Hepatology* 2003; 38 (suppl1): 724A
2-Adefovir dipivoxil (Hypsera)
Adefovir dipivoxil (Hypsera) used in a dose of 10 mg once daily.

It is highly indicated in case of emerging of YMDD variant strain during Lamivudine therapy (YMDD characterized by elevation of ALT & HBV-DNA above pre-treatment levels).

Adefovir dipivoxil 10mg (Hypsera) is adding on Lamivudine for 3 months and then stopping Lamivudine and continue on Adefovir dipivoxil 10mg.

If (Hypsera) is not available, patient should on Lamivudine even on emerging of YMDD.
Adefovir - Conclusion

- Adefovir treatment results in long-term viral suppression, ALT normalisation and histological improvement
- Resistance to adefovir is delayed and infrequent
- Addition of adefovir to patients with lamivudine-related clinical breakthrough leads to resumption of disease control
HBV DNA when adefovir is added to ongoing lamivudine with YMDD mutant HBV

Perrillo R et al, Gastroenterology 2004; 126: 81-90
Adefovir dipivoxil 10mg safety summary

- Safety and tolerability of ADV 10mg similar to placebo through 48 weeks
  - Increases in ALT and AST more frequent on placebo
- Safety may be similar with extended dosing
- Incidence of increases in serum creatinine is low
  - One patient discontinued
- No hypophosphatemia
- Increases in serum ALT after stopping treatment
  - Liver function should be closely monitored for at least 12 weeks after discontinuation of therapy
3- Entecavir
It has similar mode of action of Adefovir dipivoxil, also used once daily in case of emerging of YMDD variant strain during Lamivudine therapy. But this molecule still in phase 2 (Under trails) & not available in the market yet.