Treatment Strategies for Hepatitis B in the West

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Key Questions

• When to start?
• Which treatment to use?
• How to monitor for response?
• When to stop?
Hepatitis B Treatment Strategies
East vs. West

• Are the strategies different?
• Are the differences related to differences in
  – Disease patterns
  – Responsiveness to treatment
  – Availability or affordability of treatment
  – Physician and patient preference
Who Should be Treated?

- Not a question of whom to treat but when: treat now or monitor and treat later when indicated

- All HBV carriers are potential treatment candidates

- A patient who is not a treatment candidate now can be a treatment candidate in the future
  - Changes in HBV replication status and/or activity/stage of liver disease
  - Availability of new and better treatments
When to Start Treatment?

Benefits
- Likelihood of adverse outcome
- Long-lasting response

Risks
- Side effects
- Drug resistance

Patient’s age and preference

Costs

Likelihood of adverse outcome without treatment
- Activity and stage of liver disease at presentation
- Risk of cirrhosis / HCC in the next 10-20 yrs

Likelihood of long-term benefit with treatment
# Stages of Chronic HBV Infection

<table>
<thead>
<tr>
<th>Immune tolerance</th>
<th>Immune clearance</th>
<th>Low replicative phase</th>
<th>Reactivation phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBeAg + (wild)</td>
<td>HBeAg - / anti-HBe + (PC/CP variants)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HBV-DNA</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>10^9-10^{10} cp/ml</td>
<td>10^7-10^8 cp/ml</td>
<td>&lt;10^5 cp/ml</td>
<td>&gt;10^5 cp/ml</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ALT</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal / mild CH</td>
<td>moderate/severe CH</td>
<td>Normal/mild CH</td>
<td>moderate/severe CH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>cirrhosis</td>
<td>Inactive cirrhosis</td>
<td>cirrhosis</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| HBeAg +          | Inactive-carrier state | HBeAg – |
| Chronic hepatitis |                       | Chronic hepatitis |
Treatment indication should be based on HBV DNA NOT ALT

- Positive HBeAg and high serum HBV DNA (>4 log_{10} copies/mL) had been reported to be associated with increased risk of cirrhosis and HCC
- Moderate inflammation, fibrosis and even cirrhosis can be found in patients with normal ALT
- ALT 0.5-1x ULN is associated with increased risk of hepatic complications vs. those with ALT <0.5x ULN
## REVEAL HBV Study

3653 HBsAg+ patients, mean FU 11.4 yr  
Mean age 43 yr, 15% HBeAg+, 6% elevated ALT, 2% cirrhosis

<table>
<thead>
<tr>
<th>HBV DNA Entry</th>
<th>(c/mL) Last FU</th>
<th>No. of Participants</th>
<th>No. of HCC Cases</th>
<th>Adjusted HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 4 log</td>
<td>ND</td>
<td>2034</td>
<td>26</td>
<td>1.0</td>
</tr>
<tr>
<td>4-5 log</td>
<td>&lt;4 log</td>
<td>256</td>
<td>6</td>
<td>1.3 (0.5 – 3.1)</td>
</tr>
<tr>
<td></td>
<td>4-5 log</td>
<td>161</td>
<td>1</td>
<td>0.4 (0.1 – 3.2)</td>
</tr>
<tr>
<td></td>
<td>≥ 5 log</td>
<td>110</td>
<td>5</td>
<td>2.9 (1.0 – 9.8)</td>
</tr>
<tr>
<td>≥ 5 log</td>
<td>&lt; 4 log</td>
<td>146</td>
<td>8</td>
<td>1.9 (0.8 – 4.4)</td>
</tr>
<tr>
<td></td>
<td>4-5 log</td>
<td>120</td>
<td>10</td>
<td>4.3 (2.0 – 9.3)</td>
</tr>
<tr>
<td></td>
<td>≥ 5 log</td>
<td>537</td>
<td>55</td>
<td>5.3 (2.9 – 9.7)</td>
</tr>
</tbody>
</table>

Adjusted for gender, age, smoking, alcohol, HBeAg, cirrhosis & ALT

Chen CJ, JAMA 2006; 295:65
REVEAL – HBV Study: Limitations

• Is Serum HBV DNA $\geq 4$ log 10 copies / ml a strong risk predictor of HCC?
  – 4-5 log - Marginal increase in risk
  – $>5$ log – Significant increase in risk, especially if persistent

• Can the result be generalized to other HBV carriers?
  - Adult acquired HBV infection
  - Perinatally acquired HBV infection, age < 40 years

• Can assessment at a single time point predict the prognosis of an individual with chronic HBV infection?
Histology during the Immune Tolerant Phase is Generally Benign

• 40 patients, median age 29 (17-59)
  – 20 F0, 20 F1
    • Andreani T, Clin Gastro & Hepatol 2007; 5:636

• 57 patients, median age 31 (18-41)
  – 19 F0, 38 F1
  – 48 remained immune tolerant, 3 had increase, 4 had decrease, and 41 had unchanged fibrosis score after 5 yr
    • Hui C, Hepatology 2007; 46:395
Short-term Outcome of Patients who Presented in the Immune Tolerant Phase is Favorable

• 240 patients (130 M: 110 F), mean age 27.6 yr
• Mean FU 10.5 yr (3-20)
• Spontaneous HBeAg seroconversion: 85%
• Reactivation of hepatitis after HBeAg seroconversion: 2.2%/yr
• Cirrhosis: ~1.5% after 10 yr
• HCC: none

Baseline ALT is the Best Predictor of Response to Treatment of HBeAg+ Patients

Perrillo R et al, Hepatology 2002;36:186 * 1/2 patients
What are the Indications to Start Treatment?

AASLD Practice Guidelines 2007

• Evidence of liver disease – abnormal ALT (>2x ULN) in the presence of high serum HBV DNA (>20,000 IU/mL for HBeAg+ patients and >2,000 IU/mL for HBeAg- patients)
  – Lower threshold if
    • Older age
    • Active inflammation or advanced fibrosis on biopsy
    • Clinical evidence of cirrhosis
• Borderline ALT or HBV DNA – monitor, if persistent, consider biopsy
• Others – monitor, treat later when indication arises or more effective treatment available

Lok & McMahon, Hepatology 2007; 45: 507
Which should be the primary treatment?

Long-term Benefits:
- Antiviral potency
- Durability of response

Long-term Risks:
- Contraindications
- Ease of administration
- Duration of Rx
- Costs of Rx & monitoring
- Patient and provider preference
- Side effects
- Drug resistance
Approved HBV Treatments

- Interferon alpha 2b (Intron)
- Lamivudine (Epivir)
- Adefovir (Hepsera)
- Entecavir (Baraclude)
- Pegylated interferon alpha 2a (Pegasys)
- Telbivudine (Tyzeka)

Treatments approved for HIV with activity against HBV

- Tenofovir (Viread)
- Emtricitabine (Emtriva)
- Tenofovir + Emtricitabine (Truvada)
Virologic Response in HBeAg+ patients (undetectable HBV DNA by PCR at week 48-52)

LAM = Lamivudine, ADV = Adefovir, ETV = Entecavir, LdT = Telbivudine, TDF = Tenofovir, PegIFN = pegylated interferon
Virologic Response in HBeAg+ patients (HBeAg seroconversion at week 48-52)

<table>
<thead>
<tr>
<th>Drug</th>
<th>% Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAM</td>
<td>~17%</td>
</tr>
<tr>
<td>ADV</td>
<td>12%</td>
</tr>
<tr>
<td>ETV</td>
<td>21%</td>
</tr>
<tr>
<td>LdT</td>
<td>22%</td>
</tr>
<tr>
<td>TDF</td>
<td>21%</td>
</tr>
<tr>
<td>Peg IFN</td>
<td>27%*</td>
</tr>
<tr>
<td>Peg IFN + LAM</td>
<td>27%*</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Virologic response in HBeAg-patients (HBV DNA undetectable by PCR at week 48-52)

- LAM: ~70%
- ADV: 51%
- ETV: 90%
- LdT: 88%
- TDF: 91%
- Peg IFN: 63%
- Peg IFN + LAM: 87%
Rates of antiviral-resistant HBV mutations reported in clinical trials

<table>
<thead>
<tr>
<th>Antiviral therapy</th>
<th>Rates of genotypic resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nucleoside-naïve pts</strong></td>
<td></td>
</tr>
<tr>
<td>Lamivudine</td>
<td>15-30% after 1 yr, 70% after 5 yr</td>
</tr>
<tr>
<td>Adefovir</td>
<td>0% after 1 yr, ~30% after 5 yr</td>
</tr>
<tr>
<td>Entecavir</td>
<td>0% after 1 yr, ~1% after 4 yr</td>
</tr>
<tr>
<td>Telbivudine</td>
<td>6-12% after 1 yr, 9-22% after 2 yr</td>
</tr>
<tr>
<td><strong>Lam-experienced pts</strong></td>
<td></td>
</tr>
<tr>
<td>Adefovir</td>
<td>~20% after 2 yr</td>
</tr>
<tr>
<td>Entecavir</td>
<td>1%, 11%, 27%, 39% after 1, 2, 3 &amp; 4 yr</td>
</tr>
<tr>
<td>Treatment</td>
<td>Interferon</td>
</tr>
<tr>
<td>----------------</td>
<td>------------</td>
</tr>
<tr>
<td><strong>Route</strong></td>
<td>Parenteral</td>
</tr>
<tr>
<td><strong>Duration of treatment</strong></td>
<td>Finite duration ~ 12 mos</td>
</tr>
<tr>
<td><strong>Antiviral activity</strong></td>
<td>Modest, additional immunomodulatory effects</td>
</tr>
<tr>
<td><strong>HBsAg loss</strong></td>
<td>1-3% after 1 yr</td>
</tr>
<tr>
<td><strong>Resistant mutants</strong></td>
<td>None</td>
</tr>
<tr>
<td><strong>Side effects</strong></td>
<td>Frequent</td>
</tr>
<tr>
<td><strong>Cost/yr (USD)</strong></td>
<td>18,000</td>
</tr>
</tbody>
</table>
How to Monitor for Response?

- **Serum HBV DNA**
  - Preferably Q 3 mos, minimum Q 6 mos
  - Ideally real-time PCR, more accurate quantification of baseline HBV DNA
  - Genotypic resistance testing in patients with virologic breakthrough

- **HBeAg/anti-HBe**
  - For HBeAg+ patients only
  - Year 1, and Q 6 mos thereafter

- **HBsAg/anti-HBs**
  - Q 1 yr in HBeAg- patients
When to Stop Treatment?

- Predetermined duration regardless of patient response
- Achievement of therapeutic endpoint
- Treatment failure: modify treatment
  - Primary: inadequate initial response
  - Secondary: drug resistance
- Unacceptable adverse events
- Patient request
- Pregnancy?
- Never?
When to Stop Interferon Treatment?

• Finite duration
  – Immunomodulatory effects may persist after cessation of treatment
  – Need for parenteral administration, side effects, and high costs

• HBeAg+ patients
  – Standard IFN: 4-6 mos
  – Pegylated IFN: 12 mos, is 6 mos sufficient?

• HBeAg- patients
  – Standard IFN: 24 mos better than 12 mos
  – Pegylated IFN: 12 mos, is longer duration better?
What should be the therapeutic endpoint for stopping nucleos/tide analogue therapies?

- Ideally, viral suppression (to undetectable by sensitive PCR) that can be sustained after treatment is discontinued
- HBeAg+ patients: HBeAg seroconversion + ≥ 6 months consolidation therapy
- HBeAg- patients: HBsAg loss, after virus remained suppressed x 4-5 yr?
- Patients with cirrhosis: indefinite treatment?
Hepatitis B Treatment
Strategies are not uniform in the West

- **When to start?**
  - Treatment indication based on HBV DNA alone vs. age + HBV DNA + liver disease

- **Which treatment to use?**
  - IFN vs. nucleos/tides: higher usage of IFN in Europe
  - 1st line nucleos/tide varies with national health / individual insurance coverage

- **How to monitor for response?**
  - HBV DNA assays widely available, generally covered but often not ordered
  - Genotypic resistance testing available in reference labs, variable usage

- **When to stop?**
  - HBeAg+ patients: duration of consolidation treatment varies from 6 mos to >1 yr to indefinite
  - HBeAg- patients: stop in selected patients vs. indefinite treatment for all
Hepatitis B Treatment Strategies
East vs. West

• Disease patterns
  – HBV genotypes: B & C in Asia, A & D in Europe, A-D in USA
  – Age at infection: perinatal in Asia, childhood or adult life in the West

• Responsiveness to treatment
  – IFN: similar when stratified for pretreatment ALT, genotype A more favorable
  – Nucleos/tides: identical

• Availability or affordability of treatment
  – Availability similar
  – Affordability highly variable, wide range in price
  – Many national health policies opt for cheapest drug as 1st line treatment despite risk of drug resistance and need for rescue therapy later

• Physician and patient preference
  – IFN vs. nucleos/tides