Hepatitis B Treatment: Current Guidelines and Special Considerations

Joel Wedd
Transplant Hepatology Fellow
University of Colorado Denver
Learning Objectives

• Identify indications for antiviral therapy in chronic HBV
• Implement therapy appropriately
• Analyze the long term benefits of therapy
• Evaluate the need for therapy in special clinical situations
  – Pregnancy
  – Immunosuppression
Chronic HBV Treatment

• 350-400 million infected worldwide
  – Spectrum of disease from inactive carrier to progressive liver disease, cirrhosis, HCC
  – 0.5-1 million annual deaths

• Target for treatment
  – Those at risk for progressive disease

• Goal
  – Reduce rate/risk of progression to cirrhosis, decompensated cirrhosis, and HCC
Natural History of HBV Infection

Acute HBV Infection
- 95% of Teenagers or Adults

Recovery
- HBsAb+, HBcAb+, HBsAg -

Inactive Carrier
- BeAg to BeAb Seroconversion
- Negative DNA
- Normal ALT
- HBsAg Positive

Chronic HBV Infection
- HBsAg + > 6 months

Chronic Active Hepatitis
- Mild
- 12-20%
- Reactivation

Cirrhosis
- 6-15%

End-Stage Liver Disease
- Liver Transplantation

Hepatocellular Carcinoma
- Death

Immune Tolerant Patients
- High DNA
- Low ALT

End-Stage Liver Disease
- Death

Courtesy of Greg T. Everson
Natural Course of Chronic HBV

DNA

ALT

Immune Tolerance  Immune Clearance  Inactive Carrier  Reactivation

HBeAg  Anti-HBe
HBV Treatment

• Aims:
  – Sustained suppression of HBV replication
  – Remission of liver disease

• Goals:
  – Decrease rate of development of cirrhosis
  – Decrease rate of decompensation
  – Induce compensation in decompensated patients
  – Reduce risk of HCC
Regression of Fibrosis

- Lam, 3 yr
- Adefovir, 4.5 yr
- Entecavir, 5 yr
- Tenofovir, 5 yr

% of Pt with Dec Fibrosis
% of Pt with Reg Cirrh

Dienstag, et al Gastro 2003
Rizzetto, et al Hep 2005
Hadziyannis, et al Gastro 2006
Chang, et al Hep 2010
Marcellin, et al Lancet 2013

Courtesy of Greg T. Everson
Treatment Decisions
Chronic HBV Treatment

- If F3/F4 and + DNA: TREAT

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Monitoring</th>
<th>Treat?</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBeAg Positive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT &gt; 2 x ULN</td>
<td>Consider biopsy for treatment duration</td>
<td>YES</td>
</tr>
<tr>
<td>ALT 1-2 x ULN</td>
<td>q 3 month ALT, q 6 month HBeAg</td>
<td>Treat ≥ F2</td>
</tr>
<tr>
<td></td>
<td>Consider liver biopsy if persistent or &gt; 40</td>
<td></td>
</tr>
<tr>
<td>ALT normal</td>
<td>ALT q 3-6 months, HBeAg q 6-12</td>
<td>NO</td>
</tr>
</tbody>
</table>
### Chronic HBV Treatment

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Monitoring</th>
<th>Treat?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HBeAg Negative</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT &gt; 2 x ULN</td>
<td>Consider biopsy for treatment duration</td>
<td><strong>YES</strong></td>
</tr>
<tr>
<td>DNA &gt; 20,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT &gt; 1-2 x ULN</td>
<td>ALT and DNA q 3 months</td>
<td><strong>YES</strong></td>
</tr>
<tr>
<td>DNA 2,000-20,000</td>
<td>Consider liver biopsy</td>
<td></td>
</tr>
<tr>
<td>ALT normal</td>
<td>ALT and DNA q 3 months x 3 Q 6-12 if persistently normal</td>
<td><strong>NO</strong></td>
</tr>
<tr>
<td>DNA &lt; 2,000</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
HBeAg -, normal ALT

- DNA > 20,000: Consider biopsy
- DNA between 2000 and 20,000: Monitor for change
- DNA < 2000: Chronic Inactive Carrier, Monitor
# Treatment Options

<table>
<thead>
<tr>
<th>PEG-IFN</th>
<th>Nucleos(t)ide Analogs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Advantages</strong></td>
<td></td>
</tr>
<tr>
<td>Finite duration</td>
<td>Potent antiviral effect</td>
</tr>
<tr>
<td>Lack of resistance</td>
<td>Well tolerated</td>
</tr>
<tr>
<td>Higher rates of seroconversion within 12 months</td>
<td>Oral administration</td>
</tr>
<tr>
<td><strong>Disadvantages</strong></td>
<td></td>
</tr>
<tr>
<td>Moderate antiviral effect</td>
<td>Indefinite duration</td>
</tr>
<tr>
<td>Inferior tolerability</td>
<td>Resistance risk</td>
</tr>
<tr>
<td>Adverse events</td>
<td>Long term safety unknown</td>
</tr>
<tr>
<td></td>
<td>Subcutaneous injections</td>
</tr>
</tbody>
</table>
Pegylated Interferon (PegIFN-α)

• Tolerability issues underscore need for selection
  – Young patient
  – No advanced fibrosis
  – Elevated ALT and low DNA
  – Genotype A and B
## PegIFN-α

<table>
<thead>
<tr>
<th>HBeAg Status</th>
<th>Response Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HBeAg Positive</strong></td>
<td></td>
</tr>
<tr>
<td>HBeAg Seroconversion</td>
<td>29-32%</td>
</tr>
<tr>
<td>Loss of HBV DNA</td>
<td>25%</td>
</tr>
<tr>
<td>ALT Normalization</td>
<td>32-41%</td>
</tr>
<tr>
<td>HBsAg Loss</td>
<td>3-7%</td>
</tr>
<tr>
<td><strong>HBeAg Negative</strong></td>
<td></td>
</tr>
<tr>
<td>Loss of HBV DNA</td>
<td>63%</td>
</tr>
<tr>
<td>ALT Normalization</td>
<td>38%</td>
</tr>
<tr>
<td>HBsAg Loss</td>
<td>4-9%</td>
</tr>
</tbody>
</table>
Nucleos(t)ide Analogs (NA)

- Better tolerated and generally better efficacy

Date of FDA approval:
- Lamivudine: 1998
- Adefovir: 2002
- Entecavir: 2005
- Telbivudine: 2006
- Tenofovir: 2008
HBeAg Positive

<table>
<thead>
<tr>
<th></th>
<th>Lamivudine 100 mg qd 48-52 wk</th>
<th>Adefovir 10 mg qd 48 wk</th>
<th>Entecavir 0.5 mg qd 48 wk</th>
<th>Tenofovir 300 mg qd 48 wk</th>
<th>Telbivudine 600 mg qd 52 wk</th>
<th>PegIFNα 180 mcg qw 48 wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss of serum HBV DNA*</td>
<td>40%-44%</td>
<td>21%</td>
<td>67%</td>
<td><strong>76%</strong></td>
<td>60%</td>
<td>25%</td>
</tr>
<tr>
<td>Loss of HBeAg HBeAg</td>
<td>17%-32%</td>
<td>24%</td>
<td>22%</td>
<td>na</td>
<td>26%</td>
<td><strong>30%/34%†</strong></td>
</tr>
<tr>
<td>HBeAg seroconversion</td>
<td>16%-21%</td>
<td>12%</td>
<td>21%</td>
<td>21%</td>
<td>22%</td>
<td><strong>27%/32%†</strong></td>
</tr>
<tr>
<td>Loss of HBsAg</td>
<td>1%</td>
<td>0</td>
<td>2%</td>
<td>3.2%</td>
<td>0%</td>
<td>3%</td>
</tr>
<tr>
<td>Normalization of ALT</td>
<td>41%-75%</td>
<td>48%</td>
<td>68%</td>
<td>68%</td>
<td>77%</td>
<td>39%</td>
</tr>
<tr>
<td>Histologic improvement</td>
<td>49%-56%</td>
<td>53%</td>
<td>72%</td>
<td>74%</td>
<td>65%</td>
<td>38%‡</td>
</tr>
<tr>
<td>Durability of response</td>
<td>50%-80%§</td>
<td>~90%§</td>
<td>69%§</td>
<td>na</td>
<td>~80%</td>
<td>na</td>
</tr>
</tbody>
</table>
### HBeAg Negative

<table>
<thead>
<tr>
<th></th>
<th>Lamivudine 100 mg qd 48-52 wk</th>
<th>Adefovir 10 mg qd 48 wk</th>
<th>Entecavir 0.5 mg qd 48 wk</th>
<th>Telbivudine 600 mg qd 52 wk</th>
<th>Tenofovir 300 mg qd 48 wk</th>
<th>Peg IFNα 180 mcg qw 48 wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss of serum HBV DNA*</td>
<td>60%–73%</td>
<td>51%</td>
<td>90%</td>
<td>88%</td>
<td>93%</td>
<td>63%</td>
</tr>
<tr>
<td>Normalization of ALT</td>
<td>60%–79%</td>
<td>72%</td>
<td>78%</td>
<td>74%</td>
<td>76%</td>
<td>38%</td>
</tr>
<tr>
<td>Histologic improvement</td>
<td>60%–66%</td>
<td>64%</td>
<td>70%</td>
<td>67%</td>
<td>72%</td>
<td>48%</td>
</tr>
<tr>
<td>Durability of response</td>
<td>&lt;10%</td>
<td>~5%</td>
<td>3%</td>
<td>na</td>
<td>na</td>
<td>~20%</td>
</tr>
</tbody>
</table>
Risk of Resistance

![Graph showing the percentage [response] of resistance over time for different treatments (LAM, ADV, ETV, LdT, TDF) across different years (Year 1, Year 2, Year 3, Year 4, Year 5).]
Endpoints

• Ideal: HBsAg seroconversion (1% at 5 yrs)
  – Sole safe criteria in cirrhotic patients

• HBeAg positive patients
  – HBeAg to HBeAb seroconversion and negative DNA, sustained > 12 months
    • Achieved in 40-50%
      – 50% relapse after stopping NA: strict monitoring posttreatment

• HBsAg levels?
Treatment Failures and Resistance

• Prevention
  – Avoid unnecessary treatment
  – Use NAs with low rate of resistance or combination therapy

• Monitoring
  – HBV DNA q 3-6 months during treatment
  – Question medication compliance
  – Confirm resistance with genotypic testing
Special Considerations
Special Considerations - Pregnancy

• Vertical transmission occurs at delivery
• Mothers with high DNA, HBeAg+
  – 10% risk of vertical transmission despite vaccination and HBIG
• PEG-IFN contraindicated
Special Considerations - Pregnancy

Pregnant woman with chronic HBV

Check HBV DNA at 28 weeks

Previous HBV + child?

NO

DNA < 10⁸/10⁹

Monitor

DNA > 10⁸/10⁹

Lamivudine, tenofovir, or telbivudine at 32 weeks

YES

DNA > 10⁶

HBIG and vaccine at birth

DNA < 10⁶

Buchanan, Tran Clin Liv Dz 2010
Chemo/IS Therapy

- HBV DNA detected in liver tissues of 13 out of 14 patients positive for cAb and sAb
- Reactivation risk is high in HBsAg +
  - Particularly with rituximab (but even in infliximab, 6-MP, azathioprine)
  - All immunosuppression candidates should be screened
- Extreme injury and even liver failure can result
Chemo/IS Therapy

HBsAg +
- High DNA: Treat until usual endpoint
- Low DNA: NA until 6 mos after therapy

HBsAg -
- Frequent ALT, DNA
  - DNA +: Rituximab R-CHOP
  - DNA -: HBsAb -
    - HBcAb +: NA
  - DNA -: BMT
Summary

- Patients with high DNA and ALT are treatment candidates
- All others can be biopsied or monitored
- Primary recommended treatments are Peg-INF, tenofovir, and entecavir
- Treatment can dramatically improve outcomes
- Treatment to reduce risk of vertical transmission from chronic HBV mothers is based on HBV DNA level
- Reactivation related to immunosuppression therapy can be catastrophic and can be avoided with prophylactic use of NAs
  - Screen your patients getting anti-TNF therapy!