Treatment Strategies of Hepatitis B in China

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Characteristic features of CHB in China

- Huge amount of patients
- Infection during early life
- Maternal to infant transmission in about 30%
- Genotype: C, B
- Long immunotolerant period
- Insidious onset of cirrhosis and HCC
- Low income per capita and limited medical expenditure
- Awareness the importance of anti-HBV therapy
- Inadequate well trained medical personnels
Epidemiology

- HBsAg carrier rates in different time period

<table>
<thead>
<tr>
<th>Time Period</th>
<th>HBsAg Positive Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1992~1995</td>
<td>9.7%</td>
</tr>
<tr>
<td>2002</td>
<td>8.2%</td>
</tr>
<tr>
<td>2007</td>
<td>7.6%</td>
</tr>
</tbody>
</table>
Age Distribution of HBsAg Positive Rate of 1992 and 2002
Disease Burden of CHB in China
Mortality of Chronic Liver Disease in China

- 2nd leading cause of death in infectious disease:
- mortality:

  Chronic Hepatitis and cirrhosis
  24.5 / 100,000 / year

  Hepatocellular carcinoma
  14.5 / 100,000 / year
Disease Burden

- DALY
  7th
- Family burden
  7th
- Society burden
  2th
## Economic Loss due to HBV Infection in China (2002)

<table>
<thead>
<tr>
<th>Disease Status</th>
<th>Direct Medical Cost (RMB)</th>
<th>Direct Non-medical Cost (RMB)</th>
<th>Indirect Cost (RMB)</th>
<th>Total Cost (RMB)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic Hepatitis B</td>
<td>12,648</td>
<td>1,625</td>
<td>6,204</td>
<td>20,477</td>
</tr>
<tr>
<td>Compensated Cirrhosis</td>
<td>22,867</td>
<td>1,581</td>
<td>11,875</td>
<td>36,323</td>
</tr>
<tr>
<td>Decompensated Cirrhosis</td>
<td>21,326</td>
<td>973</td>
<td>14,458</td>
<td>36,753</td>
</tr>
<tr>
<td>HCC</td>
<td>18,497</td>
<td>5,591</td>
<td>14,179</td>
<td>38,267</td>
</tr>
<tr>
<td>Total</td>
<td>17,474</td>
<td>2,299</td>
<td>10,431</td>
<td>30,477</td>
</tr>
</tbody>
</table>

- Total economic loss: 915 Billion (rate 8.05 RMB≈1.0 US$)
Goals of Treatment

- Sustained suppression and elimination of viral replication
- Reduce and improve liver necro-inflammation and fibrosis
- Delay or prevent the progression
- Improve quality of life and survival
## Indication of Treatment

<table>
<thead>
<tr>
<th>HBeAg Status</th>
<th>Viral Level</th>
<th>ALT Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBeAg (+) CHB</td>
<td>$\geq 10^5$ copies/mL</td>
<td>$\geq 2 \times$ ULN</td>
</tr>
<tr>
<td>HBeAg (-) CHB</td>
<td>$\geq 10^4$ copies/mL</td>
<td>$\geq 2 \times$ ULN</td>
</tr>
</tbody>
</table>
Available Anti-HBV Drugs in China

- **Interferons:**
  - Ordinary recombinant INFα1b, INFα2a, INFα2b
  - Pegylated Interferon α2a, Pegylated Interferon α2b

- **Nucleoside (nudeotide) analogous:**
  - Lamivudine, Adeforvir, Entecavir, Telbivudine

- **Thymosin α1 (efficacy?)**
Physician’s awareness, knowledge and habit

Host: Disease status, Immuno-Response, Co-morbidity, Complication

Pharmacology: Potency, PharmacobARRIER, Safety, Course

Influence by pharmaceutic company lobbying

Social Economics: Price, Cost/effectiveness, Reimbursement, Acceptability

Choices of anti HBV Treatment

Virus: Viral load, Strains: wide or mutant, Genotypes, Genetic barrier
## Anti-HBV Activity of 4 NAs in vitro

<table>
<thead>
<tr>
<th>Drug</th>
<th>Anti HBV activity (2.2.15 cell)</th>
<th>Clinical Daily Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$EC_{50}$ ($\mu$M)</td>
<td></td>
</tr>
<tr>
<td>Lamivudine</td>
<td>0.05</td>
<td>100mg</td>
</tr>
<tr>
<td>Adefovir</td>
<td>0.02</td>
<td>10mg</td>
</tr>
<tr>
<td>Entecavir</td>
<td>0.00375</td>
<td>0.5mg</td>
</tr>
<tr>
<td>Telbivudine</td>
<td>0.19</td>
<td>600mg</td>
</tr>
</tbody>
</table>
Genetic Barriers to Antiviral Drug Resistance

* In patients without lamivudine resistance mutations, emergent resistance with virologic rebound has been observed in one patient through 3 years of treatment (simultaneous emergence of 204+180+202)

Very Early Add-on Therapy to Keep Viral Load as Low as Possible

Drug A: high genetic barrier

Drug B: different cross-resistance profile

From Zoulim, F. 2006 and Lampertico, P. et al 2007
Trails in China
Lamivudine
Median HBV DNA (MEq/ml)

Abbott/Chiron conversion from WK 0 to WK 52

PLA + LAM (n=107)
LAM + LAM (n=322)

Abbott/Chiron conversion from WK 0 to WK 52
Median HBV DNA (MEq/mL) for Non-variant and YMDD Variant

**YMDD variant**

**non-YMDD variant**

A – median = 50th percentile
B – 25th & 75th percentile (50% of patients)
C – 5th & 95th percentile (90% of patients)
HBeAg seroconversion is increased in patients with elevated baseline ALT (Total patients)

HBeAg seroconversion = HBeAg negative, HBeAb positive

Patients entering observation during Year 4
Patients entering observation during Year 5
M = missing data
O = entered observation

ALT >1xULN
ALT >2xULN
ALT >5xULN

HBeAg seroconversion = HBeAg negative, HBeAb positive
Adefovir

HBV DNA Negative

HBV DNA negative: HBVDNA<300copies/ml (Roche Cobas Amplicor™ PCR)
Entecavir
HBV DNA Level After Treatment

<table>
<thead>
<tr>
<th>HBV DNA Level (copies/mL)</th>
<th>ETV N=258</th>
<th>LVD N=261</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥10^5</td>
<td>100%</td>
<td>98%</td>
</tr>
<tr>
<td>10^4 – &lt;10^5</td>
<td>4%</td>
<td>31%</td>
</tr>
<tr>
<td>10^3 – &lt;10^4</td>
<td>3%</td>
<td>31%</td>
</tr>
<tr>
<td>300 – &lt;10^3</td>
<td>0%</td>
<td>7%</td>
</tr>
<tr>
<td>&lt;300</td>
<td>76%</td>
<td>43%</td>
</tr>
</tbody>
</table>

BL: Baseline  
EOD: End Oral Dose
All Treated Patients: Cumulative Confirmed HBV DNA < 300 Copies/mL Through 96 Weeks
All Treated Patients: Cumulative Confirmed ALT ≤ 1×ULN Through 96 Weeks
All Treated Patients: Cumulative Confirmed HBeAg Seroconversion and HBeAg Loss
Telbivudine
## 015 Efficacy at Week 104: All Patients

**Strong Results in Chinese Patients**

<table>
<thead>
<tr>
<th></th>
<th>Telbivudine</th>
<th>Lamivudine</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n</strong></td>
<td>167</td>
<td>165</td>
<td></td>
</tr>
<tr>
<td>HBV DNA ↓ from baseline (mean log(_{10}))</td>
<td>– 5.48</td>
<td>– 4.00</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HBV DNA non-detectable by PCR (%)</td>
<td>63</td>
<td>39</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Therapeutic response * (%)</td>
<td>70</td>
<td>44</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ALT normalization (%)</td>
<td>76</td>
<td>61</td>
<td>0.003</td>
</tr>
<tr>
<td>HBeAg loss (HBeAg+ only) (%)</td>
<td>40</td>
<td>28</td>
<td>0.037</td>
</tr>
<tr>
<td>HBeAg seroconversion (HBeAg+ only) (%)</td>
<td>29</td>
<td>20</td>
<td>0.085</td>
</tr>
<tr>
<td>Primary treatment failure ‡ (%)</td>
<td>3</td>
<td>15</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* HBV DNA suppressed to \(\leq 5\) log\(_{10}\), with ALT normalized OR HBeAg loss

‡ Serum HBV DNA levels never below 5 logs
Viral Load Achieved by Week 24: Telbivudine vs Lamivudine

P < 0.001 for HBV DNA non-detectable at week 24, telbivudine vs lamivudine
QL < 300 copies/mL
Degree of Week 24 Viral Suppression Affects Rate of HBV DNA Non-detectability at Week 104 All Telbivudine-Treated Patients

Percent of Patients with PCR-Non-detectable Serum HBV DNA

- <QL: 83%
- QL-3 Log: 75%
- 3-4 Log: 40%
- >4 Log: 12%

HBV DNA at Week 24
Pegylated Interferon α2a
Patients with HBeAg-positive CHB: HBV DNA levels at 12 months posttreatment according to type of response. HBeAg seroconversion in the long-term follow-up study was associated with HBV DNA levels; 69% of patients with sustained HBeAg seroconversion had HBV DNA levels of <10,000 copies/ml.
Asian patients with HBeAg-negative CHB: Combined response at 24 weeks posttreatment (intention-to-treat population). A significantly higher percentage of patients administered peginterferon alfa-2a experienced a combined response of ALT normalization and HBV DNA <20,000 copies/ml than did patients given lamivudine.
## Price of Anti-HBV Drug in China

<table>
<thead>
<tr>
<th>Name</th>
<th>Dosage</th>
<th>One Year Expense (RMB)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peg-IFNα2a</td>
<td>180µg qw</td>
<td>91,000</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>100mg qd</td>
<td>5,475**</td>
</tr>
<tr>
<td>Adefovir</td>
<td>10mg qd</td>
<td>7,476</td>
</tr>
<tr>
<td>Entecavir</td>
<td>0.5mg qd</td>
<td>14,235***</td>
</tr>
<tr>
<td>Telbivudine</td>
<td>600mg qd</td>
<td>8,760</td>
</tr>
</tbody>
</table>

* 7.1 RMB = 1.0 US$
** Reimbursed
*** Reimbursed in several cities
Cost/Effective Analysis

- LAM vs Convention Treatment: 
  Spend less cost, Better outcomes
- Long term (5years) LAM+ADV or ADV+LAM: 
  Cost effective, More sustained decrease progression
- Pegylated IFNα2a: 
  Gain more QALYs, Spend more cost
- Envecavir: 
  One year of ETV gained 0.305 QALY increment cost 5,368 RMB
HBeAg-Positive

**HBV DNA <20,000 IU/mL (<10^5 copies/mL)**
- ALT Normal
  - No treatment
  - Monitor HBV DNA, HBeAg, ALT/3-6 months

**HBV DNA ≥20,000 IU/mL (≥10^5 copies/mL)**
- ALT Normal
  - No treatment
  - Monitor HBV DNA, HBeAg, ALT/3 months
- ALT 1-2 × ULN
  - No treatment
  - Monitor HBV DNA, HBeAg, ALT/1-3 months
  - Liver biopsy if patient >40 years
  - Treat if moderate or greater inflammation or fibrosis on biopsy
- ALT 2-5 × ULN
  - Treatment if persistent (3-6 months) or has concerns for hepatic decompensation
  - Interferon-based therapy, entecavir, telbivudine, lamivudine, adefovir, are all first-line options
- ALT >5 × ULN
  - Treatment indicated
  - May choose to observe closely for 3 months for seroconversion if no concerns for hepatic decompensation
  - Interferon-based therapy; entecavir, telbivudine or lamivudine recommended, particularly if there is concern for hepatic decompensation

**Response**
- Monitor HBV DNA, HBeAg, ALT/1-3 months post-therapy

**Non-response**
- Consider other strategies (including OLT)

**Patients at risk: HCC surveillance**
- AFP and ultrasonograph/6 months
HBeAg-Negative

HBV DNA <2,000 IU/mL (<10^4 copies/mL)

- ALT Normal
  - No treatment
  - Monitor HBV DNA and ALT/6-12 months

HBV DNA ≥2,000 IU/mL (≥10^4 copies/mL)

- ALT Normal
  - No treatment
  - Monitor HBV DNA and ALT/3 months

- ALT 1-2 × ULN
  - No treatment
  - Monitor HBV DNA and ALT/1-3 months

- ALT >2 × ULN
  - Treatment if persistent (3-6 months) or has concerns of hepatic decompensation
  - IFN based-therapy, entecavir, adefovir, telbivudine, lamivudine
  - Long-term oral antiviral treatment usually required

• Liver biopsy if patient >40 years
• Treat if moderate or greater inflammation or fibrosis on biopsy

Patients at risk: HCC surveillance
• AFP and ultrasonograph/6 months

Response

Monitor HBV DNA and ALT/1-3 months post-therapy

Non-response

Continued monitoring to recognize delayed response or plan other strategy
Liver cirrhosis

Compensated

HBV-DNA < 2 x 10^3 IU/ml
(< 10^4 cp/ml)

ALT (HBeAg) or HBV-DNA
/3 months

HBV-DNA > 2 x 10^3 IU/ml
(> 10^4 cp/ml)

Hepatitis flare

Yes

ETV
Ldt
LAM

No

IFN based
ETV
ADV
Ldt
LAM

Decompensated

Antiviral therapy
Consider transplant

Conventional
supportive
treatment

HCC surveillance
AFP and ultrasonography
/3-6 months
THANK YOU!