Antiviral Therapy for HBV/HCV in China: Clinical Perspective

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Capital Medical University
Beijing, May 9, 2014
Outline

• Current status
• Challenges
• Opportunities
Current Status of CHB in China

1. Successful vaccination program since 1992
2. Protect equal right for education and employment (2010)
3. Amend reimbursement list (2010)
4. Update and promote clinical guidelines (2010)
7. LIFT Project-Liver Center of Excellence (2013)
Evolution of HBV Vaccination Programs in Mainland China

1992.01.01: Routine infant HBV vaccination, vaccine & service should be paid.

2002.01.01: HBV vaccine integrated into EPI, service fee (~1 US$) should be paid.

2005.06.01: HBV vaccine fully integrated into EPI for free.

2009.04.09: HBV vaccine catch-up for children under 15 years.


Courtesy of Professor Hui Zhuang
Declining HBsAg Prevalence in China (1979, 1992 and 2006)


1. ages 1~4
2. ages 5~14
3. ages 15~59
Update and advocacy of Guideline for Prevention & Treatment of CHB in 2011
# Recommendations from CHB guidelines

<table>
<thead>
<tr>
<th>Guidelines</th>
<th>Updated</th>
<th>Recommendations for treatment-naïve CHB patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>APASL(^1)</td>
<td>2012</td>
<td>ETV or TDF are the <strong>preferred</strong> NUCs for NUC-naïve CHB patients. LAM, ADV and LdT may only be used...if more potent drugs with a high barrier to resistance are not available or appropriate.</td>
</tr>
<tr>
<td>EASL(^2)</td>
<td>2012</td>
<td>ETV and TDF are potent HBV inhibitors with a high barrier to resistance. Thus, they can be confidently used as <strong>first-line monotherapies</strong>.</td>
</tr>
<tr>
<td>AASLD(^3)</td>
<td>2009</td>
<td>Treatment may be initiated with any of the seven approved antiviral medications, but peg-IFN-, TDF or ETV <strong>are preferred</strong>.</td>
</tr>
<tr>
<td>China(^4)</td>
<td>2010</td>
<td><strong>If possible</strong>, drugs with high potency and low resistance <strong>should be chosen</strong> for NUC-naïve patients.</td>
</tr>
</tbody>
</table>

Clinical Trials on HBV antiviral Therapy in China (English Publication)
National Major Scientific Project Sponsored
4 large RCT studies

LdT (EFFORT study)

PEG-IFN (EXCEL study)

Lam (EXPLORE study)

ETV (DRAGON study)

N=1594
EFFORT study

LdT (EFFORT)

Treatment-naïve CHB

SOC

0 w12 w24 W52 W104

optimization

LDT

I-A: w24 if HBV DNA ≥300 copies/mL
Add ADV

I-B: W24 HBV DNA < 300 copies/mL
LDT monotherapy

Add ADV if viral breakthrough

## Study results

<table>
<thead>
<tr>
<th>104-week Outcomes</th>
<th>OPTIMIZE N = 300</th>
<th>MONO N = 299</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median reduction of HBV DNA, log(_{10}) copies/mL</td>
<td>-6.3</td>
<td>-6.1</td>
<td>0.009</td>
</tr>
<tr>
<td>ALT Normalization, n (%)</td>
<td>234 (80.7)</td>
<td>232 (79.2)</td>
<td>NS</td>
</tr>
<tr>
<td>HBeAg Seroconversion, n (%)</td>
<td>71 (23.7)</td>
<td>66 (22.1)</td>
<td>NS</td>
</tr>
<tr>
<td>HBsAg Clearance, n (%)</td>
<td>2 (0.7)</td>
<td>2 (0.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Virological Breakthrough, n (%)</td>
<td>18 (6.0)</td>
<td>91 (30.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Genotypic Resistance, n (%)</td>
<td>8* (2.7)</td>
<td>77 ** (25.8)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

• **Inclusion criteria for present cohort:**
  – Enrolled at one of the 50 Chinese study sites of REALM study
  – NUC–naïve
Patients with decompensated liver disease or HCV co-infection were excluded from efficacy analyses.

†Remained on study but discontinued their randomized assigned regimen and were offered alternative anti-HBV therapy at discretion of investigator.

oSOC: other standard of care (ADV, LVD, LdT)
REALM China Sub-study
Virologic Efficacy: All Patients

HBV DNA <50 IU/mL (%)

Week 48 96 144 192 240
ETV 69 79 83 85 85
oSOC 36 49 56 62 67

Non-completer = missing analysis

oSOC: other standard of care (ADV, LVD, LdT)

Chinese EVOLVE Study
6 territories, 63 sites, ~200 investigators, 3435 pts

• A 2-year Prospective and Observational Study

• To Evaluate the Effectiveness of Nucleos(t)ide Analogs (NUC) Therapy Among CHB Patients Naive to NUC in Real World Practice at Hospitals in Tier 2 Cities in China

• Started from December 2012
• Enrollments: as of end of March 2014, totally 3,431 patients have been enrolled, the target number is 3,435.

http://www.clinicaltrials.gov/ct2/show/study/NCT01726439
建立中国乙肝随访与临床科研平台
China Registry- Hepatitis B (CR-HepB)

- Up to Jan 15, 2014, 24205 cases inputted, follow-up times 105502
LIFT Project—Liver Center of Excellence

- Publication of standardized approach for liver disease management in 2013
Challenges in the treatment of CHB in China

- High disease burden
- Accessibility & affordability to treatment
- Insufficient reimbursement for rural residents
- Inadequate therapy - First line therapy not first
The Estimated Hepatitis B Infections by diseases classification in China, 2010

<table>
<thead>
<tr>
<th>Classification</th>
<th>Proportion (% )</th>
<th>Estimated in 2010 ( million )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seroclearance</td>
<td>6.91</td>
<td>6.43</td>
</tr>
<tr>
<td>HBV Carrier</td>
<td>59.23</td>
<td>55.08</td>
</tr>
<tr>
<td>Chronic Hepatitis B</td>
<td>32.44</td>
<td>30.17</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>1.04</td>
<td>0.97</td>
</tr>
<tr>
<td>HCC</td>
<td>0.38</td>
<td>0.35</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>100.00</strong></td>
<td><strong>93.00</strong></td>
</tr>
</tbody>
</table>

Courtesy of Dr FQ Cui
Total Economic Burden of CHB-Related Diseases in Beijing and Guangzhou

- **Direct medical cost**
- **Direct nonmedical cost**
- **Indirect cost**

### Cost per case/yr

<table>
<thead>
<tr>
<th>Condition</th>
<th>Beijing</th>
<th>Guangzhou</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHB</td>
<td>1636</td>
<td></td>
<td>9145*</td>
</tr>
<tr>
<td>Com cirr</td>
<td>2722</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dec cirr</td>
<td>4611</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCC</td>
<td>6615</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family income/yr</td>
<td>~8000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per capita GDP</td>
<td>7314*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHB</td>
<td>1452</td>
<td>6054</td>
<td></td>
</tr>
<tr>
<td>Com cirr</td>
<td>2065</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dec cirr</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family com/yr</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per capita GDP</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Hu M & Chen W. value in health, 2009*
Proportion of CHB Patients Receiving Antiviral Therapy

No, 81%
Yes, 19%

Study on knowledge of 452 patients with CHB from 6 cities of China, Chinese Society of Hepatology & Chinese Society of Infectious Diseases, 2004
Factors Associated with not Receiving Antiviral Treatment for CHB Patients

- Cost: 76.8%
- Side effect: 15.2%
- Not recomm: 4.8%
- Other drugs: 3.2%

Data from 115 physicians active in treatment of CHB, China Medical Tribune, 2005.
NUCs Treatment Regimens for CHB
---Real Clinical Practice in China

Chronic hepatitis B patients: 20 ~ 30 million cases
Antiviral treatment: 1,850,000 cases
TCM and others: 550,000 cases

**First Line is not First!**

Treatment survey for 2,500 chronic hepatitis B patients in 12 first and second tier cities in 2008.
Inadequate use of NAs in clinical practice

<table>
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<tr>
<th>治疗方法</th>
<th>用药情况</th>
<th>例数</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>初始就联合用药</td>
<td>ADV+LMV</td>
<td>22</td>
<td>20.8</td>
</tr>
<tr>
<td>单药序贯</td>
<td>ADV-ETV, ADV-LdT, LdT-ADV, LMV-ADV, LMV-ETV, LMV-ADV-ETV, LMV-ETV-ADV, ADV-stop-LMV, LMV-stop-ADV</td>
<td>75</td>
<td>70.7</td>
</tr>
<tr>
<td>多次换药、加药</td>
<td>ADV-LMV-ADV+LMV, LMV-ADV-ADV+LMV, LMV-ADV+LMV, LMV-ADV, LMV-ADV, LMV-ADV-LdT+ADV</td>
<td>5</td>
<td>4.7</td>
</tr>
<tr>
<td>耐药后不合理用药</td>
<td>LdT-LMV, LdT-ADV-LdT, LMV-ADV-LdT, LMV-ETV+LMV-ADV</td>
<td>4</td>
<td>3.8</td>
</tr>
<tr>
<td>合计</td>
<td></td>
<td>106</td>
<td>100.0</td>
</tr>
</tbody>
</table>

北京、山东、河北、新疆等地5家医院106例慢性乙肝患者核苷 (酸) 类似物不规范治疗情况调查
Projection of HBV antiviral market

Patients on treatment (Million)

图 7-19. 慢性乙型肝炎各类药物受治病人数 10 年预测
来源：IMS 分析总结
* 联合用药患者重复计入受治人数
Current Status of CHC in China

1. Declining prevalence of HCV infection
2. Release & promote clinical guidelines
3. Amend reimbursement list
4. National Major Research Project

Prevalence of HCV genotypes in China (CCgenos)

Distribution of IL28B host genotype in China

Clinical Trials on HCV antiviral Therapy in China (English Publication)
HCV cohorts and clinical studies in China

- Follow-up = 1200
- HCV natural history
  - SVR 24W
  - Relapse predictors
  - Novel diagnostic tech
  - Long-term outcomes
  - Efficacy predictors

- Difficult to treat CHC = 800
  - TN = 400
  - Relapsers = 120
  - Nonresponders = 80
  - Generic IFN = 200

N = 2000

Courtesy of Prof L Wei
Difficult-to-treat HCV achieves SVR of 8.7% with tailored PEGIFN+RIB therapy

Genotype 1b or HVL (HCV RNA ≥ 4 × 10^5 IU/ml)

Treatment naive

N = 438

- Peg-IFN-α-2a 180µg/wk + RBV 48W
- Peg-IFN-α-2a 180µg/wk + RBV 72W
- Peg-IFN-α-2a 180µg/wk + RBV 96W

f/u 24W

A

F/u 24W

B

F/u 24W

C

0 12W 24W 48W 72W 96W 120W

randomization

cEVR: HCV RNA < 15 IU/ml at wk 12

Courtesy of Prof L Wei
Optimized therapy with PEFIFN+RIV yields an overall SVR of 78.7% in TN CHC

Courtesy of Prof L Wei
Challenges in the treatment of CHC in China

• High diseases burden
• Accessibility & affordability to treatment
• High disease burden and Insufficient reimbursement for rural residents
Reported HCV cases is increasing
Importance of expanding testing and treatment to impact the global prevalence of HCV infection

Thomas DL. Nature Med 2013, 19:850-8
HBV & HCV treatment opportunities in China

- Highly effective drugs for CHB (ETV and TDF) are registered in China
- DAAs trials for HCV are under way
- Public health CHB treatment program provides an opportunity for significant price reduction
  - TDF negotiated at RMB 113/month for the HIV public health program (RMB 1,470/month for CHB)
- Public health approach embedded in the health reform would open new opportunities for price reduction of antiviral drugs to meet the targets of Universal Health Care Coverage
WHO WPRO Informal Technical Meeting
Manila, April 1-2, 2014
Acknowledgement