The Efficacy of Antiviral Therapy on the Regression of Liver Fibrosis in CHB

Jidong Jia, MD, PhD
Global annual mortality from hepatitis, HIV, tuberculosis and malaria 2000–2015:

Deaths from viral hepatitis, by virus and type of sequelae in 2015

VIRAL HEPATITIS B IN THE WORLD

WHO: GLOBAL HEPATITIS REPORT, 2017
Age-standardised disability-adjusted life-year rates attributable to HBV in 2013, by country

Hepatitis B

- <60.0
- 60.0-119.9
- 120.0-239.9
- 240.0-479.9
- 480.0-999.9
- ≥1000.0

Per 100 000 per year

DALY=伤残调整寿命年

## Etiology of the 8080 liver cirrhosis patients in southern China

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Total</th>
<th>Male</th>
<th>Female</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 8080)</td>
<td>(n = 6719)</td>
<td>(n = 1361)</td>
<td></td>
</tr>
<tr>
<td>Viral hepatitis</td>
<td>6514 (80.62)</td>
<td>5489 (81.69)</td>
<td>1025 (75.31)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>HBV</td>
<td>6239 (77.22)</td>
<td>5316 (79.12)</td>
<td>923 (67.82)</td>
<td></td>
</tr>
<tr>
<td>HCV</td>
<td>226 (2.80)</td>
<td>135 (2.01)</td>
<td>91 (6.69)</td>
<td></td>
</tr>
<tr>
<td>HBV + HDV</td>
<td>2 (0.02)</td>
<td>2 (0.03)</td>
<td>0 (0.00)</td>
<td></td>
</tr>
<tr>
<td>HBV + HCV</td>
<td>47 (0.58)</td>
<td>36 (0.54)</td>
<td>11 (0.81)</td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>459 (5.68)</td>
<td>451 (6.71)</td>
<td>8 (0.59)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Autoimmune</td>
<td>163 (2.03)</td>
<td>30 (0.43)</td>
<td>133 (9.77)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>AIH</td>
<td>54 (0.67)</td>
<td>13 (0.19)</td>
<td>41 (3.01)</td>
<td></td>
</tr>
<tr>
<td>PBC</td>
<td>87 (1.08)</td>
<td>15 (0.22)</td>
<td>72 (5.29)</td>
<td></td>
</tr>
<tr>
<td>AIH + PBC</td>
<td>19 (0.24)</td>
<td>1 (0.01)</td>
<td>18 (1.32)</td>
<td></td>
</tr>
<tr>
<td>PSC</td>
<td>3 (0.04)</td>
<td>1 (0.01)</td>
<td>2 (0.15)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>944 (0.12)</td>
<td>...........</td>
<td>...........</td>
<td></td>
</tr>
</tbody>
</table>

Natural history of chronic HBV infection

Acute HBV infection

95% infants\(^1\)  \rightarrow  5%-10% Adults\(^1\)

Chronic HBV infection

Chronic Hepatitis

HBeAg(+) : 8%-17% in 5y \(^2\)
HBeAg (-) : 13%-38% in 5y \(^2\)

Cirrhosis

3%-6% per y \(^1\)

HCC  \rightarrow  \approx 20% in 5y \(^2\)

Decompensation

HBV level is the major driver for disease progression

**REVEAL: Higher viral loads are associated with increased rate of cirrhosis**

- Baseline HBV DNA Level:
  - $\geq 1.0 \times 10^6$
  - $1.0-9.9 \times 10^5$
  - $1.0-9.9 \times 10^4$
  - $300-9.9 \times 10^3$
  - $<300$

Cumulative incidence of liver cirrhosis:
- Year of follow-up:
  - 0 1 2 3 4 5 6 7 8 9 10 11 12 13
  - 36.2%
  - 4.5%
  - RR=9.6

**REVEAL: Higher viral loads are associated with increased rate of HCC**

Cumulative incidence of HCC%:
- Year of follow-up:
  - 0 1 2 3 4 5 6 7 8 9 10 11 12 13
  - $>10^5\text{cpm}$ 15%
  - $10^5-10^6\text{cpm}$
  - $10^4-10^5\text{cpm}$
  - $300-10^4\text{cpm}$
  - $<300\text{cpm}$ 1.3%

Iloeje UH et al. Gastroenterology 2006; 130: 678–86.
HBV promotes expression of TGFβ by Kupffer

HBV-C, X proteins promote mRNA levels of PDGF/-R in HSCs (LX-2)

HBV increases collagen I expression in LX-2 HSCs

HBV Increase TGF-β mRNA Expression in LX-2 HSCs

HBV and liver fibrosis - a hypothesis

TLRs

HBV

TGF-β1, PDGF, IL-1β

巨噬细胞

星状细胞

肌成纤维细胞样细胞

Proliferation↑
ECM synthesis↑
ECM degradation↓

Th1/Th2

T 细胞

HBV and liver fibrosis hypothesis

Progression and regression of liver fibrosis

Fibrogenesis → Progression

Fibrolysis ← Regression
Strategies for antifibrotic therapies in CHB

- Effective causal treatment-antiviral therapy
- Prevention of HSC Activation and/or proliferation
- Inhibit fibrogenesis
- Promote resolution of fibrosis
  - Apoptosis and inactivation of HSCs
  - Degradation of extracellular matrix
# Reversal of Fibrosis: An Achievable Goal of Hepatitis B Antiviral Therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Agents</th>
<th>HBeAg</th>
<th>Biopsy/N</th>
<th>Treatment period</th>
<th>Cases achieved decrease of Ishak score (%)</th>
<th>Ishak 5-6, decrease ≥1 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dienstag et al. 2003</td>
<td>LAM</td>
<td>+</td>
<td>63/267</td>
<td>3</td>
<td>12/19 (63%)</td>
<td>8/11 (73%)</td>
</tr>
<tr>
<td>Rizzetto et al. 2005</td>
<td>LAM</td>
<td>-</td>
<td>48/76</td>
<td>3</td>
<td>8/18 (44%)</td>
<td>3/6 (50%)</td>
</tr>
<tr>
<td>Hadziyannis et al.2006</td>
<td>ADV</td>
<td>-</td>
<td>46/125</td>
<td>4-5</td>
<td>29/46 (63%)</td>
<td>3/4 (75%)</td>
</tr>
<tr>
<td>Chang et al. 2010</td>
<td>ETV</td>
<td>+/-</td>
<td>57/679</td>
<td>5</td>
<td>50/57 (88%)</td>
<td>4/10 (40%)</td>
</tr>
<tr>
<td>Marcellin et al. 2012</td>
<td>TDF</td>
<td>+/-</td>
<td>348/641</td>
<td>5</td>
<td>176/348 (51%)</td>
<td>71/96 (74%)</td>
</tr>
</tbody>
</table>

Antiviral therapy improved liver fibrosis in HBeAg-negative CHB patients

Long-term lamivudine treatment achieves regression of advanced liver fibrosis/cirrhosis in CHB patients

Telbivudine Treatment Improves Necroinflammation and Fibrosis in CHB

A: Knodell necroinflammatory score (%)
- Baseline (n=57): 16%, 4%, 51%, 20%
- Year 5 (n=57): 0%, 98%

B: Ishak fibrosis score (%)
- Baseline (n=57): 4%, 1%, 21%, 42%
- Year 5 (n=57): 0%, 37%, 21%, 42%

Telbivudine Treatment Results in Resolution of Liver Inflammation and Fibrosis in CHB

Improvement of Histology after TDF Therapy for 5 Years

348/641 (54%) with biopsy samples at year 5

Histological changes in cirrhotic CHB patients treated with TDF for 5 years

Histological outcomes in cirrhotic CHB patients treated with TDF for 240 wks

Decrease of Necroinflammation and Fibrosis Stage after Long-term Entecavir Therapy

(median: 5.6 yr, n=57)

Liver Fibrosis Regression Rate: Evaluated by Biopsy Before and After Treatment

Regress Study - 1
Liver Biopsy: S2/S3 (Liver Fibrosis)

- 2013 y
- Biopsy
- ETV

100 cases

Regress Study - 2
Liver Biopsy: S4 (Early Cirrhosis)

- 2013 y
- Biopsy
- ETV

50 cases

Beijing Friendship Hospital, CMU. “Optimized Treatment for Regression of HBV-related Liver Fibrosis or Cirrhosis”, supported by National Science and Technology Major Project (2013ZX10002004)
## TDF Recommended for HBV Therapy by Major Guidelines

<table>
<thead>
<tr>
<th>Organization</th>
<th>Year</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>AASLD</td>
<td>2015</td>
<td>PEG-IFN, TDF or ETV are preferred.</td>
</tr>
<tr>
<td>ASLM</td>
<td>2015</td>
<td>ETV, TDF, PEG IFN are the preferred</td>
</tr>
<tr>
<td></td>
<td>2015</td>
<td>ETV or TDF are the preferred NUCs for NUC-naïve CHB patients.</td>
</tr>
<tr>
<td>EASL</td>
<td>2017</td>
<td>ETV and TDF</td>
</tr>
<tr>
<td>NICE</td>
<td>2013</td>
<td>PEG-IFN /ETV/TDF first</td>
</tr>
<tr>
<td>WHO</td>
<td>2015</td>
<td>TDF, ETV</td>
</tr>
</tbody>
</table>
New Proposal on the Classification of Liver Fibrosis

Progression:
- CHB
- Fibrosis
- Cirrhosis

Regression:

Hepatology
Official Journal of American Association for the Study of Liver Diseases

New Classification of Liver Biopsy Assessment for Fibrosis in Chronic Hepatitis B Patients Before and After Treatment

New Proposal on the Classification of Liver Fibrosis

CHB → Fibrosis → Cirrhosis

Regression → Progression

On Beyond Staging and Grading: Liver Biopsy Evaluation in a Posttreatment World

David E. Kleiner, M.D., Ph.D.
Laboratory of Pathology, National Cancer Institute
Bldg 10, Room 2S235, MSC 1500
10 Center Dr.
Bethesda, MD 20892
E-mail: kleinerd@mail.nih.gov
Tel: +1-301-480-8487

### Post-treatment P-I-R Score versus Ishak Stage to Evaluate Disease Progress or Reverse

<table>
<thead>
<tr>
<th>Ishak (pre-post)</th>
<th>Post-treatment P-I-R score</th>
<th>n=71</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Progressive n=8</td>
<td>Indeterminate n=8</td>
</tr>
<tr>
<td>Increase, n=3</td>
<td>67% (2/3)</td>
<td>0</td>
</tr>
<tr>
<td>Stable, n=35</td>
<td>17% (6/35)</td>
<td>11% (4/35)</td>
</tr>
<tr>
<td>Decrease, n=33</td>
<td>0</td>
<td>12% (4/33)</td>
</tr>
</tbody>
</table>

Improve Liver Fibrosis after Long-Term Antiviral Therapy Assessed by Fibroscan in CHB Patients With Advanced Fibrosis

• NA-naive CHB with Lx ≥ F3, HBV DNA ≥ 2,000 IU/ml, & ALT < 2 × ULN
• LSM at baseline and annually for 5 years during antiviral therapy
• Five-year fibrosis improvement was defined as LS value < 7.2 kPa (<F3) at year 5.
• LSM changes: from baseline to year 1, 2, 3, 4 and 5.
  • 14.5 ➔ 11.3 ➔ 9.62 ➔ 9.3 ➔ 8.6 ➔ 8.3 kPa
• Patients with baseline LSM < 12.0 kPa had a greater probability of experiencing significant fibrosis improvement than those with baseline LSM ≥ 12.0 kPa (81.5% vs. 29.0%, P < 0.001).

Summary

• HBV may cause liver fibrosis through direct and indirect pathways

• Effective antiviral therapy is the currently available most efficacious anti-fibrotic therapy for CHB

• Antiviral therapy combined with novel therapeutic approaches may needed to treat advanced fibrosis/cirrhosis.
中国慢性肝病注册研究 (China Registry, CR)

- CHB
- Fibrosis
- Cirrhosis

中国乙肝注册系统–CR-HepB
- 参加单位47家
- 录入患者139,443例
- 随访患者521,672人次

中国遗传代谢性肝病注册网–CR-GMLD
- 开展12种基因检测：
  - 血色病
  - Wilson病
  - Gaucher病
  - 糖原累积症
  - PFIC
  - BRIC
  - Citrin缺乏症
- 为肝移植提供基因诊断依据
