Impact of antiviral therapy on the outcome of chronic hepatitis B

Yun-Fan Liaw

Liver Research Unit
Chang Gung Memorial Hospital
Chang Gung University College of Medicine
Taipei, Taiwan

6th Paris Hepatitis Conference
Paris, France, Jan 15 2013
Extended immune clearance phase leads to higher risk of cirrhosis and HCC

HBV DNA

HBeAg-positive

Anti-HBe-positive

Pre C/BCP
Wild type
Wild > Mutant
Mutant > Wild

HBsAg loss

Histology
Minimal
Active hepatitis
Minimal/inactive

Liver HBcAg
Nucleus
Nucleus/cytoplasm
Absent

ALT

Cirrhosis

HCC

Liaw & Chu Lancet 2009;373:582-592

HBV is the deriver!
Short-term impact in compensated CHB

HBe seroconversion

Undetectable HBV DNA

Normal ALT

EASL J Hepatol 2009;50:227-242
Lamivudine improves clinical, biochemical, virological markers and reduces need for OLT, prolongs survival in decompensated cirrhosis

*\( p < 0.05 \) compared with baseline

# Nuc therapy in hepatic decompensation

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug(s) used</td>
<td>ETV</td>
<td>ETV/ADV</td>
<td>TDF/TDF+ FTC/ETV</td>
<td>LdT/LAM</td>
<td>ETV/LAM</td>
<td>ETV/LAM</td>
</tr>
<tr>
<td>No. patients</td>
<td>70</td>
<td>100/91</td>
<td>45/45/22</td>
<td>114/114</td>
<td>45/41</td>
<td>53/73</td>
</tr>
<tr>
<td>CTP score</td>
<td>8.4</td>
<td>8.8/8.4&lt;sup&gt;g&lt;/sup&gt;</td>
<td>7/7/7&lt;sup&gt;b&lt;/sup&gt;</td>
<td>8.1/8.5&lt;sup&gt;c&lt;/sup&gt;</td>
<td>9.6/9.1</td>
<td>NR</td>
</tr>
<tr>
<td>MELD score</td>
<td>11.5</td>
<td>17.1/15.3</td>
<td>11/13/10.5</td>
<td>14.7/15.5</td>
<td>16.7/16.1</td>
<td>18.6/20.4</td>
</tr>
<tr>
<td>1-year survival, (%)</td>
<td>87</td>
<td>77/67</td>
<td>96/96/91</td>
<td>94/88</td>
<td>91/92</td>
<td>64/55</td>
</tr>
<tr>
<td>↓ CTP score ≥ 2, (%)</td>
<td>49</td>
<td>35/27</td>
<td>26/48/42</td>
<td>32/39</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>MELD score ↓</td>
<td>-2.2</td>
<td>-2.6/-1.7</td>
<td>-2/-2/-2</td>
<td>-1.0/-2.0</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

*The earlier the better!*
Decline in the Need for LT for ESLD Secondary to HBV in the US

1st Nuc approval in 1998

Kim WR. Hepatology. 2009;49:S28-S34
Impact of 1-yr Peg IFN on 3-5 yr serological outcomes

* **HBeAg seroconversion:** 37% at EOT; 60% at 5 yr

Wong VWS et al Hepatology 2010

---

**3 yr FU/Peg IFNα2b responders**

- Initial responders (%)
  - HBeAg negative: 81%
  - HBV DNA <10,000 cp/mL: 58%
  - HBV DNA <400 cp/mL: 45%
  - ALT normal: 78%
  - HBsAg negative: 30%

- Patients with HBsAg clearance (%)
  - Years after EOT:
    - 1: 11%
    - 2: 5%
    - 3: 6%
    - 4: 9%
    - 5: 11%

- Patients with HBsAg clearance overall: 12%

---

**HBeAg(-)/Peg IFNα2a**

- N=230
- Years after EOT:
  - 1: 5%
  - 2: 6%
  - 3: 9%
  - 4: 11%
  - 5: 12%

---

* 23% if qHBsAg ↓ ≥ 10% at wk 12, 28% if HBV DNA ≤ 2000 IU/mL 1yr after EOT

Buster et al. Gastroenterology 2008

Marcellin et al. APASL 2009; Hepatol Int 2012 (in press)
Long-term impact of IFN-based therapy

* HBeAg response and HBsAg loss increase over time
  
  Lampertico Hepatology 2003; van Zonneveld Hepatology 2004

* Cirrhosis reduced 35%
  
  Yang YF et al JVH 2009*

* HCC reduced 41% (49% in cirrhotics)
  
  Yang YF et al JVH 2009*

• only 1/230 or 1/55 F$_{3,4}$ HBeAg (-) patients developed HCC 3-yr after Peg IFN$_{\alpha2a}$ therapy
  
  Marcellin et al Gastroenterology 2009

* Liver death reduced 37% (80% in initial responders)
  
  Wong GLH Aliment Pharmacol Ther 2010*

* Meta-analysis
Maintained HBV suppression by ETV/TDF

ETV (Italy)

ETV (Hong Kong)

adapted from Plo & Lampertico JVH 2012;19:377-86
# Fibrosis regression during Nuc therapy

<table>
<thead>
<tr>
<th>Nucleos(t)ide</th>
<th>n</th>
<th>HBeAg</th>
<th>Duration</th>
<th>Fibrosis Regression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamivudine</td>
<td>63</td>
<td>+</td>
<td>3 yrs</td>
<td>33%</td>
</tr>
<tr>
<td>Entecavir</td>
<td>21</td>
<td>+/-</td>
<td>3 yrs</td>
<td>57%</td>
</tr>
<tr>
<td>Adefovir</td>
<td>15/24</td>
<td>+/-</td>
<td>5 yrs</td>
<td>60%/71%</td>
</tr>
<tr>
<td>Entecavir(^a)</td>
<td>57</td>
<td>+/-</td>
<td>6 yrs</td>
<td>88%</td>
</tr>
<tr>
<td>Tenofovir(^b)</td>
<td>348 (96(^b))</td>
<td>+/-</td>
<td>5 yrs</td>
<td>51% (74%(^b))</td>
</tr>
</tbody>
</table>

adapted from Liaw YF Liver Int 2013

a. ETV improved Ishak fibrosis (-1.53) \(\geq 2\) in 58% and in all 4 cirrhotics  
   Chang et al Hepatology 2010

b. Cirrhosis at baseline, \(\geq 2/3\) ↓ in 73/58%  
   Marcellin et al Lancet 2013
3-yr LAM therapy reduced disease progression but effect negated with LAMr

Liaw YF NEJM 2004; Sem Liver Dis 2005
Nuc therapy starting with LAM reduced complications in HBV-cirrhosis

Hepatic decompensation

145 (60.4%) of 240: HBeAg (+); Fu 46.4 mo

Cumulative survival rates

Duration (month)
LAM therapy reduced HCC in CHB

A systematic review: 3381 patients /21 studies

Papatheodoridis GV J Hepatol 2010;53:348
Maintained HBV suppression reduced HCC in HBeAg (-) cirrhosis

* 20 centers, Italy, 27 HCC in 303 patients / 1-66 mo

P<0.001

LAM alone

145 (60.4%) of 240: HBeAg (+); Fu 46.4 mo

P = 0.074

LAM±ADV

* HEPNET Greece cohort (209) Fu 4.5yr

P=0.327

LAM±ADV

Kim et al JGH 2012;27:1589-95

Papatheodoridis et al Gut 2011;60:1109-16
Cumulative development rates of HCC (%)

No cirrhosis

Cirrhosis

43% HBeAg (+)

"Propensity score matched controls"

Hosaka T et al Hepatology 2013 in press
Survival of ETV treated patients with compensated cirrhosis

* Kaplan-Meier estimates

Overall survival: 11 patients
Death for HCC: 2 patients
OLT for HCC: 4 patients

HCC=17
HCC rate/year: 2.8%
Decompensation rate/year: 0%

Complication-free survival (%)

Survival (%)

Months

 Patients at risk

155 153 149 145 135 125 115 105 92 58 20

Overall death: 11 patients
Death for HCC: 2 patients
OLT for HCC: 4 patients

Liver–related survival: 95%
Overall survival: 91%

Months

Patients at risk

155 154 151 147 142 133 124 111 98 61 21

* Kaplan-Meier estimates; OLT=death

83% HBeAg (-); Fu 53 mo

Courtesy of Lampertico P 2012 AASLD poster 366
Nuc therapy starting with LAM reduced mortality even in child B and C cirrhotic patients

40% HBeAg (-); Fu 46.4 mo

adapted from Kim et al JGH 2012;27:1589-95
HCC-free survival in ETV/ADV treated patients with hepatic decompensation

Survival

Time (weeks)

ETV 100/ADV 91

60%

ETV - Actual Data  ETV - fitted  ADV - Actual Data  ADV - fitted

Courtesy of Tsai N et al Clinicoecon Outcomes Res 2012;4:227)
Nuc therapy reduced post-resection HCC recurrence and mortality

A nation wide cohort study based on Taiwan National Health Insurance Research Database (99% coverage) 2003-2010

adapted from Wu CY et al JAMA 2012:308;1906-1913
Goals of therapy for chronic HBV infection

**short-term goal**
- Initial response
  - HBeAg(+) patients
  - Anti-HBe seroconversion
  - HBeAg loss
  - Prevent/rescue decompensation
  - HBV DNA undetectable
  - ALT normalization

**long-term goal**
- HBsAg clearance/conversion
  - Inactive HBsAg carrier
  - Durable response
    - Reduce progression
    - Prevent complications
    - Prolong survival

**TIME**

Adapted from Liaw YF et al Hepatol Int 2012;6:531-561

Goals achievable but not satisfactory!!