Management of Decompensated Chronic Hepatitis B

Dr James YY Fung, FRACP, MD
Department of Medicine
The University of Hong Kong
Liver Transplant Center
Queen Mary Hospital
State Key Laboratory for Liver Research
The University of Hong Kong
Natural History of HBV Cirrhosis

Active cirrhosis (HBV-DNA >2000 IU/ml)

Compensated cirrhosis

~10%/yr

Inactive cirrhosis

~1.5%/yr

HBsAg loss

~7 to 10%/yr

Acute flare of CHB

~4%/yr

Hepatitis flare

~14%

De-compensation

~15%/yr

Death/transplantation

~8%/yr

Hepatocellular carcinoma

~1%/yr

~6%/yr

~2%/yr

~10%/yr

?
Long term Benefits in Compensated Cirrhosis treated with Lamivudine

651 patients – 41 sites (Asia-Pacific) – Randomized 2:1 LAM:Placebo

All P values ≤ .05

- Placebo (n = 215)
- Lamivudine (n = 436)

- Overall Disease Progression: 18% Placebo, 8% Lamivudine
- CPT Increase: 9% Placebo, 3% Lamivudine
- HCC: 7% Placebo, 4% Lamivudine

Beneficial Effects of Antiviral Effects Diminished with Resistance

Antiviral Resistance in Oral Therapies in Chronic Hepatitis B

Cirrhotic patients and patients with decompensated liver disease are unlikely to tolerate further flares if resistance occurs.

Virological Response for ETV According to Severity of Liver Disease

Tenofovir vs Placebo in Acute on Chronic Liver Failure from HBV

Tenofovir (n=14) vs placebo (n=13)
INR > 1.5; bilirubin > 85 mmol/L, ascites/encephalopathy
Tenofovir vs Placebo in Acute on Chronic Liver Failure from HBV

A

HBV DNA reduction in Tenofovir Group
- ≥2 Log Reduction
- <2 Log Reduction

8

1

5

B

HBV DNA reduction in Placebo Group
- ≥2 Log Reduction
- <2 Log Reduction

0

2

7

Survived

Died

Survived

Died

Cumulative probability of survival (%)

Follow up in 90 days

P value <0.05 (Log rank test)

Number of patients:
- Tenofovir: 14
- Placebo: 13

TDF vs FTC + TDF vs ETV in HBV Pts With Decompensated Liver Disease

**Outcome at 48 weeks**

<table>
<thead>
<tr>
<th></th>
<th>TDF (n = 45)</th>
<th>TDF/FTC (n = 45)</th>
<th>ETV (n = 22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV DNA &lt;400 cpm</td>
<td>71%</td>
<td>88%</td>
<td>73%</td>
</tr>
<tr>
<td>Median log HBV DNA</td>
<td>3.11</td>
<td>3.92</td>
<td>3.40</td>
</tr>
<tr>
<td>Child Pugh score ≥2</td>
<td>26%</td>
<td>48%</td>
<td>42%</td>
</tr>
<tr>
<td>Median MELD score</td>
<td>-2</td>
<td>-2</td>
<td>-2</td>
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</tbody>
</table>

Viral suppression and Mortality in Decompensated Cirrhosis treated with ETV

70 patients with HBV decompensated cirrhosis treated with ETV 0.5mg

Shim JH et al. J Hepatol 2010;52:176-182
Changes in CTP and MELD Score at 12 Months with ETV

Shim JH et al. J Hepatol 2010;52:176-182
ETV vs ADV in CHB Decompensation – Randomized Open Label Study

- Primary efficacy endpoint: mean reduction in serum HBV DNA at Wk 24

Liaw YF et al. Hepatology 2011;54:91-100
ETV vs ADV in CHB Decompensation – Randomized Open Label Study

Mean HBV DNA (log_{10} copies/mL)

Treatment (Wks)

Limit of detection 300 copies/mL

$P < .0001$

-3.40

-4.48

Patients With Measurements

ETV 100 98 92 87 76 71 69
ADV 91 88 80 80 73 66 61
ETV vs ADV in CHB Decompensation – Randomized Open Label Study

1 ETV patient had lactic acidosis

<table>
<thead>
<tr>
<th></th>
<th>ADV (N=91)</th>
<th>ETV (N=100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Δ MELD score (median)</td>
<td>-1.7</td>
<td>-2.6</td>
</tr>
<tr>
<td>↓ CPT score ≥2 pts</td>
<td>27%</td>
<td>35%</td>
</tr>
</tbody>
</table>
ETV vs LAM in Decompensated CHB
ALT normalization & HBV DNA suppression

*Retrospective study on Decompensated HBV*
Hyperbilirubinemia >2x ULN
Coagulopathy (Prolonged >3 secs)
Antiviral therapy with LAM/ETV >1 week

\[ P = 0.06 \]

\[ \begin{array}{ccc}
\text{ALT normalization} & \text{HBV DNA undetectability} \\
\text{LAM} & 21/40 & 26/34 \\
\text{ETV} & 7/12 & 8/8 \\
\end{array} \]

\[ P = 0.05 \]

Hsu YC et al, 2012. Antiviral Ther; doi:10.3851/IMP2027
ETV vs LAM in Decompensated CHB
Overall Survival & Liver-Related Mortality

Hsu YC et al, 2012. Antiviral Ther; doi:10.3851/IMP2027
ETV & LAM in Severe Acute Flares of CHB

ALT >10x ULN, Br >3x ULN
ETV (n=36)
LAM (n=117)

Wong VWS et al. J Hepatol 2011(54):236-242
ETV & LAM in Severe Acute Flares of CHB

Outcomes

Overall Survival

Liver-related Mortality

Wong VWS et al. J Hepatol 2011(54):236-242
ETV & LAM in Severe Acute Flares of CHB Deaths Within 48 Weeks

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender/Age</th>
<th>Treatment</th>
<th>Cirrhosis</th>
<th>Baseline ALT (IU/L)</th>
<th>Bilirubin (μmol/L)</th>
<th>INR</th>
<th>MELD score</th>
<th>HBV DNA (log copies/ml)</th>
<th>Survival (Weeks)</th>
<th>Cause of death</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M/70</td>
<td>Entecavir</td>
<td>No</td>
<td>2290</td>
<td>325</td>
<td>3.95</td>
<td>35</td>
<td>8.68</td>
<td>0.6</td>
<td>Liver failure</td>
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<tr>
<td>2</td>
<td>M/48</td>
<td>Entecavir</td>
<td>No</td>
<td>282</td>
<td>194</td>
<td>1.09</td>
<td>18</td>
<td>3.51</td>
<td>16.3</td>
<td>Pancreatic cancer</td>
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<tr>
<td>3</td>
<td>M/61</td>
<td>Entecavir</td>
<td>No</td>
<td>285</td>
<td>601</td>
<td>2.07</td>
<td>28</td>
<td>3.33</td>
<td>2.4</td>
<td>Liver failure</td>
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<tr>
<td>4</td>
<td>F/55</td>
<td>Entecavir</td>
<td>No</td>
<td>2180</td>
<td>251</td>
<td>4.15</td>
<td>33</td>
<td>8.91</td>
<td>3.3</td>
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<tr>
<td>5</td>
<td>F/70</td>
<td>Entecavir</td>
<td>No</td>
<td>1105</td>
<td>331</td>
<td>3.08</td>
<td>32</td>
<td>8.37</td>
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<tr>
<td>6</td>
<td>M/57</td>
<td>Entecavir</td>
<td>Yes</td>
<td>908</td>
<td>55</td>
<td>1.27</td>
<td>14</td>
<td>9.83</td>
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<tr>
<td>7</td>
<td>M/52</td>
<td>Entecavir</td>
<td>Yes</td>
<td>377</td>
<td>89</td>
<td>1.24</td>
<td>15</td>
<td>7.30</td>
<td>20.3</td>
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<tr>
<td>8</td>
<td>F/79</td>
<td>Lamivudine</td>
<td>Yes</td>
<td>278</td>
<td>102</td>
<td>2.17</td>
<td>22</td>
<td>6.26</td>
<td>16.3</td>
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<tr>
<td>9</td>
<td>M/45</td>
<td>Lamivudine</td>
<td>No</td>
<td>2210</td>
<td>205</td>
<td>1.88</td>
<td>23</td>
<td>7.42</td>
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<tr>
<td>10</td>
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<td>Lamivudine</td>
<td>Yes</td>
<td>1552</td>
<td>322</td>
<td>2.09</td>
<td>26</td>
<td>9.43</td>
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<tr>
<td>11</td>
<td>M/42</td>
<td>Lamivudine</td>
<td>No</td>
<td>1513</td>
<td>166</td>
<td>3.19</td>
<td>41</td>
<td>9.32</td>
<td>11.4</td>
<td>Liver failure</td>
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<tr>
<td>12</td>
<td>M/44</td>
<td>Lamivudine</td>
<td>No</td>
<td>2100</td>
<td>195</td>
<td>1.93</td>
<td>23</td>
<td>8.15</td>
<td>23.3</td>
<td>Acute myeloid leukemia</td>
</tr>
</tbody>
</table>

ALT, alanine aminotransferase; HBV, hepatitis B virus; INR, international normalized ratio; MELD, Model for End-stage Liver Disease.
**ETV & LAM in Severe Acute Flares of CHB**

**Factors Associated with Deaths Within 48 Weeks**

Wong VWS et al. J Hepatol 2011(54):236-242

<table>
<thead>
<tr>
<th>Liver-related mortality</th>
<th>Univariate</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th>Multivariate</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Hazard ratio</td>
<td>95% CI</td>
<td>P-value</td>
<td>Hazard ratio</td>
<td>95% CI</td>
<td>P-value</td>
<td></td>
<td></td>
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<tr>
<td>Age (years)</td>
<td>1.07</td>
<td>1.02-1.12</td>
<td>0.004</td>
<td></td>
<td>1.05</td>
<td>1.00-1.11</td>
<td>0.058</td>
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<td></td>
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<tr>
<td>Male gender</td>
<td>0.29</td>
<td>0.082-1.03</td>
<td>0.056</td>
<td></td>
<td>1.00</td>
<td>1.00-1.00</td>
<td>0.58</td>
<td></td>
<td></td>
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<tr>
<td>Baseline ALT (IU/L)</td>
<td>1.00</td>
<td>1.00-1.00</td>
<td>0.58</td>
<td></td>
<td>1.00</td>
<td>1.00-1.01</td>
<td>0.56</td>
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<tr>
<td>Baseline bilirubin (μmol/L)</td>
<td>1.00</td>
<td>1.00-1.01</td>
<td>0.038</td>
<td></td>
<td>1.00</td>
<td>1.00-1.01</td>
<td>0.56</td>
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</tr>
<tr>
<td>Baseline albumin (g/L)</td>
<td>0.91</td>
<td>0.82-1.00</td>
<td>0.057</td>
<td></td>
<td>4.2</td>
<td>2.1-8.5</td>
<td>&lt;0.001</td>
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<tr>
<td>Baseline INR</td>
<td>6.4</td>
<td>3.3-12.5</td>
<td>&lt;0.001</td>
<td></td>
<td>4.2</td>
<td>2.1-8.5</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
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<tr>
<td>Baseline HBeAg</td>
<td>0.14</td>
<td>0.017-1.06</td>
<td>0.057</td>
<td></td>
<td>1.17</td>
<td>0.78-1.76</td>
<td>0.46</td>
<td></td>
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</tr>
<tr>
<td>Baseline HBV DNA (log copies/ml)</td>
<td>1.17</td>
<td>0.78-1.76</td>
<td>0.46</td>
<td></td>
<td>2.8</td>
<td>0.79-9.9</td>
<td>0.11</td>
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<tr>
<td>Cirrhosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5.2</td>
<td>1.5-18.6</td>
<td>0.010</td>
<td>4.0</td>
<td>1.0-15.7</td>
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<tr>
<td>Antiviral therapy</td>
<td></td>
<td>Referent</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lamivudine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Entecavir</td>
<td>5.2</td>
<td>1.5-18.6</td>
<td>0.010</td>
<td></td>
<td>4.0</td>
<td>1.0-15.7</td>
<td>0.044</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time from presentation to starting antiviral drugs (days)</td>
<td>0.97</td>
<td>0.80-1.17</td>
<td>0.73</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
Could there be a possible cause for mortality associated with ETV use?

Severe Lactic Acidosis During Treatment of Chronic Hepatitis B with Entecavir in Patients with Impaired Liver Function

Christian M. Lange, Jörg Bojunga, Wolf Peter Hofmann, Katrin Wunder, Ulrike Mihm, Stefan Zeuzem, and Christoph Sarrazin

- 16 patients with HBV cirrhosis treated with ETV
  - 5 developed lactic acidosis
- The MELD score (and not CPS) correlated with development of lactic acidosis
  - All had MELD >18
  - All had impaired CrCl
- Important to dose-adjust for renal impairment

TDF vs FTC + TDF vs ETV in HBV Pts With Decompensated Liver Disease

- No cases of lactic acidosis reported in any treatment arm

LDT & LAM in Decompensated CHB Clinical Response

Multicenter Phase III Randomized Double Blind Trial
Cirrhotics with CTP score $\geq 7$, HBV DNA $\geq 5$ log cpm

LDT & LAM in Decompensated CHB
Overall Survival

![Survival Rate Graph]

- Survival rates at key weeks:
  - Week 104: Lamivudine 87%, Telbivudine 79%
  - Week 84: Lamivudine 85%, Telbivudine 85%
  - Week 48: Lamivudine 92%, Telbivudine 88%
  - Week 24: Lamivudine 96%

- Sample sizes:
  - Lamivudine: 116
  - Telbivudine: 115

- Statistical comparison:
  - $P = 0.16$ (log-rank test)

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Chan HLY et al., 2012. J Viral Hep; doi:10.1111/j.1365-2893.2012.01600.x
LDT & LAM in Decompensated CHB

Renal Function

Biphasic Pattern of Survival in Decompensated HBV Patients

154 HBV decompensated patients treated with LAM
6-month survival independent of early treatment efficacy

Poor Survival
↑Br
↑Cr
↑HBV DNA

Fontana RJ et al. Gastroenterology 2002;123:719-727
Oral Therapy in Decompensated HBV Cirrhosis
1 year survival

Fontana RJ et al. Gastroenterology 2002;123:719-727
Schiff ER et al. Liver Transplant 2007;13:349-360
Schiff ER et al. Hepatology 2009;50:222 (Abstract)
Shim et al. J Hepatol 2010;52:176-182

*Non-head to head comparisons
LAM and ETV in Decompensated Cirrhosis

86 HBV decompensated patients (CTP ≥7) Treated with either LAM or ETV

**No difference in early mortality rates**

Clinical Events for those with Cirrhosis and Without Virological Response

N=372 ETV treated patients
Clinical events = HCC, decompensation, death

HBV DNA threshold of 2000 IU/mL was not associated with lower disease progression in cirrhotic patients

HBV Cirrhosis
Who Do We Treat?

Liver cirrhosis

Compensated

- HBV-DNA < 2 x 10^3 IU/ml
  - ALT, HBeAg or HBV-DNA /3 months

- HCC surveillance
  - AFP and ultrasonography /3-6months

Decompensated

- HBV-DNA ≥ 2 x 10^3 IU/ml
  - ALT ≥ 5X ULN
    - Yes
      - ETV
      - TDF
    - No
      - IFN based
      - ETV
      - TDF

Conventional supportive treatment

Antiviral therapy
Consider transplant

ETV
TDF
Treatment of Decompensated CHB Summary I

• The short term outcome is not likely to be altered by antiviral therapy
  – Determined by underlying liver reserve

• IFN-based therapy are contraindicated

• Oral NAs are comparable in
  – Reducing viral load
  – Improving MELD score and CTP score
  – Short term survival
Treatment of Decompensated CHB Summary II

• All cirrhotics who are HBsAg+ should be considered for treatment

• Treatment should be lifelong

• Treat with a highly potent antiviral agent with high genetic barrier to resistance
  – Patients unlikely to tolerate any further breakthrough flares
  – Selection of mutant strains likely to limit choice of further treatment
Treatment of Decompensated CHB
Summary III

• Early referral to a transplant unit is recommended for those with evidence of decompensation
  – ↑Br, ↑Cr, ↑INR, ↑HBV DNA
  – Hepatic encephalopathy

Thank You