Cornerstones of Hepatitis B: Past, Present and Future

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The University of Hong Kong
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Outline

• Past
  • Natural history studies
    • Development of HBV-related complications
    • Treatment Endpoints
  • Therapeutic options

• Present
  • Effects of long-term treatment

• Future
  • Treatment goals
  • New treatment options
• Past
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Difference Phases Of CHB: Development Of Complications

- Healthy/ asymptomatic carriers
  - If persistent HBeAg +ve: complications will develop
  - No risk
HBeAg Seroconversion To Anti-HBe

- 11,893 Taiwan males; FU 92,359 person-years

**Relative risk of developing HCC**

<table>
<thead>
<tr>
<th>Cumulative incidence (%)</th>
<th>Years</th>
<th>HBsAg+, HBeAg+</th>
<th>HBsAg+, HBeAg-</th>
<th>HBsAg-, HBeAg-</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>60.2*</td>
<td>9.6*</td>
<td>1*</td>
</tr>
</tbody>
</table>

* p<0.001

- HBeAg / anti-HBe status only on entry to study, NOT at time of HCC development.

Natural History Of CHB

• A study with 3,233 CHB patients in Hong Kong
  • All were asymptomatic without complications on presentation
  • Median age: 38 yrs
  • HBeAg: anti-HBe ratio 1: 1.5
  • Mean follow up: 46.9 months
    • 307 (10%) had FU > 10 yrs

HBeAg Seroconversion To Anti-HBe

- Development of cirrhosis complications and HCC
  - 3,233 Chinese patients
  - Mean follow-up 46.9 months

<table>
<thead>
<tr>
<th>Condition</th>
<th>Median age in yrs</th>
<th>% anti-HBe</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBeAg seroconversion</td>
<td>35</td>
<td>-</td>
</tr>
<tr>
<td>All complications</td>
<td>57.2</td>
<td>73.5%</td>
</tr>
<tr>
<td>Ascites</td>
<td>57.7</td>
<td>68.8%</td>
</tr>
<tr>
<td>SBP</td>
<td>60.0</td>
<td>76.7%</td>
</tr>
<tr>
<td>Varices</td>
<td>54.3</td>
<td>76.3%</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>58.5</td>
<td>65.0%</td>
</tr>
<tr>
<td>HCC</td>
<td>59.0</td>
<td>81.1%</td>
</tr>
</tbody>
</table>

HBV DNA Level And HCC

Yuen MF et al., J Hepatol 2009;50:80-8

N = 820

Cumulative risk of HCC

HBV DNA levels (log)

≥6
5 - 5.99
4 - 4.99
<3 logs or 3 - 3.99

p=0.028

Months of follow-up

0 12 24 36 48 60 72 84 96 108 120
Natural History Of Chronic Hepatitis B: Update

Decade of life | 1st – 3rd | 3rd – 5th | 4th – 5th onwards
---|---|---|---
Disease phase | Immune tolerant | Immune clearance | Residual

HBsAg +ve

HBeAg + ve

HBeAg - ve

HBV DNA

ALT

Occult hepatitis B

Cirrhosis and HCC

Reactivation

Hepatitis flare

Death

Modified from Yuen MF, occult hepatitis B infection, Hepatitis B Virus and Liver Disease
Endpoints In Chronic Hepatitis B Treatment

**Virologic response**
1) ↓ HBV DNA to undetectable
2) ↓ cccDNA

**Biochemical and liver synthetic test improvement**
ALT, bilirubin, albumin

**Serologic responses**
HBeAg loss/ seroconversion
HBsAg loss/seroconversion

**Histologic improvement**

**Aims:**
Prevent progression to cirrhosis, HCC and death

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Long Term Effects Of Interferon Treatment
Prevention Of HCC By IFN In CHB

- 208 IFN-treated vs. 203 controls
- Median follow up 107 vs. 108 months
  - HCC in 7 IFN-treated patients and none in controls (p=NS)

Prevention Of HCC By IFN In CHB

Prevention Of HCC By IFN In CHB

- Prevention of HBV-related HCC
  - Interferon vs. no treatment
    - 10 studies: only 3 showed some improvement; 7 showed NO difference

- Conclusion: inconsistent results; beneficial effect of IFN possibly in responders (ie, ~30%) with pre-existing cirrhosis

Lai CL, Yuen MF. Hepatology 2013;57:399–408.
Long Term Effects Of First Generation Of Nucleoside Analog Treatment
Prevention Of HCC By Lamivudine In CHB

## Prevention Of HCC By Lamivudine In CHB

<table>
<thead>
<tr>
<th>Study, Year (Reference)</th>
<th>Nucleotide/side analogues n/N</th>
<th>Placebo / no treatment n/N</th>
<th>RR (random) 95% CI</th>
<th>RR (random) 95% CI</th>
<th>Years of follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liaw, 2004 (29)</td>
<td>17/436</td>
<td>16/215</td>
<td>0.52 [0.27, 1.02]</td>
<td>0.22 [0.10, 0.50]</td>
<td>2.7</td>
</tr>
<tr>
<td>Matsumoto, 2005 (30)</td>
<td>4/377</td>
<td>50/377</td>
<td>0.08 [0.03, 0.22]</td>
<td></td>
<td>2.7</td>
</tr>
<tr>
<td>Papatheodoridis, 2005 (31)</td>
<td>5/201</td>
<td>15/195</td>
<td>0.32 [0.12, 0.87]</td>
<td></td>
<td>3.8</td>
</tr>
<tr>
<td>Yuen, 2007 (32)</td>
<td>1/142</td>
<td>3/124</td>
<td>0.29 [0.03, 2.76]</td>
<td></td>
<td>8.2</td>
</tr>
<tr>
<td>Eun, 2007 (33)</td>
<td>5/111</td>
<td>36/111</td>
<td>0.14 [0.06, 0.34]</td>
<td></td>
<td>4.4</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>1267</strong></td>
<td><strong>1022</strong></td>
<td><strong>0.22 [0.10, 0.50]</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 32 (Nucleotide/side analogues), 120 (Placebo/no treatment)

Test for heterogeneity: $\chi^2 = 12.57$, df = 4 ($P = 0.01$), $I^2 = 68.2$

Test for overall effect: $Z = 3.65$ ($P = 0.0003$)

Nucleos(t)ide Analogs

• Prevention of HBV-related HCC

  • Lamivudine/adeovir vs. no treatment:
    • 5 studies: ALL showed beneficial effects

  • Conclusion: consistent reduction of HCC in patients with and without cirrhosis (effect blunted but still present with resistance development)

Lai CL, Yuen MF. Hepatology 2013;57:399–408.
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Long Term Effects Of More Potent Nucleoside Analogs
Rates Of Virologic Suppression, HBeAg Seroconversion, ALT Normalization And Genotypic Resistance – 7-year Entecavir Data

ALT=alanine aminotransferase; HBeAg=hepatitis B envelop antigen.

Lam FY…Yuen MF. manuscript submitted.
ETV Reduced HCC Incidence

- ETV therapy reduced the 5-year HCC risk by > 60% compared with control group

- Multivariate Cox regression analysis:* HR 0.37 (95% CI 0.15–0.91); P = 0.030

Risk Of HCC Is Predicted To Be Decreased With Long-term TDF

Kim WR et al., Cancer 2015;121:3631-8.

<table>
<thead>
<tr>
<th>Time of Incident</th>
<th>Cumulative HCC Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Predicted</td>
</tr>
<tr>
<td>Week (Year)</td>
<td></td>
</tr>
<tr>
<td>17.3 (0.33)</td>
<td>0.74</td>
</tr>
<tr>
<td>28.1 (0.54)</td>
<td>1.19</td>
</tr>
<tr>
<td>46.1 (0.88)</td>
<td>1.92</td>
</tr>
<tr>
<td>111.7 (2.14)</td>
<td>5.03</td>
</tr>
<tr>
<td>172.3 (3.30)</td>
<td>6.79</td>
</tr>
<tr>
<td>206.0 (3.95)</td>
<td>8.63</td>
</tr>
<tr>
<td>242.4 (4.65)</td>
<td>11.45</td>
</tr>
<tr>
<td>318.1 (6.10)</td>
<td>16.62</td>
</tr>
<tr>
<td>End of week 384b</td>
<td>20.11</td>
</tr>
</tbody>
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<tr>
<td></td>
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</tr>
<tr>
<td>Week (Year)</td>
<td></td>
</tr>
<tr>
<td>50.0 (0.96)</td>
<td>1.17</td>
</tr>
<tr>
<td>113.9 (2.18)</td>
<td>2.91</td>
</tr>
<tr>
<td>114.1 (2.19)</td>
<td>2.92</td>
</tr>
<tr>
<td>124.6 (2.39)</td>
<td>3.04</td>
</tr>
<tr>
<td>174.6 (3.35)</td>
<td>4.02</td>
</tr>
<tr>
<td>194.1 (3.72)</td>
<td>4.67</td>
</tr>
<tr>
<td>End of week 384b</td>
<td>11.67</td>
</tr>
</tbody>
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Treatment Goals

1) Entering disease residual phase $\rightarrow$ HBeAg seroconversion

2) Total elimination of HBV $\rightarrow$ no covalently closed circular (ccc) DNA

3) Functional cure $\rightarrow$ loss of HBsAg
cccDNA reduction/ elimination
cccdna Reduction On Long Term Nucleoside Treatment

HbsAg Seroclearance: Development Of Complications

HBsag Sero clearance As Endpoint

- Treatment guidelines from APASL, EASL and AASLD all agree that this is the optimal endpoint
The new treatment paradigm is to continue CHB treatment until HBsAg seroclearance is achieved for both HBeAg-positive and HBeAg-negative CHB patients.

## HBsAg Loss With Current Therapies

<table>
<thead>
<tr>
<th>Drug</th>
<th>At 1 Year</th>
<th>At 2 Years</th>
<th>At 3-10 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamivudine</td>
<td>0%</td>
<td>2.8%</td>
<td>10% (10 years)</td>
</tr>
<tr>
<td>Entecavir</td>
<td>0%</td>
<td>5.1% *</td>
<td></td>
</tr>
<tr>
<td>Telbivudine</td>
<td>-</td>
<td>-</td>
<td>6% (3 years)</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>3%</td>
<td>6%</td>
<td>12% (7 years)</td>
</tr>
<tr>
<td>Peginterferon</td>
<td>3-7%</td>
<td>-</td>
<td>8% (3 years)</td>
</tr>
<tr>
<td>Teno + PegIFN</td>
<td>9.1%</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

* Continuous treatment stopped at year 2
Decades Of NA Treatment Are Required Before Patients Achieve HBsAg Loss...

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Investigational Drugs Enhancing HBsAg Seroclearance
HBV Life Cycle And Therapeutics Currently Undergoing Clinical Trials In Humans

- **cccDNA inhibitors:** Pending clinical studies
- **Entry inhibitors:** Myrcludex B
- **Nucleos(t)ide analogues:** Already available
- **Nucleocapsid assembly inhibitors:** NVR 3-778, JNJ379, GLS4
- **HBsAg release inhibitors:** REP 2139, GC 1102

**Immune modulation:**
- **Therapeutic vaccines**
  - GS-4774
  - ABX-203
  - TG-1050
  - INR-1800
  - FP-02.2
- **Others**
  - GS-9620
  - SR-9200
  - AIC649
  - Birinapant

**mRNA silencers:**
- siRNA
- ARC-520
- ARBi-1467
- **Others**
  - GSK3228836
  - RO7020322

Seto WK & Yuen MF. Clinical Liver Disease 2016 (in press).
siRNA (ARC-502)—Reduction in HBsAg in Treatment Naive CHB Patients: A Single Dose of 4 mg/kg

Final Goal: Possible Future Curative Regimen For CHB

- **Nucleos(t)ide analogue**
  - To control viral replication and cccDNA re-amplification

- **Viral antigen inhibitor**
  - To inhibit HBV life cycle processes (e.g. entry, mRNA transcription, capsid assembly, viral protein secretion)

- **Immune modulation**
  - To activate or restore HBV targeting immune responses

- **cccDNA inhibitor**
  - To silence or eliminate cccDNA

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**Functional cure**

**Complete cure?**

*Seto WK & Yuen MF. Clinical Liver Disease 2016 (in press).*
Conclusions

• Past:
  – Natural history of chronic hepatitis B was better defined
  – Nucleos(t)ide analog (NA) treatment was a great milestone of drug development for chronic hepatitis B

• Present:
  – Long-term NA treatment is very effective in reducing the risk of development of complications from the disease

• Future:
  – Drug development programs to enhance HBsAg seroclearance are actively underway
Thank you!!