The long term impact of NA treatment on the outcome of liver disease in CHB

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Hepatitis Research Center, 
Department of Internal Medicine, 
National Taiwan University College of Medicine and Hospital
Outline

• Current treatment of CHB
• Impact of long-term NA therapy on HCC reduction in Asian CHB patients
  – Japan
  – Hong Kong
  – Korea
• C-TEAM (Taiwan)
• Perspectives
Clinical goals of CHB therapy

- Mortality reduction
- Transplant need reduction
- HCC reduction
- Cirrhosis reduction
- Fibrosis regression
- HBsAg seroclearance
- Histologic improvement
- HBeAg loss/seroconversion (HBeAg-positive patient only)
- HBV DNA negativity
- ALT normalization

Su and Kao. ERGH 2014.
<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
<th>Manufacturer</th>
<th>Date Approved for Hepatitis B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interferon alfa</td>
<td>INTRON® A ROFERON ®</td>
<td>Schering Hoffman La-Roche</td>
<td>1991</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>ZEFFIX®</td>
<td>GlaxoSmithKline</td>
<td>1998</td>
</tr>
<tr>
<td>Adefovir dipivoxil</td>
<td>HEPSERA™</td>
<td>GlaxoSmithKline</td>
<td>2002</td>
</tr>
<tr>
<td>*Entecavir</td>
<td>BARACLUDE™</td>
<td>Bristol-Myers Squibb</td>
<td>2005</td>
</tr>
<tr>
<td>*Peginterferon alfa-2a</td>
<td>PEGASYS®</td>
<td>Hoffman La-Roche</td>
<td>2005</td>
</tr>
<tr>
<td>Telbivudine</td>
<td>SEBIVO™</td>
<td>Novartis</td>
<td>2006</td>
</tr>
<tr>
<td>*Tenofovir</td>
<td>VIREAD™</td>
<td>Gilead Sciences</td>
<td>2008</td>
</tr>
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</table>

*Preferred agents
# High virological responses with long-term ETV or TDF

<table>
<thead>
<tr>
<th>Response</th>
<th>ETV</th>
<th>TDF</th>
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<tbody>
<tr>
<td></td>
<td>HBeAg+ Patients Year 5&lt;sup&gt;1&lt;/sup&gt;</td>
<td>HBeAg+ Patients Year 7&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>HBeAg- Patients Year 3&lt;sup&gt;2&lt;/sup&gt;,&lt;sup&gt;a&lt;/sup&gt;</td>
<td>HBeAg- Patients Year 7&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td>HBV DNA suppression&lt;sup&gt;b&lt;/sup&gt;</td>
<td>94% (88/94)</td>
<td>99% (159/160)</td>
</tr>
<tr>
<td></td>
<td>95% (54/57)</td>
<td>99% (271/273)</td>
</tr>
<tr>
<td>Resistance</td>
<td>1% (n=1)</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>HBsAg loss (seroconversion)</td>
<td>1.4% (0%)</td>
<td>12% (10%)</td>
</tr>
<tr>
<td></td>
<td>NR</td>
<td>&lt;1% (&lt;1)</td>
</tr>
</tbody>
</table>

*Neither Truvada (TVD=TDF + FTC) nor emtricitabine (FTC) are licensed for use in CHB; <sup>a</sup>ETV re-treatment (relapsed <6 months post-treatment in ETV-027 study);<sup>b</sup>TDF: HBV DNA <400 copies/mL, ETV: HBV DNA <300 copies/mL; HBeAg: hepatitis B e antigen; NR: not reported; ETV: entecavir; TDF: tenofovir disoproxil fumarate

Not head to head trials

3. Marcellin P et al. AASLD 2013 Abstract 926
Table 2. The histologic improvement and fibrosis regression after prolonged nucleos(t)ide analog therapy.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Lamivudine</th>
<th>Adefovir</th>
<th>Entecavir</th>
<th>Tenofovir</th>
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<tbody>
<tr>
<td>Treatment duration (year)</td>
<td>3</td>
<td>4–5</td>
<td>3–7</td>
<td>5</td>
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<tr>
<td>Patient number</td>
<td>63</td>
<td>45</td>
<td>57</td>
<td>348</td>
</tr>
<tr>
<td>HAI necroinflammatory score †</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improvement</td>
<td>56%</td>
<td>83–86%</td>
<td>96%</td>
<td>87%</td>
</tr>
<tr>
<td>Progression</td>
<td>11%</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Bridging fibrosis ‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improvement</td>
<td>63%</td>
<td>73–75%</td>
<td>88%</td>
<td>51%</td>
</tr>
<tr>
<td>Progression</td>
<td>9%</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Advanced fibrosis/cirrhosis ‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improvement</td>
<td>73%</td>
<td>NA</td>
<td>100%</td>
<td>74%</td>
</tr>
<tr>
<td>Progression</td>
<td>2%</td>
<td>NA</td>
<td>NA</td>
<td>1%</td>
</tr>
</tbody>
</table>

†Histologic improvement is defined as ≥2 point reduction in Knodell necroinflammatory score with no worsening of fibrosis.
‡The regression of fibrosis is defined as ≥1 unit decrease by Ishak scoring system.
HAI: Histology activity index; NA: Not available.
Entecavir-treated patient with serial liver biopsies
Outline

• Current treatment of CHB
• Impact of long-term NA therapy on HCC reduction in Asian CHB patients
  – Japan
  – Hong Kong
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• Perspectives
Antiviral agents delay disease progression


Placebo (n=215)

Lamivudine (n=221)

21%, Wild-type

5%, Wild-type

Patients with disease progression, %

Months after randomisation

Pooled data from 5 studies showed about four-fold reduction of HCC in NA group (2.5%) against the control group (11.7%).

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

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

Test for heterogeneity: \( \chi^2 = 12.57, \text{df} = 4 (P = 0.01) \), \( P = 68.2\% \)

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

• Current treatment of CHB
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HCC incidence is lower in patients treated with ETV vs. control

All patients

Cirrhotics

Hosaka et al. Hepatology
Outline

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Entecavir therapy reduces clinic events in cirrhotic patients

Hepatocellular carcinoma

Changes in risk scores and HCC

CU-HCC

- 5 at both time points (P<0.001)
- 5 at baseline and <5 at 2 years (P=0.002)
- <5 at baseline (referent)

GAG-HCC

- 101 at both time points (P<0.001)
- 101 at baseline and <101 at 2 years (P=0.07)
- <101 at baseline (referent)

REACH-B

- 8 at both time points
- <8 at baseline and/or 2 years (P=0.06)
Outline

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  – Korea
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Mortality, Liver Transplantation, and Hepatocellular Carcinoma Among Patients With Chronic Hepatitis B Treated With Entecavir vs Lamivudine

Young-Suk Lim,1 Seungbong Han,2 Nae-Yun Heo,3 Ju Hyun Shim,1 Han Chu Lee,1 and Dong Jin Suh1

1Department of Gastroenterology, Liver Center, 2Department of Clinical Epidemiology and Biostatistics, Asan Medical Center, Seoul, Republic of Korea; 3Department of Internal Medicine, Haeundae Paik Hospital, Inje University College of Medicine, Busan, Republic of Korea

9615 patients were consecutively treated with entecavir (0.5 mg/day) or lamivudine (100 mg/day) for hepatitis B between November 1999 and December 2011 (Source Population).

6525 started treatment with lamivudine

3151 were excluded
- 203 had age < 20 years or > 80 years
- 735 died within 6 months of treatment
- 228 received transplantation within 6 months of treatment
- 90 had HCC within 12 months of treatment
- 77 lost HBsAg within 6 months of treatment
- 40 had anti-HCV, anti-HDV, or anti-HIV antibody
- 354 were treated for less than 6 months
- 647 received other treatments previously
- 777 had serum HBV DNA < 2000 IU/mL or undetectable

3374 lamivudine study population

3090 started treatment with entecavir

1090 were excluded
- 23 had age < 20 years or > 80 years
- 374 died within 6 months of treatment
- 149 received transplantation within 6 months of treatment
- 57 had HCC within 12 months of treatment
- 36 lost HBsAg within 6 months of treatment
- 36 had anti-HCV, anti-HDV, or anti-HIV antibody
- 129 were treated for less than 6 months
- 81 received other treatments previously
- 205 had serum HBV DNA < 2000 IU/mL or undetectable

2000 entecavir study population

Lim et al. Gastroenterology 2014.
Outline

• Current treatment of CHB
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  – Korea
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Reduction of hepatocellular carcinoma in hepatitis B-related cirrhosis patients with long-term entecavir therapy - A follow-up report of C-TEAM study


Su and Kao et al. AASLD 2013; oral #189
Su and Kao et al. AASLD 2014; LB-30
Study design (I)

- Multi-center, observational, cohort study with long-term FU to evaluate the prognosis of ETV-treated HBV-related cirrhosis patients
- Primary endpoint
  - HCC reduction
- Secondary endpoint: reduction in the incidence rates of
  - EV/GV bleeding
  - Spontaneous bacterial peritonitis
  - Hepatic encephalopathy
  - Ascites
  - Liver-related mortality

Su and Kao et al. AASLD 2013; oral #189
Study Design (II)

- Inclusion criteria of Treatment group
  - HBsAg (+) > 6 months, anti-HCV (-)
  - Baseline serum HBV DNA $\geq 2000$ IU/mL
  - Child A cirrhosis
    - Liver biopsy (Metavir F4 or Ishak $> 5$) or
    - Ultrasonographic evidence of cirrhosis with signs of portal hypertension (splenomegaly or presence of EV/GV)
  - Treatment naïve
  - No HCC development within the first year
  - Long-term ETV monotherapy

- Historical control group: Untreated compensated cirrhotic controls collected from 1985-1995
Cirrhosis Taiwanese EntecAvir Multicenter Study

24 academic centers in Taiwan

Chung-Shan Med Univ Hosp
Changhua Christian Hosp
China Med Univ Hosp
Tungs’ MetroHarbor Hosp
Taichung Vet Gen Hosp

Chia-Yi Christ Hosp
Tzu-Chi Gen Hosp, Chiyi
Natl Taiwan Univ Hosp, YL

Chang-Gung Mem Hosp, Kaohsiung
Kaohsiung Med Univ Hosp
E-Da Hosp

Natl Taiwan Univ Hosp
Taipei Vet Gen Hosp
Tzu-Chi Gen Hosp, Taipei
Chang-Gung Mem Hosp, Keelung
McKay Mem Hosp, Taipei
Cathy Gen Hosp
Shuang-Ho Hosp
Taipei City Hosp, Ren-Ai
Wan Fang Hosp
Tri-service Gen Hosp
Far Eastern Mem Hosp

Tzu-Chi Gen Hosp, Hualien
McKay Mem Hosp, Taitung

Su and Kao et al. AASLD 2014; LB-30
Kao 2015
Results- Patients enrolment

Entecavir group
Compensated CHB-LC patients
Treated with ETV 0.5mg, 2006-2014
n=1023
Mean follow-up: 3.6 years
HCC cases: 85

Historical control group
Untreated CHB-LC patients
Followed-up, 1993-2008
n=503
Mean follow-up: 6.8 years
HCC cases: 121

Data updated on May 31, 2014
Baseline characteristics of patients in ETV treatment and untreated control groups

<table>
<thead>
<tr>
<th></th>
<th>ETV</th>
<th>Control</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>1123</td>
<td>503</td>
<td></td>
</tr>
<tr>
<td>Age, year</td>
<td>54.8(11.3)</td>
<td>50.5(11.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Male</td>
<td>826 (74)</td>
<td>385 (77)</td>
<td>0.202</td>
</tr>
<tr>
<td>ALT, U/L</td>
<td>115(222)</td>
<td>59(60)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Albumin, g/dL</td>
<td>3.9(0.6)</td>
<td>4.2(0.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>T-bil, mg/dL</td>
<td>1.4(2.0)</td>
<td>1.0(0.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Platelet, K/uL</td>
<td>122(52)</td>
<td>141(53)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>HBeAg-negative</td>
<td>795</td>
<td>354</td>
<td>0.576</td>
</tr>
<tr>
<td>HBV DNA, log IU/mL</td>
<td>5.6(1.3)</td>
<td>5.5(1.3)</td>
<td>0.325</td>
</tr>
<tr>
<td>AFP, ng/mL</td>
<td>23(85)</td>
<td>48(348)</td>
<td>0.159</td>
</tr>
<tr>
<td>Prior cirrhotic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>complications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EV/GV bleeding</td>
<td>37 (3)</td>
<td>14 (3)</td>
<td>0.584</td>
</tr>
<tr>
<td>Spontaneous bacterial peritonitis</td>
<td>2</td>
<td>0</td>
<td>0.344</td>
</tr>
<tr>
<td>Hepatic encephalopathy</td>
<td>2</td>
<td>1</td>
<td>0.928</td>
</tr>
<tr>
<td>Liver decompensation</td>
<td>4</td>
<td>0</td>
<td>0.180</td>
</tr>
<tr>
<td>Follow-up duration, year</td>
<td>3.6(1.3)</td>
<td>6.8(4.5)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>
The lifetime incidence of HCC development between entecavir and no-treatment group

Kaplan-Meier failure estimates

Adjusted HR: 0.40 (95%CI: 0.27-0.60)
Log-rank test P<0.001

Su and Kao et al. AASLD 2014; LB-30
### Multivariate analysis to predict HCC by Cox regression model

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (1 year increment)</td>
<td>1.04</td>
<td>0.99-1.09</td>
<td>.151</td>
</tr>
<tr>
<td>Male (vs. female)</td>
<td>1.89</td>
<td>1.24-2.88</td>
<td>.003</td>
</tr>
<tr>
<td>Entecavir treatment (vs. no treatment)</td>
<td>0.40</td>
<td>0.27-0.60</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>ALT (1 U/L increment)</td>
<td>1.00</td>
<td>1.00-1.00</td>
<td>.221</td>
</tr>
<tr>
<td>T-bil (1 mg/dL increment)</td>
<td>1.04</td>
<td>0.92-1.17</td>
<td>.513</td>
</tr>
<tr>
<td>PLT (1 k/uL increment)</td>
<td>0.996</td>
<td>0.99-0.9996</td>
<td>.030</td>
</tr>
<tr>
<td>Albumin (1 g/L increment)</td>
<td>0.61</td>
<td>0.43-0.87</td>
<td>.006</td>
</tr>
<tr>
<td>AFP (1 ng/mL increment)</td>
<td>1.00</td>
<td>1.00-1.00</td>
<td>.855</td>
</tr>
<tr>
<td>HBeAg positive (vs. negative)</td>
<td>1.38</td>
<td>0.94-2.03</td>
<td>.099</td>
</tr>
<tr>
<td>HBV DNA (1 log IU/mL increment)</td>
<td>1.02</td>
<td>0.89-1.16</td>
<td>.800</td>
</tr>
</tbody>
</table>

Entecavir treatment was associated with **60% reduction of HCC risk** (adjusted hazard ratio: 0.40, 95% CI: 0.27-0.60) in cirrhosis patients.

Su and Kao et al. AASLD 2014; LB-30
The effects of entecavir on cirrhotic complications

- Variceal bleeding

Nelson-Aalen cumulative hazard estimates

Log-rank test P=0.057

Su and Kao et al. AASLD 2014; LB-30
The effects of entecavir on cirrhotic complications

• Spontaneous bacterial peritonitis

Nelson-Aalen cumulative hazard estimates

Log-rank test $P < 0.001$

<table>
<thead>
<tr>
<th>Analysis Time</th>
<th>Number at Risk</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>ETV 1121</td>
</tr>
<tr>
<td>2</td>
<td>control 503</td>
</tr>
<tr>
<td>4</td>
<td>ETV 1121</td>
</tr>
<tr>
<td></td>
<td>control 502</td>
</tr>
<tr>
<td>6</td>
<td>ETV 1030</td>
</tr>
<tr>
<td></td>
<td>control 492</td>
</tr>
<tr>
<td>8</td>
<td>ETV 787</td>
</tr>
<tr>
<td></td>
<td>control 434</td>
</tr>
<tr>
<td>10</td>
<td>ETV 368</td>
</tr>
<tr>
<td></td>
<td>control 368</td>
</tr>
</tbody>
</table>

Su and Kao et al. AASLD 2014; LB-30
The effects of entecavir on cirrhotic complications

- Hepatic encephalopathy

Nelson-Aalen cumulative hazard estimates

Log-rank test $P=0.393$

Number at risk

<table>
<thead>
<tr>
<th></th>
<th>ETV</th>
<th>control</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1121</td>
<td>502</td>
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<tr>
<td>2</td>
<td>1116</td>
<td>502</td>
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<tr>
<td>4</td>
<td>1023</td>
<td>492</td>
</tr>
<tr>
<td>6</td>
<td>780</td>
<td>434</td>
</tr>
<tr>
<td>8</td>
<td>336</td>
<td>370</td>
</tr>
<tr>
<td>10</td>
<td>186</td>
<td>325</td>
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<tr>
<td>12</td>
<td>73</td>
<td>282</td>
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<td>14</td>
<td>19</td>
<td>227</td>
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<tr>
<td>16</td>
<td>0</td>
<td>187</td>
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<td>18</td>
<td>0</td>
<td>148</td>
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<tr>
<td>20</td>
<td>0</td>
<td>127</td>
</tr>
</tbody>
</table>

Su and Kao et al. AASLD 2014; LB-30
The effects of entecavir on liver transplantation

Nelson-Aalen cumulative hazard estimates

Log-rank test P=0.161

No Treatment

Entecavir

Number at risk

ETV 1123 1123 1031 788 336 185 73 19 0 0 0
control 503 503 493 436 370 324 282 227 188 150 129

Su and Kao et al. AASLD 2014; LB-30
Summary

• In this large cohort study, long-term entecavir therapy significantly reduced the development of HCC and spontaneous bacterial peritonitis in hepatitis B-related cirrhosis patients
Outline

• Current treatment of CHB
• Impact of long-term NA therapy on HCC reduction in Asian CHB patients
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Goals of therapy for chronic HBV infection

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

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

goals achievable but not satisfactory!!

→ We need novel agents to cure HBV

Courtesy of Prof. YF Liaw
<table>
<thead>
<tr>
<th>Drug name</th>
<th>Mechanism of action</th>
<th>Clinical trial status</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nucleoside analog</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emtricitabine</td>
<td>DNA polymerase inhibition</td>
<td>Should combine with other antiviral agents</td>
</tr>
<tr>
<td><strong>Nucleotide analog prodrug</strong></td>
<td></td>
<td></td>
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<tr>
<td>Besifovir</td>
<td>DNA polymerase inhibition</td>
<td>Phase III, NCT01937806 [119]</td>
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<tr>
<td>Tenofovir alafenamide fumarate</td>
<td>DNA polymerase inhibition</td>
<td>Phase III, NCT01940471 NCT01940341 [116,117]</td>
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<td><strong>Non-nucleos(t)ide analog</strong></td>
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<tr>
<td>Myrcludex-B</td>
<td>Viral entry inhibitor</td>
<td>Phase II</td>
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<tr>
<td>Bay 41–4109</td>
<td>Inhibits viral core formation</td>
<td>Phase I</td>
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<tr>
<td>REP 9AC</td>
<td>Blocks HBsAg release</td>
<td>Phase II</td>
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<tr>
<td>NVR-1221</td>
<td>Capsid inhibitor</td>
<td>Phase Ia</td>
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<td><strong>Immunomodulator</strong></td>
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<td>GS-9620</td>
<td>TLR-7 agonist</td>
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<tr>
<td><strong>Other</strong></td>
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<tr>
<td>ARC-520</td>
<td>RNA interference</td>
<td>Phase II, NCT02065336 [121]</td>
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Persistence of hepatitis B virus covalently closed circular DNA in hepatocytes: molecular mechanisms and clinical significance

Hung-Chih Yang\textsuperscript{1,2,3} and Jia-Horng Kao\textsuperscript{2,3,4,5}

Covalently closed circular DNA (cccDNA) is the transcriptional template of hepatitis B virus (HBV). Extensive research over the past decades has unveiled the important role of cccDNA in the natural history and antiviral treatment of chronic HBV infection. cccDNA can persist in patients recovering from acute HBV infection for decades. This explains why HBV reactivation occasionally occurs in patients with resolved hepatitis B receiving intensive immunosuppressive agents. In addition, although advances in antiviral treatment dramatically improve the adverse outcomes of chronic hepatitis B (CHB), accumulating evidence demonstrates that current antiviral treatments alone, be they nucleos(t)ide analogs (NAs) or interferon (IFN), fail to cure most CHB patients because of the persistent cccDNA. NA suppresses HBV replication by directly inhibiting viral polymerase, while IFN enhances host immunity against HBV infection. Viral rebound often occurs after discontinuation of antiviral treatment. The loss of cccDNA can be induced by non-cytolytic destruction of cccDNA or immune-mediated killing of infected hepatocytes. It is known that NA has no direct effect on viral transcription or cccDNA stability. Therefore, the long half-life of hepatocytes leads to a very slow decline in cccDNA in patients under antiviral therapy. Novel antiviral agents targeting cccDNA or cccDNA-containing hepatocytes are thus required for curing chronic HBV infection.