Understanding new medicines to treat chronic hepatitis B: toward a cure

October 26, 2016
Define an HBV cure

**Functionally (practical):**
- Sustained, off drug response (loss of viremia and antigenemia)

**Clinically:**
- Return an individual to the risk of death and disease due to liver disease to that of an age and gender adjusted uninfected individual

- Block, Gish et al, AVR, 2015
- Liang, Block et al, Hepatology, 2016
Categories of HBV therapeutics

Direct Acting Antivirals (DAA)  Indirect (Host) Acting Antivirals (Host)

Timeline of Approved Drugs for Chronic HBV

- Interferon approved for CHB
- Lamivudine
- Adefovir
- Entecavir
- PEG-IFN
- Telbivudine
- Tenofovir

REVEAL Study: The Relationship Between Virus Number and Hepatocirrhosis/Hepatocellular Carcinoma

4006 Study: antiviral therapy could slow down the development of CHB


Tenofovir approved in US for HBV, in 2008, but not yet approved in China for HBV

All are Direct Acting Antivirals (DAA)
Functional cures do occur with current therapeutics, although rarely.

Table 2. Results of main studies for the treatment of HBeAg-positive chronic hepatitis B at 6 months following 12 months (48 or 52 weeks) of pegylated interferon alpha (PEG-IFN) and at 12 months (48 or 52 weeks) of nucleos(t)ide analogue therapy.

<table>
<thead>
<tr>
<th></th>
<th>PEG-IFN-2a</th>
<th>PEG-IFN-2b</th>
<th>Lamivudine</th>
<th>Telbivudine</th>
<th>Entecavir</th>
<th>Adefovir</th>
<th>Tenofovir</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose</strong></td>
<td>180 µg</td>
<td>100 µg</td>
<td>100 mg</td>
<td>600 mg</td>
<td>0.5 mg</td>
<td>10 mg</td>
<td>245 mg</td>
</tr>
<tr>
<td><strong>[Ref.]</strong></td>
<td>[63]</td>
<td>[64]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-HBe seroconversion (%)</td>
<td>32</td>
<td>29</td>
<td>16-18</td>
<td>22</td>
<td>21</td>
<td>12-18</td>
<td>21</td>
</tr>
<tr>
<td>HBV DNA &lt;60-80 IU/ml (%)</td>
<td>14</td>
<td>7</td>
<td>36-44</td>
<td>60</td>
<td>67</td>
<td>13-21</td>
<td>76</td>
</tr>
<tr>
<td>ALT normalisation (%)</td>
<td>41%</td>
<td>32%</td>
<td>41-72</td>
<td>77</td>
<td>68</td>
<td>48-54</td>
<td>68</td>
</tr>
<tr>
<td>HBsAg loss (%)</td>
<td>3</td>
<td>7</td>
<td>0-1</td>
<td>0.5</td>
<td>2</td>
<td>0</td>
<td>3</td>
</tr>
</tbody>
</table>

*PEG-IFN were given as percutaneous injections once weekly and nucleos(t)ide analogues as oral tablets once daily.

#The definition of ALT normalisation varied among different trials (i.e. decrease of ALT to ≤1.25-times the upper limit of normal (ULN) in the entecavir or ≤1.3-times the ULN in the telbivudine trial).
Failure to cure with NUCs is because
Nests of infected cells (cccDNA containing) remain; HBsAg continues to be made: T cells exhausted B cells: no detectable HBsAb
Need

• Something new that complements current compounds
• *Different mechanism DAA*
  +
• *An immuno-enhancer*
# Categories of Anti-HBV Strategies

## Direct Acting Antivirals
- **In Use**
  - Polymerase
- **Potential**
  - RNaseH
  - RNAi
  - Capsid inhibitors
  - sAg
  - eAg
  - Virus attachment
  - CRISPR/CAS

## In-Direct Acting Antivirals
- **Immuno-modulatory**
  - **In Use**
    - Interferons
  - **Potential**
    - Therapeutic vaccines
    - PD-1 blockade
    - Toll R agonists
    - STING, other innate defense
    - Interleukins, other cytokines

- **Essential host functions**
  - **In Use**
    - None for HBV
  - **Potential**
    - Epigentic modifiers
    - Entry
    - Morphogenesis
    - Exit
    - Glycan processing
The HBV Therapeutic Development Landscape as of Jan, 2016

Pre-clinical

- TTP sAg
- GLS-4 capsid
- RNase H inhib
- Benza capsid
- CpAM S capsid
- cccDNA forma
- NV100
- Editope
- HDAC
- Chimgene HBV
- Altravax HBV
- STING

Human Phase Trials

- Isis HBV antisense
- ARC520 RNAi
- AGX1009 prodrug
- CMX157 prodrug
- NVIR21 capsid
- RepA9 sAg
- Bay41109 capsid
- TKM-HBV
- NVR1221 capsid
- Roche 7795
- GS9620 Toll
- DV501 Vac
- GS4774 vac
- *HDV active

Indirect Host modifier

- Indirect Immunomodulator
Entry
Heptera

cccDNA
Novartis, Arbutus

Cytoplasm
subviral particles
secretion

endocytosis
entry/uncoating
inhibitor
uncoating
cccDNA formation
inhibitor

Capsid
Arbutis, Gilead, Roche, Novera, Assembly, Jansen

Morph
Neurovive, Cyclophilin

Pol
Gilead, Contravir

RNAi
Alnylam, Arbutus, Arrowhead, IsisBenetec

Immuno
Gilead, Arbutus, Roche, Inovio, Akshaya, Springbank
Pol inhibitors:

Currently Available:
- Ten
- ADF
- LAM
- ETV
- TEL
  (FMAU in Korea)

In development:
- TAF
- CMA157
Pol inhibitors:

Currently Available:
- Ten
- ADF
- LAM
- ETV
- TEL
  (FMAU in Korea)

In development:
- Gilead: TAF
- Contravir: CMA157
- Arbutus (RNaseH inhibit)
cccDNA: “natural” source of all viral gene products
cccDNA: natural source of all viral gene products
Repress cccDNA, and repress all natural gene products.
But cccDNA is a small, tough target
HBV

**Biologicals**

*Approved:*
IFNs

*New:*
Immunenhancers:
Inovia, Gilead: Thera vaccines
Gilead, Roche: Toll R
Arbutus: STING

*Other:*
Arbutus (ARB)
Intellia: CRISPR CAS

---

**Block & Guo, 2015, Gastroenterology**
But some HBV DNA is “integrated” and not free cccDNA, and thus might be missed by drugs acting on cccDNA.
RNAi transcript inhibition

In development:

**Antisense:**
Ionis/GSK3228836*

**shRNA:**
- Alnylam (ALNHBV)*
- Arrowhead (ARC520,521)*
- Arbutus (ARB 1467,1740)*
- Benitec

*Human Trials
RNAi / sh RNA leads to degradation of HBV RNA transcripts from cccDNA and integrated DNA
RNAi: Complete shut down: cccDNA
Entry Inhibitors

Entry Inhibitor (oilgopeptide)
MyrcludexB*
Human Trials

Liang, Block et al 2016
Entry Inhibitors
Capsid inhibition

Capsid Inhibitors
- Novira NVR 778*
- Arbutus ARB423
- Sunshine*
- Assembly ABI H101
*Human trials
sAg inhibition: antiviral, anti-antigenemnic, and ?immuno restoration
Hepatitis Delta Virus

- Needs co-infection with HBV
- Mycludex B and Eiger’s Lornafarnib in human trials for HDV
Adaptive & Innate host defense

**Indirect treatment**
- RAW 264.7 cells
- Two cell chamber transfer
- Awaken, stimulate

**Adaptive**
- Gilead GS4774*
- Inovio Roche INO1800*
- Altimmune*
- Transgene TG1050*

**Innate**
- Gilead Toll GS9620*
- Roche Toll RO6884018*
- SpringBank RIGI SB9200*
- Arbutus STING A
- Contravir Cyclophil CPI421

*Human Trials

**T cells (exhausted)**

**B cells** (No detectable Antibody to HBs)

**macrophage**

**hepatocyte-derived cells**

**HBV**
Inhibiting the virus life cycle at any step should be equal in eliminating infection.

Break HBV down into at least 12 different “assayable”, “targetable” steps. Grouped into 6, here…
Current Guidelines

- Rx Rec vary
- Rx recommended
- Rx Rec varies

**Immune tolerance**
- High infectivity

**Immune elimination**
- Chronic hepatitis

**Low-viraemic**
- HBsAg carrier

---

**HBV DNA**
- \(>10^7\) IU/ml

**HBsAg**
- \(>30,000\) IU/ml

**HBeAg**
- Highly positive

---

**ALT**
- Normal

Source: Gerlich, W. 2013. Virology Journal, 10:239
Hepatitis B Foundation
Goal

• No one will die from HBV by 2030

• A cure is possible, necessary, and expected