New Anti-HBV Strategies Towards HBV CURE?

Edward Gane

Professor of Medicine
New Zealand Liver Transplant Unit
Auckland, New Zealand
Disclosures

• Ed Gane is Investigator/Advisor for:
  – Alios, Alnylam, Arbutus, Arrowhead, Assembly, BMS, Eiger, Gilead, Janssen, GSK, Novartis and Roche
The New Goal: Functional Cure

Finite treatment duration

Cessation of all treatment

Absence of HBV DNA and HBsAg

Clearance of cccDNA

“Naturally Resolved”

“Never Infected”
Why is HBV CURE important?

- 5409 CHB patients on long-term LAM or Entecavir
- After 6 years, 110 (2%) lost HBsAg (0.3% per annum)

HBsAg loss improves survival and lowers HCC incidence in patients on long-term NUCs

Disadvantages of long-term oral antiviral therapy

1. Treatment limited to only patients in immune active phase (high ALT, HBV DNA, fibrosis)
2. High cost limits access in low-income countries, \( \Rightarrow \) LAM, ADV use \( \Rightarrow \) high rate of treatment failure
3. No clear stopping criteria, especially in eAg neg
4. Viral breakthrough from non-adherence or resistance \( \Rightarrow \) flares \( \Rightarrow \) liver failure
5. Cumulative toxicity from long-term use

Disadvantages of long-term oral antiviral therapy

6. Slow rate of HBsAg loss and cccDNA decline

- 124 patients on OAV, paired liver biopsies for cccDNA

- Need to treat for 35-50 years to clear HBsAg

Can we do better with current therapies?

1. **Combine different NUCs**
   - No synergistic viral suppression or HBsAg loss
     *Lok et al, Gastroenterology 2012; Zoulim et al, J Hepatol 2015*

2. **Stop NUCs after long-term suppression**
   - HBsAg loss is rare
   - HBeAg loss $\Rightarrow$ off-treatment rebound and flares
     *HBsAg levels may be best predictor of durability*

3. **Add Pegylated-IFN to long-term NUCs**
Add Pegylated-IFN to Nucleotide Analogue Study GS-US-174-0149

740 CHB patients
No cirrhosis
Randomised 1:1:1:1
Stratified by GT

Primary endpoint: HBsAg loss

Switch from Long-term NUC to Peg-IFN in Genotype C CHB

144 CHB patients
Long-term ETV
Randomised 1:1

<table>
<thead>
<tr>
<th></th>
<th>PegIFN alfa 2a</th>
<th>NA</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg decline (log)</td>
<td>0.3</td>
<td>0.014</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HBeAg seroconversion (%)</td>
<td>24.5</td>
<td>0</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>HBsAg loss (%)</td>
<td>1.9</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>HBV DNA &lt;2000 IU/ml (%)</td>
<td>66.7</td>
<td>100</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HBV DNA &lt;20 IU/ml (%)</td>
<td>35.2</td>
<td>90.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ALT flare (%)</td>
<td>4</td>
<td>1.9</td>
<td>NS</td>
</tr>
</tbody>
</table>

Woo HY, et al. AASLD 2016, Boston. #71
Why can’t antiviral therapy cure HBV?

High Viral Burden

Weak Immune Response
Therapeutic Strategies for HBV Cure

Reduce Viral Burden

Activate Antiviral Immunity
HBV Life Cycle offers many targets for Antivirals

- NTCP
- pgRNA
- HBx
- HBs
- HBe
- Pol
- Core
- RT Step
- siRNA
- Entry Inh
- Capsid Inh
- Pol Inh
- cccDNA Inh
- α-HBsAg
- HBsAg Secretion
- REP-2139
New Targets: Block HBV DNA production

- **Entry Inh** ➔ Block hepatocyte infection

- **NTCP**

- **Pol Inh**
  - **ETV**
  - **TDF**

- **cccDNA Inh** ➔ silence/degrade cccDNA

- **NUCs don’t block 100% viral production**

- **Deacetylase activators**
- **Demethylase inhibitors**
- **Nucleases (ZFNs, CRISPR-Cas9)**

- **pgRNA** ➔ **Pol Core** ➔ **HBe** ➔ **HBs** ➔ **HBx**
New Targets: cccDNA- challenges and risks

- No standardised assays to assess cccDNA
  - Delivering the drug to the target
    • into hepatocyte nucleus
    • Into every infected hepatocyte

- Host epigenetic modulators have risks
  - Direct toxicities
  - Off-target effects of drug on host DNA
  - Long-term risks in young patients

Viral epigenetic modulators should be safer
- X-protein
- Capsid protein
New Targets: Block HBV Capsid Assembly

Capsid Inhibitors
1. GLS-4
2. HAP-12
3. AT-130
4. NVR 3-778
5. NVR 3-1983
6. NVR 26-0617
7. GLP-26
8. BAY41-4109
9. AB-423
10. ABI-H0731
11. JNJ-56136379
12. RO7049389
Oral HBV capsid assembly inhibitor NVR 3-778
Clinical Profile: synergism with Peg-IFN

- Phase 1b study of NVR 3-778 ± PegIFN for 28 days in HBeAg+ CHB

- 0.4 log reduction in HBeAg in 600mg bid

- No effect on HbsAg levels after 28 days

- Phase II: Combine with NUC ± Peg-IFN for 52 wks

- More potent capsid inhibitors in development
New Targets: Block HBV antigen production

- NTCP
- pgRNA
- Pol
- Core
- HBe
- HBs
- HBx
- siRNA/LNA
  1. ARC-520
  2. ARC-521
  3. TKM-HBV
  4. ARB-1740
  5. ALN-HBV
  6. ISIS-HBV
  7. LUNAR™-HBV
  8. RO7062931
Single IV dose ARC-520 in patients reduces all HBV proteins and HBV DNA (HEPARC-1)

(1) HBV DNA

(2) HB core Ag

(3) HBeAg

(4) HBsAg
Multiple dosing of ARC-520
Effect on HBsAg reduced in HBeAg neg CHB

(i) Chimps

(ii) Patients

ARCC-521 includes siRNA in S open reading frame outside DR1-DR2, targeting HBV RNA expressed from integrated HBV DNA

Xu Z, et al. EASL 2016, Barcelona. THU-213

Yuen M, et al. AASLD 2014; Poster #LB-21
Yuen M, et al. AASLD 2015; Poster #LB-9
ARC-521 reduces HBsAg in HBeAg- chimps

- 3 monthly IV doses ARC-521 administered to 2 HBeAg neg chimps after 6 monthly doses of ARC-520

- ARC-520/521 on FDA hold due to toxicity in preclinical studies and infusion reactions in clinical studies
Therapeutic Strategies for HBV Cure

- **Reduce Viral Burden**

- **Activate Antiviral Immunity**

  - CD8+
  - CD8+
  - B
  - B
Ways to activate Antiviral Immunity against HBV

1. Stimulate Antiviral Effector Cells
   - CD8+, NK, Mφ, pDC, B
   - TLR-7, TLR-8, RLRs, CLR, NLRs
   - DNA sensors

2. Generate New T cells
   - CD8+
   - Therapeutic vaccines

3. “Rescue” Exhausted T cells
   - CD8+
   - Reduce viral antigens
   - Modulate immune receptors (PD-1)
   - Relieve suppression of T cells
   - Inhibit T regs
Ways to activate Antiviral Immunity against HBV

1. Stimulate Antiviral Effector Cells
   - TLR-7, TLR-8, RLRs, CLRs, NLRs
   - DNA sensors

2. Generate New T cells
   - Therapeutic vaccines

3. “Rescue” Exhausted T cells
   - Reduce viral antigens
   - Modulate immune receptors (PD-1)
   - Relieve suppression of T cells
   - Inhibit T regs
TLRs: Pattern Recognition Receptors that Recognize Pathogen-Associated Molecular Patterns.
GS-9620 Toll-like Receptor 7 (TLR7)

1. **Adaptive immunity**
   - Kill infected cells
   - Antiviral cytokines (e.g. IFN-γ)
   - Neutralizing antibodies

2. **Innate Immunity**
   - Kill infected cells
   - Antiviral cytokines (e.g. IFN-γ)

3. **Antiviral cytokines**

Intrahepatic TLR7+ Cells

- pDCs
- B cells

APCs

- CD8+
- B cell
- NK

pDC, Plasmacytoid dendritic cell
APC, Antigen presenting cell.
IFN, interferon
GS-9620 Phase 2 study in suppressed CHB

- ISG15 Expression
- Change in HBsAg level

- More potent TLR-7 agonists?
- Other TLR/PRR agonists?

- Dose-related increase ISGs
- Peripheral T-cell/NK cell activation by 8 weeks
- No systemic IFN, no flares, no cytopenias

- BUT Minimal change in HBsAg levels

Janssen HL, et al. AASLD 2016, Boston. #1851
Ways to activate Antiviral Immunity against HBV

1. Stimulate Antiviral Effector Cells
   - TLR-7, TLR-8, RLRs, CLRs, NLRs
   - DNA sensors

2. Generate New T cells
   - Therapeutic vaccines

3. “Rescue” Exhausted T cells
   - Reduce viral antigens
   - Modulate immune receptors (PD-1)
   - Relieve suppression of T cells
   - Inhibit T regs
**T-cell Vaccine (GS-4774)**

- No change in HBsAg levels
- No change in HBV-specific T-cell responses

⇒ Need to overcome T-cell exhaustion?
Ways to activate Antiviral Immunity against HBV

1. Stimulate Antiviral Effector Cells
   - TLR-7, TLR-8, RLRs, CLRs, NLRs
   - DNA sensors

2. Generate New T cells
   - Therapeutic vaccines

3. “Rescue” Exhausted T cells
   - Reduce viral antigens
   - Modulate immune receptors (PD-1)
   - Relieve suppression of T cells
   - Inhibit T regs
Role of PD-1:PD-L1 Interactions for HBV

- Persistent HBV infection has exhausted CD8 T-cell phenotype
  - PD-1 most strongly expressed among inhibitory markers\(^1\)
- PD-L1 ligand is up-regulated in HBV-infected liver\(^2\)
- PD-1:PD-L1 blockade reverses immune dysfunction in murine and woodchuck HBV models\(^3\)\(^-\)\(^5\)
- PD-1 inhibitors suppress HBV in patients with HBV-HCC\(^6\)

Are PD-1 Inhibitors safe in Chronic Hepatitis B?

- CheckMate 040 Study: Nivolumab in Advanced HCC
  - Included 51 patients with chronic hepatitis B

  - >1 log reduction in HBsAg in 3 patients over 6 months
  - No ALT flares

Sangro B, et al. AASLD 2016
Are PD-1 Inhibitors safe in Chronic Hepatitis B?

- GS-US-330-1938 Study: PD-1 inhibition with or without therapeutic vaccine in suppressed CHB patients

**Cohort A, n=10**

- GS-4774 40 YU

**Cohort B, n=10**

- Nivolumab 0.3 mg/kg

**Primary Endpoints**
- log10 HBsAg decline at 12 weeks post-dose
- Safety and tolerability

**Exploratory Endpoints**
- Changes in HBV-specific immune responses, T-cell subsets and cytokine level after treatment

Gane E, et al. EASL 2017
Combination strategy to achieve Functional Cure

Boost Immune response

Boost specific T-cell responses
- Therapeutic vaccines
- TLR agonists
- Checkpoint modulation

Boost Innate Immunity
- TLR agonists

Reduce Viral Burden

1. Block cccDNA production
   - Capsid assembly modulators

2. Reduce antigen load (sAg, capsid)
   - siRNA
   - Antisense

cccDNA silencing & degradation

- TALENs
- CRISPR / CAS9
Conclusions
HBV CURE

- HBV CURE will require combination therapies which inactivate cccDNA and overcome T-cell exhaustion
- HBV CURE could provide treatment for ALL HBsAg+
- HBV CURE could prevent most HCC
- SAFETY will be the priority in order to avoid hepatitis flares and off-target toxicities
- Will HBV CURE expedite global eradication?

Short duration, convenience (sc/oral), affordability, will be crucial for uptake in low-
Global Health Sector Strategy on Viral Hepatitis (2016-2021)

WHO Global Targets for 2030

Do we need an HBV CURE?

- In 1990, HBsAg prevalence in Chinese children was 9.8%
- Neonatal vaccination rolled out since 1992
- HBV Vaccine coverage 1990-2013
- HBsAg Prevalence 1992 and 2003

Neonatal vaccination 99% (BD 94%)
Childhood HBsAg prevalence <1%


1WHO/UNICEF Joint Reporting Form for Immunization
Do we need an HBV CURE?

Impact on Total Cost of Global Eradication

CURE reduces total costs by >10% (>USD$5Billion)

Infant Vaccine/Birth Dose + PPT + OAV

Infant Vaccine/Birth Dose + PPT + OAV + CURE

Thank you!

1. Stephen Locarnini, Doherty
2. Antonio Bertoletti, Duke/NUS
3. Jeff Glenn, Stanford
4. Anuj Gaggar, Gilead Sciences
5. Bruce Given, Arrowhead
6. John Fry, ALIOS
7. Michael Schlag, Janssen