New Therapies in the Treatment of HBV Infection

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Chronic Hepatitis B: Globally Significant Disease

- In 2016
  - Worldwide estimated prevalence 3.5% (257 million)
    - Western Pacific region 6.2% (115 million)
    - African region 6.1% (60 million)

- In 2015
  - Number of deaths due to
    - Viral hepatitis 1.34 million
    - Tuberculosis 1.37 million
    - Malaria 0.44 million

Seto WK... Yuen MF. The Lancet 2018;10161:2313-24
Chronic Hepatitis B Infection: Complex Disease

Complex Viral Life Cycle

Complex Disease Phase

Seto WK... Yuen MF. The Lancet 2018;10161:2313-24
HBV Treatment Goals and Definitions of Cure
Current Goal: Partial Cure

Finite treatment duration

Cessation of all treatment

HBsAg+ but sustained normal ALT and low/undetectable HBV DNA

No active liver disease
New Goal: Functional Cure

- Finite treatment duration
- Cessation of all treatment
- Absence of HBV DNA and HBsAg

- No active liver disease
- No viral replication
Future Goal: Complete Cure

- **Finite treatment duration**
- **Cessation of all treatment**
- **Absence of HBV DNA and HBsAg**
- **Clearance of cccDNA**

- No active liver disease
- No viral replication
- No risk of reactivation
Future Goal: Sterilising Cure

- Finite treatment duration
- Cessation of all treatment
- Absence of HBV DNA and HBsAg
- Clearance of cccDNA
- Clearance of integrated HBV DNA

- No active liver disease
- No viral replication
- No risk of reactivation
- No risk of HCC and no ongoing surveillance
HBsAg Seroclearance = Functional Cure

- Important disease/treatment milestone
  - associated with better prognosis if it occurs at an early age
  - treatment can be stopped
Approved Treatment Agents For Chronic HBV Infection

IFNα-2b

1990

Interferon therapy

Lamivudine

1998

NUCs therapy

Adefovir

2002

Entecavir

2005

PEG-IFNα

2006

TAF

2008

Telbivudine

2016

Nature Reviews | Disease Primers

Yuen MF et al., Nat Rev Dis Primers. 2018;4:18035
Slow HBsAg Decline by Long-term Entecavir Treatment

Log HBsAg (log IU/ml)

Baseline | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 | Year 6 | Year 7
--- | --- | --- | --- | --- | --- | --- | ---
3.41 | 3.36 | 3.32 | 3.19 | 3.04 | 2.95 | 2.96 | 2.78

p <0.01

Data on file from Lam YF... Yuen MF. Clin Transl Gastroenterol 2017; 8(10): e125
Slow HBsAg Decline by Long-term Nucleos(t)ide Treatment

The Hong Kong Association for the Study of Liver Diseases

Low Rate of HBsAg Seroclearance by Existing Treatment

Nucleos(t)ide Analogs

<table>
<thead>
<tr>
<th>Drug</th>
<th>HBsAg seroclearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entecavir</td>
<td>2.5% (7 years follow-up)</td>
</tr>
<tr>
<td>TDF</td>
<td>11.8% for HBeAg+ and 1.3% for HBeAg- (7 years follow-up)</td>
</tr>
<tr>
<td>TAF</td>
<td>NA</td>
</tr>
</tbody>
</table>

PEG - IFN

2.4% at 5 years (n= 85, HBeAg+)
8% at 3 years (n=230, HBeAg-)

Yuen MF et al., Nat Rev Dis Primers. 2018;4:18035
Decades of NUC Treatment Before Achieving HBsAg Seroclearance

The Hong Kong Association for the Study of Liver Diseases


- HBeAg +ve: 3 years for 1 log decline in HBsAg from baseline, 18 years for HBsAg clearance
- HBeAg -ve: 10 years for 1 log decline in HBsAg from baseline, 42 years for HBsAg clearance

Estimated years of Nuc therapy required to achieve HBsAg endpoints
Possible Future Curative Regimen For CHB

NUC analogue + Viral antigen inhibitor + Immune modulation + cccDNA inhibitor

To control viral replication and cccDNA re-amplification
To inhibit HBV life cycle processes (e.g. entry, mRNA transcription, capsid assembly, viral protein secretion)
To activate or restore HBV-targeting immune responses
To silence or eliminate cccDNA

Functional cure

Complete cure?

Seto WK & Yuen MF. Clinical Liver Disease 2016;8(4):83-8
Agents Under Clinical Trials to Enhance “Functional Cure”

**Nucleocapsid assembly inhibitors:**
- NVR 3-778
- JNJ379
- ABI-H0731
- GLS4

**HBsAg release inhibitors:**
- REP 2139
- GC 1102

**Entry inhibitors:**
- Myrcludex B

**cccDNA inhibitors:**
- Pending clinical studies

**Immunomodulators:**
- Therapeutic vaccines
  - GS-4774
  - ABX-203
  - TG-1050
  - INR-1800
  - FP-02.2
- Others
  - GS-9620
  - SB-9200 (Inarigivir)
  - AIC649
  - Birinapant

**mRNA silencers:**
- siRNA
  - ARC-520
  - ARO-HBV
  - ARB-1467
- Others
  - GSK3228836
  - RO7020322

**HBV virion**

**NUC analogues:**
- Already available

**Others:**
- GS-9620
- SB-9200 (Inarigivir)
- AIC649
- Birinapant

**siRNA silencers:**
- ARC-520
- ARO-HBV
- ARB-1467

**Others:**
- GSK3228836
- RO7020322

**Modified from Seto WK & Yuen MF. Clinical Liver Disease 2016;8(4):83-8**
Simplified Theory of HBV siRNA Therapeutic

1. “HBsAg Theory”
   - Reducing HBsAg enables host immune system derepression and long term control of virus

2. Destabilizing Viral Function
   - Silencing all antigens could destabilize normal viral function
   - Enable host immune system de-repression and long term control of virus
HBsAg Reduction by Multiple Doses of siRNA (ARC-520)

Yuen MF (unpublished data)
Profound HBsAg Reduction with 3-dose siRNA (ARO-HBV)

Mean Log HBsAg change from day 1 (n=4 per cohort)

NADIR HBsAg responses for patients with > 6 weeks of HBsAg data

- > 1 log (90%) reduction: 100%
- > 1.5 log (97%) reduction: 83%
- > 2 log (99%) reduction: 38%
- > 3 log (99.9%) reduction: 3%

Gane E...Yuen MF AASLD 2018 (LB 25)
Individual changes in HBV DNA, HBV RNA, HBeAg and HBcrAg in patients receiving 3-dose siRNA (ARO-HBV)
CpAM under Clinical Trials

HBV capsid assembly pathway and examples of capsid inhibitors

Class I
- Forms aberrant non-capsid polymers
- RO7049389
- BAY-41-4109
- RG7907
- GLS-4

Class II
- Forms empty capsid devoid of pgRNA/rcDNA
- NVR 3-778
- AB-423
- AB-506
- JNJ-6379
- ABI-H0731

HAP: heteroaryldihydropyrimidines; | SBA: sulfamoylbenzamides; | PP: phenylpropenamides
CpAM: Dual mechanism of action

JNJ-6379 is a CAM that binds to HBV core protein and disrupts early and late-stage processes in the HBV life-cycle.

**“Primary” mechanism (“empty capsid” CAM)**
Interference with capsid assembly kinetics, preventing encapsidation of (pg)RNA and blocking HBV replication (late step in viral life cycle)

JNJ-6379 median EC\textsubscript{50}/EC\textsubscript{90} = 102 nM/376 nM

**“Secondary” mechanism**
Inhibition of the de-novo formation of cccDNA, potentially by interfering with the capsid disassembly process (early step in viral life cycle)

JNJ-6379 median EC\textsubscript{50}/EC\textsubscript{90} = 876 nM/4019 nM

Berke JM et al. AASLD 2016; Abstract 234

Dane particle (infectious DNA containing)
RNA containing particle (pgRNA, spliced RNA)
Subviral particles (HBsAg)
NAs block HBV replication but do not inhibit the production of RNA-containing particles
Objective: To evaluate the antiviral activity, safety and PK of escalating doses of JNJ-6379 following 4 weeks’ oral administration in treatment-naïve adults with CHB who meet the following criteria:

- HBeAg-positive or -negative
- Plasma HBV DNA >2,000 IU/mL
- Non-cirrhotics (F0–F2)
- ALT less than 2.5x ULN

Session 8 (EU)
(8 drug; 4 placebo)
100 mg 25 mg QD 8-week follow-up

Session 9 (EU)
(8 drug; 4 placebo)
75 mg QD 8-week follow-up

Session 10 (EU/AP)
(9 drug; 3 placebo)
150 mg QD 8-week follow-up

Session A (EU/AP)
(9 drug; 3 placebo)
250 mg QD 8-week follow-up

Session 11 (AP)
(7 drug; 2 placebo)
75 mg QD 8-week follow-up

Data being presented today

AP Asia-Pacific; EU Europe

Sessions 1 to 7 were performed in healthy volunteers (Zoulim F et al., AASLD 2017; Abstract LB-15)
HBV DNA Change

Mean (±SD) HBV DNA change from baseline (log_{10} IU/mL)

Time (weeks) 6 8 10 12

Follow-up period

-0.06 (0.93)
-0.08 (0.42)
-0.57 (0.62)
-0.77 (0.69)
-1.39 (1.18)*

LLOQ = Lower limit of quantification (20 IU/mL) of the HBV DNA assay

No patients had values <LLOQ

* One patient started tenofovir at Week 8

Zoulim F et al. AASLD 2018 (Abstract 74)
ABI-H0731: Study Design

**Treatment (28 days)**
- 100 mg (n=10 + 2 PBO)
- 200 mg (n=10 + 2 PBO)
- 300 mg (n=10 + 2 PBO)
- 400 mg (n=2)

**Objectives**

**Primary**
- Dose-related safety and tolerability

**Secondary**
- Steady state human PK
- Dose-related antiviral effects
  - HBV DNA/RNA
  - HBsAg and HBeAg
  - Pre-existing and emergent resistance

**Once-daily oral dosing**
- HBeAg Pos and Neg patients (stratified 7:5)

*Yuen MF et al. AASLD 2018 (Abstract 73)*
HBV DNA Change

- Dose responsive declines; Reductions of up to 4 logs at 300 and 400 mg PO QD
- All subjects rebounded post therapy

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>N</th>
<th>Mean (Range)</th>
<th>N</th>
<th>Mean (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 mg</td>
<td>6</td>
<td>1.3 (0.8 - 1.7)</td>
<td>4</td>
<td>2.2 (0.7 - 3.6)</td>
</tr>
<tr>
<td>200 mg</td>
<td>5</td>
<td>1.9 (1.0 - 2.6)</td>
<td>5</td>
<td>2.4 (1.5 - 3.8)</td>
</tr>
<tr>
<td>300 mg</td>
<td>6</td>
<td>2.9 (1.8 - 3.9)</td>
<td>3*</td>
<td>2.5* (0.8 – 4.1)</td>
</tr>
<tr>
<td>400 mg</td>
<td>0</td>
<td>NA</td>
<td>2</td>
<td>3.9 (3.9 –4)</td>
</tr>
</tbody>
</table>

*Excludes subject with known resistance at baseline
Parallel Reductions in HBV RNA Levels

- HBV RNA reductions (1-2 logs) seen at all dose levels, and correlated with HBV DNA reductions (p <0.001)
- Mechanism-based reduction in viral RNA levels is a differentiating feature of Core inhibitors

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>N</th>
<th>Mean Copies/µL (Range)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 mg</td>
<td>6</td>
<td>1.2 (0.7 - 1.6)</td>
</tr>
<tr>
<td>200 mg</td>
<td>5</td>
<td>1.7 (1.1 - 2.2)</td>
</tr>
<tr>
<td>300 mg</td>
<td>6</td>
<td>2.3 (1.7 – 2.6)</td>
</tr>
<tr>
<td>400 mg</td>
<td>0</td>
<td>NA</td>
</tr>
</tbody>
</table>

*Internal HBV RNA RT-qPCR assay, for HBeAg positive: LOQ = 10 copies/µL

HBeAg Neg patients
- RNA levels were lower at baseline and more difficult to quantitate
- All subjects with detectable RNA at baseline had RNA declines on treatment
INARIGIVIR: A NOVEL, ORAL SELECTIVE IMMUNOMODULATOR WITH A DUAL MECHANISM OF ACTION

INARIGIVIR is a RIG–I AGONIST which is designed to:

• Restore hepatic selective innate and adaptive immune response stimulating the production of type I and III IFNs

• Inhibit the HBV replication complex via a direct acting anti-viral effect

• Result in significant anti-HBV activity with reduction in HBV DNA, HBV RNA, HBsAg and cccDNA

HBV, hepatitis B virus; IFN, interferon; pgRNA, pregenomic RNA; RIG-I, retinoic acid-inducible gene-I.

Yuen MF et al. AASLD 2018 (Abstract 75)
ACHIEVE PHASE 2 (PART A) MONOTHERAPY DOSE ESCALATION STUDY

Clinical trial collaboration with Gilead to evaluate inarigivir followed by tenofovir 300 mg

Up to 80 non-cirrhotic HBV subjects, randomized 4:1 between inarigivir and placebo (Adaptive trial design)

12 weeks (inarigivir monotherapy QD)
- Inarigivir - 25 mg
- Inarigivir - 50 mg
- Inarigivir - 100 mg
- Inarigivir - 200 mg
- Placebo

Cohort 1

Cohort 2

Cohort 3

Cohort 4

12 weeks

All patients switch to Gilead's Viread® 300 mg monotherapy

Safety and antiviral activity at 12 weeks

PK, change in serum HBV DNA, HBsAg, HBV RNA and HBeAg from baseline to weeks 6, 12, 14, 16, and 24

HBsAg predefined response: > 0.5 log HBsAg reduction at week 12 or 24

Yuen MF et al. AASLD 2018 (Abstract 75)
Inarigivir demonstrates a continuing positive dose response in HBeAg-ve patients at week 12.

**HBV DNA**

- Placebo
- 25 mg
- 50 mg
- 100 mg

All groups $p<0.01$

5 patients undetectable HBV RNA at baseline

**HBV RNA**

- Placebo
- 25 mg
- 50 mg and 100 mg

All groups $p<0.01$

Yuen MF et al. AASLD 2018 (Abstract 75)
INARIGIVIR DEMONSTRATES A CONTINUING POSITIVE DOSE RESPONSE IN HBeAg +VE PATIENTS AT WEEK 12

Yuen MF et al. AASLD 2018 (Abstract 75)
**HBeAg negative patients (n=10) – Inarigivir effect on HBV RNA persists on TDF**

- **HBV DNA**
  - Inarigivir to week 12
  - Tenofovir week 12 - 24

- **HBV RNA**
  - Inarigivir to week 12
  - Tenofovir week 12 - 24

6 patients LLOQ

_Yuen MF et al. AASLD 2018 (Abstract 75)_: The Hong Kong Association for the Study of Liver Diseases
HBeAg Positive Responder Patients > 0.5 $\log_{10}$ Reduction

**HBsAg decline in HBeAg positive responders**

- Inarigivir
- Tenofovir

**HBV RNA decline in HBeAg positive responders**

- Inarigivir
- Tenofovir

$-0.9 \log_{10}$

$-1.5 \log_{10}$

Yuen MF et al. AASLD 2018 (Abstract 75)
Summary of HBsAg Response

- Overall, 13 of 47 (28%) patients experienced a $0.5 \log_{10}$ reduction on inarigivir alone or at 24 weeks after TDF switch.

- HBsAg response seen in 6 out of 32 HBeAg +ve and 7 out of 15 HBeAg –ve patients.

- Mean and median HBsAg reduction $0.8 \log_{10}$ (range $0.5 – 1.4 \log_{10}$) in 13 responder patients.

Yuen MF et al. AASLD 2018 (Abstract 75)
Summary for New Agents

Most of the new HBV agents have now undergone/ completed phase II studies

Coming HBV agents to the clinic

• RNA inhibition (IV or SC)
  • Profound effect on HBsAg level
    (also HBeAg/ HBcrAg) and HBV RNA
  • Cases of HBsAg seroclearance were observed

• Capid protein modulation/ inhibition (oral)
  • Proven efficacy on HBV DNA and HBV RNA reduction
  • According to the MOA, reduction on cccDNA expected

• RIG-I agonist (oral)
  • Positive effects on HBV DNA and HBV RNA
  • Effects on HBsAg reduction maintained/ potentiated even after switching to NUC monotherapy
Shortening the Time of CHB Treatment by New Agents

For now

NUCs → Viral suppression undetectable HBV DNA → ? > 10 yrs → Functional control/cure HBsAg loss → ? > 30-40 yrs → Complete cure cccDNA clearance

1-3 yrs

Slow HBsAg decline
Natural hepatocyte turn-over

For the future

NUCs → Viral suppression undetectable HBV DNA → ? 3 yrs → Functional control/cure HBsAg loss → ? 10, 20 yrs → Complete cure cccDNA clearance

1-3 yrs

RNA knock-down
RIG-I agonist
CpAM
NAP ± Immune modulators
Thank you