New anti-HBV drugs in the pipeline

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Next HBV Treatment Goal

Functional Cure = HBsAg seroclearance

Finite treatment duration

Cessation of all treatment

Absence of HBV DNA and HBsAg

- No active liver disease
- No viral replication
Loss of HBsAg (HBsAg seroclearance): Good Outcome

Better prognosis if HBsAg seroclearance at younger age

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

Potential New Agents: Enhance “Functional Cure”

**NUC analogues:**
- Already available
- NVR 3-778
- JNJ379
- ABI-H0731
- GLS4

**Nucleocapsid assembly inhibitors:**
- Pending clinical studies
- Myrcludex B

**cccDNA inhibitors:**
- REP 2139
- GC 1102

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

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

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

**Entry inhibitors:**
- Myrcludex B

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

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

Modified from Seto WK & Yuen MF. Clinical Liver Disease 2016;8:83-8
Knock Down Viral Proteins (HBsAg) by RNA Interference (RNAi)
Antisense Therapeutic Approach

1) Short Single Stranded Anti-sense Oligonucleotide (DNA)

“Killing the messenger”
Antisense Oligonucleotides: GSK3389404 and ISIS 505358

- ISIS 505358
- GSK3389404 is a GalNAc conjugated prodrug of ISIS 505358 – intended to enhance delivery to the hepatocyte
- target all 4 HBV mRNA transcripts
- both are delivered by subcutaneous injection
Effective Reduction of HBsAg in Transgenic Mouse Model


GSK836 = ISIS 505358
GSK404 = GSK3389404
2) Double Stranded RNA (siRNA)

Therapeutic Gene Silencing

- mRNA degradation
- cleaved mRNA
- cleavage
- complementary pairing
- strand separation
- RISC
- siRNAs
- dsRNA
- dicer
- Natural Process of RNAi

Synthetic siRNAs

(A)_n

(A)_n

mRNA degradation

cleaved mRNA

cleavage

(A)_n

mRNA

complementary pairing

strand separation

RISC

siRNAs

dsRNA

dicer

dicer
First siRNA (ARC-520) for chronic HBV infection

ARC-520 consists of 2 vials

- Vial 1: ARC-520 Excipient
  - contains a masked, hepatocyte-targeted peptide (NAG-MLP) that aids in the delivery of the HBV chol-siRNAs.
- Vial 2: ARC-520 API
  - contains the HBV chol-siRNAs.
- The liquid in Vial 2 is used to dissolve the powder in Vial 1, resulting in ARC-520 for Injection (IV)
- DPC and the chol-siRNAs are targeted to the liver. When they are in the same endosome, the DPC facilitates chol-siRNA escape resulting in RNAi.
Single Dose ARC 520: First-in-patient Study

HBeAg +ve patients

HBeAg -ve patients

Multiple Dose of ARC-520 In HBeAg +ve Patient: Robust & Sustained Reduction of All Viral Antigens & HBV RNA

Yuen MF (data on file)
Multiple Doses of ARC-520: Sustained HBsAg Reduction & HBsAg seroclearance

**HBeAg positive patients**

- Single dose
- HBsAg reduction (Log IU/mL)
- Month
- Pt. 708
- Pt. 710
- Pt. 711

**HBeAg negative patients**

- Single dose
- HBsAg reduction (Log IU/mL)
- Month
- Pt. 701
- Pt. 705
- Pt. 706
- Pt. 709
- Pt. 712

Yuen MF (data on file)
Common Deleted Regions (Between DR2 & DR1) after HBV DNA Integration to Human DNA

Target Sites for ARC-520 siRNAs can be Deleted in Integrated HBV DNA

- 520 siRNAs can be Deleted in Integrated HBV DNA
- Designed to reduce all transcripts from HBV cccDNA
- Integration into host chromosome
- HBV dsDNA
  - S promoter
  - X promoter
- S mRNA
- DR1
- DR2
- ARC-520
- precore, core promoters
- integrated HBV DNA
  - S mRNA
  - ARC-520
JNJ-3989 (ARO-HBV)

- Addresses full HBV transcriptome
  - Two hepatocyte targeted RNAi molecules
  - Works for cccDNA and integrated-derived transcripts
  - Previously shown to reduce HBV DNA, HBV RNA, HBsAg, HBeAg, & HBcrAg $^{1,2}$
- Multiple triggers to avoid resistance development and increase coverage of viral genomes


Yuen MF et al. ILC 12 April 2019, PS-080
JNJ-3989/ ARO-HBV

Profound HBsAg Reduction for both HBeAg +ve & -ve patients

- Range of HBsAg NADIR: -1.3 to -3.8 Log_{10}
- Mean HBsAg NADIR: -2.0 Log_{10}
- All CHB patient’s HBsAg responded
  - Mean HBeAg positive (n=11): -2.5 Log_{10}
  - Mean HBeAg negative (n=13): -1.8 Log_{10}

Gane E...Yuen MF APASL 2019 (Abstract 638)
All patients receiving 3 monthly doses have achieved > 1 log reduction in HBsAg

- NADIR in HBsAg is reached around 4 months post start of therapy
- Duration of pharmacologic effect persisted for > 4 months after last dose

Yuen MF et al. EASL 2019, PS-080
Distribution of quantitative HBsAg pre and post 3 doses of JNJ-3989/ARO-HBV

Baseline
Median: 1263 IU/mL
Min: 7.0 IU/mL
Max: 392,800 IU/mL

NADIR
Median: 14.5 IU/mL
Min: 0.05 IU/mL
Max: 8950 IU/mL

Yuen MF et al. EASL 2019, PS-080
Individual Changes in HBV DNA, HBeAg, HBcrAg and HBV RNA

Gane E...Yuen MF APASL 2019 (Abstract 638)
HBcAg inhibition: Core Protein Allosteric Modulator (CpAM)

HBV capsid assembly pathway and examples of capsid inhibitors

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
Effects of First-in-class CpAM (NVR3-778) +/- Peg IFN on HBV DNA and HBV RNA

Yuen MF et al. Gastroenterology 2019;156:1392-1403
JNJ-6379: HBV DNA Change

Mean (±SD) HBV DNA change from baseline (log₁₀ IU/mL)

Time (weeks)

Follow-up period

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

No patients had values <LLOQ

* One patient started tenofovir at Week 8

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

Zoulim F et al. AASLD 2018 (Abstract 74)
ABI-H0731: HBV DNA Change in HBeAg +ve patients

ABI-H0731: HBV DNA Change in HBeAg –ve patients

ABI-H0731: HBV RNA Change

After 4 weeks of treatment with RO7049389, a robust HBV DNA decline was observed across all five cohorts with a median reduction of 2.66-3.20 Log_{10} IU/mL.

13/16 (81.3%) patients who were HBeAg negative at baseline achieved HBV DNA levels lower than LLOQ (<20 IU/mL).

**Median HBV DNA decline from baseline over time**

<table>
<thead>
<tr>
<th>Cohort</th>
<th>n (Baseline HBeAg +/-)</th>
<th>Baseline Median(range)</th>
<th>Change from Baseline on Day 28</th>
</tr>
</thead>
<tbody>
<tr>
<td>200mg BID</td>
<td>N=6 (3/3)</td>
<td>4.5 (1.9-8.3)</td>
<td>-2.66 (-3.4, -0.6)</td>
</tr>
<tr>
<td>400mg BID</td>
<td>N=6 (3/3)</td>
<td>7.8 (4.0-8.5)</td>
<td>-3.20 (-5.3, -2.2)</td>
</tr>
<tr>
<td>200mg QD</td>
<td>N=6 (5/1)</td>
<td>7.14 (3.9-8.5)</td>
<td>-3.0 (-3.6, -2.3)</td>
</tr>
<tr>
<td>600mg QD</td>
<td>N=6 (2/4)</td>
<td>4.43 (3.3-8.4)</td>
<td>-2.92 (-3.7, -2.0)</td>
</tr>
<tr>
<td>1000mg QD</td>
<td>N=6 (1/5)a</td>
<td>5.1 (4.1-8.7)</td>
<td>-3.17 (-3.8, -2.8)</td>
</tr>
<tr>
<td>Placebo</td>
<td>N=6 (2/3)a</td>
<td>5.94 (4.8-8.2)</td>
<td>-0.26 (-1.2, 0.2)</td>
</tr>
</tbody>
</table>

a. Only include patients who completed 28 days treatment. One patient in each group was excluded from efficacy analysis. These two patients were discontinued early and were replaced.
HBV RNA decline after 28 days of RO7049389 treatment

- After 4 weeks of treatment with RO7049389, a robust HBV RNA decline was observed across all five cohorts with a median reduction of d 2.09-2.55 Log_{10} copies/mL.

![Median HBV RNA decline from baseline over time graph]

<table>
<thead>
<tr>
<th>Cohort</th>
<th>n (Baseline HBeAg +/-)</th>
<th>Baseline Median (range)</th>
<th>Change from Baseline on Day 28</th>
</tr>
</thead>
<tbody>
<tr>
<td>200mg BID</td>
<td>n=2 (2/0)</td>
<td>6.37 (5.7-7.1)</td>
<td>-2.09 (-2.5, -1.6)</td>
</tr>
<tr>
<td>400mg BID</td>
<td>n=4 (3/1)</td>
<td>7.01 (6.5-7.4)</td>
<td>-2.55 (-4.0, -2.0)</td>
</tr>
<tr>
<td>200mg QD</td>
<td>n=5 (5/0)</td>
<td>6.9 (4.5-7.5)</td>
<td>-2.55 (-3.1, -0.4)</td>
</tr>
<tr>
<td>600mg QD</td>
<td>n=2 (2/0)</td>
<td>7.02 (6.8-7.2)</td>
<td>-2.54 (-2.9, -2.2)</td>
</tr>
<tr>
<td>1000mg QD</td>
<td>n=2 (1/1)</td>
<td>4.64 (4.3-7.4)</td>
<td>-2.43 (-3.0, -1.9)</td>
</tr>
<tr>
<td>Placebo</td>
<td>n=3 (2/1)</td>
<td>6.37 (4.7-7.3)</td>
<td>-0.26 (-0.5, 0.2)</td>
</tr>
</tbody>
</table>

a. LLOQ=4.04 Log_{10} copies/mL.

Yuen MF et al. EASL (abstract 219) 2019
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.
Achieve Phase 2 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

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

12 weeks

Safety and antiviral activity at 12 weeks

SECONDARY ENDPOINT

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

Responders: > 0.5 log HBsAg reduction at week 12

Yuen MF et al. EASL 2019 (Abstract 75)
Mean Change from Baseline in HBV DNA to Week 12 in Placebo (PL) and IRIG cohorts

Yuen MF et al. EASL 2019 (Abstract 75)
Mean Change from Baseline in HBV RNA to Week 12 in Placebo (PL) and IRIG cohorts

Yuen MF et al. EASL 2019 (Abstract 75)
Quantitative HBsAg in Responder Patients > 0.5 log₁₀ Reduction at Week 12 or Week 24 from Baseline

**Mean Change in HbsAg**
- Week 12: 0.4 log₁₀
- Range 0.1 – 0.9 log₁₀

- Week 24: 0.72 log₁₀
- Range 0.15 - 1.4 log₁₀

**Yuen MF et al. EASL 2019 (Abstract 75)**
HBsAg release inhibitor
Nucleic Acid Polymer (NAP) : REP 2139/2165

- 40 nucleotide phosphorothioate oligoribonucleotide (RNA)
- Hydrophobic interactions drive delivery to the liver and provide pharmacologic effect

NAPs block subviral particle release (cccDNA and integration derived)
Efficient HBsAg clearance from blood

- Efficient HBsAg clearance from blood

HBeAg negative treatment naïve chronic HBV infection

**REP 2019/2165 + Tenofovir + Peg-IFN**

Week 1
Week 25
Week 49
Week 73
Week 97

- EXPERIMENTAL (20 patients)
  - REP 2139-Mg / REP 2165-Mg (1:1)
  - TDF
  - Pegasys
  - Follow-up

- ADAPTIVE COMPARATOR CONTROL (20 patients)
  - REP 2165-Mg / REP 2165-Mg (1:1)
  - TDF
  - Pegasys
  - Follow-up

- Patients with < 3 log HBsAg response at 49 weeks

Dosing:
- TDF 300mg PO qD
- Pegasys 180ug SC qW
- NAPs: REP 2139-Mg or REP 2165-Mg 250mg IV qW
- REP 2165 = REP 2139 variant with improved tissue clearance

Initial follow up scheduled 4, 12, 24 and 48 weeks after all treatment is stopped

Valliant A et al., AASLD 2018
REP 2139/2165 + Tenofovir + Peg-IFN

REP 401 Treatment and Follow-up Summary

<table>
<thead>
<tr>
<th>Patients entered into trial</th>
<th>40</th>
</tr>
</thead>
<tbody>
<tr>
<td>End of treatment HBsAg response</td>
<td></td>
</tr>
<tr>
<td>&gt; 1 log from baseline</td>
<td>36 (90%)</td>
</tr>
<tr>
<td>&lt; 1 IU/mL</td>
<td>27 (67%)</td>
</tr>
<tr>
<td>≤ 0.05 IU/mL</td>
<td>24 (60%)</td>
</tr>
<tr>
<td>Patients currently completed treatment and 24-48 weeks of follow-up</td>
<td>34</td>
</tr>
<tr>
<td>Stable, inactive HBV (HBV DNA ≤ 2000 IU/mL, normal ALT)</td>
<td>15 (44%)</td>
</tr>
<tr>
<td>Functional cure (HBsAg and HBV DNA target not detected)</td>
<td>14 (41%)</td>
</tr>
<tr>
<td>Therapy not indicated (AASLD / EASL guidelines)</td>
<td>29 (85%)</td>
</tr>
<tr>
<td>Clinical benefit (Low risk of fibrosis progression and HCC)</td>
<td></td>
</tr>
</tbody>
</table>

Valliant A et al., AASLD 2018
Conclusions

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

- **HBsAg release inhibition (IV or ? SC)**
  - Profound effect on HBsAg level
  - Able to achieve full blown HBsAg seroconversion (detectable anti-HBs)

- **RIG-I agonist (oral)**
  - Positive effects on HBV DNA and HBV RNA
  - Effects on HBsAg reduction maintained/ potentiated even after switching to NUC monotherapy