Hepatitis B
New Therapies

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Outline

• Definitions of endpoints of therapy
• Current therapy
• New therapies
Endpoints Of HBV Therapy

Three options:

• **Complete Cure:**
  • Eradication of the virus and replicative intermediates after stopping treatment

• **Functional Cure:**
  • Sustained viral suppression off treatment with decreased HBV related liver mortality

• **Partial cure:**
  • Sustained viral suppression on treatment
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<thead>
<tr>
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Proposed Definition Of Functional Cure

- Loss of HBsAg with or without anti-HBs 6 months after stopping therapy
Functional Cure

**Advantages**
- Is a feasible endpoint
- Easy to assess
- Associated with reduced rates of disease reactivation
- Once achieved, no requirement for therapy

**Limitations**
- Rarely achieved with current therapy
- Which assay should be used to measure HBsAg
- Small risk of HBV-related complications
Current Treatments for HBV

- Interferon
- Lamivudine
- Adefovir
- Telbivudine
- Tenofovir
- Entecavir

Issues with current treatments:
- Can maintain long term viral suppression but cannot cure CHB
- Requirement for long term administration
- Only partial cure in most
What Do We Mean By Cure?

• Eradication of cccDNA
• Clearance of HBsAg +/- anti-HBs
• Sustained HBV DNA suppression with normal ALT levels off therapy
Entry Inhibitors
- Myrcludex
- Cyclosporine
- Ezetimibe

Inhibit protein translation by siRNA

cccDNA silencing

HBsAg release inhibitor
- NAP

Polymerase inhibitors
- Nucleotide analogues
- Non-Nuc analogues
- RNAseH Inhibitors

Core protein allosteric modulators

Immunomodulators
- TLR 7 and 9 agonists
- T-cell vaccines
- PD-1/PD-L1 blockade
HBV Entry Inhibitors Myrcludex B

- Large surface protein-derived synthetic lipopeptide
- Acts as an entry inhibitor by binding to and inactivating the HBV receptor
Myrcludex B Proof Of Concept Phase 2a Trial

HBeAg (-), median HBV DNA $4.7 \log_{10}$, no cirrhosis

- Myrcludex B 0.5 mg qd n=8
- Myrcludex B 1 mg qd n=8
- Myrcludex B 2 mg qd n=8
- Myrcludex B 5 mg qd n=8
- Myrcludex B 10 mg qd n=8

- HBV DNA levels declined in all treatment groups
- >1 log reduction observed in 6/8 patients in the 10 mg dose group
- >1 log reduction in HBV DNA observed in 7/40 patients in the lower dosing groups
- No HBsAg loss

Urban S AASLD 2014
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Core protein allosteric modulators

Immunomodulators
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Novel Target For HBV “Cure”
Core Protein Allosteric Modulators

- Phenylpropenamide derivatives (AT-61, AT-131, GLS-4)
- Heteroaryldihydropyrimidines (Bay 41-4109)
- Sulfamoyl benzamides (**NVR 3-778**)
- Two mechanisms of action to dysregulate or selectively inhibit encapsidation of pregenomic RNA or nucleocapsid assembly or both
- Active against wild type and lamivudine resistant HBV *in-vitro*
NVR 3-778 Proof Of Concept Phase 1b Trial

- HBeAg (+)
- median HBV DNA 7.8 log\(_{10}\)
- No cirrhosis

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<thead>
<tr>
<th>Treatment</th>
<th>Description</th>
<th>Patients</th>
<th>HBV DNA log(_{10}) Reduction</th>
</tr>
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<tr>
<td>NVR 3-778 100 mg qd x 28 days n=12</td>
<td></td>
<td></td>
<td>&lt;.5</td>
</tr>
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<td></td>
<td></td>
<td>&lt;.5</td>
</tr>
<tr>
<td>NVR 3-778 400 mg qd x 28 days n=10</td>
<td></td>
<td></td>
<td>&lt;.5</td>
</tr>
<tr>
<td>NVR 3-778 600 mg bid x 28 days n=10</td>
<td></td>
<td></td>
<td>1.72</td>
</tr>
<tr>
<td>NVR 3-778 600 mg bid &amp; pegIFN 180 ug q week x 28 days n=10</td>
<td></td>
<td></td>
<td>1.97</td>
</tr>
<tr>
<td>Placebo &amp; pegIFN 180 ug q week x 28 days n=10</td>
<td></td>
<td></td>
<td>1.06</td>
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- <1 log reductions observed in HBV RNA and HBeAg levels
- NVR 3-778 well tolerated

Yuen MF et al  EASL 2016; 101B
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Novel Target For HBV “Cure”
Nucleic Acid Polymers (NAPs)

Subviral particles (bulk of serum HBsAg)

Infected hepatocyte

Nucleus

cccDNA

Capsids

Virions

HBeAg

Infection

NAPs block subviral particle release (HbsAg)

Infected hepatocyte

Nucleus

cccDNA

Capsids

Virions

HBeAg

Infection

Efficient HBsAg clearance from the blood

Vaillant, 2016. Antiviral Res. 133: 32-40
Real et al., 2016 J. Hepatol. 64: S395
Noordeen et al., 2015 PLOS One 10: e0140909
Noordeen et al., 2013 AAC 57: 5291-5298
Nooreen et al., 2013 AAC 57: 5299-5306

Slide courtesy A Vaillant
HBsAg response > 4 log: 9/10
HBsAg loss (≤0.01 IU/mL): 8/10

LLOQ = lower limit of quantification (0.05 IU / mL)
TND = HBsAg not detected (0.00 IU / mL)

LLOQ = lower limit of quantification (10 IU / ml)
TND = HBV DNA target not detected

Bazinet M et al EASL 2017 Abstract THU-154: Data courtesy A Vaillant
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Novel Target For HBV “Cure”
Inhibitors of HBV Gene Expression

High levels of HBsAg may inhibit HBV-specific immune responses

- Targeting viral mRNA
  - Antisense oligonucleotides
  - Ribozymes
  - RNA interference
ARB-1467

• Three synthetic small interfering RNA directed against mRNA at 3 sites HBV genome delivered IV
• Phase 2a study
ARB-1467 (siRNA)

Streinu-Cercel et al EASL 2017
Inhibitors Of HBV cccDNA Formation And Stability

Strategies to inhibit cccDNA:

• Blocking formation
  • Generation of sequence-specific endonucleases such as zinc finger nucleases or transcription activator-like effector nuclease to cleave cccDNA

• Elimination
  • Target RNaseH activity of HBV polymerase which is required for HBV replication and cccDNA formation with specific inhibitors

• Silencing of transcription
  • Inhibit transcription with CRISPR/cas9
## Inhibitors of HBV Gene Expression Development

<table>
<thead>
<tr>
<th>Candidate</th>
<th>Stage of Development</th>
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<tbody>
<tr>
<td><strong>Research</strong></td>
<td><strong>IND</strong></td>
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<tr>
<td>ARB-1467 RNAi</td>
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</tr>
<tr>
<td>AB-423 Capsid Inhibitor 1.0</td>
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</tr>
<tr>
<td>AB-506 Capsid Inhibitor 2.0</td>
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<tr>
<td>AB-452 HBV RNA Destabilizer</td>
<td></td>
</tr>
<tr>
<td>GalNAc RNAi</td>
<td></td>
</tr>
<tr>
<td>Checkpoint inhibitor</td>
<td></td>
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<tr>
<td>cccDNA Targeting Agent</td>
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<tr>
<td><strong>Enabling</strong></td>
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<tr>
<td>Phase I</td>
<td></td>
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<tr>
<td>Phase II</td>
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Many other studies are ongoing...

- Immunological assessment of HBeAg-negative chronic hepatitis B patient responses following anti-PD1 treatment
- TLR 7 Agonist: Safety and Efficacy of Vesatolimod (GS-9620) in Patients with Chronic Hepatitis B (CHB) Who Are Not Currently on Antiviral Treatment (phase 2)
- Sequential combination therapy with IFN, rhIL-2 and therapeutic vaccine enhanced HBsAg loss and led to partial immune restoration in entecavir-suppressed CHB patients (the Endeavor study)
• Oral capsid inhibitor: Single Dose Safety, Tolerability, and Pharmacokinetics of AB-423 in Healthy Volunteers from the ongoing Single and Multiple Ascending Dose Study AB-423-001

• TLR Agonist: Cytokines Induced by GS-9688, a Toll-Like Receptor 8 Agonist, Inhibit HBV RNA, DNA and Antigen Levels in Primary Human Hepatocytes

• Antisense Oligonucleotide: Safety, Tolerability and Pharmacokinetics of GSK3389404, an Antisense Oligonucleotide for the Treatment of Chronic Hepatitis B (CHB) Infection: A Randomized, Double-Blind, Placebo-Controlled, Dose-Escalation, First Time in Human Study

• Assembly inhibitor: Multiple Dose Study of GLS4JHS, Interfering With The Assembly Of HBV core particles, in patients Infected with Hepatitis B Virus

• Core protein modifier: Phase 1a Safety and Pharmacokinetics (PK) of ABI-H0731, a Novel Core Protein Allosteric Modifier (CpAM) For The Treatment of Chronic HBV Infection

AASLD 2017
Novel Assays

• HBV RNA
• HBVcrAg
• Ultrasensitive HBsAg
• Quantitative HBsAg
• HBsAg fragments
• HBsAg-Ab complexes
• Ultrasensitive HBV DNA
Hepatitis B core-related antigen

- **HB core related Antigen (HBcrAg)** correlates strongly with intrahepatic viral replication (including cccDNA)
  - AA sequence shared by different viral proteins: HBeAg, anti-HBc, 22 kDa precore protein
  - this sequence is independent of HBV DNA formation
  - Can be detected 19 months after HBsAg clearance

Seto AJG 2016
A Future Regimen To Achieve A Functional Cure

Likely will require combination of existing and future therapies

• Nucleos(t)ide analogue
• Immune activator
• cccDNA inhibitor
• HBV antigen inhibitor
Future Regimens To Achieve Functional And Complete Cure

- **Complete Cure**
  - cccDNA undetectable
  - Integrated HBV DNA eliminated

- **Functional Cure**
  - HBsAg negative
  - +/- anti-HBs

- **Partial Cure**
  - HBV DNA undetectable

- **NUC**
  - Novel antiviral
  - Immune-modulator
  - Gene editing

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  - Novel antiviral
  - Immune-modulator