Future Challenges in Hepatitis B Treatment

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Disclosures

- **Advisor**: AbbVie, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, Janssen, Merck Sharp & Dohme, Novartis
- **Lecturer**: Bristol-Myers Squibb, Gilead Sciences, Janssen, Merck Sharp & Dohme, Novartis
- **Clinical trials**: Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, Janssen, Merck Sharp & Dohme, Novartis, Roche
HBV can not be cured unlike HCV

<table>
<thead>
<tr>
<th>VIRUS</th>
<th>HIV</th>
<th>Hepatitis C</th>
<th>Hepatitis B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic archive</td>
<td>Yes</td>
<td>NO</td>
<td>Yes</td>
</tr>
<tr>
<td>Ability to cure most patients</td>
<td>No (Integrated viral DNA)</td>
<td>YES (No DNA integration)</td>
<td>No (cccDNA)</td>
</tr>
<tr>
<td>Current therapeutic goal</td>
<td>Lifelong suppression</td>
<td>Cure: Clearance from plasma and liver</td>
<td>Lifelong suppression</td>
</tr>
</tbody>
</table>
Pitfalls of Current Treatment

- Nucleoside Analogues are highly potent suppressing HBV DNA but
  - has little effect on HBsAg levels and depletion of cccDNA
  - Long-term therapy is the rule. Concerns on safety?

- IFN finite therapy duration but
  - Limited response
  - Low applicability
  - Side effects
Goal “Cure” of Hepatitis B

- Ultimate aim would be to ‘cure’ CHB
  - Functional cure
    - Off-therapy persistent HBV suppression
  - HBsAg loss and seroconversion
  - cccDNA eradication
  - Prevention of negative outcomes (HCC)


cccDNA: covalently closed circular DNA
New Strategies for Finite HBV therapy

• With the current available drugs

• With New Drugs
Which strategy to enhance HBsAg loss rates?

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Treatment</th>
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<tbody>
<tr>
<td>PEG-IFN</td>
<td>Simultaneously Combo</td>
</tr>
<tr>
<td>NUCs</td>
<td>PEG-IFN</td>
</tr>
<tr>
<td>NUCs</td>
<td>Switch or add-on IFN</td>
</tr>
<tr>
<td>PEG-IFN</td>
<td>NUCs</td>
</tr>
</tbody>
</table>
Tenofivir Disoproxil Fumarate plus Peginterferon Alfa-2a Combination Therapy for Chronic Hepatitis B

Study Design

- Randomized, controlled, open-label study (N=740)
  - Stratified by screening HBeAg status and HBV genotype
- Inclusion criteria
  - HBeAg+ and HBV DNA ≥20,000 IU/mL; HBeAg- and HBV DNA ≥2,000 IU/mL
  - ALT >54 and ≤400 U/L (men); ALT >36 and ≤300 U/L (women)
  - No bridging fibrosis or cirrhosis on liver biopsy or by transient elastography

Start TDF during follow-up if prespecified safety criteria met
7 patients had HBsAg seroreversion on or after Week 48 (4 [TDF + PEG 48 wk], 3 [TDF + PEG 16 wk → TDF 32 wk])
- 5/7 had ≤1 week of therapy after HBsAg loss
New Strategies for Finite HBV therapy

- With the current available drugs

- With New Drugs
What pathways or approaches might we take?

- The virus replication cycle offers many targets
Identification of NTCP as an HBV receptor


NTCP: sodium taurocholate cotransporting polypeptide
Inhibition of viral entry

Myrcludex-B is a synthetic lipopeptide consisting of a myristoylated pre-S1 domain of the large HBsAg with binding to the HBV entry receptor.


Phase 1a study completed – Phase 1b/2a study underway
# A Proof-Of-Concept Phase 2a Clinical Trial with HBV/HDV Entry Inhibitor Myrcludex B

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Treatment Arms</th>
<th>Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cohort A</strong>&lt;br&gt;Chronic HBV HBeAg negative&lt;br&gt;HBV DNA &gt; 2000 IU/mL&lt;br&gt;No Cirrhosis&lt;br&gt;• N=40</td>
<td>• Myr B, daily SC at 0.5, 1, 2, 5&amp;10 mg&lt;br&gt;• 12 wk treatment, with 12 wk follow-up (10 mg received 24 wk of treatment)</td>
<td>• Safety and tolerability&lt;br&gt;• Efficacy (ALT, HBV DNA, HBsAg)&lt;br&gt;• PK&lt;br&gt;• Immunogenicity&lt;br&gt;• Bile salt elevations</td>
</tr>
<tr>
<td><strong>Cohort B</strong>&lt;br&gt;Chronic HDV&lt;br&gt;12.5% cirrhosis&lt;br&gt;• N=24</td>
<td>• 24 wk of Myr B, daily SC at 2 mg, followed by 48 wk Peg-IFN&lt;br&gt;• 24 wk of Myr B added to 48 wk Peg-IFN&lt;br&gt;• 48 wk Peg-IFN alone</td>
<td>• Safety and tolerability&lt;br&gt;• Efficacy (ALT, HDV DNA)&lt;br&gt;• PK&lt;br&gt;• Immunogenicity&lt;br&gt;• Bile salt elevations</td>
</tr>
</tbody>
</table>

Urban S et al. AASLD 2014;LB20
A Proof-Of-Concept Phase 2a Clinical Trial with HBV/HDV Entry Inhibitor Myrcludex B

- At week 24, HBV DNA levels declined in all treatment groups
- >1 log reduction was observed in 6/8 (75%) patients in the 10 mg cohort
- 7/40 patients showed >1 log HBV DNA reduction in lower dosing groups
- No significant effect on HBsAg was observed after 24 weeks of treatment

Urban S et al. AASLD 2014;LB20
A Proof-Of-Concept Phase 2a Clinical Trial with HBV/HDV Entry Inhibitor Myrcludex B

- 6/7 vs. 7/7 patients showed >1 log HDV RNA reduction at week 24 during Myr B monotherapy vs. Peg-IFN combination therapy
- 2 vs. 5 patients became HDV RNA negative during Myr B monotherapy vs. Peg-IFN combination therapy
- Myr B/Peg-IFN combination therapy induced more preS-specific antibodies than Myr B monotherapy

Urban S et al. AASLD 2014;LB20
What pathways or approaches might we take?

- The virus replication cycle offers many targets
Tenofovir Alafenamid Fumarate (TAF)
Nucleotide Analogue Reverse Transcriptase Inhibitor (NRTI s)

Tenofovir

Tenofovir Disoproxil Fumarate

Tenofovir Alafenamide

- Improved stability in plasma:
  - Enhanced delivery of active form (TFV-DP) to hepatocytes
  - Lower doses are used; systemic exposures of TFV reduced

GUT | PLASMA | LYMPHOID CELLS/HEPATOCYTES
---|---|---
TFV | X |
TDF | TDF/TFV |
TAF | TAF | TAF

CES1 = carboxylesterase 1; DP = di-phosphate; MP = mono-phosphate.

Agarwal K et al. AASLD 2013
Murakami E et al. HepDART 2013
28 day safety, and antiviral activity of tenofovir alafenamide for treatment of chronic hepatitis B

TAF delivers high concentrations of tenofovir into primary human hepatocytes

TAF is being tested vs TDF in a Phase 3 study


TAF is an investigational agent and not licensed for use in CHB
TAF Phase III Studies

- 2 phase 3, randomized, double-blind studies
- Primary endpoint (non inferiority margin of 10%)
  - HBV DNA <29 IU/mL at Week 48
- Secondary endpoints
  - Bone mineral density
  - Renal parameters
Besifovir

- Acyclic nucleotide phosphonate (a guanosine monophosphate)
- Activity in Naïve and LAM resistant HBV
- Controlled trial comparing besifovir at 90 mg and 150 mg with entecavir has similar efficacy
- Besofovir needs oral L-carnitine supplements due to the depletion of L-carnitine through renal loss

Lai C et al Gut 2013
Two years Besifovir vs. Entecavir for Chronic Hepatitis B: A multicenter study

Similar HBV DNA suppression similar HBeAg loss. None loss HBsAg
84-100% needed L-carnitine supplements

Yuen M F et al J Hepatol 2015
What pathways or approaches might we take?

- The virus replication cycle offers many targets

Adapted from Stein LL, Loomba R. Infect Disord Drug Targets 2009;9:105–16

ER: endoplasmic reticulum
Inhibition of cccDNA formation

Conversion of relaxed circular HBV DNA into cccDNA can be inhibited

- Small molecule library screening (n=85,000) revealed disubstituted sulfonamides (CCC-0975 and CCC-0346) block production of cccDNA in cell culture and duck hepatocytes

Phase II, study of ACR-520 a short interfering RNA containing (siRNA)

- ARC-520, an RNAi therapeutic, liver targeted aimed to reduce all HBV transcripts via RNA interference
- In HBV infected chimpanzee a reduction of viral particles and decreased expression of viral proteins was observed.
- Viral proteins (HBsAg and HBeAg) have been implicated in immune tolerance, sustained infection and disease progression
Phase II, Dose-Ranging Study of ACR-520, a siRNA-Based Therapeutic, in Patients with Chronic HBV Infection

16 Chinese patients with Chronic hepatitis B

ARC-520 activity is measured by % of qHBsAg decline from baseline after a single iv dose

- In Cohort 1, mean nadir HBsAg was -39% (range -22 to -57) with a mean change on day 85 of -31% (range -14 to -39)
- In cohort 2, mean nadir HBsAg was -51% (range -46 to -59) with a mean change on day 85 of -22% (range -7 to -40)

Yuen M et al. AASLD 2014 LB-21
Phase II, Dose-Ranging Study of ACR-520, a siRNA-Based Therapeutic, in Patients with Chronic HBV Infection

- No serious AEs, no dose limiting toxicities, no discontinuations due to AEs
- Low occurrence rate of abnormal laboratory tests, with no observed relationship to timing or dose
- All reported AEs were unrelated or unlikely related to study drug

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Placebo n=4</th>
<th>Cohort 1 n=6</th>
<th>Cohort 2 n=6</th>
<th>Cohort 3 n=8 (blinded)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>0</td>
<td>1</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Flu like symptoms</td>
<td></td>
<td>1 mild</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CK elevation</td>
<td></td>
<td>1 mild</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injection extravasation</td>
<td></td>
<td>1 mild</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Near syncope</td>
<td></td>
<td></td>
<td>1 mod</td>
<td></td>
</tr>
<tr>
<td>Malaise</td>
<td></td>
<td></td>
<td>1 mod</td>
<td></td>
</tr>
<tr>
<td>Leg pain</td>
<td></td>
<td></td>
<td></td>
<td>1 mild</td>
</tr>
</tbody>
</table>

Yuen M et al. AASLD 2014 LB-21
Phase 1a Safety and Pharmacokinetics of NVR 3-778 HBV Core Inhibitor

- NVR 3-778 is a potent and selective oral HBV core inhibitor that inhibits HBV nucleocapsid assembly and potentially other core-mediated functions in the HBV lifecycle.
- HBV Core inhibitors potential to boost durable responses by inhibiting HBV DNA replication, viral assembly, cccDNA replenishment and hepatic reinfection.
- In vitro antiviral HBV activity similar to potent NAs.

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<tr>
<th>Patient Population</th>
<th>Treatment Arms</th>
<th>Endpoints</th>
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</thead>
<tbody>
<tr>
<td><strong>Part I:</strong> Healthy volunteers</td>
<td><strong>Part I:</strong> 28 days of NVR 3-778 (50-200 mg QD oral) vs. placebo</td>
<td><strong>Part I:</strong> Safety and PK</td>
</tr>
<tr>
<td><strong>Part II:</strong> Chronic HBV Treatment-naïve HBeAg positive</td>
<td><strong>Part II:</strong> 28 days of NVR 3-778 (QD oral) + Pegasys (subQ) vs. Pegasys</td>
<td><strong>Part II:</strong> Safety, PK, and antiviral activity</td>
</tr>
</tbody>
</table>

Gane E et al. AASLD 2014 LB19
Phase 1a Safety and Pharmacokinetics of NVR 3-778 HBV Core Inhibitor

- Cohort E (200 mg QD): peak levels ($C_{max}$) = ~3.5 µM, 24 hr trough levels > 1 µM
- Exposures exceed HBV inhibitory concentration in HepG2 cells ($EC_{50}$ = 0.24 µM; $EC_{90}$ = 0.62 µM)
- Doses > 200 mg may afford continuous HBV inhibition with QD dosing schedule

**Phase 1a: Mean NVR 3-778 Plasma Concentrations Over Time by Cohort**

*Gane E et al. AASLD 2014 LB19*
What pathways or approaches might we take?

- The virus replication cycle offers many targets

Adapted from Stein LL, Loomba R. Infect Disord Drug Targets 2009;9:105–16

ER: endoplasmic reticulum
Immunomodulators

- **Immune dysfunction is the basis for chronic HBV infection**
  - Immune modulation aims to induce immune control with a view to finite therapy
  - Potential for therapeutic immune modulation in CHB shown by durable responses in a low proportion of patients treated with a finite course of PEG-IFN
- **Toll-like receptors (TLRs)**
  - Recognise a variety of broadly conserved pathogen-associated molecular patterns
  - TLR agonists trigger innate and adaptive immune responses
  - Currently in Phase 1/2
- **Therapeutic vaccines**
  - Vaccination with recombinant HBV proteins overcomes diminished T-cell response in CHB

TLR-7 agonists

- TLR-7 activation leads to secretion of type I IFN, T-cell co-stimulation and B-cell differentiation
- GS-9620 is an oral TLR-7 agonist with nanomolar potency
- Preclinical studies show GS-9620 reduces HBsAg and HBV DNA in woodchucks and chimpanzees
- Phase 1a single ascending dose study complete: favourable safety profile shown in healthy volunteers (N=75)

GS-9620 is an investigational agent and not licensed for use in CHB;
IRF: interferon regulatory transcription factor;
NFkB: nuclear factor kappa B; ISG: interferon stimulating genes

Gane E, et al. AASLD 2013; Abstract 9896
TLR-7 agonism Induces sAg Seroconversion in Chronically Infected Woodchucks

![Graph showing TLR-7 agonism Induces sAg Seroconversion in Chronically Infected Woodchucks](image)

<table>
<thead>
<tr>
<th>α-sAg Ab+ (#)</th>
<th>Max Δ DNA (log₁₀)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0/7</td>
<td>- 0.6</td>
</tr>
<tr>
<td>1/7</td>
<td>- 1.0</td>
</tr>
<tr>
<td>3/7</td>
<td>- 3.9</td>
</tr>
<tr>
<td>2/7</td>
<td>- 4.7</td>
</tr>
</tbody>
</table>

**Legend:**
- 5 mg/kg
- 5/2.5 mg/kg
- Placebo

**Axes:**
- X-axis: Week
- Y-axis: Mean WHsAg Titer (ODU)
TLR-7 agonist (GS-9620) in patients with CHB

Patients with CHB: treatment naïve (N=49) or virologically suppressed (N=50)

<table>
<thead>
<tr>
<th>Day (h)</th>
<th>1 (0)</th>
<th>8 (168)</th>
<th>15 (366)</th>
</tr>
</thead>
</table>

First GS-9620 dose
- Single ascending dose (SAD cohorts)
  - SAD: Placebo 5:1

Second GS-9620 dose
- Multiple ascending doses (MAD cohorts)
  - MAD: Placebo 5:1
- 0.3 mg SD
- 1 mg SD
- 2 mg SD
- 4 mg SD
- 0.3 mg QW (2 doses)
- 1 mg QW (2 doses)
- 2 mg QW (2 doses)
- 4 mg QW (2 doses)

*Follow-up visits at 2 and 4 weeks from last dose;.
GS-9620 is an investigational agent and not licensed for use in CHB;
QW: once weekly; SD: single dose

Gane E, et al. EASL 2014; Poster 1052;
Clinicaltrials.gov NCT01590654 and NCT01590641
Significant dose dependent ISG15 mRNA induction in peripheral blood

- GS-9620 treatment was seen to have a favourable safety profile and was well tolerated
- Longer treatment durations required to assess safety and efficacy in CHB patients

Gane E, et al. EASL 2014; Poster 1052; Clinicaltrials.gov NCT01590654 and NCT01590641

GS-9620 is an investigational agent and not licensed for use in CHB
Therapeutic vaccination with GS-4774

- GS-4774 is a yeast-based vaccine expressing recombinant X, large S and core HBV antigens

<table>
<thead>
<tr>
<th>GS-4774 structure</th>
<th>GS-4774 recombinant antigen</th>
</tr>
</thead>
<tbody>
<tr>
<td>M</td>
<td>X</td>
</tr>
<tr>
<td>X = 60 amino acids</td>
<td>M = MADEAP metabolic stability tag</td>
</tr>
<tr>
<td>Large S = 399 amino acids</td>
<td>His⁶ = 6 histidine-tag</td>
</tr>
<tr>
<td>Core = 182 amino acids</td>
<td></td>
</tr>
</tbody>
</table>

- Weekly versus monthly doses for 3 consecutive months studied in healthy volunteers (n=60)
- Immune response was assessed

Gaggar A, et al. AASLD 2013; Abstract 9952; Clinicaltrials.gov NCT01779505

GS-4774 is an investigational agent and not licensed for use in CHB; env: envelope
Detectable HBV-specific immune responses in the majority of patients

Combined response to HBsAg, HBcAg and HBx

GS-4774 is an investigational agent and not licensed for use in CHB; HBcAg: hepatitis B core antigen; HBx: hepatitis B x-gene

Gaggar A, et al. AASLD 2013; Abstract 9952; Clinicaltrials.gov NCT01779505
**How may a HBV curative regimen look in the future – a combination approach?**

<table>
<thead>
<tr>
<th>Approach</th>
<th>Potential benefit</th>
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</thead>
<tbody>
<tr>
<td>Entry/release inhibitor</td>
<td>Prevent entry/spread</td>
</tr>
<tr>
<td>cccDNA inhibitor</td>
<td>Deplete cccDNA reservoir</td>
</tr>
<tr>
<td>Potent polymerase inhibitor</td>
<td>Suppress replication</td>
</tr>
<tr>
<td>Immune modulator</td>
<td>Activate or restore antiviral immunity</td>
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</tbody>
</table>