Novel Therapeutic Agents for Chronic Hepatitis B

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GRANTS
AbbVie, Bristol Myers Squibb, Gilead, Innogenetics, Janssen, Medimmune, Merck, Novartis, Roche.

CONSULTANT
AbbVie, Arbutus, Benitec, Bristol Myers Squibb, Eiger Bio, Spring Bank Pharma, Gilead, GSK, Innogenetics, ISIS Pharmaceuticals, Janssen, Medimmune, Merck, Novartis, Roche
Is HBV Treatment Paradigm changing?

**Current PARADIGM**

• Indefinite Treatment
• Poor off-Rx response
• Reduces overall mortality
• Reduce but does not eliminate the risk of HCC
• Potent NAs: suppresses viral replication but cannot cure the disease

**New PARADIGM**

• Finite treatment duration
• Sustained off-Rx response shift towards endpoint of true immune control & HBsAg seroconversion
• No increased risk of mortality and HCC
• New HBV treatments with increased chance of curing disease
Key Considerations for Current Treatment Options

- HBV nucleos(t)ides are highly effective and generally well tolerated, but with high rates of relapse after discontinuation.

- Long-term nucleos(t)ide-analogues reduce cirrhosis, liver failure and HCC; safety remains to be determined but appears very good.

- PEG-IFN monotherapy is finite but only effective in subgroup of patients and its use is limited due to toxicity.

- Thus, unlike HCV there is highly effective and safe therapy available which suppresses HBV.
Why is Finite Therapy a Goal for HBV Treatment?

- Younger patients may find lifelong treatment hard to accept.
- Women who want to become pregnant.
- Patients reluctant to start treatment.
- Working days lost to hospital visits.
- Cost savings to healthcare system.
- Long-term adherence issues.
HBV Life cycle
Towards New HBV Treatment Targets

- Myclonex-B
- Cyclosporin
- Interferon-α
- LTBR
- ZFNs
- Pegylated-Lambda
- TLR agonist
- PD-PDL1 Blocking
- Therapeutic Vaccin
- RNAi
- ASO
- ALN-HBV
- HAP
- Phenytoitramide
- Isothiophene
- NVR-1221
- TAF
- AGX-1009
- Besifovir
- Lagociclovir valactate
- NAP(Rep 9AC)
- Nitazoxanide
- TLR agonist
- Nitazoxanide
- NAP(Rep 9AC)
New HBV Treatments

**Virology**
Entry inhibitors
cccDNA Degradation/Silencing/Elimination
RNA interference (RNAi)/Gene silencing
Assembly (Nucleocapsid) inhibitors
New Nucleos(t)ide Analogues

**Immunology**
PEG-IFN Lambda
TLR agonists
Therapeutic vaccination
PD-1, PDL-1 Blocking
New HBV Treatments

**Virology**

Entry inhibitors  
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Scientists from National Institute of Biological Sciences (NIBS), Beijing discovered a functional receptor for Hepatitis B virus (HBV) infection

- It opens doors for future high throughput drug screen
- as well as revealed an important new target for treating HBV infection and related diseases

the receptor-binding region of pre-S1 specifically interacts with sodium taurocholate cotransporting polypeptide (NTCP), a multiple transmembrane transporter predominantly expressed in the liver.

Myrcludex B: Acylated HBV preS1-derived peptides block HBV infection in vitro – entry inhibitor

Myrcludex B: Myt-GQNL STSMP LGFFD DHQLD PAFRA NTAMD DWDFN DNKD'T WPDAN KVG

Chemically synthesized lipopeptides derived from the envelope of HBV block virus infection in cell culture (HepaRG & PTH, PHH)

Gripou et al., PNAS, 99 (24) 2002
Urban et al., J. Virol, 79 (3), 2005
Glebe et al., Gastroenterology, 129, 2005
Engelke et al., Hepatology, 43, 2006
Schulze et al., Hepatology, 46, 2007
### Phase 2a clinical trial with the HBV/HDV entry inhibitor Myrcludex B

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Treatment Arms</th>
<th>End points</th>
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<tbody>
<tr>
<td>- CHB HBeAg negative</td>
<td>- Myr B daily S.C (0.5, 1, 2, 5, 10 mg) for 12 w (10mg for 24w) -12 weeks follow-up</td>
<td>- Safety and tolerability - Efficacy (HBV DNA, ALT, HBsAg) - PK - Immunogenicity - Bile acids levels</td>
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<td>- HBV DNA &gt; 2000IU/ML</td>
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<td>- No cirrhosis</td>
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<td>- N = 40</td>
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- At 24w, HBV DNA declined in all treatment groups
- >1 log reduction in HBV DNA in 6/8 (75%) of the 10mg (24w) group
- 7/40 patients >1 log reduction HBV DNA in lower dose groups
- ALT normalization in 55%
- No significant effect on HBsAg at 24 weeks

*Urban S et al, AASLD 2014*
Strategies to control/eliminate cccDNA

Pharmacological (small molecules)

Immune control

Gene therapy

Host factors
Non-cytotoxic degradation of cccDNA by IFN-alfa and lymphotoksin β receptor agonists

Lucifora J et al, Science 2014
cccDNA Degradation/Silencing/Elimination

- Zinc finger nucleases and Sulfonamide compounds: direct destruction of cccDNA, inhibiting rcDNA conversion to cccDNA and by targeting the epigenetic control of cccDNA
- Early development: cell culture/primary duck hepatocytes
- **CRISPR**: use target RNA with sequence specificity for conserved regions of DNA to guide nuclease to cleave the DNA at that site
- Suppression of cccDNA in HBV transgenic mice
- CRISPR strategy holds promise for human gene therapy and may be useful targeting a stable viral genome like HBV

*Kennedy et al. Virology 2015*
RNA Interference/ Gene Silencing

- HBV susceptible to RNAi because it replicates via an RNA intermediate
- Delivery is now possible through different platforms (LNA, nano particles)
- SI RNA can knockdown production of all HBV genes and thereby significantly decrease the number of infectious viral particles and Ag’s
- This reduction in viral and antigen load is designed to permit the immune system to mount an effective response to CHB
- Phase II ARC 520 (Arrowhead): Single IV dose 1-4 mg/kg with ETV; mean max HBsAg decline of 1.1 log in HBeAg pos and 0.2 log in HBeAg neg; response less good in those pre-treated with ETV. 23% reported mild to moderate AE

Capsid Inhibitors

Capsid inhibitors disrupt the HBV lifecycle by destabilizing the nucleocapsid and/or by blocking RNA packaging thus producing empty capsids lacking genetic information.

Potentially inhibit viral assembly, HBV genome replication, cccDNA replenishment and hepatic reinfection cycles.

NVR 3-778
- No adverse events in volunteers
- Phase 1b: 100 to 600 mg BD
- Mean HBVDNA decline 1.72 log in highest dose group after 28 days
- One patient serious rash hand and feet
- Studies with higher doses and combination with PEG-IFN ongoing

Tenofovir Alafenamide Fumarate (TAF)
Nucleotide Analogue Reverse Transcriptase Inhibitor (NRTIs)

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

Agarwal K et al. J Hep 2015
Murakami E et al. HepDART 2013

CES1 = carboxylesterase 1; DP= di-phosphate; MP= mono-phosphate.
Tenofovir Alafenamide Fumarate (TAF)
Nucleotide Analogue Reverse Transcriptase Inhibitor (NRTIs)

• 25 mg TAF similar antiviral activity but reduces systemic exposure to < 8% of exposures generated by 300 mg tenofovir
• Probably less nefrotoxic than tenofovir
• Also beneficial for HBV+HIV co-infected
• Phase 3 study:
  – Primary endpoint HBV DNA <29 IU/mL at Week 48
  – Secondary endpoints: bone mineral density and renal parameters

Agarwal et al. J Hep 2015
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<th><strong>Virus Targeting</strong></th>
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<tr>
<td><strong>Entry Inhibitors</strong></td>
<td>Targets NTCP receptor to inhibit viral infection</td>
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<tr>
<td><strong>Assembly Effectors</strong></td>
<td>Inhibits HBV replication by causing destabilization of viral nucleocapsid</td>
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<tr>
<td><strong>RNA Interference</strong></td>
<td>RNA molecules inhibiting gene expression and release of new virions</td>
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<td><strong>New Nucleos(t)ide Analogue</strong></td>
<td>DNA polymerase inhibitor</td>
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<td><strong>HBsAg Release Inhibitor</strong></td>
<td>Inhibits the release of HBsAg SVPs and boosts restoration of the immune response</td>
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<td><strong>cccDNA Degradation</strong></td>
<td>Up-regulation of APOBEC3A and APOBEC3B causing cccDNA degradation</td>
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New HBV Treatments

**Virology**
- Entry inhibitors
- cccDNA Degradation/Silencing/Elimination
- RNA interference (RNAi)/Gene silencing
- Assembly (Nucleocapsid) inhibitors
- New Nucleos(t)ide Analogues

**Immunology**
- PEG-IFN Lambda
- TLR agonists
- Therapeutic vaccination
- PD-1, PDL-1 Blocking
Immune Modifying Agents

Innate immunity | Adaptive immunity

Hepatocyte

- Uptake viral particles/antigens
- IFNαβ
- Cytotoxicity

NK(T)

- Activation

CD8+

- CD4+
- IFNγ/TNFα: viral replication

B

- Neutralization

Anti-HBe, HBc, HBs

DC

- Viral replication

Viral replication

IFNαβ

Viral lysis
Peg-IFN Lambda vs Alfa One Year of Therapy
HBeAg Seroconversion

Week 48

Baseline

Peg-IFN Lambda 180 µg
(N = 80)

14/80 (18%)

Week 24 post-dosing

11/80 (14%)

Peg-IFN Alfa 180 µg
(N = 83)

14/83 (17%)

25/83 (30%)

Chan HL, et al. EASL 2014
Toll Like Receptor (TLR) 7 Agonist

- TLR-7 is a pattern recognition receptor in endolysosomal compartment of plasmacytoid dendritic cells (pDC) and B cells
- Agonism induces anti-viral response via innate immune activation

• GS-9620
  - Potent oral TLR-7 agonist tested in several animal models
  - Decline in HBVDNA and HBsAg during GS-9620 therapy in HBV-infected chimpanzees
  - Safe and well tolerated in 84 patients, significant dose dependant ISG-15 mRNA induction was observed in peripheral blood

Lanford R et al. Gastroenterology 2013; Gane E et al. AASLD 2013
The Oral Toll-Like Receptor-7 Agonist GS-9620 suppresses Hepatitis B Virus

- Woodchuck hepatitis B model
- Less HCC

Menne S et al, J Hep 2015

Phase Ib study - HBV patients

- Activation of ISG’s
- No clinically significant changes in HBsAg or HBV DNA levels were observed

Gane EJ et al, J Hep 2015
Therapeutic Vaccination
Tarmogen/GS-4774

- Tarmogens are made from genetically modified yeast that express one or more disease-associated antigens
- Activate T cells to specifically target and eliminate diseased cells with the same target antigen
- Elicited an immune response to recombinant antigens and peptides in healthy volunteers (independent of host HLA alleles); well-tolerated
- Further evaluation of GS-4774 in virally suppressed chronic HBV patients is ongoing

Gaggar et al. AASLD 2013
DNA vaccination to promote anti-viral immune response among HBV patients

**Phase I study**
(HBeAg positives after Lam breakthrough)

DNA vaccine containing the small and middle regions of S Ag was safe and elicited immunological response as measured by IFN gamma secretion by T cells in response to HBsAg

**Phase I/II study**
(HBV negative after cessation of NAs)

5 IM injections of surface based DNA vaccine did not prevent HBV reactivation after NUCs discontinuation and did not restore anti-HBV immune response

*Mancini M et al, Vaccine 2006; Fontaine H et al, Gut 2015*
Reversing the exhausted Phenotype of HBV-specific T cells

• Inability to eliminate virus in CHB has been attributed to high levels of expression of programmed death 1 (PD-1) and its ligand (PD-L1/B7-H1) on viral antigen-specific T-cells and APC’s

• Blocking the PD-1/PD-L1 interaction in vitro reversed exhausted cytokine production and proliferation of these HBV specific T cells
Blocking PD-1 to reverse HBV T cells exhaustion in a WHV model

- Combination therapy that included ETV, DNA vaccine and anti-PD-L1 antibody
- Combination regimen: enhanced HBV specific T cell activation and more robust and sustained suppression of HBV DNA and HBsAg
- Proof of principle to the efficacy of a combination immune modulation therapy with an anti-viral agent

Liu J et al, Plos Pathogens 2014
STING agonists induce an innate anti-viral immune response against HBV infection

- DNA sensor cGAS activates STING in response to various stimuli such as foreign DNA, that in turn generates production of anti-viral type I interferons
- in mice STING agonist (DMXAA) elicit a cytokine response (mainly IFN beta) resulting in suppression of HBV DNA in parallel to induction of cellular ISGs
HBV Curative Regimen?

Antiviral

Prevent viral spread, cccDNA re-amplification

Immune activator

Activate antiviral immunity or relieve repression of the system

HBV Functional Cure

HBV antigen inhibition

Inhibit other components in HBV life cycle [entry or cell-spread, capsid, HBX, HBsAg]

cccDNA inhibitor

Deplete or perturb cccDNA
Conclusions

- NA are effective, safe and difficult to replace
- Shift towards endpoint of true immune control, functional cure and HBsAg seroconversion
- New Viral agents: HBV entry inhibitors, small interfering RNA, capsid inhibitors promising but early in development
- Direct ccc-DNA inhibition may be needed but is difficult to reach
- Immune modification: TLR agonist, therapeutic vaccination, PD1-PDL1 blocking in development
- Combination therapy most likely needed!