HBV: What is in the Pipeline?

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No conflict of interest to disclose
New agents/drugs that are not yet FDA approved will be discussed
Persistence of Hepatitis B

Outcome: Clinical Recovery

Outcome: Chronic Hepatitis

Adapted from Rehermann B and Mascimbeni M Nat Rev Immunol 5: 1573, 2005
Current HBV Treatment

**Nucleos(t)ides**

- Tenofovir
- Adefovir
- Telbivudine
- Lamivudine
- Entecavir

**Interferons**

- Pegylated Interferon alfa 2a
- Pegylated Interferon alfa 2b
Efficacy of HBV Agents After One Year of Therapy

Data from 2012 EASL HBV Management Guidelines

ALT Normalization (% patients at 1 year)

<table>
<thead>
<tr>
<th>Agent</th>
<th>HBeAg+</th>
<th>HBeAg-</th>
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<tbody>
<tr>
<td>Tenofovir</td>
<td>80</td>
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<tr>
<td>Entecavir</td>
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<tr>
<td>Telbivudine</td>
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<tr>
<td>Lamivudine</td>
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<tr>
<td>Adefovir</td>
<td>60</td>
<td>80</td>
</tr>
<tr>
<td>PEG-IFN-2a</td>
<td>40</td>
<td>80</td>
</tr>
</tbody>
</table>

Data from 2012 EASL HBV Management Guidelines
74% of Patients with Cirrhosis at Baseline Were No Longer Cirrhotic at Year 5

Marcellin, P et al. Lancet 2013; 381(9865):468-75
Efficacy of HBV Agents After One Year of Therapy: HBsAg Loss

Data from 2012 EASL HBV Management Guidelines
Pitfalls of Current Therapy

- Nucleoside analog therapy has little effect on HBsAg levels, HBsAg loss and depletion of cccDNA

- Emergence of resistance is a potential problem with long term nucleoside analog therapy

- Long term adverse events may occur with continued use of nucleoside analogs
Goals for Eradication

- Absence of plasma HBV DNA after stopping antiviral therapy

- Loss of HBsAg with or without HBsAg seroconversion
Target the Virus and/or Target the Host

- Viral proteins or nucleic acids
- Host proteins necessary for viral replication
- Innate or adaptive immune system
Novel Strategies to Eradicate HBV

Target the Virus

- Viral proteins or nucleic acids
HBV Life Cycle, Potential Targets

Entry of HBV into cell

Core assembly and RNA packaging

Core particle minus strand synthesis

Core particle plus strand synthesis

Repair

cccDNA

Transcription

Translation

Recycling

Vesicular transport to cell membrane

HBsAg

HBeAg
Targeting HBV Entry

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HBsAg

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HBV

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HBV core particle minus strand synthesis

HBV core particle plus strand synthesis

Entry of HBV into cell

Vesicular transport to cell membrane

HBsAg

HBeAg
Inhibition of Viral Entry: Myrcludex B

Myrcludex B prevents de novo infection preclinically

Key Issues: Will it have an impact on chronic infection, or HBsAg loss?

Targeting cccDNA

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Vesicular transport to cell membrane

HBcAg

HBsAg

cccDNA
Depleting or Inactivating cccDNA

Key issues:

– cccDNA = reservoir of infection

– Formation of *new* cccDNA can be blocked by inhibiting replication

  – Existing cccDNA is not affected directly by current therapies and has a long half-life

– Is it possible to silence cccDNA epigenetically?

– Is it possible to destabilize cccDNA?
Epigenetic Silencing of cccDNA by Interferon-alfa

- cccDNA “silenced”, not depleted
- Possible to identify other ways to “silence” cccDNA?
- Zinc finger motifs in Duck Hepatitis model

Belloni L. J. Clin Invest 2012; 122:529-537
ZFP Decreases HBV Replication in Hep AD38 Cells

TALENs

- transcription activator-like effector nucleases

Chen et al, *Molecular Therapy* 2014; 22(2):303–311
Targeting Encapsidation

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HBV

HBsAg

HBeAg
HBV Capsid Inhibitors

Key Issue: Will capsid inhibitors impact HBsAg loss or only have antiviral activity like nucleosides?

Phase 1 clinical trial is planned with HBV capsid inhibitor

Targeting Envelopment and Secretion

Entry of HBV into cell

Core assembly and RNA packaging

Recycling

Core particle minus strand synthesis

Core particle plus strand synthesis

Vesicular transport to cell membrane

Translation

Transcription

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cccDNA

HBV

HBsAg

HBeAg
Inhibition of HBsAg Secretion

Key Issues:

- Will suppression of HBsAg antigenemia restore T cell responsiveness?
- Mechanism undefined, potential to inhibit host protein secretion?

Novel Strategies to Eradicate HBV

Target the Host

- Host proteins necessary for viral replication
- Innate or adaptive immune system
Mechanisms of Persistence

HBV

PAMP or Pathogen

Endocytic PRR

TLR

IFN-α/β

IFN-γ

IL-18 CCL3

Antigen presentation

Adaptive immune responses

Cytokine and chemokine production

Kupffer cells

DC

Hepatocyte

NKT cells

NK cells

Hepatocyte
GS-9620, an orally available agonist

Selective for antiviral vs proinflammatory response

Preclinical studies: Reduces sAg, viral DNA in woodchucks & chimpanzees

Phase 1a (SAD) complete: Safety shown in healthy volunteers

Lopatin U et al. *Antivir Ther* 2013; 18:409-418
Oral TLR7 Agonist GS-9620 Highlights Potential of Immunotherapy for Chronic HBV

Lanford et al. Gastroenterology 2013;144:1508-17.
Adaptive Immunity in Chronic Hepatitis B Infection

Antigen presentation to both CD4+ and CD8+ T-cells

APC

MHC II

TCR

CD80/86

CD28

Naive CD4+ T-cell

CD8+ T-cell

IL-12

Th1 CD4

IL-2

IFN-γ and TNF-α

CD4 differentiates into two subsets

Th1 CD4

Hepatocyte

Cytolytic activity and production of IFN-γ and TNF-α

HBeAb

HBeAb

HBeAb

B cell

IL-10

IL-4

IL-10

IL-4
Effect of PD-1/L1 on Antiviral Immunity

- CD80, CD86
- CD28
- MHC
- Peptide antigen
- TCR
- PD-L
- PD-1
- Costimulatory ligand
- Costimulatory receptor

Naive T cell → Activated T cell → Exhausted T cell → Reinvigorated T cell

- Activated APC
- Chronic infection, persistent antigen stimulation

Proliferation
Cytokines
Cytotoxicity

Proliferation
Cytokines
Cytotoxicity

Proliferation
Cytokines
Cytotoxicity

Proliferation
Cytokines
Cytotoxicity

Blocking antibody
Expansion of HBV-specific CD8 T Cell Response by Blocking PD-1/L1/2 Interaction In Vitro

Sherman AC et al. AIDS Res Hum Retr 2012
Effect of anti-PD-1 or PD-L1 Antibodies in Cancer

Safety, Activity, and Immune Correlates of Anti–PD-1 Antibody in Cancer
SL Topalian, M Sznol et al.

Safety and Activity of Anti–PD-L1 Antibody in Patients with Advanced Cancer
JR Brahmer, JM Wigginton et al.
Blocking PD-1/L1 to Enhance HBV Immunity

**PD-1 antibody**
- Blocks PD-1
- Acts on T cells
- More efficient blocking?
- More adverse events
- Risk benefit

**PD-L1 antibody**
- Blocks PD-L1
- Acts on APCs
- Less efficient blocking
- Less adverse events
- Risk benefit
Chimeric Antigenic Receptors (CAR)

First Generation CAR
- scFv
- VH
- VL
- Linker
- hinge
- CD3ζ

Second Generation CAR
- One Costimulation Domain (4-1BB or CD28)
- CD3ζ

Third Generation CAR
- Two costimulation domains
  - CD27
  - CD28
  - ICOS
  - 4-1BB
  - OX40

June CH et al Blood 2014
Therapeutic Vaccines

Li et al. J Biotechnology 2012
Our goal is to achieve sustained suppression of HBV and HBsAg loss after cessation of therapy.

Approaches to target virus include inhibition of viral entry, HBV antigen production, and elimination or silencing of cccDNA.

Approaches to target host include non specific inhibition of immunoregulatory pathways and boosting of HBV specific immunity.

Realistically, a combination approach may be necessary to achieve sustained virologic remission.