New Therapeutic Options for Hepatitis B in 2018: Can We Eradicate cccDNA?

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Approved HBV Treatments

- **Interferons (IFN)**
  - Standard IFN alfa - 1992
  - Pegylated IFN alfa - 2005

- **Nucleos(t)ide analogues**
  - Lamivudine (Epivir) - 1998
  - Adefovir (Hepsera) - 2002
  - Entecavir (Baraclude) - 2005
  - Telbivudine (Tyzeka) - 2006
  - Tenofovir disoproxil fumarate (Viread) – 2008
  - Tenofovir alafenamixse (Vemlidy) - 2016
Efficacy and Limitations
of Current HBV Treatment

Efficacy

• Potent virus suppression
• Reverses hepatic inflammation and fibrosis
• Prevents progression to cirrhosis and liver failure
• Decreases risk of HCC
• Excellent safety profile for NAs

Limitations

• Does not eradicate cccDNA or integrated HBV DNA
• Low rate of HBsAg loss
• Long duration of treatment required
• Risk of HCC persists albeit at lower rate

NA = nucleos/tide analogue, HCC = hepatocellular carcinoma
Is HBV Cure Possible?

Can treatment accomplish what nature can’t? HBV persists in persons who have recovered from acute hepatitis B with HBsAg to anti-HBs seroconversion

• Reactivation of HBV replication can occur during potent immunosuppressive therapy
• Transmission of HBV possible when livers are transplanted
• Long-lasting rigorous immune response to HBV possibly from continued stimulation by residual virus
Barriers to Eradicating HBV

- Covalently closed circular (ccc) DNA
  - Long half-life in non-dividing cells
  - Replenished from cytoplasmic core
  - NAs no direct inhibitory effect
- Integrated HBV DNA
- Impaired immune response

NA = nucleos(t)ide analogue
Potential paths towards cccDNA eradication

- Decrease production
  - Block infection (entry inhibitors)
  - Block conversion of relaxed circular DNA to cccDNA
- Decrease cccDNA amplification
  - Block intracellular entry of new capsids (CpAM, NA)
- Decrease persistence
  - Increase turnover of infected cells
  - Increase degradation of cccDNA: direct (CRISPR, gene editing), indirect (IFN)
- Decrease cccDNA activity
  - Epigenetic modification, HBx inhibitors
Potential paths towards cccDNA eradication

Immune-mediated mechanisms

**Cytolytic mechanism**

- Replacement by infected hepatocyte
- Dilution of ccc DNA content

**Noncytolytic mechanism**

- Replacement by uninfected hepatocyte

IFN-γ  
TNF-α

Cell ‘cure’

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**Cytolytic**  
**Non-Cytolytic**

Assessment of cccDNA eradication

• Direct assessment requires liver biopsy
• Lack of standardized method
• Need specificity for cccDNA not relaxed circular DNA
• Uncertain if small tissue sample is representative
• Surrogate serum markers not validated, no standardized assay
  – Quantitative HBsAg*
  – Hepatitis B core related antigen (HBcrAg)*
  – HBV RNA (pregenomic)

*better correlation in HBeAg+ than HBeAg- patients
Quantitative serum HBsAg correlates with hepatic cccDNA in HBeAg+ but not in HBeAg- patients

HBeAg+ (n=71); HBeAg- (n=78)

Thompson AJ, Hepatology 2010; 51: 1933
# Definitions of HBV Cure

<table>
<thead>
<tr>
<th>Clinical scenario</th>
<th>Complete/ Sterilizing cure</th>
<th>Idealistic functional cure</th>
<th>Realistic functional cure</th>
<th>Partial “cure”</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Never infected</td>
<td>Recovery after acute HBV</td>
<td>Chronic HBV with HBsAg loss</td>
<td>Inactive carrier off treatment</td>
</tr>
<tr>
<td>HBsAg</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td>Anti-HBs</td>
<td>Negative</td>
<td>Positive</td>
<td>Positive/negative</td>
<td>Negative</td>
</tr>
<tr>
<td>HBeAg</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Serum HBV DNA</td>
<td>Not detected</td>
<td>Not detected</td>
<td>Not detected</td>
<td>Low level or not detected</td>
</tr>
<tr>
<td>Hepatic cccDNA, transcription</td>
<td>Not detected Not active</td>
<td>Detected Not active</td>
<td>Detected Not active</td>
<td>Detected Low level</td>
</tr>
<tr>
<td>Integrated HBV DNA</td>
<td>Not detected</td>
<td>Detected?</td>
<td>Detected</td>
<td>Detected</td>
</tr>
<tr>
<td>Liver disease</td>
<td>None</td>
<td>None</td>
<td>Inactive, fibrosis regress over time</td>
<td>Inactive</td>
</tr>
<tr>
<td>Risk of HCC</td>
<td>Not increased</td>
<td>Not increased</td>
<td>Declines with time</td>
<td>Risk lower vs. active hepatitis</td>
</tr>
</tbody>
</table>

- **Clinical scenario**:
  - Never infected
  - Recovery after acute HBV
- **Idealistic functional cure**:
  - Chronic HBV with HBsAg loss
- **Realistic functional cure**:
  - Inactive carrier off treatment
- **Partial “cure”**:
  - Inactive, fibrosis regress over time
  - Inactive
  - Risk lower vs. active hepatitis
Decline in Serum HBV DNA Levels during Myrcludex B (Entry Inhibitor) Treatment in CHB Patients

HBV DNA decrease >1 log in 6/8 in 10 mg dose group and in 7/40 in lower dose groups
No HBsAg decline

S Urban, AASLD 2014
RNA Interference or Anti-sense Oligonucleotides

Decrease production of virions and HBsAg
May in turn help to restore immune response
Decrease in Serum HBsAg Levels in Patients Receiving ARC-520 Every 4 Weeks with Daily Entecavir

IV administration of siRNA targeting co-termini of HBV RNAs + PO Entecavir

HBeAg+ patients

HBeAg- patients

Effect of ARC 520 on serum HBsAg levels attenuated in HBeAg- patients compared to HBeAg+ patients

Yuen MF et al, EASL ILC 2017
Mapping of HBV S Transcripts from HBeAg+ and HBeAg- Chimpanzees

Integrated HBV DNA not cccDNA appears to be predominant source of HBsAg in HBeAg- patients and chimpanzees

Region targeted by ARC520 frequently missing in integrated HBV DNA
Marked Reduction in Serum HBsAg Levels in HBeAg- Chimpanzees Treated with siRNA Targeting Upstream of DR1-DR2 Region

Received siHBV-75

Wooddell CI, Sci Transl Med 2017
Capsid Assembly Modulators (CpAM)

Result in dysfunctional or empty capsids preventing HBV DNA replication and recycling of capsids to amplify cccDNA

Antiviral Activity of JNJ-379, CpAM in Non-cirrhotic Treatment-Naïve Chronic Hepatitis B

• JNJ-379 binds with core protein, inhibits capsid assembly and disassembly
• Decrease in serum HBV RNA suggests decrease in cccDNA transcription

Mean decrease in HBV RNA log c/mL
- Placebo -0.18
- 25 mg -2.30
- 75 mg -1.85

Three patients with HBV DNA <LLOQ of the HBV DNA assay.

Zoulim et al. HEPATOLOGY. 2017 66(1)39
Nucleic Acid Polymers (NAPs)

- NAPs target host factors involved in assembly/secretion of subviral particles
- Secretion of virions and HBeAg not affected
- Intracellular HBsAg not increased but ALT flares common
Rapid decline in quantitative HBsAg
Response maintained in 8/10 patients in experimental group after stopping treatment
But frequent hepatitis flares, some severe

Bazinet M, J Hepatol 2017; 66:S256
Restoration of T Cell Response to HBV is Observed in CHB Patients Who Responded to IFN or NA

Rehermann B, J Clin Invest 1996; 97: 1655

Boni C, Gastroentrol 2012; 143: 963
Immune Liver Microenvironment and Immunotherapeutic Targets

**Therapeutic vaccination**

- Blockade of immunosuppressive pathways, Checkpoint inhibitors
- Stimulation of innate immunity
  - TLR agonists
  - Small molecules
  - cIAP inhibitors
- Recovery of exhausted adaptive immunity
  - Engineering of T cells (HBV-specific TCR or CARs) Naïve T cells priming to HBV antigens

Lok A, Hepatology 2017; 66: 1296
Multiple Steps to Achieve Functional HBV Cure

**Step I**
- **Goal**: Complete inhibition of HBV replication
- **Approaches**: NUCs + novel HBV replication inhibitors
- **Outcomes**: HBsAg-Anti-HBs+

**Step II**
- **Goal**: Reduce viral antigen production/ increase clearance
- **Approaches**: Target cccDNA siRNA
- **Outcomes**: HBsAg-Anti-HBs+

**Step III**
- **Goal**: Activation of a functional antiviral immune response
- **Approaches**: Therapeutic vaccine
- **Outcomes**: HBsAg-Anti-HBs+

Adapted from Guo JT, AASLD-EASL HBV Treatment Endpoint Workshop 2016