HBV - NEW AGENTS

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Outline

• What are we aiming for?

• Can we do better with what we have got already?
  • Nucleos(t)ides
  • Interferon

• What about new ‘directly acting’ antivirals?

• What about new ‘host directed’ agents?

• What other issues are there?
What are we aiming for?
Can we do better with what we have already got?

- **Nucleos(t)ides:**
  - Entecavir
  - Tenofovir

- **Interferons:**
  - Peg-interferon alpha

- So what about using them together or one after the other?
Sequential or Concurrent Nucs and Interferon...

- But not all strategies have shown a benefit...
- And those that have are small studies
- And is it enough anyway?

Marcellin P et al, AASLD 2014
So what about new drugs?
Lifecycle of HBV

Main Points
• Not as easy as the HIV lifecycle…
• But vital to understand...
Viral entry into hepatocyte

Binding:
• HBV grabs hold of heparan sulfate proteoglycans
• Then binds to Sodium-Taurocholate Co-Transporting Polypeptide (NTCP) receptor

Entry:
• Via endocytosis or fusion
• Nucleocapsid released into cytoplasm
Viral entry into hepatocyte

Myrcludex B
- Synthetic lipopeptide that blocks NTCP

Main Points
- Small studies
- Well tolerated but ?concern at high doses:
  - Hyperbilirubinaemia, interactions etc
- Unlikely effective on its own
  - But may have vital role in combination
  - Perhaps important in liver transplantation

Phase 2a:
- 10mg daily:
  - >1log_{10} drop in VL at wk12 in 6/8 HBeAg-ve patients

Lutgehetmann et al., Hepatology 2012; Urban et al., AASLD 2014
Entry into nucleus, conversion to cccDNA and then transcription

DNA enters nucleus → converted to the highly stable cccDNA
- ‘covalently closed circular’ DNA
  - like a HBV mini-chromosome

cccDNA is template for transcription of viral mRNAs:
- Surface proteins
- HBV X protein
- Pregenomic RNA

cccDNA is the key to HBV ‘cure’….
Directly attacking cccDNA...

- In development:
  - Zinc-finger nucleases
  - Disubstituted sulfonamide compounds
    - Degrade cccDNA, inhibit rcDNA to cccDNA conversion, target epigenetic control of cccDNA
  - APOBEC proteins
    - Degrade cccDNA
  - CRISPR/Cas9
  - RNA-interference etc.

Promising but only in-vitro and animal work to date.

Reduction of HBsAg in treatment-naïve CHB patients after a single dose of 4 mg/kg ARC-520

Hepatocyte Targeting - ALN-HBV
- N-acetyl galactosamine (GalNAc) ligand binds to asialoglycoprotein receptor (ASGPR)

Main Points
- Early promising results
- However need further improvements in stable drug delivery systems

Yuen M-F et al. EASL 2016, Barcelona. THU-193
Sepp-Lorenzino L, et al. AASLD 2015, San Francisco. #36
Translation of mRNA and formation of capsids

mRNAs translated:
- Surface proteins
- X protein
- Pregenomic RNA
  - Core and polymerase proteins
  - RNA template for conversion to genomic DNA

There are drugs developed to destabilise the nucleocapsid
Capsid assembly modulators

- CAMs induce the formation of two types of capsids \textit{in vitro}
  - Empty capsids with normal geometry and size
    - Phenylpropenamides (e.g. AT130) and sulfamoylbenzamide derivatives
  - Empty capsids with abnormal geometry and size
    - Heteroaryldihydropyrimidines (e.g. BAY41-4109)

\textbf{Electron microscopy}

Recombinant HBV core dimers + 150mM NaCl +/- 30µM CAM (24h)
HBV core inhibitors

HBeAg-positive CHB patients
- Serum HBV DNA >20,000 IU/mL
- ALT levels 1-7 times upper limit of normal
- Randomized to NVR 3-778 capsules at 4 doses (vs placebo) x 28 days

Main Points
- Still only very early and small studies for capsid and core inhibitors

Mean viral load change (HBV DNA)

NVR 3-778 600 mg bd associated with mean 1.72 log_{10} IU/mL HBV DNA reduction in 28 days

Yuen M-F et al. AASLD 2015, San Francisco. #LB-10
Coated with surface proteins, RNA in capsid converted to relaxed circular DNA, and released.

Main Points
- What benefit will they have over existing nucs?
  - Already have good control of virus & very low resistance
  - No extra impact on cccDNA expected

This is where nucleos(t)ides work

And there are potentially more on the way:
- Besifovir, CMX 157, AGX-1009, MIV-210
But let's think for a moment about sAg

Why?
- Absorb neutralising antibodies
- Induce T cell tolerance & immune exhaustion

So what if we could inhibit sAg secretion?
sAg release inhibitors

9/9 HBsAg response > 1 log

6/9 HBsAg response > 1 log

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

Bazinet et al. AASLD 2016
Prot. Imm. = Architect defined threshold for protective immunity (10 mIU / mL)
absent = no significant anti-HBs present (≤ 0.1 mIU / mL)

Elevation in serum anti-HBs correlated with extent of sAg release inhibitors

**Main Points**
- Small studies
- Is there a potential toxicity concern?
  - Akin to a storage disease?
There is also the X-protein
There is also replenishment of the cccDNA *within* the cell.
There is also replenishment of the cccDNA *within* the cell.
Capsid Assembly Inhibitor - JNJ-379: Effect on cccDNA in HBV-infected PHHs

Dose-dependent inhibition of cccDNA formation in presence of JNJ-379

Berke et al. AASLD 2016
Host-Directed Therapies

OK – what about optimising the immune response?
Immune Stimulators?

• New Interferons
  • Interferon lambda
    • Better VL and ALT drop and better tolerated
    • However poorer off-treatment/longer-term responses than IFN-alpha

• Toll-like receptor agonists
  • TLR 7
  • TLR 9

• Lymphotoxin-B receptor
  • Possibly acting via APOBEC family

• Others…
  • IL-7, IL-12, IL-18, IL-1, STING agonists etc
TLR agonists

**IN VITRO HBV-SPECIFIC T CELL ANALYSIS**

GS 9620 can induce a transient improvement of IL2 production by HBV-specific T cells

**CLINICAL EFFICACY**

HBsAg changes during GS 9620 therapy

- HBsAg changes were minimal in all cohorts (no patients with >0.5-log10 declines in HBsAg at week 24)
- No patients had HBsAg loss at week 24

Boni et al. AASLD 2016
Correction of immune exhaustion?

Checkpoint inhibitors

- PD-1, PD-L1, CTL-4 inhibitors etc.

Main Points

- Small studies
- Toxicity profile of current generation therapies
Vaccination?

Therapeutic vaccines
- S and Pre-S antigen vaccines
- DNA vaccines (especially of S)
- T cell vaccines
- Adenoviral vectors
- And many more…

Main Points
- But probably need to break immune tolerance and exhaustion first…
- May be issues with genotype specificity
But there are major issues...

It is quite likely that a single drug or target will not be sufficient. Therefore, some kind of combination...

- But how do we decide what to combine with what?

How do we assess response?
What are we aiming for and how do we know we have got there?

What is our endpoint for studies?

What are we aiming to achieve?
Regardless – the future is bright and exciting...

<table>
<thead>
<tr>
<th>Targets</th>
<th>Compounds</th>
<th>Developer</th>
<th>Stage of development</th>
<th>ClinicalTrials.gov identifier</th>
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<td>Gilead</td>
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There is a full pipeline for HBV drugs in development

Durante D et al. J Hepatol. 2016 Apr;64(1 Suppl):S117-31
Not yet clear what will work, in which combination, in which patient, at what time etc. . . .