Why do we need new HBV treatment and what is our definition for cure?

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Disclosures for HLA Janssen

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
Advances in HBV treatment

1957
Discovery interferon

1990
Discovery PMEA

1991
Discovery lamivudine (3TC)

1991
Interferon alfa-2b licensed

1998
Discovery entecavir

1999
Lamivudine (3TC) licensed

2001
Discovery telbivudine

2003
Adefovir dipivoxil (PMEA prodrug) licensed

2005
Peginterferon alfa-2a
Peginterferon alfa-2b* licensed

2006
Entecavir licensed

2007
Telbivudine licensed

2008
Tenofovir licensed

2017
TAF licensed

* Specific countries only

Adapted from: ClinicalCareOptions.com
Key Considerations for Current Treatment Options

- HBV nucleos(t)ides are highly effective and generally well tolerated, but with low rates of successful 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
What can be considered as a defined cure?

- **Virological cure**
  - elimination of cccDNA
  - lowering or silencing cccDNA
  - Undetectable HBV DNA in serum
  - Off-therapy HBsAg loss

- **Disease cure**
  - No risk of progression to liver failure or HCC
  - Identifiable by clinical parameters, biomarkers or gene signatures

- **State achieved where remission of CHB is achieved with improved long term survival**
### Is HBV Treatment Paradigm Changing?

<table>
<thead>
<tr>
<th><strong>Current PARADIGM</strong></th>
<th><strong>New PARADIGM</strong></th>
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<tbody>
<tr>
<td><em>Indefinite Treatment</em></td>
<td><em>Finite treatment duration</em></td>
</tr>
<tr>
<td><em>Poor off-Rx response</em></td>
<td><em>Sustained off-Rx response shift towards endpoint of true immune control &amp; HBsAg seroconversion</em></td>
</tr>
<tr>
<td><em>Reduces overall mortality</em></td>
<td><em>No increased risk of mortality and HCC</em></td>
</tr>
<tr>
<td><em>Reduce but does not eliminate the risk of HCC</em></td>
<td><em>New HBV treatments with increased chance of curing disease</em></td>
</tr>
<tr>
<td><em>Potent NAs: suppresses viral replication but cannot cure the disease</em></td>
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## Defining HBV Cure

<table>
<thead>
<tr>
<th>Functional cure</th>
<th>Complete cure</th>
</tr>
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<tbody>
<tr>
<td>Associated with clinical benefit (disease progression and HCC)</td>
<td></td>
</tr>
<tr>
<td>Off-therapy sustained HBV suppression and disease remission</td>
<td></td>
</tr>
<tr>
<td>HBsAg seroconversion and cccDNA inactivation/reduction</td>
<td></td>
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<tr>
<td>Risk under immunosuppression</td>
<td></td>
</tr>
<tr>
<td>Feasible</td>
<td></td>
</tr>
<tr>
<td>Associated with clinical benefit (disease progression and HCC)</td>
<td></td>
</tr>
<tr>
<td>HBsAg seroconversion and cccDNA eradication</td>
<td></td>
</tr>
<tr>
<td>Feasibility uncertain</td>
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</tbody>
</table>

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
HBV Life cycle
Towards New HBV Treatment Targets

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
How to assess treatment efficacy
Endpoints: The ideal biomarker...

- Predictive (visible early, and indicative of, clinical outcome)
- High specificity
- High sensitivity, also correlation with severity
- Reflective of durable response
- High reproducibility
- Non-invasive/accessible
- Rapid/simple
- Inexpensive

Biomarkers Definitions Working Group, 2001
Current endpoints in HBV treatments

Biochemical: ALT normalization
Virological: HBV DNA decline/undetectability
Serological: HBsAg/HBeAg loss/seroconversion
Histological: Reduction of necrosis, inflammation, fibrosis
Combined: Most often HBeAg, HBVDNA and ALT
## Virological Markers to Follow CHB Patients

<table>
<thead>
<tr>
<th>Marker</th>
<th>Applicability</th>
<th>Immune Control</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HBV DNA</strong></td>
<td>Applicable to both HBeAg+ and HBeAg-</td>
<td>Not really indicative of sustained immune control</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Standardized assays available</td>
</tr>
<tr>
<td><strong>Quantitative HBeAg</strong></td>
<td>Applicable only in HBeAg+</td>
<td>More indicative of sustained immune control</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Commercial assays not currently available</td>
</tr>
<tr>
<td><strong>Quantitative HBsAg</strong></td>
<td>Applicable to both HBeAg+ and HBeAg-</td>
<td>Most indicative of sustained immune control</td>
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Immune control: HBeAg neg and low HBVDNA
Serum HBsAg Quantification

- HBsAg loss associated with better outcome
- Reflects number of infected hepatocytes
  - Association with transcriptionally active cccDNA level in HBeAg pos
- Easily measured in serum
  - Produced in excess of virus particles
  - Standardized assays available

Endpoints: Key considerations

- Phase 2 or 3 studies
- Primary & secondary endpoints
- Antiviral vs. immunomodulatory drugs
- Treatment naive vs. virally suppressed patients
- Timing of endpoint assessment: on- or off-treatment
- Efficacy criteria for further development of drug
Clinical trial phases

**Phase 1**
Safety
- Phase 1a: Safety of single ascending dose
- Phase 1b: Safety of multiple ascending doses

**Phase 2**
Efficacy & Safety
- Phase 2a: Optimal dose
- Phase 2b: Efficacy prescribed dose

**Phase 3**
Efficacy & Safety
Comparison to standard of care

**Phase 4**
Post-marketing
Safety surveillance in ‘real-life’ patients

**Pharmacokinetics & pharmacodynamics**

100-200 patients
500-2000 patients

20-100 volunteers
Survey: Surrogate for HBV cure (true/false)

<table>
<thead>
<tr>
<th>Best endpoint for HBV cure</th>
<th></th>
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<tr>
<td>HBsAg seroconversion</td>
<td>61 (92.4%)</td>
</tr>
<tr>
<td>HBsAg loss</td>
<td>43 (65.2%)</td>
</tr>
<tr>
<td>HBsAg decline</td>
<td>22 (33.3%)</td>
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Survey AASLD/EASL HBV Treatment Endpoints Workshop: respondents n=66 about 45% academic, 45% industry, 10% rest group
Primary endpoint catered to treatment modality and patient group?

- Antiviral Therapy
- Immunomodulatory Therapy
- Combination Therapy

- Treatment naive
- Virally suppressed
# Experimental treatment in naive vs virally suppressed patients

<table>
<thead>
<tr>
<th>Treatment Naive</th>
<th>Suppressed</th>
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<tr>
<td>Younger</td>
<td>Have safe and effective therapy with reduction of HCC and improved survival</td>
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<tr>
<td>Active Disease</td>
<td>Partial immune restoration may benefit immune modifying therapy</td>
</tr>
<tr>
<td>HBVDNA can be used as a biomarker</td>
<td>Potentially better protection against flares</td>
</tr>
<tr>
<td>No resistance</td>
<td>May have more objections to accept experimental therapy</td>
</tr>
<tr>
<td>May be more likely to accept finite therapy</td>
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Endpoint differentiation based on treatment modality?

In principle, rather not:
- All HBV treatments aimed at common clinical goal
- Association with clinical endpoint is essential

But:
Different mechanism of action → different response durability
- HBsAg loss with immune modifying treatment vs. viral treatments such as RNA interference

Different validated endpoints could be used for different treatments in phase 2 studies (proof of concept) also because drugs with different MOA and endpoints could potentially be combined into one regimen
HBeAg (+) patients: More HBsAg decline with PEG-IFN than ETV

**HBV DNA decline**

<table>
<thead>
<tr>
<th>Week</th>
<th>Mean change in HBV DNA (log IU/mL)</th>
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<tr>
<td>0</td>
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</tr>
<tr>
<td>12</td>
<td>-4.5</td>
</tr>
<tr>
<td>24</td>
<td>-2.2</td>
</tr>
<tr>
<td>36</td>
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**HBsAg decline**

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<tr>
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<td>-0.94</td>
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Reijnders et al. J Hepatology 2011
Sustained Response: ETV Peg-IFN add-on vs. ETV ARES Study

**ETV PEG-IFN add-on**
- 81% Continue ETV therapy
- 19% Stop Rx
- 21% Sustained Response
- 79%

**ETV monotherapy**
- 90% Continue ETV therapy
- 10% Stop Rx
- 75%
- 25%

Response: HBeAg loss, normal serum ALT and HBV DNA <2000 IU/mL

*Brouwer et al. Hepatology 2015*
Endpoint differentiation based on clinical study phase?

**Phase 2a, b**
- Proof of concept
- Dose finding
- Safety very important
- On- and off-treatment efficacy

**Phase 3**
- Aim is functional cure
- Comparison to standard treatment
- Sustained response off-treatment
Other Potential Viral and Immunologic Endpoints in Phase 2 and 3 Studies

**Viral**
- Hepatitis B core-related antigen (HBcrAg)
- HBV RNA in serum
- (Quantitative) cccDNA in liver/blood
- HBsAg epitope mapping

**Immunologic**
- HBV-specific T & B-cell response
- T-lymphocyte markers
- Expression of inhibitory molecules (PD-1, Tim-4, CTLA4)
- Quantitative anti-HBs
- Anti-HBc (IgM/total)
New Kits on the Block

• Further standardization and validation of tests needed

• Association with clinical outcome is preferred for further use

• Of interest to dissect mechanism of response in treatments targeting host and virus
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!
Conclusions

- Quantitative HBsAg and HBVDNA will be the most important biomarkers used for endpoint in phase 2 and 3 studies

- Endpoints are different in naive vs suppressed patients

- Endpoints may not have the same meaning for different drugs

- For proof of concept (phase 2) studies different validated endpoints can be used for different compounds depending on their MOA, also to allow future combination therapy
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Global Hepatitis Summit &
Introducing
The Hepatitis Global Village