Treatment endpoints to guide clinical development of novel therapies
EASL-AASLD workshop, March 2018, London

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Goals of future therapies to cure HBV infections

From Testoni et al, Sem Liver Dis, 2017
Nomenclature and endpoint definitions

• For now, the majority of participants agreed to keep the term ‘functional cure’.

• Defined as durable HBsAg loss (assays with LLOD ~0.05 IU/mL) with / without HBsAg seroconversion and undetectable serum HBV DNA after completing a course of treatment.

• It is recognized that cccDNA is still present in the liver in very small amounts or in a transcriptionally inactive state, and integrated HBV DNA is still present. HBV reactivation can occur spontaneously or upon immunosuppression.

• For the patient community, HBsAg loss is an important goal because it removes the stigma of HBV infection
<table>
<thead>
<tr>
<th>Clinical scenario</th>
<th>Sterilizing ‘cure’</th>
<th>Idealistic functional ‘cure’</th>
<th>Realistic functional ‘cure’</th>
<th>Attainable Partial ‘cure’</th>
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</thead>
<tbody>
<tr>
<td>Never infected</td>
<td>HBsAg Negative</td>
<td>Recovery after acute HBV</td>
<td>Chronic HBV with HBsAg loss</td>
<td>Inactive carrier off treatment</td>
</tr>
<tr>
<td>Anti-HBs</td>
<td>Negative/Positive</td>
<td>Positive</td>
<td>Positive/negative</td>
<td>Negative</td>
</tr>
<tr>
<td>HBeAg</td>
<td>Negative</td>
<td>Negative</td>
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</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</td>
<td>Detected</td>
<td>Detected</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>
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*Cornberg, Lok, Terrault, Zoulim, J Hepatol, in press*
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| HBsAg                     | Negative           | Negative                     | Negative                    | Positive                 |
| Anti-HBs                  | Negative/Positive  | Positive                     | Positive/negative           | Negative                 |
| HBeAg                     | Negative           | Negative                     | Negative                    | Negative                 |

| Serum HBV DNA             | Not detected       | Not detected                 | Not detected                | Low level or not detected|

| Hepatic cccDNA, transcription | Not detected | Detected                    | Detected                    | Detected                 |
| Liver disease              | None            | None                         | Inactive, fibrosis regress over time | Inactive                 |
| Risk of HCC                | Not increased    | Not increased                | Declines with time          | Risk lower vs. active hepatitis |
Improving response rates with current treatments – Stopping NUCs

Potential outcome predictors

- Age, time to undetectable HBV DNA, and duration of viral suppression under NA, HBsAg levels at NA baseline and NA cessation, type of NA (TDF vs. ETV), HBV DNA levels during reactivation phase, re-treatment strategy, and HBV genotype

- Treatment phase (> 3 years)
  - Lag-phase (variable <1-12 months)
  - Reactivation phase (~ 3 months)
  - Consolidation phase (~ 12 months)
  - Long-term outcome

Outcome categories A-D

A) HBsAg loss (~20% after 2-3 years of follow-up)
B) Sustained virologic response (true „healthy carrier“ state) ± HBsAg level decline ~ 20-30%
C) Indeterminate state not fulfilling immediate re-treatment criteria (~10-20%)
D) Chronic hepatitis B requiring re-treatment (~40%)

Evidence:

- Small European studies: HBsAg loss rates approx. 20-30% within 3 years.
- Asian studies: lower rates of HBsAg loss (<10%).
- Risk of clinical relapse, hepatitis flares, and hepatic decompensation.
- Prediction of outcome: low HBsAg level?
- Most studies were retrospective.
- Few prospective studies (e.g. Germany, Canada) with conflicting results.
- More robust data are needed to serve as a reference for RCT

Lampertico & Berg, Hepatology 2018
New Therapies in pre-clinical and clinical development

Curative approaches: Targeting the pool of cccDNA

Entry inhibitors
- Controlling viral replication: Pre- & Post-cccDNA targets

Inhibitors of HBsAg release

Antiviral approaches
- Targeting cccDNA
- Targeting HBx

Immunomodulatory approaches
- RNA interference
- CpAMs: "Capsid inhibitors"

Curing hepatocytes
- IFNs and other antiviral cytokines
- IL12
- IFN-α
- pDC

Innate immunity modulation
- Toll-like receptor agonist
- RIGI
- STINGs

Adaptive immunity modulation
- Anti-PD-1 mAb
- TCR engineering
- Vaccine therapy

Specific hepatocyte killing
- Dysfunctional T-cell response
- Insufficient B-cell response

Virus neutralization


CpAM: core protein allostERIC modulators; HBx: hepatitis B X protein; IFN: interferon; IL: interleukin; KC: Kupffer cells; mAb: monoclonal antibody; NA: nucleos(t)ide analogue; NK: natural killer; NKT: natural killer T cell; pDC: plasmacytoid dendritic cell; PD-1: programmed cell death-1; TCR: T cell receptor
Selected novel therapies that have been investigated in humans

### Direct antivirals

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Sponsor</th>
<th>Mechanism of action</th>
<th>Class</th>
<th>Clinical stage</th>
<th>Notes</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myxovirus B (Buleviride)</td>
<td>MYRX Pharmaceuticals</td>
<td>Blocks NTCP</td>
<td>Peptide II</td>
<td>2 mg Myxovirus B + Raltegravir treatment resulted in 40% responders with HBsAg loss observed in 26.7% of the cohort</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>CRY431</td>
<td>Contravir</td>
<td>Blocks NTCP and protein folding</td>
<td>Small molecule</td>
<td>Single-ascending dose study performed up to a dose of 520 mg</td>
<td>271</td>
<td></td>
</tr>
</tbody>
</table>

### Translational inhibitors

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<tr>
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<th>Mechanism of action</th>
<th>Class</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>JNJ3990</td>
<td>Janssen</td>
<td>mRNA degradation</td>
<td>siRNA II</td>
<td>Most patients had HBsAg loss ≤300 IU/ml after 3 doses, Range of 1.3-2.8 (at nadir) log decrease in HBsAg levels</td>
</tr>
<tr>
<td>ARB-1467</td>
<td>Arbutus</td>
<td>mRNA degradation</td>
<td>siRNA II</td>
<td>7 of 11 patients had &gt;1 log decrease in HBsAg levels after 30 weeks of dosing (respondents). Biweekly dosing better than monthly dosing</td>
</tr>
</tbody>
</table>

### Capsid assembly inhibitors

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<th>Mechanism of action</th>
<th>Class</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABI-H0731</td>
<td>Assembly</td>
<td>Core binding</td>
<td>Small molecule</td>
<td>Combined with entecavir, ABI-H0731 caused a 4.54 log decrease in HBV DNA levels at 12 weeks and a 5.94 log decrease at 24 weeks</td>
</tr>
</tbody>
</table>

### Immune modulators

#### Innate immunity activators

<table>
<thead>
<tr>
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<th>Class</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inamivir</td>
<td>Springbank</td>
<td>RIG-I agonist and polymerase inhibitor</td>
<td>Small molecule</td>
<td>Dose-dependent decrease in HBV DNA levels (1.54 log decrease with 200 mg). After switch to 750 mg, 96% of participants had HBV DNA levels below the LOQ</td>
</tr>
<tr>
<td>RO7029181</td>
<td>Roche</td>
<td>TLR3 agonist</td>
<td>Small molecule</td>
<td>Immune activation observed in all patients. No viral data reported</td>
</tr>
<tr>
<td>GS-9201</td>
<td>Gilead</td>
<td>TLR7</td>
<td>Small molecule</td>
<td>No change in HBsAg levels. Transient dose-dependent induction of ISG15 and change in NK cell and T cell phenotype observed</td>
</tr>
<tr>
<td>GS-9688</td>
<td>Gilead</td>
<td>TLR8</td>
<td>Small molecule</td>
<td>Dose-dependent IL-12 and IL-1β production noted in healthy volunteers</td>
</tr>
</tbody>
</table>

#### Adaptive immunity activators

<table>
<thead>
<tr>
<th>Drug name</th>
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<th>Mechanism of action</th>
<th>Class</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>TG-1056 (T1013)</td>
<td>Genentech/Takeda</td>
<td>Vaccine</td>
<td>Ad5 delivery</td>
<td>HBV T cell responses induced by vaccine. Anti-Ad5 antibodies seen with higher dose. Mean 3.45 log decrease in HBsAg levels observed at day 137</td>
</tr>
<tr>
<td>HepTcell</td>
<td>Allimmune</td>
<td>Vaccine</td>
<td>Peptide plus</td>
<td>T cell responses strongest for vaccine plus adjuvant. Safe, but no decline in HBsAg levels was observed after three administrations of vaccine</td>
</tr>
</tbody>
</table>

Ad5, adenovirus type 5; anti-HBs, anti-hepatitis B surface protein; ASO, antisense oligonucleotide; BID, twice daily; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; INHAs, interferon-α; IU, infectious units; LOQ, limit of quantification; NK, natural killer; NTCP, sodium-taurocholate cotransporting polypeptide; QD, once daily. RIG-I, retinoic acid-inducible gene 1 protein; siRNA, small interfering RNA; TDF, tenofovir disoproxil fumarate; TID, thrice daily; TLR, Toll-like receptor.
Assessment of safety

• Given the well-established safety of NUCs, the safety of new therapies will need to be comparable
• If additional risk is anticipated, it should be well justified for the endpoints achievable
• A major concern in HBV drug development is occurrence of ALT flares
### Types of ALT flares during treatment

<table>
<thead>
<tr>
<th></th>
<th>“Antiviral flare”</th>
<th>“Virus-induced flare”</th>
<th>“Drug-induced flare”</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Timing of flare</strong></td>
<td>Variable depending on mechanism of drug</td>
<td>May be early if due to lack of efficacy, and variable if due to antiviral drug resistance</td>
<td>Any time during treatment</td>
</tr>
<tr>
<td><strong>Course of flare</strong></td>
<td>Usually self-limiting within weeks</td>
<td>Progressive if not recognized and remedied</td>
<td>Static or progressive</td>
</tr>
<tr>
<td><strong>Association with HBV DNA</strong></td>
<td>After HBV DNA decline</td>
<td>Preceded by HBV DNA increase</td>
<td>Unrelated</td>
</tr>
<tr>
<td><strong>Alkaline phosphatase level</strong></td>
<td>Normal</td>
<td>Normal</td>
<td>Normal or elevated</td>
</tr>
<tr>
<td><strong>Bilirubin level</strong></td>
<td>Usually normal</td>
<td>May be elevated</td>
<td>Normal or elevated</td>
</tr>
<tr>
<td><strong>Liver biopsy</strong></td>
<td>Not needed</td>
<td>Not needed</td>
<td>May be needed for diagnosis</td>
</tr>
</tbody>
</table>

*Cornberg, Lok, Terrault, Zoulim, J Hepatol, in press*
HBV cure - New treatment concepts - Will we need combination of DAA and immune therapy?

Antivirals

Therapy

HBV DNA change from baseline (log_{10} c/mL)

0.0 - 1.0 - 2.0 - 3.0 - 4.0

Antivirals

Immune restoration

Check point inhibitors

Tx Vaccine

Anti-HBsAb

HBsAg

HBVDNA

NUC

Capsid

SiRNA Ag load

TLR agonist

Vaccine

Check point inhibitors

Anti-HBsAb

Testoni et al, Sem Liver Dis 2017
Design of Trials

• Careful consideration of the study populations
  • Heterogenous disease and not all therapies may be expected to be effective in all patient groups.
  • The challenge in phase 2 studies is identifying patient groups with sufficient homogeneity to allow efficacy to be accurately evaluated.
  • The population studied should align with the investigational drug’s mechanism of action.

• Many phase 2 studies initially target patients who are virally suppressed on NUCs; an easily accessible population that is more homogenous and with lower risk of hepatitis flares.

• Regardless of the type of trial design chosen, a study to demonstrate superiority is generally preferred for the HBsAg loss endpoint.

• However, non-inferiority might also be an option, e.g. rates of sustained viral suppression with a finite treatment similar to maintained viral suppression during long-term NUC treatment.
Prioritization of patients for enrolment in phase 2 and 3 trials

Prioritization of Patient Populations for Study

- High replication with inflammation: Immune active (IA) HBV and HDV
  - Low replication, low inflammation: Inactive CHB and those on NA therapy
  - High replication; low inflammation (Immune tolerant)
  - Special populations: cirrhosis, HIV, transplant, children,

- High need and greatest gain from effective therapy
- Greatest dynamic range to assess treatment effect
- Modest need (but high life-long impact)
- Beyond phase 3

Stratification possible on a few factors: HBeAg status, viral genotypes, viral suppression, etc.

Cornberg, Lok, Terrault, Zoulim, J Hepatol, in press
New Clinical Trials Options: Master Protocols

- Most commonly used in cancer trials

Table 1. Types of Master Protocols.

<table>
<thead>
<tr>
<th>Type of Trial</th>
<th>Objective</th>
</tr>
</thead>
<tbody>
<tr>
<td>Umbrella</td>
<td>To study multiple targeted therapies in the context of a single disease</td>
</tr>
<tr>
<td>Basket</td>
<td>To study a single targeted therapy in the context of multiple diseases or disease subtypes</td>
</tr>
<tr>
<td>Platform</td>
<td>To study multiple targeted therapies in the context of a single disease in a perpetual manner, with therapies allowed to enter or leave the platform on the basis of a decision algorithm</td>
</tr>
</tbody>
</table>

Platform Protocol for CHB when Multiple New Therapies Being Tested

Key features of platform trial:
- Single infrastructure; ongoing over time
- No fixed stopping date
- Maps out adding and dropping strata
- Common control arm to aid in efficiency

Primary endpoint & desired response rates in Phase 2 trials

• Some proposed setting a high bar, i.e. requiring HBsAg loss in at least a small percent of participants to minimize the likelihood of negative phase 3 trials.

• Others argued for a lower bar in early phase trials, e.g. a >1 or >2 log reduction in HBsAg level or a decrease to <100 IU/mL, to minimize the risk of abandoning promising drugs that need to be administered for longer duration or in combination with other antiviral or immune modulatory therapies to achieve the desired effects.

• Phase 2 trials should be looking for an early signal of finite treatment efficacy.
Primary endpoint & desired response rates in Phase 3 trials

- HBsAg loss with or without anti-HBs seroconversion 6 months after completion of treatment should be the primary endpoint for phase 3 trials (with suppression of serum HBV DNA).
- HBsAg loss in ≥30% of patients after 1 year of therapy as the desired response rate for phase 3 trials;
- Arbitrary target, but required to guide the first wave of drug development.
- A ‘one-size fits all’ approach should be avoided: clinical trial design and target response rates to be tailored to patient characteristics.
- Sustained off-treatment HBV DNA suppression after a short course of therapy in a high percentage of patients could be considered an improvement even if without HBsAg.
Decline in HBsAg levels as predictor for HBsAg loss in early phase trials

- Early declines in serum HBsAg on treatment are associated with HBsAg loss during or after treatment (higher negative than positive predictive value).
- Accuracy of HBsAg decline in predicting HBsAg loss may be affected by HBeAg status, HBV genotype, and the type/target of the HBV therapy used.
- Decline in HBsAg levels in phase 2 trials: exploratory endpoint, not a surrogate endpoint.
- A decline of HBsAg as a surrogate marker in phase 3 trials can only be accepted if it is demonstrated to reliably predict HBsAg loss. Another predictor for HBsAg loss may be a reduction in HBsAg level to a low level, e.g. <100 IU/ml HBsAg.
- More data are required to determine whether a specific threshold level predicts HBsAg loss and if this can be applied to all antiviral and immune-modulatory therapies regardless of mechanism of action.
Novel Biomarkers to Assess Target Engagement and Treatment Endpoints

Serum
- HBV DNA
- qHBsAg
- Circulating RNAs
- HBcrAg

Liver
- cccDNA
- Integrated DNA

Standardization & validation
- Target engagement
- Prediction of HBsAg loss
- Guiding therapy

Prerequisites for testing a new therapy in combination with other (new or existing) therapies

• The FDA and EMA requires data on antiviral activity, mechanism of action, safety, and drug-drug interactions.

• In situations where a new drug is being combined with a pre-existing drug, animal toxicity studies are not required unless there is some non-clinical data indicating that there might be overlapping toxicity.

• Some drugs in development that do not demonstrate the intended antiviral activity in phase 1 or 2 trials may work synergistically in combination with other drugs. Those drugs may be tested if there are no safety concerns and if there is scientific rationale for combination.