Hepatitis B Cure: from discovery to regulatory endpoints in HBV clinical research
A summary of the AASLD/EASL statement

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From viral suppression to cure

**UNTREATED**

Liver Blood

- ccc-DNA
- Rc-DNA
- HBV-DNA
- HBsAg

- Integrated HBV DNA

**NUCs**

Liver Blood

- ccc-DNA
- Rc-DNA
- HBV-DNA
- HBsAg

- Integrated HBV DNA

**NMEs**

Liver Blood

- ccc-DNA
- Integrated HBV DNA

- Integrated HBV DNA

**“Cure”**

Direct Antiviral Agents

Immunomodulatory strategies

Normal Cirrhosis Hepatocellular carcinoma

Risk of HCC reduced (after 5 yrs) but not eliminated

Normal Cirrhosis Hepatocellular carcinoma

Normal Cirrhosis Hepatocellular carcinoma

Zoulim & Levrero
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 is possible when these livers are transplanted

• Long-lasting rigorous immune response to HBV possibly from continued stimulation by residual virus
Barriers to eradicating HBV

- cccDNA reservoir
  - Long t1/2
  - Continuous replenishment
  - Not affected by NAs and IFN

- Integrated forms

- HBV persistence

- Defective CD8+ responses
- Defective B cell responses
- Inefficient innate response
- Defective immune responses

Persistence of intrahepatic viral DNA synthesis during Tenofovir therapy (HIV-HBV cohort)

New round of infection and/or replenishment of the cccDNA pool occur despite « viral suppression »

Boyd et al, J Hepatol 2016
HBsAg Loss Decreases Subsequent Risk of HCC

REVEAL study 2964 HBsAg+, no cirrhosis

Hazard ratio for HCC after seroclearance during follow up
- HBeAg 0.63
- HBV DNA 0.24
- HBsAg 0.18

after adjustment for age, gender ALT

Among HBeAg- lifetime cumulative incidence of HCC for those with clearance of
- Both HBV DNA and HBsAg 4.0%
- HBV DNA only 6.6%
- Neither 14.2%

Liu J, Gut 2014; 63: 1648
Lack of impact of current antivirals on cccDNA

Levrero et al, Current Opinion Virology, 2016
The main targets & drug discovery efforts

- Entry inhibitors
- Targeting cccDNA
- RNA interference
- NUCs “Polymerase inhibitors”
- CpAMs “Capsid inhibitors”
- Inhibitors of HBsAg release

Immune modulation
- Toll-like receptors agonists
- Anti-PD-1 mAb
- Vaccine therapy

The introduction of novel compounds for chronic hepatitis B necessitates:
1) a standardized appraisal of the **efficacy and safety** of these treatments,
2) definitions of **new or additional endpoints** to inform clinical trials.

To move the field forward, and to expedite the pathway from discovery to regulatory approval, a workshop with key stakeholders was held in September 2016 to develop a consensus on treatment endpoints **to guide the design of clinical trials aimed at hepatitis B cure.**
Definition of cure

**SEROUS**

- HBV DNA change from baseline (log $10$ c/mL)
  - $0.0$ to $-1.0$
  - $-1.0$ to $-2.0$
  - $-2.0$ to $-3.0$
  - $-3.0$ to $-4.0$

**THERAPY**

- Therapy

**HBsAg**

**PARTIAL CURE**

**FUNCTIONAL CURE**

**STERILIZING CURE**

**LIVER**

- cccDNA

**COMPLETE CURE**

Lok et al, Hepatitis B Cure: From Discovery to Regulatory Approval; Hepatology / J Hepatol joint publication; 2017
Virologic Cure vs. Liver (Clinical) Cure

**Partial Cure**
- HBsAg+, HBV DNA UD
- cccDNA+, integrated HBV DNA+

**Decreased necroinflammation**
- Fibrosis persists
- HCC risk persists

**Functional Cure**
- HBsAg-, HBV DNA UD
- cccDNA+, integrated HBV DNA+

**Regression of fibrosis**
- HCC risk decreases

**Sterilizing Cure**
- HBsAg-, anti-HBs+, HBV DNA UD
- cccDNA & integrated HBV DNA eliminated

**Restoration of liver to normal**
- HCC risk eliminated

- Decreased necroinflammation
- Decreased necroinflammation
- Decreased necroinflammation
- Decreased necroinflammation
- Decreased necroinflammation
Definition of cure

• The vast majority (87.9%) of survey respondents selected **functional cure** (sustained HBsAg loss) as the goal for new HBV therapies. Advantages: easy to assess, associated with improved clinical outcomes & lower rates of disease reactivation, and once achieved, no further requirement for therapy.

• Less consensus regarding the necessity of achieving **anti-HBs seroconversion**

• Discussion: is elimination or silencing of cccDNA a mandatory criterion for functional cure? Uncertainties whether new therapies in development can silence or clear cccDNA, as well as pragmatic difficulties in measuring cccDNA.

• Partial cure: acceptable intermediary step toward functional cure (more achievable in the short-term, reduction in clinical outcomes, and could expedite drug development).
Durability of HBsAg Loss in Patients Treated with NUC ± PEG-IFN

74 patients with HBsAg loss during NUC +/- PEG-IFN treatment

>95% durable if HBsAg loss confirmed ≥24 weeks apart, seroconversion to anti-HBs not important

Chan H, EASL 2017
Efficacy endpoints for clinical trials

- The use of a biochemical endpoint is problematic because of the lack of a standardized definition of normal ALT.

- With increasing prevalence of obesity and non-alcoholic fatty liver disease, failure to normalize ALT may not necessarily indicate ongoing liver inflammation induced by HBV.

- Non-invasive assessments of liver fibrosis have replaced liver biopsies in assessing liver disease in clinical practice and a histological endpoint would no longer be practical or necessary for assessing functional cure.

- Liver biopsies may be required in proof-of-concept studies to confirm a novel mode of action and/or to validate noninvasive surrogate markers of antiviral activity.
Efficacy endpoints: clearance of HBsAg

- For both antiviral and immune modulatory therapy trials, suppression of serum HBV DNA to undetectable and loss of HBsAg were ranked as the most important primary efficacy endpoint for phase 2 and phase 3 trials.
- No consensus whether the kinetics of decline in HBsAg level can predict ultimate HBsAg loss.
- The most appropriate time to assess the primary efficacy endpoint for phase 3 trials of novel antiviral or immune modulatory therapies should be month 6 post-treatment, i.e. durable response.
- For Phase 2 studies: depends on the MoA of the drug.

Lok et al, Hepatitis B Cure: From Discovery to Regulatory Approval; Hepatology / J Hepatol joint publication; 2017
Diagnostic assays for new markers to determine therapeutic efficacy

• There was consensus on the need for standardized assays to provide mechanistic insights into the effects of novel antiviral or immune modulatory agents and to have new surrogate markers to assess HBV “cure”
Dane particles

cccDNA

Subgenomic RNAs

Exosomes

Rc-DNA  cccDNA  pgRNA  Encapsidated pgRNA  Subgenomic RNAs  Exosomes

Testoni, Levrero & Zoulim, Seminars Liver Dis 2017
Need for standardized clinical immunology assays

- **Goals of Tx**
  - Restoration of T cell activity
  - Restoration of B cell functions
  - Boosting innate immunity

- **Clinical assays needed for:**
  - Phenotypic characterization of patients
  - Monitoring of immune activity of novel Tx
  - ICE-HBV immunology working group
Assessment of safety and stopping rules

• The remarkable safety profile of current NAs imposes a **stringent requirement for the safety of new HBV therapies**.

• A unique concern in the development of hepatitis B therapies is the **risk of severe hepatitis flares**, which can result in hepatic decompensation and death. The U.S. FDA has explicit recommendations on managing drug-induced liver injury; however, these recommendations do not apply to patients with underlying liver disease.

• **Transient hepatitis flares are not always harmful and may portend immune clearance of infected hepatocytes**

• **Severe flares**: accompanied by increase in bilirubin or prothrombin time and flares in patients with cirrhosis

• Any death or liver transplantation, hepatic decompensation, irreversible autoimmunity, or incidence of severe hepatitis flare in >5% of patients could prompt a halt

Lok et al, Hepatitis B Cure: From Discovery to Regulatory Approval; Hepatology / J Hepatol joint publication; 2017
Design of clinical trials for HBV cure

• Combination of antiviral and immune modulatory therapies most likely needed.

• Antiviral activity and safety of individual new agents used as monotherapy, and drug interactions should be first established before progressing to combination therapy trials.

• However, demonstration of efficacy as a monotherapy need not be required.

• Randomized controlled trials needed to establish efficacy (heterogeneity of the natural course of CHB).

• Trials should aim to demonstrate superiority of the investigational therapy

• Initially conduct trials in treatment-naïve HBeAg-(+) patients with active disease or in virally suppressed patients. Proof of principle and safety to be established first in patients without cirrhosis.
Summary and recommendations

- **A functional cure** (sustained loss of HBsAg with or without anti-HBs seroconversion) after a finite course of novel therapies in a higher proportion of patients than currently achieved with existing treatments, is an attainable goal.

- Need for **surrogate markers for cure** to assist clinical trials

- **Limited proof-of-concept monotherapy studies** to evaluate safety and antiviral activity should be conducted prior to proceeding to combination therapy.

- **The safety** of any new curative therapies will be paramount given the excellent safety of currently approved NAs.

Lok et al, Hepatitis B Cure: From Discovery to Regulatory Approval; Hepatology / J Hepatol joint publication; 2017
HBV cure: An attainable goal within the next decade!

- Collaboration between Academia, Industry, Regulatory Agencies and Stakeholders
- International HBV cure programs