Review

EASL JOURNAL OF HEPATOLOGY

Hepatitis B cure: From discovery to regulatory approval

Anna S. Lok[1,*], Fabien Zoulim[2], Geoffrey Dusheiko[3], Marc G. Ghany[4]

Summary

The majority of persons currently treated for chronic hepatitis B require long-term or lifelong therapy. New inhibitors of hepatitis B virus entry, replication, assembly, or secretion and immune modulatory therapies are in development. The introduction of these novel compounds for chronic hepatitis B necessitates a standardised appraisal of the efficacy and safety of these treatments and 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. The consensus reached was that a complete sterilising cure, *i.e.*, viral eradication from the host, is unlikely to be feasible. Instead, a functional cure characterised by sustained loss of hepatitis B surface antigen with or without hepatitis B surface antibody seroconversion, which is associated with improved clinical outcomes, in a higher proportion of patients than is currently achieved with existing treatments is a feasible goal. Development of standardised assays for novel biomarkers toward better defining hepatitis B virus cure should occur in parallel with development of novel antiviral and immune modulatory therapies such that approval of new treatments can be linked to the approval of new diagnostic assays used to measure efficacy or to predict response. Combination of antiviral and immune modulatory therapies will likely be needed to achieve functional hepatitis B virus cure. Limited proof-of-concept monotherapy studies to evaluate safety and antiviral activity should be conducted prior to proceeding to combination therapies. The safety of any new curative therapies will be paramount given the excellent safety of currently approved nucleos(t)ide analogues.

Keywords: Chronic hepatitis B; Antiviral therapy; Immune modulatory therapy; Hepatitis B surface antigen; Covalently closed circular DNA.

Received 11 May 2017; accepted 11 May 2017

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Introduction

The advent of several novel antiviral and immune modulatory therapies for chronic hepatitis B now necessitates a standardised appraisal of the efficacy and safety of these therapies, and 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, the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver jointly organised the Hepatitis B Treatment Endpoints Workshop on September 8-9, 2016, in Alexandria, Virginia. The primary goal of this workshop was to assemble key stakeholders from regulatory agencies (US Food and Drug Administration and European Medicines Agency), biopharmaceutical and biotechnology companies engaged in development of diagnostic tests and therapeutic agents for hepatitis B, and academia in order to develop a consensus on treatment endpoints to guide the design of clinical trials aimed at hepatitis B cure.

Sixty-six (33%) of 202 participants completed a premeeting survey, including four from regulatory agencies, 31 from industry, 28 from academia, and three from other health care sectors. During the workshop, experts reviewed the natural history of chronic hepatitis B virus (HBV) infection, efficacy of currently approved treatments, potential antiviral targets and approaches to restore immune responsiveness to HBV, and preclinical and early-phase clinical trial data on novel antiviral and immune modulatory therapies for chronic HBV. The workshop concluded with a session on the definition of HBV cure; efficacy endpoints, safety assessments, target populations, and design of clinical trials; and diagnostic assays needed to support develop-

[1]*Division of Gastroenterology and Hepatology, University of Michigan, Ann Arbor, MI, United States*;
[2]*Cancer Research Center of Lyon–INSERM U1052, Hospices Civils de Lyon, Lyon University, Lyon, France*;
[3]*University College London Medical School and Kings College Hospital, London, UK*;
[4]*Liver Diseases Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD, United States*

* Corresponding author. Address: Division of Gastroenterology and Hepatology, University of Michigan Health System, 1500 East Medical Center Drive, 3912 Taubman Center, SPC 5362, Ann Arbor, MI 48109, United States.
E-mail address: aslok@med.umich.edu (A.S. Lok).

Please cite this article in press as: Lok AS et al. Hepatitis B cure: From discovery to regulatory approval. J Hepatol (2017), http://dx.doi.org/10.1016/j.jhep.2017.05.008

ment of curative therapies. These topics were further discussed during a closed session involving 23 experts (including the four authors) representing all constituent groups. This report summarises the discussions and consensus opinions of the 2-day meeting.

Definition of HBV cure

The goal of developing new therapies is to achieve HBV cure, *i.e.*, elimination of HBV, thereby allowing treatment to be stopped with no risk of virological relapse and no risk of liver disease progression. However, a true cure may not be feasible because HBV DNA is integrated into the host genome; even among persons who have recovered from acute HBV, viral covalently closed circular DNA (cccDNA) can be detected in the liver, explaining the reactivation of HBV replication when these "recovered" persons are profoundly immunosuppressed. However, the observation that hepatitis B surface antigen (HBsAg) may become undetectable in serum after clinical recovery from acute hepatitis B, spontaneously during the course of chronic HBV infection, and during or after nucleosid(t)e analogue (NA) or interferon (IFN) therapy, despite the likelihood of persistent integrated HBV genomes, argues for the feasibility of achieving undetectable levels of HBsAg.

A key objective of the meeting was to establish a definition of cure. Three definitions of HBV cure were proposed at this meeting: (i) *complete sterilising cure* with undetectable HBsAg in serum and eradication of HBV DNA including intrahepatic cccDNA and integrated HBV DNA; (ii) *functional cure* with sustained, undetectable HBsAg and HBV DNA in serum with or without seroconversion to hepatitis B surface antibody (anti-HBs) after completion of a finite course of treatment, resolution of residual liver injury, and a decrease in risk of hepatocellular carcinoma (HCC) over time (several levels of functional cure including complete shutdown of cccDNA transcription, elimination of cccDNA, complete resolution of liver damage, and elimination of risk of HCC were discussed); (3) *partial cure* with detectable HBsAg but persistently undetectable HBV DNA in serum after completion of a finite course of treatment.

The vast majority (87.9%) of survey respondents selected functional cure (sustained HBsAg loss) as the goal for new HBV therapies. This selection was endorsed by other participants and the expert panel as a feasible goal. In addition, functional cure offers several other advantages: it is easy to assess and tests are widely available, it is associated with improved clinical outcomes and lower rates of disease reactivation, and once achieved, there is no further requirement for therapy.

There was less consensus regarding the necessity of achieving anti-HBs seroconversion because it is unclear whether durability of HBsAg loss and clinical benefits of HBsAg loss are dependent on the development of anti-HBs. Importantly, few of the participants believed elimination of cccDNA was a mandatory criterion for functional cure, and less than half required that cccDNA be rendered transcriptionally inactive, reflecting uncertainties over whether new therapies in development can silence or clear cccDNA, as well as pragmatic difficulties in measuring cccDNA.

Some members of the expert panel considered partial cure (sustained suppression of HBV replication off treatment but persistent presence of HBsAg) an acceptable intermediary step toward functional cure because partial cure is more achievable in the short term, has been shown to lead to a reduction in clinical outcomes,[1] and could expedite drug development.

Natural history of chronic HBV infection

The natural history of chronic HBV infection is variable and dependent on a complex interplay between the host immune response and the virus. Chronic HBV infection comprises four phases defined by three clinical parameters: serum alanine aminotransferase (ALT) concentrations, serum HBV DNA levels, and hepatitis B e antigen (HBeAg) status (Fig. 1). The first phase is characterised by the presence of HBeAg and high serum HBV DNA but normal ALT levels. It has been called the "immune-tolerant" phase, though recent studies have challenged the concept of immune tolerance. HBV-specific T-cell responses have been observed in patients in the immune-tolerant phase with similar frequency as in patients in the immune-active phase. This finding has led some to propose that the immune response is better characterised as low inflammatory during the immune-tolerant phase (as opposed to inflammatory during the immune-active phase).[2–4] The immune-tolerant phase is followed by the "HBeAg-positive immune-active" phase, when ALT levels become elevated. After varying intervals, seroconversion from HBeAg to hepatitis B e antibody occurs, and a majority of patients transition to the "inactive carrier" phase, during which ALT levels return to normal and serum HBV DNA levels are low or undetectable. In some patients, serum HBV DNA and ALT levels become elevated again, after years or decades. These patients are considered to be in the "HBeAg-negative immune-active" phase, which is characterised by fluctuating HBV DNA and ALT levels. The annual incidence of HBeAg-negative immune-active hepatitis among inactive carriers is estimated to be 0.37%.[5] Some patients do not fit into any of these conventional phases. Serum HBsAg levels are highest during the immune-tolerant phase and lowest during the inactive carrier phase. Consequently, quantification of serum HBsAg levels may help in determining the phase of infection, particularly for HBeAg-negative persons,[6] and to predict the risk of disease progres-

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