Hepatology Publish Ahead of Print
DOI:10.1097/HEP.0000000000000496

EDITORIAL: RE-ASSESSING ANTIVIRAL TREATMENT CRITERIA FOR CHRONIC HEPATITIS B

James Lok[+] and Geoffrey Dusheiko[+]

Affiliation:

+ Kings College Hospital
Denmark Hill
London SE59RS
United Kingdom

Corresponding author Geoffrey Dusheiko

email g.dusheiko@ucl.ac.uk
Kings College Hospital
Denmark Hill
London SE59RS
United Kingdom

Geoffrey Dusheiko advises GSK, Vir, Janssen, Aligos, Arbutus, and Precision Biosciences. He consults for Roche.

Chronic hepatitis B virus (HBV) infection is a global health problem affecting than 260 million people worldwide. Persistent infection predisposes patients to life-threatening complications such as cirrhosis, hepatic decompensation and hepatocellular carcinoma (HCC).[1] To facilitate risk stratification, chronic hepatitis B is broadly divided into four phases based on biochemical tests (alanine aminotransferase; ALT), viral markers (HBeAg, HBV DNA) and fibrosis stage.[2] Antiviral therapy is generally recommended for HBeAg-positive and -negative patients with active disease as they have a greater risk of fibrosis and dysplasia;[2] however, the current standards of care (i.e. nucleos(t)ide analogs, or pegylated interferon) rarely achieve functional cure and viral reactivation is common after treatment withdrawal.[3,4] Up to 40% of patients reside outside of the classification of traditional disease phases (such as HBeAg-negative patients with HBV DNA concentrations between 2000-20,000 IU/ml and persistently normal aminotransferases), and the indications for treating this "grey zone" cohort remain contentious.[5]

In this issue of *Hepatology*, Huang et al. report a retrospective analysis of outcomes in 855 patients with CHB infection.[6] The cumulative HCC incidence was compared between those who received antiviral therapy versus those who remained off-treatment. 59% were male, 20% were HBeAg-positive and the baseline mean HBV DNA was 4.5 ± 2.1 $\log_{10}$ IU/ml. All patients were classified into an "indeterminate" category of chronic hepatitis B if they failed to meet the criteria for the standard phases of infection specified in 2018 American Association for the Study of Liver Diseases (AASLD) guidelines. The study was conducted across 14 sites in the U.S.A, Europe and Asia between August 1992 and November 2021 (total follow-up of 4,714 person-years). Two percent of treatment naïve individuals transitioned to the "immune active" phase by year 10 of follow-up and were censored at the point of transition. Amongst the treated population in this "indeterminate" group, the 5-, 10- and 15-year incidence of HCC was 2.5%, 3.9% and 9.4%, respectively, compared with 2.7%, 14.7% and 19.1% in the untreated cohort.[6] Antiviral therapy was a strong predictor of reduced HCC risk (adjusted hazard ratio 0.3, 95% CI 0.1-0.6, p=0.001), but the protective effect was mainly observed in males, HBeAg-positive individuals, those aged >35 years and possibly patients with HBV DNA concentrations of >1000 IU/ml. The incidence of HCC was low in both groups (5.2 per 1000 person years in the treated group; 11.6 per 1000 person years in the untreated group) and five years of antiviral treatment was required to achieve a significant reduction in oncogenic risk (years 0-5 p=0.67; year 5 onwards p=0.007). A

reduction was *not* observed amongst females or HBeAg-negative individuals, and larger studies may be required to explore these lower risk populations.[6]

The main strength of this study is the balancing of baseline characteristics by inverse probability of treatment weighting; however, 94% of individuals were Asian and extrapolation of these results to other populations (including those infected with genotypes A, D or E) may be tenuous. An important risk factor for oncogenesis, namely a family history of HCC, was omitted during data collection and the rationale for starting antiviral therapy in some patients was unclear. This was recognised by the authors who commented on the heterogeneity of clinical practice and scope for physician discretion.[6]

The current definitions of "Immune tolerant," "immune active" and "inactive" disease phases utilize an imprecise nomenclature that fails to fully reflect the host immune response and intrahepatic HBV activity, and the loose conglomeration of patients into an "indeterminate" or leftover category (without specifying the exact clinical, biochemical, and virological parameters) is problematic. In this study, the "indeterminate" cohort likely comprised a heterogeneous population, including those with (i) high HBV DNA concentrations > $1x10^6$ IU/ml and abnormal serum ALT, (ii) HBV DNA >2000 (HBeAg-negative) or > 20,000 IU/ml (HBeAg positive) and serum ALT less than twice the upper limit of normal or (iii) HBV DNA concentrations <2000 IU/ml and abnormal ALT. Many individuals in this cohort could be recommended for treatment (e.g., HBeAg-negative patients with HBV DNA concentrations >20,000 IU/ml), and it is hard to discern why some patients were left untreated for up to 15 years.

Nevertheless, the results of this study highlight the potential benefits of antiviral treatment in this population. Nucleos(t)ide analogues may limit cellular transformation through a reduction in viral integration, gradual decline of hepatocyte clone size and slower transition to "immune active" states.[7] In addition, they may reduce the risk of developing liver fibrosis; for example, in the placebo controlled, double-blinded TORCH-B study, 160 patients with HBV DNA concentrations of >2000 IU/ml and ALT between 1-2 times the upper limit of normal were randomised to receive tenofovir disoproxil fumarate (n=79) or placebo (n=81) for three years. Antiviral treatment achieved a significant reduction in progressive liver fibrosis (RR 0.56, 95% CI 0.35-0.88, p=0.013).[8]

Newer peripheral biomarkers, such as hepatitis B RNA (HBV RNA) and core related antigen (HBcrAg) may allow a more refined approach to stratification and pharmacotherapy, as they

reflect cccDNA transcriptional activity.[9] Several studies have demonstrated a positive correlation between HBcrAg titres and the risk of HCC development; in a untreated cohort of HBeAg-negative patients from the ERADICATE-B cohort, who had concentrations of HBV DNA ranging from 2000-19,999 IU/ml and normal ALT concentrations, HBcrAg levels ≥10 kU/ml were associated with an increased risk of hepatic oncogenesis (HR 6.29, 95% CI 2.27-17.48). After 10 years of follow-up, an AUROC of HBcrAg for predicting HCC development was 0.73 (95% CI 0.69-0.78).[10] These newer markers could potentially divide HBeAg-negative patients with lower levels of HBV replication into those with more active or less active cccDNA transcriptional activity, and further refine prognostication.

International HBV guidelines are due for renewal, and the manuscript by Huang helps energise the debate around expanding antiviral therapy (and simplifying treatment paradigms). In the HBeAg negative population, HBV DNA titres ≥2000 IU/ml are generally considered to be the threshold for initiating treatment as prospective and retrospective studies have shown this ceiling to be an important relative predictor of cirrhosis and HCC. Many experts now advocate for a more liberal and expanded approach to antiviral therapy to accommodate patients' preferences, and the argument for expanding treatment is supported by the tolerability, affordability, and relative safety of nucleos(t)ide analogues. Ultimately, a patient centred approach should be adopted that carefully considers virological parameters, risk factors for disease progression, age, as well as individual preferences.

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