

# Five Decades of Research in Chronic Hepatitis B Infection-Have We Reached the Endpoint?

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## 2. Commentary

Being a practicing hepatologist in Asia for almost thirty years, my most distressing clinical experience is the need to confront patients with chronic hepatitis B (CHB) infection, being undiagnosed and presented with advanced/late hepatocellular carcinoma (HCC). Many of these patients subsequently died at their middle-age. With the discovery of hepatitis B surface antigen[1]coupled with subsequent large scale epidemiology study[2] and the substantial reductions of HCC with universal hepatitis B vaccination[4] the causal relationship of CHB with HCC, has been clearly established. In the subsequent REVEAL study, high baseline HBV DNA associated with increased risk of HCC [5].In addition, CHB infection is also the major culprit of end-staged liver cirrhosis and its reactivation, either spontaneously or with the use of immunosuppressive therapy could lead to fulminant liver failure[6]. The latter is aggravated by the presence of precorepoint mutation at nucleotide 1896 of the precore region[7].

From the clinical perspective, the ultimate endpoint for the treatment of CHB should be a reduction of its related morbidity and mortality i.e. HCC, end-staged liver cirrhosis and fulminant hepatic failure due to its reactivation[6, 8], with the understanding of viral life cycle and the importance of host immunity, pegylated interferon and seven nucleos (t) ide analogues: lamivudine, telbivudine, entecavir, clevudine (in South Korea), adefovir, tenofovir and tenofovir alafenamide, have been approved by various regulatory authorities for the treatment of CHB[3]. These medications were approved based on well-designed Randomized Controlled Trials (RCTs), using surrogate treatment endpoints, such as e-seroconversion, reduction of serum HBV DNA level, loss of Hepatitis B surface Antigen (HBsAg) with or without development of Hepatitis B surface antibody (anti-HBs) and improvement of liver stiffness, which are believed to be “equivalent” to reduction of HBV-related liver morbidity and mortality[6,8]. In keeping with this, long-term carefully designed and controlled studies with the use of lamivudine has been shown to be effective in reducing liver-related mortality and morbidity[9].However, in real-life over the past two decades, HBV-related morbidity and mortality has not been reduced as expected. In a recent systemic review, only moderate-quality evidence supported the effectiveness of antiviral therapy in CHB patients in reducing the risk of cirrhosis, decompensated liver disease and HCC[10].

By 2018, liver cancer (at least 80% being HCC) remains the fourth leading cause of cancer death worldwide, with about 841,000 new cases and 782,000 deaths annually (incidence/mortality ratio of 0.93). Annually, over 50% of all newly diagnosed liver cancer cases (> 90 % related to HBV) and deaths occurred in China[11]. On the other hand, due to the increase use of immunosuppressive agents for treatment of various forms of cancer, immune-related diseases and in patients who received transplantation, there is an increasing incidence of fulminant liver failure due to HBV reactivation[6, 8]. What is the missing link between science and real life? Recently, major research effort has been focused to achieve loss of HBsAg with or without development of anti-HBs and eradication of intrahepatic cccDNA as a form of “cure” in CHB. This is supported by the previous observation that in CHB patients, loss of HBsAg before the development of liver cirrhosis will drastically reduce the incidence of HCC. Will this type of “cure” be a better solution in terms of efficacy, safety and cost (with the widespread utility of much cheaper generic agents) as compared to life-long nucleos(t) ide or finite therapy with IFN (though only a minority could have sustained disease remission), to achieve the ultimate endpoints with elimination of HBV-related liver morbidity and mortality? What we really need is perhaps methods for early detection of HCC (to allow curative local ablation therapy or transplantation) based on the new technology platform in genomics[12] and proteomics,[13] raise of public and health-care professional awareness of CHB, designation of more effective algorithm to further reduce incidence of new infection and to understand and to correct the other comorbidity factors which can aggravate CHB-related morbidity and mortality. Multi-disciplinary effort, with the support of our community and governance agency, with clear understanding of the real “end-point”, will be required to alleviate the suffering of mankind from CHB infection.

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