COMMENT
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A Commentary on the Natural Disease Progression Sequence of Chronic Hepatitis B

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Hepatitis B virus (HBV), an ancient family of hepatotropic DNA viruses with origins dating back millions of years, remains a major burden to human health today, although hepatitis B vaccines have dramatically reduced the prevalence of chronic HBV infection[1-3]. It stands the leading cause of chronic viral hepatitis, end-stage liver disease (cirrhosis, liver failure, etc.) and primary hepatocellular carcinoma. Recently, a review entitled "Hepatitis B" by Jeng *et al.* in *The Lancet* summarized the latest advances in the epidemiology, natural history and treatment strategies of chronic hepatitis B (CHB)[4]. They suggest that most patients manifest HBeAg-negative chronic infection after HBeAg seroconversion, with approximately 5% reverting to the HBeAg-positive phase and 10-25% progressing directly or indirectly to HBeAg-negative CHB. This means that it is not a line development process, despite such a statement is met in major guidelines including EASL, ASSLD, and others.

HBV is a non-cytopathic hepatotropic DNA virus. The natural history of CHB is the dynamic interplay between the host immune response and viral replication. As described at EASL 2017, its natural history has been schematically divided into five phases according to virological and inflammatory features: HBeAg-positive chronic HBV infection (immune-tolerant), HBeAg-positive chronic hepatitis B (immune-active), HBeAg-negative chronic HBV infection (inactive carrier), HBeAg-negative chronic hepatitis B (reactivation), and HBsAg-negative phase[5]. However, this weakens the spatiotemporal correlation between different disease states and the natural history of CHB.

There are significant differences in HBV infection patterns and genotypes between regions. In low-prevalence regions such as Europe and the Americas, adult exposure is the primary route of infection, whereas in high-prevalence regions such as East Asia, vertical transmission from mother to child predominates. Consequently, most of these patients in East Asia should have experienced a longer period of immune tolerance before HBeAg seroconversion. As for the genotypes, A and D are globally distributed, while B and C are highly prevalent in Asia. In particular, genotype B is responsible for 27.9% and genotype C for 64.4% of HBV infections in China[2]. We therefore asked whether such differences in routes of infection and a longer natural history would result in different patterns of disease progression.

Recently, a follow-up cohort study from Taiwan in China showed that spontaneous HBeAg conversion at older age had a higher probability of persistently elevated ALT (> 6 months), suggesting that a certain proportion of patients may progress directly from HBeAg-positive CHB to HBeAg-negative CHB[6]. In addition, a follow-up study from Japan reported that up to 60% of patients had an abnormal ALT at HBeAg seroconversion, which is significantly higher than the 10-25% mentioned in the article[7]. Similarly, our recent cross-sectional study based on Chinese people found that the age of patients with HBeAg-negative CHB was younger than that of patients with HBeAg-negative chronic infection, but older than that of patients with HBeAg-positive CHB[8]. Therefore, we recommend that a subset of patients transition directly from HBeAg-positive CHB to HBeAg-negative CHB, and this proportion increase with age.

Accordingly, we have refined the presentation of chronic HBV infection to better reflect the natural history of patients worldwide. As shown in Fig.1, during HBeAg-positive chronic infection (immune-tolerant), patients typically have elevated levels of HBV DNA and HBsAg, positive HBeAg, persistently normal serum alanine aminotransferase (ALT) and liver histology without significant inflammation, necrosis or fibrosis. Subsequently, during the immune-active phase, viral replication is suppressed, leading to a gradual decline in HBV DNA and HBsAg levels with persistent or intermittent abnormal ALT levels or evident inflammation, necrosis, or fibrosis in the liver. During this period, serologic conversion of HBeAg may occur, with a transition from HBeAg-positive CHB to HBeAg-negative CHB. In chronic HBeAg-negative infection (inactive carrier), HBV DNA levels are often below the detection limit with positive HBsAg, persistently normal ALT and minimal liver histologic lesions. During this interval, 10-25% of patients may progress to HBeAg-negative CHB, while about 1% of patients may have resolved or occult HBV infection.

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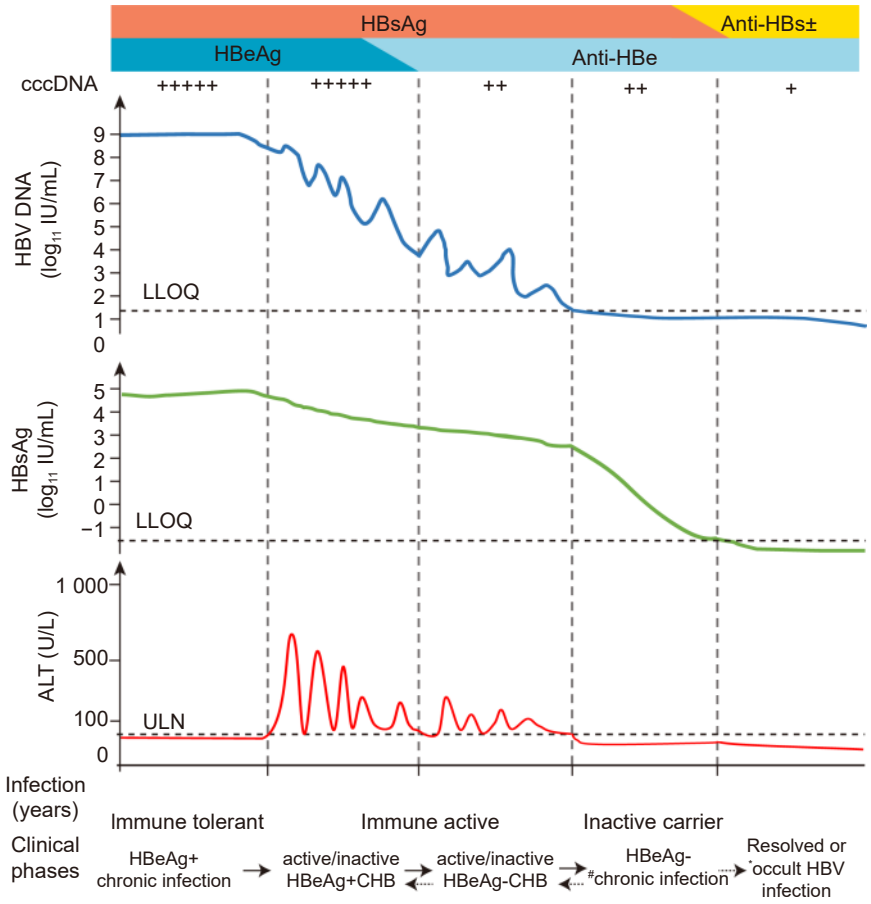

Fig. 1. Modified phases of chronic HBV infection.
#: 10%-25%[4]; *: about 1%[4].

Abbreviations

ALT, alanine aminotransferase; CHB, Chronic Hepatitis B; HBV, Hepatitis B Virus.

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Conflict of interest

The authors declare that they do not have any conflict of interest.

Authors' contributions

FML designed the study and revised the manuscripts. XL and LJW wrote the manuscripts.

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