Viral factors and outcome of chronic hepatitis B revisited

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Virus-host interactions during chronic hepatitis B virus (HBV) infection allow the distinction of several phases, defined according to virological, biochemical and histological profiles: immune-tolerant (IT) [HBeAg-positive, very high serum level of HBV DNA, normal serum alanine aminotransferase (ALT) level without significant liver necroinflammation activity and fibrosis], immune-reactive (HBeAg-positive, high HBV DNA and ALT levels with moderate to severe liver activity and fibrosis) and the inactive carrier state, which follows HBeAg seroconversion and reflects host immune control of the HBV infection (HBeAg-negative, low HBV DNA level, normal ALT level without liver damage in most cases). An HBeAg-negative chronic hepatitis B (CHB) phase (HBeAg-negative, HBV DNA level above 2,000–20,000 IU/mL, normal/high ALT level and histological signs of CHB) occurs in patients who have achieved HBeAg seroconversion or in inactive carriers due to HBV reactivation [1]. Basal core promoter

(BCP) mutations have been reported to possibly modulate HBV replication [2–4] and could thus impact the natural course of CHB. In addition, BCP mutations (the more common are the BCP A1762T/G1764A dual mutations) and precore G1896A mutation lead to the impairment and abolishment, respectively, of HBeAg production [5], and they have been reported in patients with HBeAg-negative CHB occurring under immune pressure to control HBV infection. Importantly, the more common BCP dual mutations have been shown to increase the risk of developing hepatocellular carcinoma (HCC) [6, 7].

Turyadi et al. [8] carried out a cross-sectional study to characterize the relationships between viral factors and the natural history of CHB within the Indonesian population. In their study, Turyadi et al. assessed the correlations between viral parameters [serum HBsAg, HBeAg and HBV DNA levels, HBV genotype and BCP (A1762T/G1764A)/precore (G1896A) mutations] in different stages of HBV infection within a cohort of 152 treatment-naïve Indonesian patients. Patients were categorized into the four phases of CHB, denoted IT, immune-clearance (IC, i.e., immune-reactive phase), low/non-replicative (LR, i.e., inactive carrier state) and HBeAg-negative CHB (ENH). The authors showed that HBsAg and HBV DNA serum levels were both at a high level and strongly correlated in the early phases of CHB (i.e., IT and IC), but a tendency to separate from one another occurred after HBeAg seroconversion. A moderate correlation between serum HBV DNA and serum HBsAg titers was found in the ENH phase, and no correlation was observed in the LR phase. These important results are consistent with previous studies [9, 10] and suggest that the control of HBV replication by the immune system does not hamper HBsAg production. In this study, a temporal relationship between HBeAg seroconversion and an increase of prevalence of patients with

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Table 1 HBV viral parameters and frequencies of BCP/precore mutations in the different phases of CHB in 152 Indonesian patients

	<i>n</i> = 152			
	HBeAg positive		HBeAg negative	
	IT phase (<i>n</i> = 33)	IC phase (<i>n</i> = 32)	LR phase (<i>n</i> = 34)	ENH phase (<i>n</i> = 53)
HBsAg level (log ₁₀ IU/mL)	+++	+++	++	+++
HBV DNA level (log ₁₀ IU/mL)	+++	+++	+	+++
HBeAg level (PEIU/mL)	++	++	N/A	N/A
Frequency (%) of BCP mutations: A1762T/G1764A	++	++	++	++
Frequency (%) of precore mutation: G1896A	–	+	++	++

High, moderate, low or absence of different HBV viral parameters are represented by +++, ++, + or –, respectively

BCP basal core promoter, CHB chronic hepatitis B, ENH HBeAg-negative CHB, IC immune-clearance, IT immune-tolerant, LR low/non-replicative, N/A not applicable

BCP/precore mutations was shown, suggesting that the immune control that occurs during CHB is instrumental in selecting variants defective for HBeAg production. As it was found that BCP mutations were similarly distributed among the CHB phases [8], immune pressures could occur at any CHB stage and select virions with BCP mutations. Turyadi et al. did not find a correlation between HBV DNA and HBeAg levels in the IT and IC phases. This may be accounted for by the impairment of HBeAg production in part caused by BCP/precore mutants, which this study already found in the early stages of CHB. Levels of the main viral factors and frequencies of BCP/precore mutations assessed in this study are summarized in Table 1.

As the authors have outlined, this study has several limitations. The number of patients was small, and virological and biochemical parameters, used to classify the patients according to CHB phases, were measured only once. However, during the course of CHB, HBV DNA and ALT levels spontaneously fluctuate, particularly in the ENH phase [11]. Thus, some patients may have been misclassified. Moreover, according to the criteria used to determine the disease stage [8], the group of patients in the LR phase possibly included both inactive carriers and patients with active ENH. Indeed, even if inactive carriers may have HBV DNA levels up to 20,000 IU/mL, ALT levels should remain normal [1]. Histological parameters are key to the proper assessment of hepatitis activity and liver fibrosis. In this study, none of the patients underwent a liver biopsy (LB), which might have increased the risk of misclassification [12]. In addition, the lack of LB precluded correlation of the CHB stage with intrahepatic viral parameters, such as covalently closed circular DNA (cccDNA). Finally, patients coinfecting with human immunodeficiency virus or hepatitis D virus, which can modulate the course of HBV infection [1], were not excluded from this study.

Aiming to address the role of viral factors in HBV pathogenesis, Turyadi et al.'s [8] study provides an interesting and extensive characterization of associations between the

main viral factors in the different stages of the natural course of CHB within an Indonesian cohort. This is a unique study involving the analysis of correlations between major HBV viral factors in the four phases of CHB and in a cohort of Indonesian patients (Table 1). Indeed, such a study has not been performed so far in this ethnic group. Interestingly, this work confirmed the results that previous studies partially addressed. Importantly, a key finding of this study is that BCP mutations were found in comparable distribution among the different CHB phases [8]. Since it was previously shown in different ethnic groups that BCP mutations increase the risk of developing HCC [6, 7], Turyadi et al.'s results reinforce the importance of performing further clinical studies with the aim to seek BCP mutations in chronically HBV-infected patients, regardless of the stage of disease, in order to determine their impact on HCC development and their usefulness in routine clinical practice.

In conclusion, in the setting of the HBV clinical cohort studies performed, most of them comprise patients with Chinese, Taiwanese and/or Korean origin (living in areas where HBV is strongly endemic); this study gives an extensive and unique overview of associations between major viral factors occurring during the natural course of CHB within an Indonesian population. Evaluation of HBV viral markers in different chronically HBV-infected populations is crucial in order to determine whether the viral correlations during the course of HBV infection are modulated by the ethnic-related background.

Conflict of interest François Habersetzer, Rémy Moenne-Loccoz, and Thomas F. Baumert report no conflicts of interest.

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