Are Hepatitis B e Antigen (HBeAg)–Positive Chronic Hepatitis B and HBeAg-Negative Chronic Hepatitis B Distinct Diseases?

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(See the article by Wu et al. on pages 1305–11)

The current algorithm for the treatment of chronic hepatitis B is primarily dependent on 3 factors: (1) hepatitis B virus (HBV) DNA levels, (2) alanine aminotransferase levels, and (3) hepatitis B e antigen (HBeAg) status [1, 2]. The presence of HBeAg is pivotal for deciding whether to start and when to stop antiviral therapy. For HBeAg-positive chronic hepatitis B, current guidelines recommend treatment if the serum HBV DNA level is $>$20,000 IU/mL and the alanine aminotransferase level is elevated or if there is significant liver disease found by examination of a liver biopsy specimen. Treatment with oral antiviral medication is continued until HBeAg seroconversion has been achieved. This occurs when serum HBeAg becomes undetectable and antibody to HBeAg is detected. After HBeAg seroconversion is achieved, antiviral therapy is most often continued for another 6–12 months (i.e., consolidation therapy) and then stopped. With consolidation therapy after HBeAg seroconversion, most patients have sustained viral suppression while not receiving medication; however, relapse, with reappearance of serum HBV DNA and detection of HBeAg, occurs in a significant proportion of patients (20%–30%) [3–6].

In this issue of Clinical Infectious Diseases, Wu et al. [7] report the rates of sustained HBeAg seroconversion in a cohort of 45 patients with HBeAg-positive chronic hepatitis B and HBeAg seroconversion after therapy with adefovir dipivoxil. Approximately three-quarters of the patients were Asian, and one-quarter were white. After a median follow-up period of 150 weeks (range, 13–252 weeks), 4 patients experienced virologic relapse. The study examined the duration of therapy before HBeAg seroconversion and consolidation therapy after HBeAg seroconversion as potential predictors of relapse, as well as the presence of precore and/or basal core promoter mutations before treatment. The authors found that a longer duration of therapy, both before and after HBeAg seroconversion, was associated with sustained HBeAg seroconversion. In a subset of 13 of the 20 patients with a serum HBV DNA level $>$1000 copies/mL at the last study visit who had stored serum samples available for genotypic analysis for precore and basal core promoter mutations (by dideoxy sequencing; sensitivity, 25%), the authors found that most (11 patients) had either precore and/or basal core promoter mutations. Eight of the 11 patients with precore and/or basal core promoter mutations during follow-up had these mutations before initiation of adefovir therapy.

Although the association of longer consolidation therapy with a higher rate of sustained HBeAg seroconversion is generally known as a result of prior published experience with lamivudine therapy [8, 9], the analysis of precore and basal core promoter mutations introduces 2 relatively new and underappreciated concepts: (1) the issue of a mixed viral population of HBeAg-producing wild-type virus and virus with precore and/or basal core promoter mutations and (2) the potential association between precore and/or basal core promoter mutations with relapse after a course of oral antiviral therapy.

The most common precore mutant virus has a point mutation from G to A at nucleotide 1896 (A1896), which creates a stop codon 28 and abolishes synthesis of HBeAg [10]. The double mutations in the basal core promoter region at nucleotide 1762 (A–T) and 1764 (G–A) are associated with reduced synthesis of HBeAg by suppressing the transcription of precore mRNA by 50%–70% [11, 12]. Although the association between precore and basal...
core promoter mutations with HBeAg-negative chronic hepatitis B is well established [13–15], their presence in HBeAg-positive chronic hepatitis B is much less appreciated. Precore and/or basal core promoter mutations were found in approximately one-half of HBeAg-positive patients with chronic hepatitis B [14, 15]. In recent years, the clinical significance of precore and basal core promoter mutations in HBeAg-positive patients has been studied with regard to spontaneous HBeAg seroconversion, but little is known regarding the potential role of these variants in treatment-associated HBeAg seroconversion [16–22].

During spontaneous HBeAg seroconversion, the prevalence of both the precore mutation G1896A and basal core promoter mutations A1762T/G1764A appears to increase in patients who experience HBeAg seroconversion. The prevalence of these mutations is also increased in patients with persistently or intermittently elevated alanine aminotransferase levels, compared with immune tolerant patients with persistently normal alanine aminotransferase levels [21]. None of these studies, however, examined the association between the presence of precore and basal core promoter mutations and HBeAg seroconversion with complete HBV DNA suppression (i.e., undetectable HBV DNA by PCR techniques).

The study by Wu et al. [7] in this issue of Clinical Infectious Diseases revealed that 20 of 45 HBeAg-positive patients still had a serum HBV DNA level >1000 copies/mL after HBeAg seroconversion, and that, of the 13 of 20 patients with available pretreatment serum samples, 11 had virus with either precore and/or basal core promoter mutations. Eight of these 11 patients already had virus with precore and/or basal core promoter mutations before initiation of adefovir therapy. The retrospective design and small sample of the study did not allow analysis of the association of pretreatment precore and basal core promoter mutations with HBeAg seroconversion. This study, however, emphasized the relatively frequent presence of precore and basal core promoter mutations in HBeAg-positive patients, and further studies are needed to elucidate the clinical significance of these variants.

Finally, the association between precore and basal core promoter mutations with HBV genotypes should also be noted. Most of the literature concerning this association comes from Asia, where HBV genotypes B and C are the primary genotypes. In general, precore mutation A1896 is known to be more common in patients with HBV genotype B than in patients with HBV genotype C, whereas basal core promoter mutation T1762/A1764 is more common in patients with HBV genotype C [21, 23–25]. Precore and, especially, basal core promoter mutations have been shown to be risk factors for hepatocellular carcinoma, independent of HBV genotype status, age, sex, and HBV DNA level (OR, 2.4 [95% CI, 1.1–5.3] and 12.8 [95% CI, 5.9–27.8], respectively) [26, 27]. The presence of precore and basal core promoter mutations is associated with a higher risk of advanced liver disease in HBeAg-positive chronic hepatitis B than in HBeAg-negative chronic hepatitis B [20].

In summary, precore and basal core promoter mutations occur in both HBeAg-negative and HBeAg-positive chronic hepatitis B. In addition to their association with more advanced liver disease, hepatocellular carcinoma, and spontaneous HBeAg seroconversion, the clinical significance of these mutations remain to be defined in the context of antiviral therapy. Virologic relapse after complete viral suppression in HBeAg-negative chronic hepatitis B is well known, which accounts for the recommendation of long-term therapy for this patient population by treatment guidelines [1, 2]. Despite receiving consolidation therapy after successful HBeAg seroconversion, only a few patients still exhibit significant viremia and HBeAg seroconversion. Additional studies are needed to examine the relationship between baseline precore and basal core promoter mutations and treatment response to antiviral therapy in patients with HBeAg-positive chronic hepatitis B; specifically, the durability of treatment-induced HBeAg seroconversion in the presence of a mixed precore and/or basal core promoter mutant viral population needs to be studied. The results of such studies may lead to reassessment of the current distinct division between the management of HBeAg-positive chronic hepatitis B and the management of HBeAg-negative chronic hepatitis B [1, 2].

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