Influence of hepatitis B virus genotypes on the response to antiviral therapies

Norio Akuta* and Hiromitsu Kumada

Department of Gastroenterology, Toranomon Hospital, 2-2-2 Toranomon, Minato-ku, Tokyo, 105-0001, Japan

Hepatitis B virus (HBV) has been classified into eight genotypes (A–H) based on genome sequence divergence. Genotypes of HBV have distinct geographical distributions, and two genotypes account for most HBV worldwide. Hepatitis B e antigen expression lasts longer and liver disease is more severe with graver outcomes in carriers of genotype C than B in Asia. Accumulating lines of evidence indicate a better response to interferon and lamivudine in patients with chronic hepatitis B who are infected with genotype B rather than C. The therapeutic response may differ, however, in patients infected with HBV of the same genotype. For example, the response to lamivudine is poorer in patients infected with subtype Ba, which contains a recombination with genotype C, than in those with subtype Bj without such a recombination. Influence of genotypes on therapeutic response needs to be examined in patients infected with the other genotypes, particularly in those with genotype A or D infection.

Keywords: chronic hepatitis, genotypes, hepatitis B e antigen, hepatitis B virus, interferon, lamivudine

Introduction

Worldwide, 350 million people are estimated to be persistently infected with hepatitis B virus (HBV),1 and three-quarters of these people reside in Asia. The morbidity and mortality of persistent HBV infection are a major public health concern. More than one million deaths every year are due to end-stage HBV liver disease, such as decompensated liver cirrhosis and hepatocellular carcinoma (HCC). The carrier state of HBV is established mainly through mother-to-baby infection in Japan, where the prevalence of hepatitis B surface antigen carriage (HBsAg) in the general population used to be less than 2%, while horizontal transmission during infancy plays an additional role in the other countries in Asia and accounts for most persistent infections in Africa where HBsAg prevailed in > 8% of the general population during the past. Although much less efficient, horizontal transmission can lead to persistent HBV infection in Western countries through sexual contact and illicit intravenous drug use. Individuals with persistent HBV infection need to be identified early and receive efficient antiviral therapy in order to prevent the development of serious liver disease.

Genotypes of HBV

The response to antiviral therapy in HBV infection is influenced by many host and viral factors. Recently, HBV genotypes have attracted increasing attention since they influence the activity and outcome of HBV-associated chronic liver disease, as well as the response to antiviral therapies. In 1988, four genotypes of HBV (A–D) were proposed based on sequence divergence of > 8% in the entire HBV genome, which consists of approximately 3200 base pairs.2 Later, an additional four genotypes (E–H) were identified by the same criteria.3–5 HBV genotypes have distinct geographical distributions,6 and the full picture awaits further epidemiological surveys in many as yet unexamined countries. Overall, genotype A prevails in Northwest Europe, sub-Saharan Africa, India and the United States, B and C are frequent in Southeast Asia, Japan and Oceania, and D is common in the Mediterranean countries. Genotype E is restricted to Africa, and F is found mainly in Central and South America. The distribution of genotypes G and H is yet to be determined. Since persistent HBV infection is frequent in Asia, genotypes B and C prevailing there have been studied most extensively with their clinical and therapeutic differences unfolding rapidly. Differences between genotypes A and D prevailing in Western countries, India and the United States, also, are increasingly coming to the fore.

Clinical manifestations of persistent HBV infection with distinct genotypes

Prospective, case-controlled and cross-sectional studies predominantly but not entirely indicate that the severity and outcome of chronic hepatitis B are more serious in patients infected with
Influence of HBV genotype on the response to antiviral therapy

Until lamivudine was developed for clinical use, interferon had remained the sole practical antiviral for chronic hepatitis B, ever since initial clinical trials by Hoofnagle and colleagues in the mid-1980s. The response to interferon, judged by the loss of HBsAg from serum, is achieved in at most 20% of treated patients.25 Moreover, Asian patients who have acquired the HBV carrier state at birth or in early infancy respond to interferon more poorly than Caucasian patients who contracted it in adulthood.26 To make matters even worse, patients with chronic hepatitis B positive for anti-HBc antibodies are much less responsive to interferon than those with serum HBsAg.27 Limited experience indicates that HBV genotypes make a difference in the response to interferon in patients with chronic hepatitis B.

Zhang et al. compared the response between 10 patients with genotype A infection and 21 patients with genotype D or E infection.28 Since all patients they studied were positive for anti-HBe antibodies, the negative influence of genotype A on seroconversion to anti-HBe was excluded. They found the response to interferon was higher in patients infected with genotype A compared with D or E (70% versus 40%, $P<0.001$).29 Likewise, Kao et al.29 reported the response to interferon to be higher in patients infected with genotype B rather than C [13/32 (41%) versus 4/26 (15%), $P=0.045$]. More recently, Wai et al.30 compared the response between patients randomized to interferon or placebo. They found the response was better in patients with genotype B than C infection who were allocated to interferon treatment [12/31 (39%) versus 7/42 (17%), $P=0.034$]; the response rate did not differ in those who received placebo.

Lamivudine [(-)-β-L-2',3'-dideoxy-3'-thiacytidine] is a nucleoside analoge with a potent antiviral activity. Since its approval in 1998, lamivudine has gained wide popularity for the treatment of chronic hepatitis B due to high efficacy with minimal untoward effects.31-35 We believe in continued lamivudine treatment for patients with or without serum HBeAg,36-39 and have accumulated experience with 286 patients including seven who have received lamivudine for 7 years or longer.40 HBV genotype also makes a difference in the response to lamivudine in patients with chronic hepatitis B. Among the 16 patients who had received lamivudine for 3 years or longer, the virological response with the loss of HBV DNA detectable by non-amplified method was achieved in two of the three (67%) patients infected with genotype B and in seven of the 13 (54%) patients infected with genotype C.

Kao et al.41 reported on the response to lamivudine in patients treated for 6–30 months infected with genotype B compared with C [3/13 (23%) versus 2/18 (11%), no significant differences]. They found resistance to lamivudine in two (15%) patients with genotype B and in four (22%) with genotype C. Chien et al.42 reported that the sustained response to lamivudine was much higher in patients infected with genotype B compared with genotype C [38/62 (61%) versus 5/20 (20%), $P=0.009$]. We monitored 213 patients on continued lamivudine treatment for drug-resistant HBV variants for mutations in the tyrosine-methionine-aspartate-aspartate (YMDD) motif in the viral DNA polymerase/reverse transcriptase.43 The emergence of YMDD mutants was no different amongst patients infected with genotype A, B or C. However, YMDD mutants developed significantly more frequently in patients infected with subtype Ba
than Bj during 2 years on lamivudine [3/4 (75%) versus 1/14 (7%), P < 0.05]. Severe acute exacerbation of hepatitis occurred in four of the 185 (2%) patients with genotype C along with the emergence of YMDD mutants, but in none of the 28 patients with the other genotypes. In patients with chronic hepatitis B in Germany, risk of lamivudine resistance was significantly higher in carriers of HBsAg of serotype adw than ayw [7/13 (54%) versus 1/13 (8%), P = 0.03];44 serotype adw corresponded to genotype A and ayw to D.51

Conclusion

HBV genotypes influence the severity of liver disease and response to interferon and lamivudine. They are also expected to influence the response to adefovir dipivoxil, which has recently been approved for treatment of chronic hepatitis B,46 as well as the emergence of resistant mutants;53 although as yet no differences have been observed in the response to adefovir dipivoxil in relation to HBV genotypes.53 Should poor responses to a given antiviral be predicted in patients infected with HBV of certain genotypes, they can be directed to the other therapeutic options to spare the cost and burden of treatment. In evaluating the association of HBV genotypes with the response to antiviral therapies, however, it needs to be taken into account that patients visiting hospitals are biased for severe liver disease. Moreover, once full-blown disease develops, it would become refractory to any antiviral treatments. Thus, genotype differences may be attenuated in patients with severe liver disease seen in hospitals, probably due to exclusion of patients with less severe disease who can still benefit from treatments. This view would be supported by different distributions of genotypes B (12% and 54%, respectively) and C (84% and 47%) between patients visiting hospitals and individuals found with HBV infection at routine check-ups in the same district of Japan.51,52 Therefore, in evaluating the influence of HBV genotypes on response to antiviral therapies, one has to keep in mind not only patients with liver disease who visit hospitals, but also those who have not and who may benefit from early treatment.

References

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