

Hepatitis B Virus Genotypes and Response to Antiviral Therapy in Chronic Hepatitis B

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Hepatitis B virus (HBV) has been classified into eight genotypes (A–H), based on divergence in the entire HBV genomic sequence of >8%.¹⁻³ Genotypes A and D are most frequently observed in Europe, Africa, and North America, while genotypes B and C are prevalent in Asia. Genotype E is restricted to West Africa, and genotype F is found in Central and South America. Genotype G was identified in France, Germany, and North America. Recently, genotype H has been described in Central America.

Clinical significance of HBV genotypes has most extensively been studied in patients with chronic HBV infection in Asia. These studies show that compared to genotype C, genotype B is associated with spontaneous HBeAg seroconversion at younger age and lower serum HBV DNA.^{4,5} Furthermore, infection with genotype B has been reported to result in less active liver disease, a slower rate of progression to cirrhosis, and less frequent development of HCC compared to genotype C.⁵⁻⁷ Sustained biochemical remission and clearance of serum HBV DNA were more frequently observed in patients with genotype A compared with genotype D.⁸

HBV genotype has been suggested to influence response to both nucleoside analogue and interferon-based treatment. In lamivudine-treated patients, infection with genotype B has been reported to result in increased virological response rates compared to genotype C,⁹ while other studies contradicted this finding.^{10,11} No difference in response to lamivudine between genotype A and D, or in emergence of lamivudine resistance across the most prevalent genotypes (A-D), has been reported.^{11,12} Initially, in adefovir-treated patients, no influence of genotype on response to antiviral therapy was observed.¹³ A recent study, however, demonstrated that genotype D was found to be significantly more frequent in adefovir-resistant patients compared to non-resistant patients.¹⁴ Response rates in entecavir-treated patients were comparable across genotypes in both HBeAg-positive and HBeAg-negative patients.¹⁵ In patients treated with standard interferon, HBeAg-seroconversion was found to occur more often in patients with genotype A and B than in those with genotype C and D.^{16,17} HBV genotype also seems to predict response to pegylated interferon. A higher rate of HBeAg-loss and HBsAg-loss has been observed in patients with genotype A and B compared to genotype C and D,¹⁸⁻²⁰ with loss of HBeAg and HBsAg in 47% and 14%, 44% and 9%, 28% and 3%, and 25% and 2% of patients infected with genotypes A to D, respectively.^{19,20} Another study in HBeAg-positive chronic HBV partly confirmed these findings and only demonstrated a superior response in genotype A.¹⁰

In conclusion, HBV genotype appears of influence on the natural course of HBV infection, with more severe disease in patients with genotype C compared to genotype B, and genotype D compared to genotype A. Genotype A or B seems to be associated with a higher likelihood of response compared to infection with genotype C or D in the treatment with peg-interferon. Stratification of peg-interferon for genotype A patients versus nucleos(t)ide analogues for other genotypes should thus be considered in treatment algorithms. HBV genotype does not seem to influence response to most nucleos(t)ide analogues. In future trials, testing for HBV genotype should be included in the routine baseline evaluation of patients to gain more insight in the relation between genotypes and outcome of therapy.

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