Factors associated with hepatitis B virus DNA breakthrough in patients receiving prolonged lamivudine therapy.

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Factors associated with hepatitis B virus (HBV) DNA breakthrough and the significance of YMDD variants without the presence of wild-type YMDD during prolonged lamivudine treatment are unknown. We studied the amino acid sequence of codon 552 (YMDD motif) and codon 528 by means of a line probe assay in 159 chronic HBV patients (median follow-up 29.6 months). Pretreatment HBV DNA levels and alanine transaminase (ALT) levels correlated inversely with the time to HBV DNA breakthrough with YMDD variants (r = -0.46, P = .001; r = -0.45, P = .001 respectively). Patients harboring YMDD variants 3 months before HBV DNA breakthroughs had higher HBV DNA breakthrough levels compared with those without YMDD variants 3 months before HBV DNA breakthroughs (18.9 x 10^6 vs. 5.4 x 10^6 copies/mL, P = .007). Patients with HBV DNA breakthroughs had higher percentages of YMDD variants without the presence of wild-type YMDD compared with patients without HBV DNA breakthrough (25.6% vs. 9%, P = .007 for single M552I variant; 20.9% vs. 8.1%, P = .026 for single M552V variant; 30.2% vs. 9.9%, P = .004 for M552I/M552V variants). Patients with HBV DNA levels of more than 10^3 copies/mL after 6 months of lamivudine therapy had a 63.2% chance of subsequently developing YMDD variants. HBeAg seroconversion occurred in 2 patients after the emergence of YMDD variants. Only one patient developed YMDD variant after HBeAg seroconversion. There was no increase in the rate of development of YMDD variants or L528M mutation in patients receiving lamivudine 25 mg daily or famciclovir 500 mg 3 times a day before being given lamivudine 100 mg daily.