Rapid re-emergence of YMDD mutation of hepatitis B virus with hepatic decompensation after lamivudine retreatment

So Young Kwon, Won Hyeok Choe, Chang Hong Lee, Jong Eun Yeon, Kwan Soo Byun

Abstract

Lamivudine has a high rate of antiviral resistance. Sequential treatment of anti-hepatitis B virus (HBV) is commonly used for lamivudine resistance. We report 4 cases of patients with rapid redetection of HBV mutants during the lamivudine retreatment. The four patients received lamivudine as an initial treatment of HBV and adefovir and lamivudine as a rescue therapy consecutively. HBV-DNA level, YMDD mutations and adefovir-resistant mutations (RFMP) were tested every 3 mo during the sequential treatment. All the patients showed YMDD mutations during the initial lamivudine therapy. After adefovir therapy for lamivudine resistance, they showed viral breakthrough. Adefovir was switched to lamivudine, however, it did not induce viral suppression at all, rather increased HBV-DNA with rapid reemergence of the YMDD mutations. All the patients had ALT flares, and hepatic decompensation occurred in two patients. After switching to adefovir combined with entecavir or lamivudine for a rescue therapy, the patients had reduction in HBV DNA and ALT improvement. These cases demonstrated that lamivudine retreatment of patients with preexposed lamivudine resistance leads to rapid reemergence of YMDD mutation with significant viral rebounds and subsequent hepatic decompensation. Sequential administration of lamivudine in patients with a prior history of YMDD mutation should be abandoned.

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Viral responses and clinical courses in a 46-year-old man with cirrhosis, received lamivudine as an initial treatment. Lamivudine was switched to adefovir, however, there was no decrease in HBV-DNA level but ALT elevation. After reintroduction of lamivudine for adefovir resistance, ALT level decreased without a significant drop in HBV-DNA level initially. Adefovir-resistant mutant was replaced by wild type, however, reemergence of the rtM204I/V mutation followed by HBV-DNA rebound and ALT fluctuation were observed. Adefovir was added to the ongoing lamivudine therapy.

Patient 3 (Figure 3), a 50-year-old woman with decompensated cirrhosis (patient 3). The underline represents sequential evolution of lamivudine- or adeforvir- resistant genotypic mutations in HBV polymerase gene. LMV: Lamivudine; ADV: Adefovir; ALT: Alanine aminotransferase.

After lamivudine was switched to adefovir, HBV-DNA dropped by 2 logs with ALT normalization. Viral breakthrough (defined as a ≥ 1 log_{10} increase in HBV DNA from nadir after initial viral response) and rtN236T mutation developed after 30 mo of adefovir therapy. Lamivudine was restarted with discontinuation of adefovir. After lamivudine was restarted, the rtM204I mutation reemerged and rtN236T adefovir-resistant mutants disappeared 1 mo after the treatment. He showed persistently high levels of HBV-DNA, ALT and total bilirubin. Lamivudine was changed to adefovir and entecavir combination treatment as a rescue therapy. After the combination treatment, HBV-DNA and ALT dropped significantly.

Patient 2 (Figure 2), a 49-year-old man with compensated cirrhosis (patient 2). The underline represents sequential evolution of lamivudine- or adefovir- resistant genotypic mutations in HBV polymerase gene. LMV: Lamivudine; ADV: Adefovir; ALT: Alanine aminotransferase.

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Patient 4 (Figure 4), a 50-year-old man with cirrhosis, received lamivudine for 14 mo. He had viral breakthrough with mild elevation of ALT, therefore lamivudine was changed to adefovir. However, he had no viral response though he showed a normal ALT level during the adefovir treatment. Adefovir was switched to lamivudine due to the high viral load. The ALT level was stable despite no decrease in HBV-DNA. After 2 mo
of lamivudine retreatment, HBV-DNA rebound with ALT flare developed. HBV mutation rtM204I was reappeared at this time. Adefovir was added to the ongoing lamivudine treatment.

All the patients were positive for HBeAg and had no seroconversion of HBeAg during the sequential antiviral treatment except for patient 3. Patient 3 had HBeAg loss after the lamivudine/adefovir combination therapy. No death occurred, however, two of them showed hepatic decompensation following the reemergence of YMDD mutations and viral breakthrough.

DISCUSSION

These cases showed that reintroduction of lamivudine could induce rapid reemergence of lamivudine-resistant mutations in chronic hepatitis B patients with prior lamivudine resistance. Lamivudine is well tolerated and significantly reduces HBV-DNA level[10]. However, lamivudine resistance associated with mutations in the polymerase gene, particularly in rtM204I/V known as YMDD mutant, occurs at a rate of 14%-30% annually[14]. Development of lamivudine resistance is associated with high baseline HBV-DNA level, duration of lamivudine treatment, precore variant, insufficient serum HBV-DNA suppression and elevated serum ALT level during treatment[11][13]. All the cases had positive HBeAg and high viral load at the time of lamivudine resistance. The high viral replication status may predispose to develop antiviral resistant mutations and subsequent viral breakthrough.

Adefovir is an effective rescue therapy for lamivudine-resistant HBV and significantly improves biochemical, virological, and histological features of lamivudine-resistant patients[10][14]. Compared with lamivudine, adefovir is associated with a low rate of antiviral resistance[14]. However, adefovir resistance occurs more common in patients with preexisting lamivudine resistance[7]. Among our cases, rtN236T mutation was detected in two patients at the time of viral breakthrough after adefovir rescue therapy. The other two showed no virologic response, and rtA181V was found in one patient.

YMDD mutations, mainly rtM204I in our cases, disappeared after the adefovir treatment, suggesting that cessation of antiviral therapy leads to disappearance of drug-resistant mutations. However, it was reported that lamivudine-resistant HBV mutants reappear rapidly after reinitiation of lamivudine[15]. Once antiviral-resistant HBV mutants have been selected, the mutants are archived even if treatment is stopped. In our cases, YMDD mutation reemerged within 3 mo after reinitiation of lamivudine, suggesting that re-treatment to which the virus has been previously resistant has a limited efficacy even after wild-type YMDD has restored. It could not be excluded that the adefovir-resistant mutations may affect the rapid emergence of lamivudine-resistant mutation.

The emergence of lamivudine resistance can result in viral breakthrough, flares of hepatitis and worsening of the initial histological improvement[12][13]. In patients with cirrhosis, severe exacerbation of hepatitis may result in hepatic failure[13]. It was reported that patients with YMDD mutations experience a higher rate of hepatitis flares than those without YMDD mutations[17], which is possibly because the YMDD locus takes part in cellular immune response in some cases.

Serum HBV DNA level was higher than baseline in the cases after emergence of the YMDD mutant before exacerbation occurred. Two patients experienced a very rapid deterioration of hepatic function accompanying the reemerging YMDD mutants only a few months after lamivudine reintroduction. These findings clearly demonstrate that sequential monotherapy, particularly retreatment with the antiviral agent to which the HBV has been previously resistant, should be avoided.

Combination therapy with adefovir and lamivudine or other antiviral agents could be a better option to prevent the emergence of antiviral-resistant mutations in patients with lamivudine- or adefovir-resistance. Combination therapy is not likely to improve virologic response, but rather decrease the rate of viral resistance[18][19]. Unfortunately, combination therapy could not be commonly used in Korea so far because of the high cost of antiviral agents. Other antiviral agents, such as tenofovir or pegylated interferon, could be promising agents for multi-drug resistant HBV[20][21]. All the patients in this study received combination therapy with adefovir and lamivudine or entecavir as a rescue therapy for lamivudine resistance. After the combination treatment, the HBV DNA and ALT level dropped and hepatic function was restored. It was reported that entecavir has a potent antiviral efficacy against naive HBV and lamivudine-refractory HBV[22]. Case 1 received adefovir and entecavir as the rescue therapy. These two agents have antiviral activity on wild type or YMDD mutants without cross resistance. The other three patients received adefovir and lamivudine combination treatment. Case 3 showed a rapid reduction in HBV DNA level and HBeAg seroconversion soon after the combination
therapy. Long-term data are not available from cases 2 and 4. However, they showed a significant decrease in HBV DNA level and improvement in hepatic function after combination therapy.

Taken together, lamivudine retreatment may induce rapid reemergence of the YMDD mutation and significant viral rebound and subsequent hepatic flare in patients with preexposed YMDD mutants. Sequential lamivudine treatment of those with a prior history of YMDD mutation should be abandoned.

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