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LETTER TO THE EDITOR

Multidrug resistance after lamivudine therapy for chronic hepatitis B

Besides interferon, five oral nucleos(t)ide analogues are currently approved for the treatment of chronic hepatitis B (CHB): lamivudine (LAM), adefovir dipivoxil (ADV), entecavir (ETV), tenofovir (TDF) and telbivudine (LdT). Treatment of CHB with any single nucleoside reverse transcriptase inhibitor (NRTI) generally leads to rapid suppression of viral replication in the short term; however, long-term therapy can cause the emergence of drug-resistant mutants.[1,2] Lamivudine, the first NRTI approved for CHB therapy, is still commonly used as the first-choice therapy for its potency, relatively low cost and safety profile. Mutations conferring resistance to LAM have been mapped to the C domain of the viral reverse transcriptase (RT)[3] and are often associated with compensatory mutations in the conserved B domain that partially restore the capacity of mutants *in vitro*.[4,5] When drug resistance occurs during LAM therapy, the most appropriate management is the early combination of LAM with ADV[6] or possibly TDF. ADV usually does not exhibit cross resistance with LAM and undetectable viremia is obtained after three months in 100% of patients who started combined therapy with viremia of <6log cp/ml.[7] Also, ETV is effective in patients with LAM resistance. However, its efficacy is lower than in naïve patients and it needs to be administered in high dose. Also, the likelihood of resistance is higher than that observed in naïve patients, because two of the three mutations conferring resistance to ETV are usually present in LAM-resistant hepatitis B virus (HBV).[8]

Here, we report the case of a 47-year-old male with CHB, HBeAg-negative and anti-HBe-positive, and negative for HCV (hepatitis C virus), HDV (hepatitis D virus) and HIV. He presented with advanced liver disease (Ishak grading 10 and staging 5), elevated HBV DNA (528 000 UI/ml) and increased ALT. He refused PEG-interferon and, according to the national guidelines at that time, started therapy with LAM in February 2006, without performing genotyping. After three months, HBV DNA was below 200 UI/ml and ALT was normal. HBV DNA and ALT measurements, performed every three months, were normal until November 2007, when, despite high adherence to the therapy regime, HBV DNA was 412 UI/ml with a normal ALT value. After a further month, HBV DNA had increased to 1028 UI/ml. HBV genotyping by in-house nested PCR was performed, obtaining the following results: four primary RT mutations, L180M, A181V, M204V, Q215S, and several other secondary mutations, R114H, F122L, N124H, Q130P, Q149K, F221Y, S246H, I253V, W257Y, T259S, D263E, W287C, A317S, S332C, M336I. For HBV sequencing, HBV DNA was extracted using a commercially available kit (QIAmp DNA blood mini-kit, QIagen Inc, USA) and then amplified with Amplitaq-Gold polymerase enzyme using primer pairs that amplify the A to E domains of RT. The sequences were obtained by an ABI-3100 automated sequencer and analyzed using SeqScape-v.2.0 software. These mutations not only confer resistance to LAM and LdT, but also greatly reduce sensitivity to ADV and ETV, leaving only TDF as a potentially suitable therapy.

This case confirms that, as recently recommended by the American Association for the Study of Liver Diseases (AASLD),[9] when possible LAM, despite its high viral potency, should not be used as first-line therapy for CHB, because it can increase the likelihood of resistance to other NRTIs.

Conflict of interest: No conflict of interest to declare.

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