Abstract: 8

Antiviral drug resistance to other (non HIV) viruses

Frequencies of Hepatitis b surface-antigen mutations in drug resistant Hepatitis b virus isolates

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Background: A chronic HBV infection is an important risk factor for development of liver cirrhosis or hepatocellular carcinoma. Therefore an increasing number of HBV infected patients are treated with a growing number of drugs. A major impediment for achieving sustained suppression of viral replication is the evolution of drug resistance. Due to overlapping reading frames treatment-associated mutations also influence the HBV surface-antigen (HBsAg). Little is known about the co-evolution of both viral proteins in drug-resistant HBV.

Material & Methods: We analysed 85 HBV isolates in the polymerase and surface-antigen reading frame, either harbouring treatment-associated mutations or failing antiviral therapy. Additionally, the initial genotype of 15 patients could be compared with following genotypes. HBsAg mutants were expressed in hepatocytes and tested in different routine HBsAg diagnostic assays.

Results: 14% (10/73) of the HBV isolates harbouring treatment-associated polymerase mutations had at least one stop codon in the surface-antigen reading frame at different positions (sW172: n=5, sW182: n=4, sW196: n=1, sW199: n=2, sL216: n=2). Moreover, in 4 of these patients two stop codons were detected. Interestingly, mutation rtM204I resulted only once in sW196* whereas 23 HBV isolates harboured sW196L. HBsAg mutations conferring immune-escape were found in 30% (22/73) of these HBV isolates. 11 HBV isolates had mutations in two epitopes (aa120-125/aa137-145) of the α-determinant potentially conferring detection-escape in commercial tests. These mutations significantly decreased the detection of in vitro expressed HBsAg with commercial test assays, which was most prominent for the test assay using monoclonal antibodies for the capture and detection phase. In some cases the detection was hampered at all. In one patient a HBsAg immune-escape mutation (sP120T) developed, whereas pre-existing resistance-associated mutations (rtL180M, rtM204I/V) maintained. Interestingly, in another patient HBV resistance profiles changed from sP120T, rtL180M, rtM204V after lamivudin failure to sQ101R, sP120S, sW172*, sT189I, rtV173F, rtQ181V, rtL215S after failure of a following adefovir therapy.

Conclusions: After failing antiviral therapy treatment-associated polymerase and HBsAg mutations were often found together in HBV. HBsAg mutations can confer immune-escape and detection-escape in commercial tests or even result in truncated proteins, which might enhance the pathogenicity. More functional analyses of HBsAg mutations in treatment failures are needed to understand the mechanism of selection.

No conflict of interest

Presented at the 8th European HIV Drug Resistance Workshop – 17-19 March 2010, Sorrento, Italy