Hepatitis B Virus Mutants Resistant to Tenofovir

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Abstract
Hepatitis B virus is a DNA virus that replicates via reverse transcription. The reverse transcriptase lacks proofreading capacity. This increases the error rate during replication of the hepatitis B virus genome. Mutated hepatitis B virus genomes could lead to anti-viral drug resistant viruses. Tenofovir is newly approved for treatment of chronic hepatitis B virus infection. Tenofovir resistant hepatitis B virus mutants are rare but could be produced in vitro. Furthermore nucleos(t)ide treatment-experienced and nucleos(t)ide treatment-naïve patients that carried tenofovir resistant hepatitis viruses were described. This review summarizes the actually known mutation sites of tenofovir resistant hepatitis B viruses and their geographic distribution.

Keywords: Hepatitis B virus; Mutants; Tenofovir; Nucleotide analogues; Resistance

Introduction
Chronic Hepatitis B Virus (HBV) carriers are exposed to severe liver diseases like cirrhosis or hepatocellular carcinoma with an increasing number of HBV-related deaths [1]. HBV replicates via reverse transcription. The reverse transcription of the pregenomic RNA to the double stranded DNA is catalyzed by the reverse transcriptase, also called HBV polymerase (for a review) [2]. The Nucleoside Analogue Entecavir (ETV), and the nucleotide analogue tenofovir that inhibit the reverse transcriptase are recommended as the first-line pharmacologic therapy for chronic hepatitis B [3].

Low Tenofovir Resistance Rate of HBV and In vitro Findings
The active drug tenofovir is formed from the prodrugs Tenofovir Disoproxil Fumarate (TDF) or Tenofovir Alafenamide Fumarate (TAF) [4,5].

Mutations of the HBV polymerase could lead to TDF-resistance and therefore to therapy failure. Although the incidence of such mutations generally is low some cases were reported in the last years [6-11]. No resistance mutations have been found to TAF, so far [12,13].

In vitro experiments showed that the rtA181T/V mutation and the combination of the mutations rtA181T with rtN236T increased the resistance to TDF [14]. HBV mutants with rtP177G and rtF249A had reduced TDF-susceptibility in vitro and in vivo [15].

Mutation Sites in Nucleos(t)ide Treatment-Experienced Patients
TDF-resistance was detected in a male patient with chronic hepatitis B in the republic of Korea [16]. This patient had been treated with sequential nucleos(t)ide therapy and the treatment was switched to TDF-monotherapy after virological breakthrough. The following mutations were found: rtL80M, rtL180M, rtM204V/I, rtA200V, rtF221Y, rtS223A, rtT184A/L, rtR153Q, and rtV191I. Another treatment-experienced patient in China showed virological breakthrough during TDF monotherapy [17]. The mutant genotype rtL180M/T184L/A200V/M204V was preponderant in this patient. After addition of ETV the replication of this tenofovir-resistant mutant could be suppressed.

Mutation Sites in Nucleos(t)ide Treatment-Naive Patients
A treatment-naive patient that developed TDF-resistance was described in South Korea [18]. He was infected with genotype C. His HBV polymerase gene was mutated as follows: rtY9H, rtL91I, rtQ267L, rtI269L, rtA317S, rtK333Q, and rtN337H. The sites 106 and 118 showed 2 different mutations: rtS106C, rtS106G, and rtT118G. It remains unclear if all these nine mutations are required for TDF-resistance. Two patients with viral breakthrough under TDF in the republic of Korea had the combinations rtS106C, rtH126Y, rtD134E and rtS106C, rtH126Y, rtD134E, and rtD269I that increased tenofovir IC50 4-times and 15-fold vs. the wild typ IC50 [19].

Two treatment-naive patients in France showed the mutation rtA194T that could be related to TDF-resistance [20,21]. It was described in vitro that the combination of the rtA194T mutation with precore and basal core promoter mutations that lead to HBeAg negativity could restore the viral replication rate to wild-type level [22]. Therefore the rtA194T mutation might lead to viral breakthroughs but, so far, its clinical significance remains unclear. Interestingly the rtA194T mutation has only been detected in a low prevalence area but not in high prevalence areas.

The fact that the mutation sites of the treatment-naive patients are different to those described in the treatment-experienced patients partially could be explained by the selection of nucleos(t)ide resistant mutants during previews therapy [16-21].

Discussion
The high genetic barrier that tenofovir imposes to drug resistance is a new milestone for treatment of chronic hepatitis B. Due to the high mutation rate of the HBV genome tenofovir resistant mutants may occur before or be selected during therapy with nucleos(t)ides. This requires a meticulous supervision of chronic HBV carriers, especially during long-term treatment. It remains unclear if tenofovir...
resistant HBV mutants show a different geographic distribution in high and low prevalence areas. Further studies are necessary to detect other tenofovir resistant HBV mutants and to evaluate more about their geographic distribution.

References


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