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HBV Flare Under Tenofovir Treatment in Chronic Hepatitis B: Case Report

Kronik Hepatit B'de Tenofovir Tedavisi Altında HBV Alevlenmesi: Olgu Sunumu

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ABSTRACT

The purpose of chronic hepatitis B treatment is to stop the progression of the disease and prevent cirrhosis and liver cancer that may occur with the progression of the disease. In the current treatment, one of the nucleosis (t) id analogs, tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide fumarate and entecavir (ETV), is preferred due to its high genetic barriers. In this study; HBV flare was detected in a patient who received TDF treatment and rtN236T, sP120T and sC124R mutations were identified as a result of the resistance analysis. A logarithmic reduction in HBV-DNA level was achieved by adding ETV to the current treatment. As a result, acyclic phosphonate mutations can reduce the clinical response in the treatment of CHB with TDF. HBV drug resistance analysis should definitely be used in rational use of TDF, a potent drug, and in determining the direction in KHB treatments.
Keywords: Chronic hepatitis B, hepatitis B virus, tenofovir, treatment failure, drug resistance

ÖZ

Kronik hepatit B tedavisinin amacı, hastalığın ilerlemesini durdurmak ve hastalığın ilerlemesi ile oluşabilecek siroz ve karaciğer kanserini önlemektir. Mevcut tedavide, yüksek genetik bariyerleri nedeniyle nükleoz (t) id analoglarından biri olan tenofovir disoproksil fumarat (TDF) veya tenofovir alafenamid fumarat ve entekavir (ETV) tercih edilmektedir. Olgumuzda; TDF tedavisi almakta iken HBV alevlenmesi tespit edilmiştir ve direnç analizi sonucunda rtN236T, sP120T ve sC124R mutasyonları tespit edilmiştir. Mevcut tedaviye ETV eklenerek HBV-DNA seviyesinde logaritmik azalma sağlanmıştır. Sonuç olarak, asiklik fosfonat mutasyonları, CHB'nin TDF ile tedavisinde klinik yanıtı azaltabilir. HBV ilaç direnç analizi, güçlü bir ilaç olan TDF'nin akılcı kullanımında ve KHB tedavilerinde yön belirlemede mutlaka kullanılmalıdır.
Anahtar Kelimeler: Kronik hepatit B, hepatit B virus, tenofovir, tedavi başarısızlığı, ilaç direnci

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Introduction

Chronic hepatitis (CHB) remains a global public health problem in changing epidemiology due to various factors such as vaccination policies and migration. It is estimated that 2 billion people worldwide are infected with the hepatitis B virus (HBV) and approximately 248 million people live with CHB (1,2). According to the global hepatitis B surveillance of the World Health Organization, our country is among the middle endemic regions (2-7%). Although the prevalence of hepatitis B surface antigen (HBsAg) positivity is 4% in people over the age of 18, this rate can be up to 10% in the Southeastern Anatolia region of Turkey (3).

The purpose of CHB treatment is to increase the life quality and duration of the patient by preventing complications such as cirrhosis, liver failure and hepatocellular carcinoma that may occur with the progression of the disease (4). Although this goal can be achieved by permanently suppressing HBV replication, eradication of the virus is not possible due to the persistence of cccDNA in the hepatocyte nucleus. Therefore, the achievable goal is the suppression of HBV-DNA in the bloodstream and normalization

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of alanine aminotransferate (ALT). With or without anti-HBs seroconversion, HBsAg negativity is defined as optimal treatment success (5). Many agents such as recombinant interferons (IFN) (conventional and pegylated IFN), nucleos(t)ide analogs [lamivudine, telbivudine, adefovir, entecavir (ETV), and tenofovir] can be used in the treatment of CHB (5). Even though rare cases with sustained virologic responses were been, pegylated IFN was abandoned due to side effects and lamivudine due to drug resistance issues (6). Likewise, adefovir has limited use because of its low genetic barrier and nephrotoxicity. The use of telbivudine is also limited due to its slow effectiveness (7). Today, drugs with high resistance barrier like TDF, ETV, and tenofovir alafenamide fumarate (TAF) is preferred according to the patients' comorbid conditions. In our country, 1,206,000 boxes of NA were used from 2018 to 2019. 15% of this distribution is original TDF drug, 43% is generic TDF drugs, 12% is original (ETV) drug and 19% is generic ETV drugs. TAF, which is new to use, seems to have been used at 3% (8). On the other hand, HBsAg negativity can be achieved at a low rate (0.6-4.6) and the duration of the treatment can be lifelong in hepatitis B e antigen (HBeAg) negative patients with NA treatments (5). Therefore, the long-term side effects of NA treatments and drug resistance that may develop should be managed well (9).

The main cause of drug resistance in NA treatments is mutations in the HBV polymerase (pol) gene. This mutation may occur in individuals naive to treatment because of the natural viral kinetics of HBV and may cause drug unresponsiveness (primary drug resistance mutations) or repair the replication capacity of HBV variants (compensatory mutations) (10). Due to the circular and double- stranded genome organization of HBV, the pol gene overlaps the envelope (S) gene (11). Therefore, pol gene mutations in NA treatments of CHB can also lead to changes in the "a" determinant (between 124th-149th aminoacids) encoding the HBsAg protein (12,13). This problem can lead to the emergence of variants that can escape from anti-HBs antibodies after HBV vaccination, inactivation of passive immunization with HBIg and pseudo-HBsAg negativity in diagnostic tests (14).

In this study, we aimed to present the management of HBV flare in an HBeAg positive and TDF treated CHB patient.

Case Report

Twenty-eight-years-old male patient was admitted to our outpatient clinic upon detection of HBV-DNA level 1.70+E8 IU/mL while being examined for infertility at the urology clinic. The patients HBsAg and HBeAg test results were positive. Anti-HBs, anti HBc IgM, anti HBe, anti HCV, anti-HIV, and HDV-RNA results were negative. Although the patient with normal ALT level was evaluated in the immune tolerant phase, a liver biopsy was performed because of family history. The biopsy result was classified as grade: 4, stage: 3 according to modified Knadell scoring. In the monthly follow-ups of the patient whose TDF treatment was started, regular logarithmic HBV DNA decrease was observed. However, the 7th month of treatment (October 2018), HBV-DNA level was defined as above 1.70+E8 IU/mL. Thereupon, HBV drug resistance analysis was requested. HBV-DNA and ALT levels and drug resistance analysis results over time are shown in Figure 1.

HBV drug resistance analysis was done by Sanger dideoxy sequencing method. Pol gene in HBV-DNA isolated from patient plasma sample (forward primer: 5'-TCGTGGTGGACTTCTCTC AAT T-3' - reverse primer: 5'-CGTTGACAGACTTTCCAATCA AT-3') was amplified with primers. Genafor/Arevir (http://coreceptor.bioinf.mpi-inf.mpg.de/) program was used to identify mutations responsible for drug resistance. Eleven months after ETV was added to the treatment, the patient's HBV-DNA level decreased to 3.52+E3 IU/mL. AST and ALT levels returned to normal.

Discussion

In our case, rtN236T mutation was detected in the pol gene of HBV isolated from the plasma sample which could explain NA non-response or suboptimal response. The rtN236T mutation is associated with acyclic phosphonate drugs but also reduces TDF sensitivity (15). Various mutations have been identified in TDF clinical applications leading to decreased sensitivity in vitro conditions (16,17). To manage viral flare in TDF treatment of CHB, HBV drug resistance analysis must be performed and drug class can be changed or combined according to the nature of the

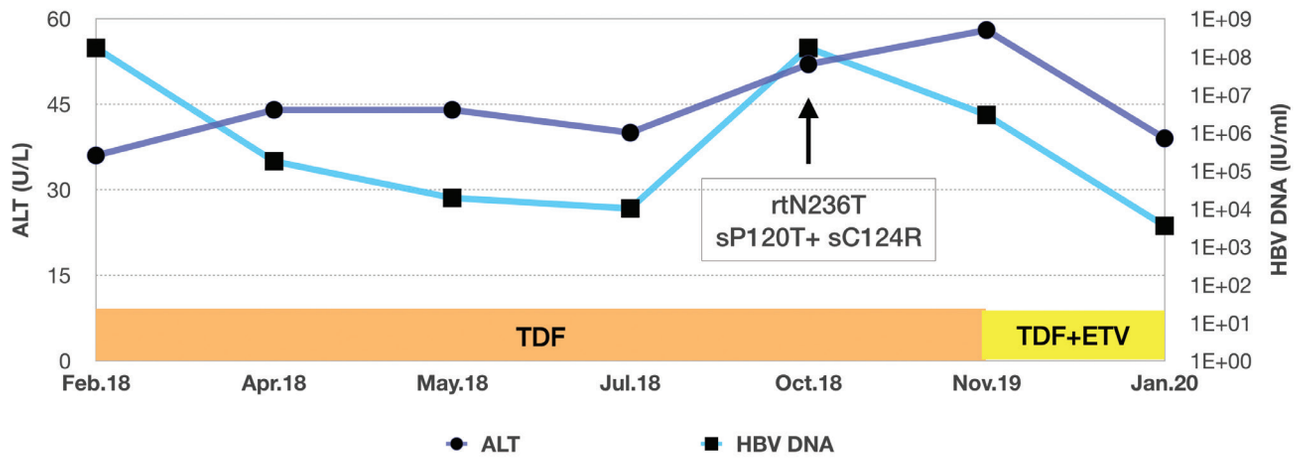

Figure 1. HBV-DNA, ALT levels and clinically important mutations detected in the patient over time
HBV: Hepatitis B virus, ALT: Alanine aminotransferate, TDF: Tenofovir disoproxil fumarate, ETV: Entecavir

detected mutation. In our case, the sP120T and sC124R mutations detected in the HBV-S gene indicates variant characteristics that can escape from the vaccine, HBIg treatment, and HBs Ag diagnostic tests. Carefully monitoring of HBV variants in CHB treatment with NA and analyzing S gene as well as the pol gene for treatment failure will be beneficial for public health (13,18).

As a result, acyclic phosphonate mutations reduce the clinical response. HBV drug resistance analysis should definitely be used in the national use of TDF, a potent drug, and in determining the direction in the treatment of CHB.

Ethics

Informed Consent: It was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: M.D.T., M.S., S.A., Design: M.D.T., M.S., S.A., Data Collection or Processing: M.D.T., M.S., S.A., Analysis or Interpretation: M.D.T., M.S., S.A., Literature Search: N.Z., N.E., Writing: M.D.T., M.S., S.A.

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