DOI: https://doi.org/10.47391/JPMA.1135

The partial virological response to Tenofovir monotherapy in naïve patients with chronic hepatitis B

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Abstract

We report two treatment-naïve cases, a 26-year-old female patient and a 59-year-old male patient who were followed up for chronic hepatitis B (CHB) at the Department of Infectious Diseases and Clinical Microbiology. A partial response subsequent to 12 months of Tenofovir Disoproksil (TDF) monotherapy presumably due to an antiviral-drug resistance was noted. A sustained viral response with TDF (245 mg) or Tenofovir Alafenamide (TAF, 25 mg) + Entecavir (ETV, 1 mg) combination therapy was observed after failure with TDF monotherapy. A combination therapy with TDF (245 mg) or TAF (25 mg) +ETV (1 mg) is efficacious in naïve patients with a partial response to TDF monotherapy.

Keywords: Chronic hepatitis B, Tenofovir, partial response, Entecavir, combination therapy

Introduction

Tenofovir Disoproxil Fumarate (TDF) achieves a sustained viral response and regression in liver fibrosis and inflammation in the treatment of chronic hepatitis

B.[1] Resistance against Tenofovir has not been reported yet.[2] A decrease of less than 1 log_{10} in serum HBV-DNA after three months of therapy is specified as a primary non-response. A decrease in HBV-DNA values of more than 1 log_{10} IU/m is specified as a partial virological response, but HBV-DNA values continue to be detectable in compliant patients after at least 12 months of treatment. [3]

We report the treatment-naïve cases with chronic hepatitis B (CHB) who accomplished a partial response with TDF monotherapy; our aim was to investigate an antiviral drug-resistance.

Case Series

Case 1: A 26-year-old female was admitted to the Department of Infectious Diseases and Clinical Microbiology at the Bakırköy Dr Sadi Konuk Training and Research Hospital in 2015 with a diagnosis of chronic Hepatitis B (CHB) infection. At the time of admission, laboratory tests were positive for HBs Ag and HBe Ag, and negative for Anti-HDV total. The HBV-DNA value was 400594927 IU/ml, while other laboratory and ultrasonography findings were normal. She did not have any comorbidity and was not on any medication. A liver biopsy was performed, which resulted in ISHAK score of 6/18 and fibrosis score of 2/6. TDF treatment (245 mg) was postponed until 32 weeks of pregnancy and then initiated. The HBV-DNA values were 730 IU/mL at month 12, and 417 IU/mL at month 18 of TDF therapy. We could not measure the TDF blood level of the patient, as the facility is not available in Turkey. Generic product was chosen for TDF therapy to be sure of the standard dose and drug adherence of the patient was complete. She accepted to receive TDF and ETV (1 mg) combination therapy, as HBV-DNA values increased to 14743 IU/ml. After five months of combination therapy, HBV-DNA value decreased to 11 IU/ml. The mutation analysis was performed under ETV monotherapy and 700 IU/ml of HBV-DNA values were checked for the susceptibility of Lamivudine (LAM), Adefovir (ADV), Entecavir (ETV), Tenofovir (TDF), and Telbivudin (LdT) in microbiology laboratory of

Istanbul Cerrahpaşa School of Medicine by using the Genafor/Arevir–geno2pheno drug resistance tool (Centre of Advanced European Studies and Research, Bonn, Germany, http://coreceptor.bioinf.mpi-inf.mpg.de/). The geno2pheno kit explores HBV drug-resistance mutations in the RT domain of the polymerase gene at H124Y, Y135S, and N248H as well as at SHB protein T127P. No mutation was found. She has undergone 24-hour urine test and dual emition X-ray absorbtiometry (DEXA) every year to detect side effects of TDF on bones and kidneys, such as nephrotoxicity and osteoporosis and no side-effect has been detected. She continues to receive a TDF+ETV combination therapy accompanying an undetectable HBV-DNA value (Table 1).

Case 2: A 59-year-old male patient, who was admitted to the Department of Infectious Diseases and Clinical Microbiology at the Bakırköy Dr Sadi Konuk Training and Research Hospital in 2013 for the examination of HBV infection subsequent to acute Hepatitis B infection in his wife. He was diagnosed with CHB infection without a history of comorbidity and medications, as his test results showed HBs Ag (+), HBe Ag (+), Anti-HDV total (-), HBV-DNA value of 287243345 IU/mL, and the liver biopsy revealed a ISHAK score of 4/18 and a fibrosis score of 2/6. TDF monotherapy was initiated, after which HBV-DNA values were 7910 IU/mL at month 12, and 12439 at month 24, respectively. We could not measure the TDF blood levels, as that could not be performed in Turkey. Generic product was chosen for TDF therapy to be sure of the standard dose and the patient's drug adherence was complete. No mutation in the aforementioned gene regions was found, as HBV-DNA value was 700 IU/mL. He received TDF and ETV (0.5 mg) combination therapy and his HBV-DNA titer decreased to 63 IU/mL after 24 months of combination therapy. When the patient asked for discontinuation of combination therapy, he started to receive only ETV (1 mg) treatment for three months. His HBV-DNA titer increased to 10449IU/mL and then he agreed to receive TDF and ETV (1 mg) combination therapy once

again. At month six of TDF+ETV combination therapy, his HBV-DNA titer decreased to 6 IU/mL. He has undergone 24-hour urine test and dual emission X-ray absorbtiometry (DEXA) every year. Although his renal function has been normal, osteoporosis was diagnosed and then calcium plus Vitamin-D supplementation was initiated. TDF was switched to TAF (25 mg), that has been available in Turkey since 2019, at month 63 of CHB treatment due to osteoporosis (Table 2). HBe Ag remained positive during follow-up.

Discussion

A virological response was not attained with TDF-monotherapy in two treatment-naïve cases and HBV-DNA levels decreased to undetectable level with ETV-TDF combination therapy. That partial response suggested an antiviral drug-resistance or an inadequate bioavailability of TDF. The TDF blood levels of both the cases could not be measured because of unavailability of monitoring test. Generic product of TDF was chosen to be sure about the standard dose of tablet, as our cases were compliant with TDF therapy. Higher TDF plasma concentrations in patients with HIV depend on ABCC2 and ABCC4 polymorphisms that cause renal toxicity.[4, 5] Although examination of HBV drug-resistance, performed in the RT domain of the polymerase gene at H124Y, Y135S, and N248H as well as at SHB protein T127P in a reference laboratory of Turkey, resulted in negative, there could exist other regions related to drug-resistance, since some gene areas related to viral resistance were reported. Marhoon et al reported that A194T mutation was associated with the TDF-resistance, and L180M, A181T/V, M204V/I/S and N236T mutations were related to multidrug resistance in 20 patients who had CHB and high viral loads after six months of TDF + ETV treatment.[6] The rtA194T mutation was believed to decrease TDF sensitivity owing to an increase in the IC50 value *in vitro* analysis, although it did not cause either a TDF-resistance *in vivo* nor a partial TDF drug-resistance.[7-9] Park et al reported two chronic hepatitis B cases that showed TDF-

resistance in consequence of seven common mutations, including rtL269I [I], rtH126Y [Y], rtM204I/V [V], rtD134E [E], rtL180M [M], rtS106C [C] and rtV173L [L]. The results indicated that the CYE mutation assures a diminished TDF-susceptibility (by 3.7-fold), and the CYEI mutation renders HBV to have a complete resistance (by 15.3-fold) against TDF. The TDF-resistance owing to the CYEI mutation (i.e. CYELMVI) was boosted by ETV-resistance with a previous resistance mutation against LMV.

AST and ALT values remained normal since the beginning of the treatment in Case 1, and recovered in the 26th month of treatment in Case 2. The continuation of inflammatory process and virological response to antiviral therapy are important in the development of long-term complications. Biochemical and virological tests remained within normal range after switching to TAF (25 mg) therapy in Case 2 owing to osteoporosis. On the other hand, Agarwal et al reported that 120 mg/day TAF, which was 4.8-fold higher than the standard dose and safe in the short-term, might not be an optimal salvage therapy for patients who have TDF-resistance.[10]

Conclusion

A combination therapy with TDF (245 mg) or TAF (25 mg) +ETV (1 mg) is efficacious in treatment-naïve patients with a partial response to TDF mono-therapy.

Disclaimer: None to declare.

Conflict of interest: There is no conflict of interest.

Funding disclosure: Any support or funding was not received for this study

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Table 1: The findings of case 1 with chronic hepatitis B

	ALT (N:0-40 U/L)	**AST (N:0-40 U/L)**	**HBV-DNA (IU/ml)**	**Anti-HDV total**	**Treatment**
One year before the treatment)	37	25	773816718	NEGATIVE	Pregnancy
Initiation of treatment at 28th weeks of pregnancy	17	17	400594927	NEGATIVE	Tenofovir disoproksil (TDF)
3 months of treatment (one month after birth)	33	25	23842	NEGATIVE	TDF
6 months	25	19	1795	NEGATIVE	TDF
9 months	34	23	7509	NEGATIVE	TDF
12 months	35	25	730	NEGATIVE	TDF
18 months	34	20	417	NEGATIVE	TDF
21 months	37	24	14743	NEGATIVE	Entecavir (ETV) 1 mg
23 months	34	25	112	NEGATIVE	TDF + ETV 1 mg

26 months	34	24	11	NEGATIVE	TDF + ETV 1 mg

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186 **Table 2: The findings of the son of case 1**

	ALT (N:0-40 U/L)	**AST (N:0-40 U/L)**	**HBV-DNA (IU/ml)**	**Anti-HDV total**	**Treatment**
12 months of age	66	58	216342929	NEGATIVE	
18 months of age	50	37	34425914	NEGATIVE	
24 months of age	123	79	154648738	NEGATIVE	
28 months of age	100	73	196762495	NEGATIVE	
29. months of age	33	25	40689773	NEGATIVE	Interferon alfa-2b initiated
33 months of age	25	19	36883059	NEGATIVE	Interferon alfa-2b discontinued and lamivudine (LAM) initiated
36 months of age	34	23	95967	NEGATIVE	Month 3 of LAM therapy
39 months of age	44	52	116916		Month 6 of LAM therapy

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190 **Table 2: The findings of case 2 with chronic hepatitis B**

	ALT (N:0-40 U/L)	**AST (N:0-40 U/L)**	**HBV-DNA (IU/ml)**	**Anti-HDV total**	**Treatment**

Initiation of treatment	79	45	287243345	NEGATIVE	Tenofovir disoproksil (TDF)
1 month	70	44	915959	NEGATIVE	TDF
3 month	63	39	58413	NEGATIVE	TDF
6 month	69	37	10033	NEGATIVE	TDF
12 month	87	41	7910	NEGATIVE	TDF
15 month	71	38	15999	NEGATIVE	TDF
16 month	65	32	12573	NEGATIVE	TDF
18 month	54	31	15951	NEGATIVE	TDF
21 month	48	29	12439	NEGATIVE	TDF + Entecavir (ETV) 0.5 mg
26 month	36	22	185	NEGATIVE	TDF + ETV 0.5 mg
33 month	20	16	74	NEGATIVE	TDF + ETV 0.5 mg
36 month	34	16	245	NEGATIVE	TDF + ETV 0.5 mg
43 month	18.2	14	74	NEGATIVE	TDF + ETV 0.5 mg
45 month	24	20	63	NEGATIVE	TDF + ETV 0.5 mg
48 month	22	18	140	NEGATIVE	ETV 1 mg
49 month	25	23	9473	NEGATIVE	ETV 1 mg
50 month	16	16	10449	NEGATIVE	ETV 1 mg
53. month	25	20	109	NEGATIVE	TDF + ETV 1 mg
57 month	21	18	6	NEGATIVE	TDF + ETV 1 mg

63 month	18	22	5	NEGATIVE	**Tenofovir Alafenamide** + ETV 1 mg

Abbreviations:
CHB: chronic hepatitis B, TDF: Tenofovir Disoproksil, Tenofovir Alafenamide: TAF, Entecavir: ETV, Hepatitis B virus: HBV, Aspartate Aminotransferase: AST, Alanine Aminotransferase: ALT, Gamma-glutamyl Transpeptidase: GGT, hepatitis D virus: HDV, hepatitis A virus: HAV, hepatitis C virus: HCV, Lamivudine: LAM, Adefovir: ADV, Telbivudin: LdT, dual emission X- ray absorbtiometry: DEXA
