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Case Report

Successful Treatment of a Pregnant Woman with Chronic Active Hepatitis B using Tenofovir Disoproxil Fumarate

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Abstract

***Background*:** Infection with hepatitis B virus (HBV) infection during pregnancy occasionally raises several issues such as acute exacerbation and the potential for vertical mother-to-child transmission.

Case report: Here, we present the case of a female patient with chronic HBV infection who was treated with tenofovir disoproxil fumarate (TDF) and had a normal pregnancy and delivery. Furthermore, the use of TDF, HBV vaccination and passive immunization of her child with hyperimmune hepatitis B immunoglobulin successfully prevented vertical transmission of HBV.

***Conclusions*:** During pregnancy, women with chronic active HBV infections may require additional care and interventions, such as the administration of TDF after the birth remain unsolved.

Keywords
Acute exacerbation; HBV; pregnancy; tenofovir disoproxil

Introduction

Hepatitis B virus (HBV) infection is a major health concern worldwide, with the highest rates in Africa and Asia. HBV is a leading cause of hepatocellular carcinoma (HCC) and end-stage liver disease [1]. Although HBV vaccination is available worldwide, HBV can infect humans through vertical transmission and affects females of childbearing age [1]. Although detection of hepatitis B e antigen (HBeAg) indicates active HBV replication, HBeAg-positive patients have been reported to be younger than HBeAg-negative patients [2]. Clearly, it is important to prevent vertical HBV transmission from mother-to-child at delivery [3].

Oral nucleoside/nucleotide analogs (NUCs) as well as PEGylated interferon (PEG-INF) are effective treatments for chronic HBV infection [1, 4]. However, during pregnancy, safety has not been established for the use of PEG-INF and NUCs other than tenofovir disoproxil fumarate (TDF), which is an acyclic adenine nucleotide analog effective against both HBV and human immunodeficiency virus (HIV) [1]. TDF is classified as a category B medication (no risk in animal studies, but unknown risk in humans) by the United States Food and Drug Administration [1]. In Japan, TDF has been available since 2014 [5].

We here present the case of a 37-year-old HBeAg-positive female patient with a chronic HBV genotype C infection who was treated with TDF and had a normal pregnancy and delivery. Furthermore, the use of TDF, HBV vaccination and passive immunization of her child with hyperimmune hepatitis B immunoglobulin (HBIg) successfully prevented vertical transmission of HBV to her child.

Ethics statement

Our institution does not require ethical approval for reporting individual cases or case series. Written informed consent was obtained from the patient for publication of her information in this article.

Case report

In September 2014, a 37-year-old woman with chronic hepatitis B who was planning to start a family was referred to our department. The patient had no other relevant medical history, did not drink alcohol and had no drug allergies. Both her mother and brother were HBV carriers. Her height and body weight were 1.78 m and 60 kg, respectively, and her laboratory findings are shown in Table 1. The patient had a long history of treatment with antivirals for chronic hepatitis B.In June 2003, she was diagnosed with HBeAg-positive hepatitis with aspartate aminotransferase (AST) levels of 160 IU/L, alanine transaminase (ALT) levels of 244 IU/L and HBV DNA > 7.6 log10 copies/mL. The patient was found to be infected with HBV genotype C. In August 2003, a liver

biopsy showed chronic hepatitis (F1/A2) type B, and she was started on 100 mg of lamivudine (LAM) daily for acute exacerbation of chronic hepatitis B, with AST levels of 1,139 IU/L, ALT levels of 1,040 IU/L and HBV DNA 7.2 log10 copies/mL. In November 2006, viral breakthrough occurred, and in December 2008 she was started on 10 mg of adefovir (ADF) daily. In June 2009, LAM and ADF were stopped and the patient received natural interferon-α (6 MIU, three times per week) for 6 months. In June 2010, she was started on LAM plus ADF again because of elevated transaminase levels. In July 2013, transient elastography revealed a value of 4.8 kPa, indicating no cirrhosis. In March 2014, she started entecavir (ETV) plus ADF. No drug resistance mutations of HBV DNA polymerase were detected by INNO-LiPA HBV Multi-DR tests (LAM: 80L, 173V, 180L, 204M; ADF: 181A, 236N; ETV: 184T, 202S, 250M; and TDF: 194A) [6], although her HBV DNA level was 2.4 log10 copies/mL.

Table 1 Laboratory findings 4 months before conception (September 2014)

Item	Value	Item	Value	Item	Value
AST	13 IU/L	WBC	4400 /μL	HBs Ag	801.77 IU/mL
ALT	7 IU/L	RBC	399×10^6 /μL	anti-HBs	Negative
LDH	134 IU/L	Hemoglobin	13.2 g/dL	anti-HBc	Positive
γ-GTP	9 IU/L	Hematocrit	40.3%	HBeAg	Positive
T.BIL	1.0 mg/dL	Platelets	16.0×10^4 /μL	anti-HBe	Negative
D.BIL	0.1 mg/dL	PT	105%	HBcrAg	4.7 log10 U/mL
TP	6.4 g/dL	PT-INR	1.05	HBV Genotype	C
Albumin	3.9 g/dL	Glucose	92 mg/dL	HBV DNA	<2.1 log10 copies/mL
T.CHO	128 mg/dL	AFP	3.2 ng/mL	anti-HCV	Negative
Creatinine	0.63 mg/dL			anti-HIV	Negative

AST, aspartate aminotransferase; ALT, alanine transaminase; LDH, lactate dehydrogenase; γ-GTP, γ-glutamyltransferase; T.BIL, total bilirubin; D.BIL, direct bilirubin; TP, total protein; T.CHO, total cholesterol; WBC, white blood cell count; RBC, red blood cell count; PT, prothrombin time; PT-INR, PT international normalized ratio; HBsAg, hepatitis B virus surface antigen; anti-HBs, anti-hepatitis B virus surface antibody; anti-HBc, anti-HBV core antibody; HBeAg, HBV e antigen; anti-HBe, anti-HBeAg antibody; HBcrAg, HBV core-related antigen; anti-HCV, anti-hepatitis C virus antibody; anti-HIV, anti-human immunodeficiency virus antibody.

In September 2014, after expressing her desire to conceive and after informed consent was obtained, her treatment regimen was changed to 300 mg of TDF daily. In January 2015, she became pregnant (Table 2). Abdominal ultrasonography showed chronic liver disease with mild fatty changes. In October 2015, she gave birth to a healthy girl who tested hepatitis B surface antigen (HBsAg) negative. The patient's liver function remained within the normal range at

delivery (Table 3). The use of an HBV vaccine and passive immunization of her child with hyperimmune hepatitis B immunoglobulin (HBIg) prevented vertical transmission of HBV.

Table 2 Laboratory findings in January 2015.

Item	Value	Item	Value	Item	Value
AST	18 IU/L	WBC	3300 /μL	HBs Ag	937.71 IU/mL
ALT	12 IU/L	RBC	439×10^6 /μL	anti-HBs	Negative
LDH	168 IU/L	Hemoglobin	14.3 g/dL	HBeAg	Positive
γ-GTP	10 IU/L	Hematocrit	43.9%	anti-HBe	Negative
T.BIL	1.1 mg/dL	Platelets	20.2×10^4 /μL	HBV DNA	Undetectable
D.BIL	0.1 mg/dL	PT	111%		
TP	7.0 g/dL	PT-INR	0.99		
Albumin	4.2 g/dL	Glucose	81 mg/dL		
T.CHO	158 mg/dL	AFP	3.6 ng/mL		
Creatinine	0.65 mg/dL				

AST, aspartate aminotransferase; ALT, alanine transaminase; LDH, lactate dehydrogenase; γ-GTP, γ-glutamyltransferase; T.BIL, total bilirubin; D.BIL, direct bilirubin; TP, total protein; T.CHO, total cholesterol; WBC, white blood cell count; RBC, red blood cell count; PT, prothrombin time; PT-INR, PT international normalized ratio; HBsAg, hepatitis B virus surface antigen; anti-HBs, anti-hepatitis B virus surface antibody; anti-HBc, anti-HBV core antibody; HBeAg, HBV e antigen; anti-HBe, anti-HBeAg antibody.

Table 3 Laboratory findings 1 month after delivery (November 2015).

Item	Value	Item	Value	Item	Value
AST	17 IU/L	WBC	4900 /μL	HBs Ag	1054.93 IU/mL
ALT	11 IU/L	RBC	404×10^6 /μL	HBeAg	Positive
LDH	220 IU/L	Hemoglobin	11.3 g/dL	anti-HBe	Negative
γ-GTP	7 IU/L	Hematocrit	36.4%	HBeAg	Positive
T.BIL	0.9 mg/dL	Platelets	32.9×10^4 /μL	HBcrAg	4.7 log10 U/mL
D.BIL	0.1 mg/dL	PT	115%	HBV DNA	Undetectable
TP	7.1 g/dL	PT-INR	0.98		
Albumin	4.0 g/dL	Glucose	91 mg/dL		
T.CHO	212 mg/dL	AFP	8.9 ng/mL		
Creatinine	0.64 mg/dL				

AST, aspartate aminotransferase; ALT, alanine transaminase; LDH, lactate dehydrogenase; γ-GTP, γ-glutamyltransferase; T.BIL, total bilirubin; D.BIL, direct bilirubin;

TP, total protein; T.CHO, total cholesterol; WBC, white blood cell count; RBC, red blood cell count; PT, prothrombin time; PT-INR, PT international normalized ratio; HBsAg, hepatitis B virus surface antigen; anti-HBs, anti-hepatitis B virus surface antibody; anti-HBc, anti-HBV core antibody; HBeAg, HBV e antigen; anti-HBe, anti-HBeAg antibody.

In March 2016, seroconversion from HBeAg to hepatitis B e antibody (HBeAb) was observed. In June 2017, her laboratory results were as follows: AST, 18 IU/L; ALT, 10 IU/L; and HBV DNA was not detected. Although she was advised to abstain from breastfeeding while using TDF, her daughter was hepatitis B surface antibody (HBsAb)-positive and showed no evidence of liver disease.

Discussion

Before her pregnancy, the woman in the present case had a long history of treatment for chronic hepatitis B infection, including NUCs or interferon-α for 12 years. We selected TDF to treat the patient because she experienced acute exacerbation of chronic hepatitis B and viral breakthrough during treatment with LAM. A previous report [7] showed significant benefits of the use of NUCs to rapidly reduce of viral DNA for the treatment of acute exacerbation of chronic hepatitis B. In the present case, we were unsuccessful in our attempt to discontinue NUCs by replacement with interferon-α sequential therapy [4]; therefore, NUCs were not stopped before her pregnancy.

TDF use has been shown to be safe for women and their infants during pregnancy [3, 8, 9]. We recommended that breastfeeding should be avoided during her treatment with TDF based on the TDF label information. The incidence of TDF-associated renal dysfunction in Japanese HIV-infected patients is high [10] and low body weight has been identified as an independent risk factor for TDF-associated renal dysfunction [10].

It has recently been reported that tenofovir alafenamide (TAF) has the potential to be as effective as TDF, but with greater safety [11]; however, further studies are required to determine the safety of TAF during pregnancy and breastfeeding. Consequently, TDF plays a central role in the treatment of HBV infection during pregnancy.

Antiviral therapy improves HBV DNA suppression and reduces mother-to-child transmission in women with chronic HBV infection and high viral loads compared to HBIg therapy and HBV vaccination alone [12]. Furthermore, during the third trimester in mothers with high HBV DNA levels, the rate of mother-to-child transmission has been reported to be lower in patients undergoing TDF therapy than among those who receive standard care without antiviral therapy [3, 13].

Conclusions

Women with chronic HBV infection require additional care and monitoring during pregnancy. We report the case of a chronic HBV infected-patient treated with TDF who had a normal pregnancy and delivery. Careful attention and follow-up are necessary during the use of TDF for HBV infection in pregnancy as the remote effects of TDF after the birth remain unsolved.

Author contributions

Seeing the patients: Tatsuo Kanda, Osamu Yokosuka.

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Competing interests

Tatsuo Kanda received research grants from Merck Sharp and Dohme (MSD), Chugai Pharm and AbbVie. The other authors declare no conflict of interest.

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