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RAPID SUPPRESSION OF HBV REPLICATION BEFORE LIVING DONOR LIVER TRANSPLANTATION IN A PATIENT WITH HDV SUPERINFECTION. CLINICAL CASE REPORT

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Chronic hepatitis B virus (HBV) infection is one of the main problems of modern transplantology and transplant hepatology, often leading to potentially fatal complications. The only definitive treatment for HBV-related cirrhosis is liver transplantation. However, recurrence of HBV after transplantation may jeopardize both recipient and graft survival. Therefore, all HBsAg-positive recipients should receive prophylactic therapy with nucleos(t)ide analogues with or without hepatitis B immune globulin (HBIG), regardless of the hepatitis B e-antigen (HBeAg) status and HBV DNA level before transplantation. However, HBIG therapy has a number of disadvantages, and nucleos(t)ide analogues do not inhibit replication of super and co-infection. In addition, there is no unified understanding of the time limits for achieving a virologic response. In our clinical case, we report a rapid suppression (5 days) of high HBV (560,000 copies/mL) viral load in a patient suffering from HBV- and HDV-related cirrhosis, who was operated on with positive HBeAg at the time of transplantation. In our study, the use of standard therapy tenofovir disoproxil fumarate reduced the HBV viral load titer to undetectable values. In turn, given the positive HBeAg at the time of transplantation, HBV infection recurred in the early post-transplant period, which was eliminated without the use of HBIG therapy. The use of tenofovir disoproxil fumarate makes it possible to plan transplantation for patients with positive replication and high viral load, avoiding the use of HBIG, against the background of limited liver transplant wait time.

Keywords: liver transplantation, hepatitis B, hepatitis D, tenofovir disoproxil fumarate, tenofovir alafenamide, nucleos(t)ide analogues.

INTRODUCTION

Chronic hepatitis B virus (HBV) is one of the primary problems of modern transplantology and transplant hepatology, often leading to potentially fatal complications, including cirrhosis and hepatocellular carcinoma. Liver transplantation (LT) is the only definitive treatment for the above complications. However, recurrence of HBV infection after LT may compromise both recipient and graft survival, severely worsening treatment outcomes [1]. In addition, HBV is a necessary basis for hepatitis D virus (HDV) infection. HDV further aggravates the prognosis of chronic progressive liver disease, reducing overall survival and shortening the transplant-free survival period.

According to the latest international analysis by the Global Disease Burden, published in the Journal of Hepatology, 296 million (228–423 million) people are living with chronic HBV infection. And despite the availability of antiviral drugs, no country is yet on track to eliminate HBV infection by 2030, as outlined by the World Health Organization (WHO) and the European Association for the Study of the Liver (EASL). HDV prevalence, estimated at 12.0 million people (8.7–18.7), further clouds the statistics [2].

In turn, despite numerous studies and pharmacological developments aimed at reducing the incidence of HBV and NDV infection, including the presentation of bulevirtide, which was supposed to be a "rescue drug," HBV incidence remains high and bulevirtide is yet to receive FDA approval [3]. Thus, we currently have only two approved drug groups – nucleos(t)ide analogues (NAs) and pegylated interferon [4]. At the same time, both of these pharmacologic groups have drawbacks and limitations, and LT is still the only definitive treatment option for patients with advanced cirrhosis.

The presence of detectable HBV in the blood and/or positive HBeAg before LT are independent risk factors for recurrent HBV infection after LT. In addition, concomitant HDV infection and low patient compliance are additional risk factors for HBV relapse [1]. Therefore, pretransplant eradication of HBV infection is a universally recognized measure aimed at reducing the incidence of

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post-transplant complications. Moreover, according to recent clinical guidelines, all HBsAg-positive recipients should receive prophylactic NAs therapy with or without HBIG, regardless of pretransplant HBeAg status and HBV DNA level before transplantation [5].

However, as it has already been noted, HBIG therapy has a number of drawbacks. Besides, there is no unified understanding of the time limits for achieving virological response, and the results of achieving seroconversion and negative PCR differ significantly. According to a report from Marcellin P. et al., published in the New England Journal of Medicine, tenofovir disoproxil fumarate (TDF) resulted in HBV suppression rate of 76% and 93% in HBeAg-positive and HbeAg-negative patients at week 48, respectively [6]. In turn, the results of a phase III, double-blind RCT NCT01940471 comparing the efficacy of TDF and TAF published in The Lancet showed that HBV suppression at week 48 was achieved in 64% of HBeAg-positive patients. However, only patients with viral load >112,000 copies/mL were included in the analysis [7].

In our clinical case, we report a rapid suppression (5 days) of high HBV viral load in a patient with positive PCR titers of HBV (560,000 copies/mL), HDV (9,500 copies/mL) and positive HBeAg at the time of transplantation.

CLINICAL CASE REPORT

A 38-year-old female patient presented to the liver transplant unit for the first time in January 2023. Diagnosis at the time of admission: cirrhosis due to HBV negative, HDV positive infection. Child–Turcotte–Pugh Class A (6 points). MELD 7. No clinically significant portal hypertension. Large natural splenorenal shunt (≈2.5 cm). Splenomegaly. Biochemistry tests: total bilirubin 25 μmol/L (normal: 3.4–20 μmol/L); AST 45 IU/L (normal: 1–40 IU/L); ALT 57 IU/L (normal: 1–40 IU/L); albumin 33 (normal: 35–55 g/L); alkaline 135 (normal: 44–146 IU/L); GGT 48 (normal: 0–30 IU/L). Serology:

Table 1

Recipient pre-transplant characteristics

Recipient characteristics							
Age (years)	**Weight (kg)**	**Height (cm)**	**BMI**	**Blood group**	**GRWR**	**HBV (copies/mL)**	**HDV (copies/mL)**
38	56	160	21	0(I) Rh^+	1.1	560,000	89,000
Laboratory indicators							
Coagulation				**Biochemical parameters**			
Parameters	**Result**	**Reference range**	**Unit**	**Parameters**	**Result**	**Reference range**	**Unit**
PT	**47.2**	70–120	%	**Total protein**	**59**	65–85	g/l
INR	**1.37**	0.9–1.3	SI	**Albumin**	**28**	35–55	g/l
aPTT	**43.8**	26–31	sec	**Glucose**	4.8	3.2–6.1	mmol/L
				Urea	4	2.5–8.3	μmol/L
Fibrinogen	**1.5**	1.8–3.5	g/L	**Creatinine**	70	62–115	μmol/L
Lipid profile				**Total bilirubin**	**37.7**	3.4–20.5	μmol/L
Parameters	**Result**	**Reference range**	**Unit**	**Direct bilirubin**	**14.2**	1.7–17.1	μmol/L
Cholesterol	3.3	<5.2	mmol/L	**ALT**	**62**	<42	ME/L
Triglycerides	0.8	<2.28	mmol/L	**AST**	**81**	<37	U/l
LDL	1.05	<3.3	mmol/L	**ALP**	158	<270	U/L
HDL	1.55	1.03–1.55	mmol/L	**GGT**	29	6.1–42	U/L
Complete blood count				**K**	4.3	3.6–5.4	
Parameters	**Result**	**Reference range**	**Unit**	**Na**	137	135–150	
HB	14	11.7–15.5	g/dl	**Ca^+**	2.2	2.0–2.6	mmol/L
WBC	**2.78**	4.1–10	10^9/L	**Mg**	1.1	0.7–1.2	mmol/L
RBC	4.28	3.5–5.5	10^9/L	**CRP**	1.5	0–5	U/L
PLT	**150**	180–320	10^9/L	**LDH**	221	81–234	U/L
MCV	97	81–100		**α-Amylase**	59	25–125	U/L

Note: aPTT, activated partial thromboplastin time; INR, international normalized ratio; PT, prothrombin time; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HB, hemoglobin; WBC, white blood cells; RBC, red blood cells; PLT, platelets; MCV, mean corpuscular volume; ALP, alkaline phosphatase; GGT, gamma-glutamyl transferase; LDH, lactate dehydrogenase; CRP, C-reactive protein; LT, liver tranplantation; BMI, body mass index; GRWR, graft-to-recipient weight ratio; HBV, chronic hepatitis B virus; HDV, hepatitis D virus; LDH, lactate dehydrogenase; ALT, alanine transaminase; AST, aspartate transaminase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transferase; K, potassium; Na, sodium; Ca^+, calcium; Mg, magnesium.

positive HBsAg and anti-HDVAg. HBV PCR (quantitative, qualitative analysis) negative. HBeAg negative. HDV PCR: 12,000 copies/mL. The patient has been taking TDF 300 mg for the past two years, once a day. Considering the compensation of the process, the patient was recommended outpatient follow-up. After 6 months of follow-up, several episodes of hepatic decompensation were noted, manifested by a decrease in albumin to 28 g/L, an increase in serum total bilirubin to 37.7 μmol/L, and ascites formation (Table 1). Due to disease progression and transition to subcompensated stage (Child–Turcotte–Pugh class B (7)), MELD 3.0–15, she was recommended to undergo related liver transplantation.

The examination revealed a relapse of HBV infection: HBV 560,000 copies/mL; HBeAg positive. HDV PCR 9,500 copies/mL. Self-induced withdrawal from TDF was identified and confirmed. Given the known high antiviral efficacy of TDF and high barrier to HBV resistance [8], the administration of TDF 300 mg, once a day was resumed. A repeat blood PCR was obtained 5 days later, showing a more than 1000-fold reduction in viral load, less than 500 copies/mL. A subsequent PCR test performed 10 days after starting TDF, revealed no detectable HBV infection by quantitative and qualitative assays. However, the patient's HBeAg remained positive (Table 2). Given the latest published clinical protocols that allow for LT in HBeAg-positive patients, the patient underwent related LT.

***Transplantation:** The donor was the patient's 38-year-old sibling, with negative virological and serological HBV at the time of LT. In accordance with local protocol, as well as recommendations from recent publications, HBIG prophylaxis was not administered. Immunosuppression protocol: methylprednisolone 1000 mg intra-*

Table 2

Dynamic virological and serological indicators

Pre-transplant assessment (17 days before LT)				**During LT**			
Virology				**Virology**			
Parameters	**Result**	**Reference range**	**Unit**	**Parameters**	**Result**	**Reference range**	**Unit**
HBV (qty.)	**560,000**	Negative	copies/mL	HBV (qty.)	Negative	Negative	copies/mL
HBV (qual.)	**Positive**	Negative		HBV (qual.)	Negative	Negative	
HDV (qty.)	**9,500**	Negative	copies/mL	HDV (qty.)	Negative	Negative	copies/mL
HDV (qual.)	**Positive**	Negative		HDV (qual.)	Negative	Negative	
Serology				**Serology**			
Parameters	**Result**	**Reference range**	**Unit**	**Parameters**	**Result**	**Reference range**	**Unit**
HbsAg	**>100**	<1		**HbsAg**	**>100**	<1	
antiHBsAg		<10	IU/mL	antiHBsAg	<3	<10	IU/mL
HbeAg	**22.5**	<15		**HbeAg**	**21.3**	<15	
AntiHBeAg	38.6	<100		AntiHBeAg	29.6	<100	
AntiHBcoreAg		<100		**AntiHBcoreAg**	**>500**	<100	

Post-transplant day 5			
Parameters	**Result**	**Reference range**	**Unit**
HBV	**230**	Negative	copies/mL

Post-transplantation period (10 days after LT)				**Post-transplantation period (22 days after LT)**			
Virology				**Virology**			
Parameters	**Result**	**Reference range**	**Unit**	**Parameters**	**Result**	**Reference range**	**Unit**
HBV (qty.)	Negative	Negative	copies/mL	HBV (qty.)	Negative	Negative	copies/mL
HBV (qual.)	Negative	Negative		HBV (qual.)	Negative	Negative	
HDV (qty.)	Negative	Negative	copies/mL	HDV (qty.)	Negative	Negative	copies/mL
HDV (qual.)	Negative	Negative		HDV (qual.)	Negative	Negative	
Serology				**Serology**			
Parameters	**Result**	**Reference range**	**Unit**	**Parameters**	**Result**	**Reference range**	**Unit**
HbsAg	**>100**	<1		HbsAg	**>100**	<1	
antiHBsAg		<10	IU/mL	antiHBsAg	<3	<10	IU/mL
HbeAg		<15		HbeAg	3.1	<15	
AntiHBeAg		<100		AntiHBeAg	10.7	<100	
AntiHBcoreAg	**>500**	<100		**AntiHBcoreAg**	**>500**	<100	

Note: HBsAg, hepatitis B surface antigen; HBeAg, hepatitis B e-antigen; antiHBsAg, hepatitis B surface antigen antibody; AntiHBeAg, hepatitis B e-antigen antibody; AntiHBcoreAg, hepatitis B core antigen antibody; LT, liver transplantation; HBV, chronic hepatitis B virus; HDV, hepatitis D virus.

venously, intraoperatively, followed by conversion to oral form in the post-transplant period and maintaining a dosage of 20 mg a day; tacrolimus tablets at a dose of 1.0 mg once a day, starting from day 2 after surgery, with further increase up to 2.0 mg, once a day, keeping blood tacrolimus level within 8–11 ng/mL; mycophenolate mofetil 250 mg capsules, twice a day, on day 7 after surgery, with further increase up to 500 mg twice a day. Resumption of TDF orally was planned on day 8 after LT, but blood PCR on day 5 after surgery showed reactivation of HBV infection – 230 copies/mL. TDF 300 mg orally, once a day, was administered. On day 13 after surgery, control PCR (quantitative + qualitative) was negative for both HBV and HDV infection.

The post-transplant period was uneventful, the patient was safely discharged on day 19 after surgery.

DISCUSSION

HBV infection is a global public health problem. It is most prevalent in the Western Pacific and African regions [9]. Despite WHO's goal to eliminate viral hepatitis as a public health problem by 2030, annual global deaths from HBV are projected to increase by 39% from 2015 to 2030 if the status quo remains [10].

Nucleos(t)ide analogues (NAs) have significantly altered the clinical course of liver disease by halting the progression of liver injury and preventing HBV-related decompensated cirrhosis [11]. On the other hand, we still face some epidemiological challenges in global diagnosis of HBV infection, and effective measures aimed at preventing infection and disease progression are not always used rationally [10]. In addition, in patients with advanced cirrhosis, LT is still the only definitive treatment option. However, it is known that a high viral load before transplantation is associated with a high risk of HBV relapse after LT. In this regard, absence of HBV DNA is a necessary rule for all LT candidates [11].

At the same time, despite the prevalence of HBV infection and the existing risks of graft loss in case of HBV infection relapse, there is still no unified consensus among the global community on HBV relapse prophylaxis. For instance, combination therapy with high-dose HBIG and NAs has become standard in most European centers [12, 13]. However, the use of HBIG is subject to a number of serious limitations and drawbacks, such as high cost, risk of complications, and often limited availability. In contrast, the availability and high efficacy of third-generation NAs, such as ETV, TDF and TAF have led to the formation of alternative strategies for the prevention of HBV graft relapse aimed at avoiding the long-term use of HBIG therapy [13]. Today, an increasing number of hospitals, mainly located in Central Asia and Asia-Pacific region (India, China, Japan), are advocating the use of NAs monotherapy as an effective, safe, and simple tool to prevent post-LT recurrent HBV infection. At the same time, despite these reports advocating "mononucleos(t)ide" doctrines, the time limits for HBV eradication remain unclear, and are highly dependent on viral load, degree of diffuse liver injury, viral genotype, and many other factors.

Thus, in the present case, several eye-catching events are presented at once. In particular, a more than 1000-fold reduction in HBV infection (from 560,000 to 500 copies) was achieved in 5 days. HBV was completely eradicated in less than 10 days. In our opinion, additional data explaining such a rapid virological response can be provided by genotyping the described HBV. These studies, however, are available only in a few laboratories in the world.

In addition, even though a prolonged virological response was attained prior to transplant, recurrent HBV occurred as a result of the infection and the ensuing immunosuppression. However, TDF at a standard dosage was able to totally control this HBV, negating the need for HBIG.

CONCLUSION

The use of TDF allows planning for LT in patients with positive replication and a high viral load, without the need for HBIG, against the background of limited waiting time for LT. The case study highlights the remarkable efficacy of NAs monotherapy in preventing pre-transplant recurrent HBV as well as in treating the illness right away.

The authors declare no conflict of interest.

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