

Hepatitis B Virus/Hepatitis D Virus–Coinfected Liver Transplant Candidate Receiving Hepatitis B Virus–Deoxyribonucleic Acid–Positive Allograft and Treated With High-Dose Hepatitis B Immune Globulin

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ABSTRACT

Liver transplantation (LT) for patients with hepatitis D virus (HDV) and hepatitis B virus (HBV) coinfection is uncommon in the United States. Previous case reports described poor outcomes when hepatitis B surface antigen (HBsAg)-positive grafts are transplanted in HBV/HDV-coinfected recipients. However, LT from an HBsAg-negative/HBV-deoxyribonucleic acid–positive donor in an HBV/HDV-coinfected recipient has not been reported. We describe the clinical course and management of an HBV/HDV-coinfected recipient who had LT from an HBsAg-negative/HBV-deoxyribonucleic acid–positive deceased donor and was treated with high-dose hepatitis B immune globulin in combination with an oral tenofovir alafenamide.

INTRODUCTION

Hepatitis D virus (HDV) infection is caused by defective ribonucleic acid (RNA) virus that requires hepatitis B surface antigen (HBsAg) for replication.¹ In patients with compensated liver disease, HDV treatment is limited to pegylated-interferon alfa and is associated with a low virological response rate and high relapse rate.^{1,2} However, when indicated, liver transplantation (LT) may be effective in hepatitis B virus (HBV)/HDV-coinfected patients.³ Furthermore, the availability of highly effective and well-tolerated antiviral agents against HBV, in combination with hepatitis B immune globulin (HBIG), has significantly reduced the risk of HBV/HDV reinfection after LT and improved prognosis.^{4,5} The prevalence of HDV coinfection with HBV in the United States is about 12%; however, LT for HDV infection is uncommon, and most published data are from international centers.^{3,4,6–9} Previous case reports described poor outcomes when HBsAg-positive grafts are transplanted in HBV/HDV-coinfected recipients.^{10–12} However, LT from an HBsAg-negative/HBV-deoxyribonucleic acid (DNA)–positive donor in an HBV/HDV-coinfected recipient has not been reported. We describe the clinical course and management of an HBV/HDV-coinfected recipient who had LT from an HBsAg-negative/HBV-DNA–positive deceased donor and was treated with high-dose HBIG in combination with tenofovir alafenamide (TAF).

CASE REPORT

A 34-year-old man from Central Asia had liver cirrhosis secondary to chronic HBV/HDV coinfection who was referred for LT evaluation. His disease was complicated with ascites and hepatic encephalopathy, and he was started on oral tenofovir disoproxil fumarate 300 mg daily 4 years previously. His Model of End-stage Liver Disease–Sodium score was 19 with B blood type. He was

Table 1. Recipient's and donor's hepatitis B and D serology before LT

Measure	Recipient	Donor
HBsAg	+	–
HBsAb	–	–
HBcAb IgG + IgM	+	–
HBV-DNA	Undetectable	Detectable
HDV-RNA	Detectable	–

HBcAb, hepatitis B core antibody; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HBV-DNA, hepatitis B virus-deoxyribonucleic acid; HDV-RNA, hepatitis D virus-ribonucleic acid; IgG, immunoglobulin G; IgM, immunoglobulin M; LT, liver transplantation.

HBsAg-positive, hepatitis B core antibody (HBcAb) immunoglobulin G (IgG) + immunoglobulin M–positive, and hepatitis B surface antibody (HBsAb)-negative. He had undetectable HBV-DNA but detectable HDV-RNA (Table 1). Hepatitis C virus antibody and hepatitis C virus RNA were negative.

He consented to receive an LT from a 34-year-old deceased, white, Centers for Disease Control and Prevention–increased risk donor (active intravenous [IV] drug use). The donor was negative for HBsAg and HBcAb IgG + immunoglobulin M but positive for HBV-DNA based on nucleic acid testing (Table 1). There were no noticeable pathologic changes in donor liver morphology. The recipient received HBIG 9,360 IU/mL IV daily for 7 days starting in the anhepatic phase and oral TAF 25 mg daily starting the first day after LT. Initial immunosuppression consisted of tacrolimus, mycophenolate mofetil, and steroids. On day 4 after LT, the recipient had negative HBsAg with HBsAb titer >1,000 mIU/mL and undetectable HDV-RNA and was discharged on day 7 after LT (total bilirubin 0.4 mg/dL, aspartate aminotransferase 13 U/L, alanine aminotransferase 45 U/L, alkaline phosphatase 75 U/L, albumin 2.7 g/dL, and international normalized ratio 1.0) (Table 2).

HBsAg and HBsAb titers were checked weekly for the first 4 months after LT, then every 2 weeks for 4 months and monthly thereafter. HBIG 9,360 IU/mL IV was readministered if HBsAb titer was <500 mIU/mL. Two months after LT, HDV-RNA was undetectable (Table 2). Twelve months after LT, the recipient

continued to have negative HBsAg with HBsAb titer >500 mIU/mL and undetectable HBV-DNA with excellent liver graft function, no episodes of rejection, biliary complications, or opportunistic infections.

DISCUSSION

Our recipient had decompensated liver cirrhosis secondary to chronic HBV/HDV coinfection and thus was not candidate for HDV treatment. Because of lower chance of timely liver allocation and a Model of End-stage Liver Disease–Sodium score of 19, HBsAg-negative/HBV-DNA-positive graft was offered. His LT was performed before the COVID-19 pandemic. An LT from an HBsAg-negative/HBV-DNA-positive donor in an HDV/HDV-coinfected recipient has not been reported to the best of our knowledge.

Because of worldwide organ shortage, HBV-positive grafts have been increasingly used.¹³ Our donor most likely had seronegative occult hepatitis B infection, defined as negative HBsAg and HBcAb IgG but detectable HBV-DNA in serum and/or liver tissue.¹⁴ Occult hepatitis B infection may cause the transmission of HBV infection to organ transplant recipients, especially when the recipient is negative for all HBV serum markers.^{15,16}

Most studies on LT for HDV were conducted when HBIG was the only prophylactic therapy to prevent HBV reinfection.³ The risk of HBV/HDV reinfection after LT has significantly decreased with the availability of effective HBV antiviral agents.^{2,4,5} Furthermore, outcomes were better among patients with HBV/HDV coinfection compared with HBV infection alone, probably through suppression of HBV replication.^{7–9,17} Three cases of LT of HBsAg-positive donor liver grafts in HDV/HDV-coinfected recipients were associated with poor outcomes, despite treatment with high-dose HBIG combined with lamivudine or lamivudine/adefovir dipivoxil.^{10,11}

Preventing HBV reinfection is the most effective means of preventing HDV reinfection.² The strongest predictor of HBV reinfection in HBsAg-positive patients who underwent LT was high level of HBV-DNA (>10⁵ copies/mL).¹⁸ However, it is recommended that all HBsAg-positive LT recipients should

Table 2. Recipient's hepatitis B and D serology before and after LT

Measure	Before LT	POD 4	POD 7	2 months after LT	12 months after LT
HBsAg	+	–	–	–	–
HBsAb	–	+	+	+	+
HBsAb titer (mIU/mL)	–	>1,000	>1,000	566.2	766.5
HBV-DNA	Undetectable	–	–	Undetectable	Undetectable
HDV-RNA	Detectable	Undetectable	–	Undetectable	–

HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HBV-DNA, hepatitis B virus-deoxyribonucleic acid; HDV-RNA, hepatitis D virus-ribonucleic acid; LT, liver transplantation; POD, postoperative day.

receive prophylactic therapy with nucleos(t)ide analogs with or without HBIG after LT, regardless of hepatitis B e-antigen (HBeAg) status or HBV-DNA level before LT.² Entecavir, tenofovir disoproxil fumarate, and TAF are the preferred and should be continued indefinitely after LT, regardless of HBeAg or HBV-DNA status.² The usage, dosage, route of administration, and duration of HBIG therapy depend on several factors including viremia level and presence of HBV/HDV coinfection and vary across transplant centers.^{2,5} A trough anti-HBs titer of at least 100 IU/L is believed to be protective,¹⁹ and reinfection rate can be reduced by maintaining anti-HBs titers consistently above 500 IU/L.²⁰ At our center, HBIG is usually administered IV, at a dose of 1,560 IU/mL during the anhepatic phase followed by 3 daily doses after LT. Since our recipient had HBV/HDV coinfection and our donor was HBV-DNA-positive, our multidisciplinary care team decided to use a higher dose of HBIG (9,360 IU/mL) for a total of 7 days and to follow HBsAb titers periodically to maintain levels above 500 mIU/mL.

This case report provides further evidence that adequate suppression of HBsAg with high-dose HBIG in combination with HBV antiviral treatment can prevent both HBV and HDV recurrence in HBV/HDV-coinfected LT recipients. Future studies are required, investigating the duration and frequency of HBIG as well as specific HBsAb titer level, to prevent HDV reinfection after LT.

DISCLOSURES

Author contributions: MB Hammami wrote the manuscript and reviewed the literature. R. Kohli edited the manuscript and reviewed the literature. T. Woreta reviewed the literature. MS Sulkowski and JP Hamilton edited the manuscript. L. Toman, B. Saberi, J. Laurin, JG Wang, B. Philosophie, AM Cameron, and A. Gurakar revised the manuscript for intellectual content. A. Gurakar is the article guarantor.

Financial disclosure: None to report.

Previous presentation: This case was presented at the American Transplant Congress; May 30–June 1, 2020; Virtual.

Informed consent was obtained for this case report.

Received September 10, 2020; Accepted December 3, 2020

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