Int J Clin Exp Med 2015;8(5):8238-8240
www.ijcem.com /ISSN:1940-5901/IJCEM0006293

Case Report

Complete withdrawal of hepatitis B virus prophylaxis after liver transplantation in a recipient at high risk of recurrence

Tian Shen, Yufu Ye, Lei Geng, Shusen Zheng

Department of Surgery, Division of Hepatobiliary and Pancreatic Surgery, First Affiliated Hospital, School of Medicine, Zhejiang University, Zhejiang, China

Received January 23, 2015; Accepted April 18, 2015; Epub May 15, 2015; Published May 30, 2015

Abstract: With the potent nucleos (t) ide analogues developed, necessity of life-long combined prophylaxis against hepatitis B virus (HBV) recurrence after HBV-related liver transplantation has been challenged. But complete withdrawal of HBV prophylaxis has not been previously observed in patients at high recurrence risk who showed active HBV replication before transplant. Herein, we describe a patient with positive HBeAg and HBV-DNA at the time of liver transplantation, who experienced complete HBV prophylaxis withdrawal after 3 years' application of hepatitis B immunoglobulin (HBIG) and entecavir, and showed no HBV recurrence during a long term of follow-up.

Keywords: Hepatitis B virus, liver transplantation, recurrence, prophylaxis, hepatitis B immunoglobulin, entecavir, withdrawal

Introduction

The life-long combination of hepatitis B immunoglobulin (HBIG) plus lamivudine has been successfully used in prophylaxis against hepatitis B virus (HBV) recurrence after HBV-related liver transplantation (LT) for years [1]. But with the widely use of newer nucleos (t) ide analogues, the necessity of long-term combined regimen with expensive HBIG has been suspected. Currently, more cost-effective schedules on bases of HBIG minimization have been attempted in patients at low risk of HBV recurrence, including entecavir monotherapy, lamivudine combined with adefovir dipivoxil, tenofovir plus emtricitabine, HBsAg vaccination and even complete withdrawal of prophylaxis [2-6]. However, whether these modified protocols are applicable and safe for those who with active HBV replication before LT is unknown, for these individuals are generally considered to be at high risk of recurrence [7]. To the best of our knowledge, no case of complete HBV prophylaxis withdrawal in patients at high recurrence risk has been reported before. Herein, we present a case of liver transplant recipient with active HBV replication at the time of LT, who received prophylaxis of HBIG and entecavir for 3 years and then completely stopped the regimens, and did not exhibit serological or histological signs of HBV recurrence in a period of 4 years' follow-up.

Case report

A 52-year-old woman was admitted to the hospital and diagnosed as HBV-related acute on chronic hepatic failure on March 6, 2007. She had never received any standard antiviral therapy such as nucleos(t)ide analogues or interferon before. HBsAg, HBeAg, HBV-DNA and HBcAb of the patient were positive at the time of admission. The peak of serum HBV-DNA level was 4×10^6 copies/mL and no mutation was detected in the "p region". After 10 days of salvage treatment with entecavir and artificial liver support system, HBV-DNA decreased to 6×10^5 copies/mL, but the condition continued to deteriorate. She underwent living donor liver transplantation (LDLT) on March 16, 2007, because of the life-threatening disease with hepatic encephalopathy, hepatorenal syndrome and

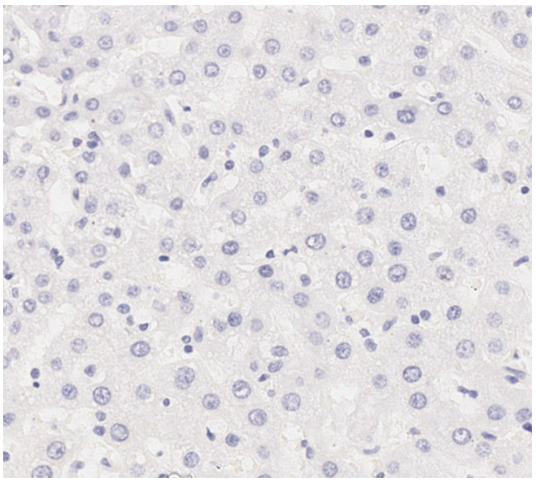

Figure 1. Pathological observation of the graft 4 years after HBV prophylaxis withdrawal (magnification × 200). Immunohistochemical staining of HBsAg and HBcAg showed no positive expression in the liver sample.

severe dysfunction of coagulation. Donated liver was obtained from her son. Donor's serum viral markers of HBV were negative, including HBsAg, HBeAg, HBcAb and HBV-DNA. While HBsAb level of the donor was positive (32 IU/L). The patient received 6000 IU of HBIG during the anhepatic phase of liver transplantation, and HBsAg turned to negative soon after transplant, as well as HBeAg and HBV-DNA level which turned to be undetectable 1 week after transplant. Then the prophylaxis schedule was 800 IU of HBIG daily for the next 6 days and weekly for 3 weeks, and followed by 400-800 IU monthly thereafter to maintain the HBsAb titer higher than 100 IU/L. Meanwhile entecavir was taken 0.5 mg per day. The patient received tacrolimus combined with mycophenolate mofetil as sustaining immunosuppression and kept tacrolimus trough level at 1-2 ng/mL since 3 years after transplant. She did not experience acute rejection, biliary complication, arterial hypertension, hypercholesterolemia, diabetes mellitus or renal function injury during the study. HBV recurrence was defined as positive HBsAg via chemiluminescence method and detectable HBV-DNA via highly sensitive PCR assay. The routine examination didn't provide any evidence for HBV recurrence. But she stopped the anti-virus prophylaxis of HBIG and entecavir for economic reason in April 2010 on her own, and refused to receive mono nucleotide analogues therapy or vaccination treatment. At the time of drug stop, serum markers of HBV showed negative HBsAg, HBeAg, HBV-DNA and positive HBsAb (108 IU/L), HBcAb and HBeAb. The HBV markers were closely monitored every month. To our surprise, she did not exhibit serological signs of HBV recurrence with normal liver graft function in the next 4 years' follow-up. Although the HBsAb level dropped gradually to negative in 1 year after drug withdrawal, HBsAg, HBeAg and HBV-DNA maintained to be undetectable during follow-up. Immunohistochemical staining of HBsAg and HBcAg revealed no positive expression in the liver sample obtained in October 2014 (**Figure 1**). The data of HBV-related immunological examination, liver function and coagulation was shown in **Table 1**.

Discussion

For HBV-related liver transplantation, risk of HBV recurrence is dependent on effective prophylaxis and the status of preoperative viral replication. Liver transplantation for HBV-related liver disease is often complicated by rapid HBV recurrence without effective prophylaxis. In the last two decades, the traditional protocol of prophylaxis against HBV recurrent infection after liver transplantation with HBIG and lamivudine has resulted in excellent outcomes [1]. But stopping life-long expensive prophylaxis is considered to be the ultimate strategy. Newer nucleos(t)ide analogues with higher efficiency and lower resistance rates such as entecavir or tenofovir could suppress HBV replication potently, and reduce the risk of HBV recurrence effectively. So, in the era of new potent nucleos(t)ide analogues, an individualized approach based on risk of reinfection is recommended. The level of HBV-DNA at the time of transplant remains to be the most significant factor predicting risk of recurrent HBV [7]. It is possible to discontinue HBIG and maintain antiviral monotherapy for patients with a low risk of HBV recurrence (i.e. undetectable HBV-DNA levels before transplant). Successful attempts focusing on HBIG cessation such as entecavir monotherapy, tenofovir plus emtricitabine, lamivudine plus adefovir dipivoxil were reported to be effective for patients at low risk of recurrence [2-4]. Moreover, previous study reported the efficacy and safety of a gradual weaning the HBIG and nucleos(t)ide analogues prophylaxis in lower recurrence risk patients [6]. But to the high risk patients (i.e. positive HBV-DNA and HBeAg before transplant, or pre-

Table 1. Data of HBV-related immunological examination, liver function and coagulation

	At LT	1 pow	1 pom	1 poy	3 poy	5 poy	7 poy
HBV-DNA (copies/MI)	6×10^5	-	-	-	-	-	-
HBsAg	+	-	-	-	-	-	-
HBeAg	+	-	-	-	-	-	-
HBsAb (IU/L)	-	501	237	152	108	-	-
HBeAb	-	-	-	+	+	+	+
HBcAb	+	+	+	+	+	+	+
ALT (U/L)	75	152	21	16	27	15	20
TB (umol/L)	692	83	17	15	17	11	13
PT (s)	57.3	12.7	11.5	11.6	11.8	11.3	11.6

LT: liver transplantation; pow: postoperative day; pom: postoperative month; poy: postoperative year; ALT: alanine aminotransferase; TB: total bilirubin; PT: prothrombin time.

existing drug resistance due to viral mutations), current concepts indicate that a more cautious approach to prophylaxis regimen is necessary, and HBIG in combination with an antiviral still remains to be significant [7, 8].

In the present study, we observed complete drug withdrawal of HBIG and entecavir in a liver transplant recipient at high risk of HBV recurrence characterized by positive HBeAg and HBV-DNA at time of transplant. This case highlights the possibility of stopping the indefinite anti-HBV agents in the patients with high risk of reinfection. What factors govern this phenomenon is as yet unknown. In this case, 3 years of antiviral therapy with entecavir, the positive HBsAb of donor and the relatively low tacrolimus level may played part role in this procedure. We report this occasional case, but larger sample size and longer period of observation are required to deeply assess the safety of complete withdrawal of HBV prophylaxis for the patients at high recurrence risk.

Acknowledgements

The authors would like to thank the staff of our immunological laboratory for performing the virologic assays. This work was supported by National Natural Science Foundation of China (No. 81373160; 81400673).

Disclosure of conflict of interest

None.

Address correspondence to: Shusen Zheng, Department of Surgery, Division of Hepatobiliary and Pancreatic Surgery, First Affiliated Hospital, School of Medicine, Zhejiang University, Zhejiang, China. E-mail: shusenzheng@zju.edu.cn

References

[1] Zheng S, Chen Y, Liang T, Lu A, Wang W, Shen Y, Zhang M. Prevention of hepatitis B recurrence after liver transplantation using lamivudine or lamivudine combined with hepatitis B Immunoglobulin prophylaxis. Liver Transpl 2006; 12: 253-258.

[2] Yi NJ, Choi JY, Suh KS, Cho JY, Baik M, Hong G, Lee KW, Kim W, Kim YJ, Yoon JH, Lee HS, Kim DG. Post-transplantation sequential entecavir monotherapy following 1-year combination therapy with hepatitis B immunoglobulin. J Gastroenterol 2013; 48: 1401-1410.

[3] Angus PW, Patterson SJ, Strasser SI, McCaughan GW, Gane E. A randomized study of adefovir dipivoxil in place of HBIG in combination with lamivudine as post-liver transplantation hepatitis B prophylaxis. Hepatology 2008; 48: 1460-1466.

[4] Wesdorp DJ, Knoester M, Braat AE, Coenraad MJ, Vossen AC, Claas EC, van Hoek B. Nucleoside plus nucleotide analogs and cessation of hepatitis B immunoglobulin after liver transplantation in chronic hepatitis B is safe and effective. J Clin Virol 2013; 58: 67-73.

[5] Takaki A1, Yagi T, Yasunaka T, Sadamori H, Shinoura S, Umeda Y, Yoshida R, Sato D, Nobuoka D, Utsumi M, Yasuda Y, Nakayama E, Miyake Y, Ikeda F, Shiraha H, Nouso K, Fujiwara T, Yamamoto K. Which patients respond best to hepatitis B vaccination after a hepatitis B virus-related liver transplantation? J Gastroenterol 2013; 48: 1373-1383.

[6] Lenci I, Tisone G, Di Paolo D, Marcuccilli F, Tariciotti L, Ciotti M, Svicher V, Perno CF, Angelico M. Safety of complete and sustained prophylaxis withdrawal in patients liver-transplanted for HBV-related cirrhosis at low risk of HBV recurrence. J Hepatol 2011; 55: 587-593.

[7] Terrault N. Prophylaxis in HBV-infected liver transplant patients: end of the HBIG era? Am J Gastroenterol 2013; 108: 949-951.

[8] Kasraianfard A, Watt KD, Lindberg L, Alexopoulos S, Rezaei N. HBIG Remains Significant in the Era of New Potent Nucleoside Analogues for Prophylaxis Against Hepatitis B Recurrence After Liver Transplantation. Int Rev Immunol 2014; [Epub ahead of print].