CASE REPORT

Liver Transplant From an ABO-Incompatible and Hepatitis C Antibody-Positive *but an HCV-RNA Negative* Living Donor in a Familial Amyloid Polyneuropathy Patient

Takayuki Takeichi, Katsuhiro Asonuma, Hidekazu Yamamoto, Yuki Ohya, Kenji Okumura, Kwang-Jong Lee, Yukihiro Inomata

Abstract

Familial amyloid polyneuropathy is a rare, progressively disabling, and ultimately fatal inherited disease. Liver transplant is currently the only available treatment proven to halt the progression of familial amyloid polyneuropathy. We report a 31-year-old woman with familial amyloid polyneuropathy who received a living-donor liver transplant from her husband who was hepatitis C virus antibody-positive *but HCV-RNA negative* and ABO incompatible. Six years after the transplant, both donor and recipient have normal liver biochemistry results; no hepatitis C viral load has been detectable in the recipient. This is the first report of a living ABO-incompatible liver transplant from an anti-hepatitis C virus antibody-positive *but an HCV-RNA negative* donor. This experience suggests that the use of an anti-hepatitis C virus antibody-positive hepatic graft is possible in select circumstances.

Key words: *Familial amyloid polyneuropathy, Hepatitis C virus, Living-donor liver transplant, ABO-incompatible transplant*

Introduction

Familial amyloid polyneuropathy (FAP) is an inherited disorder resulting in systemic deposition of amyloid fibrils containing mutant transthyretin variants.[1] The outcome of this disease is so poor that FAP has long been considered incurable. The first successful liver transplant in a patient with FAP was performed in 1990, and since then, liver transplant has become widely used for patients with FAP as a life-saving treatment.[2,3] In Japan, there is little deceased-donor liver transplant, but living-donor liver transplant (LDLT) has been done in patients with FAP. The living donor is selected from among the patient's relatives. Because FAP is an inherited disorder, candidates for living donor can be difficult to find among the relatives. This may lead to an increased use of marginal living donors. We report the outcome of an ABO-incompatible (ABO-I) liver transplant from an anti-HCV-positive donor to a recipient with FAP.

Case Report

A 31-year-old woman presented to us with no relevant history of disease during her childhood. Neurologic manifestations had appeared 5 years earlier, and she was diagnosed with FAP 3 years after that. She had a familial history of FAP, and her mother had died of FAP at 43 years of age, while her sister was a gene carrier (although no symptoms had developed). Her father had hepatitis C virus (HCV) cirrhosis. She was indicated for liver transplant, and the transplant had to be done quickly because of her 5-year history of FAP and its late diagnosis and far advanced nature. However, the possibility of deceased-donor liver transplant in Japan is not good. The only possible living-donor candidate was her 26-year-old husband, but he had an HCV infection and had received interferon therapy 5 years earlier. Furthermore, his blood type was A, and the recipient's blood type was O; thus, the blood types were incompatible. The results of his liver function tests were normal: total bilirubin, 0.8 mg/dL; aspartate aminotransferase,

From the Department of Transplantation and Pediatric Surgery, Postgraduate School of Medical Science, Kumamoto University Hospital, 1-1-1 Honjo, Kumamoto 860-8556, Japan
Acknowledgements: *No specific funding was provided for this study. The authors of this manuscript have no conflicts of interest to disclose.*
Corresponding author: *Takayuki Takeichi, MD, Department of Transplantation and Pediatric Surgery, Postgraduate School of Medical Science, Kumamoto University Hospital 1-1-1 Honjo, Kumamoto 860-8556, Japan*
Phone: *+81 96 373 5618* ***E-mail:*** *ttakeichi@fc.kuh.kumamoto-u.ac.jp*

Experimental and Clinical Transplantation (2013) 2: 182-185

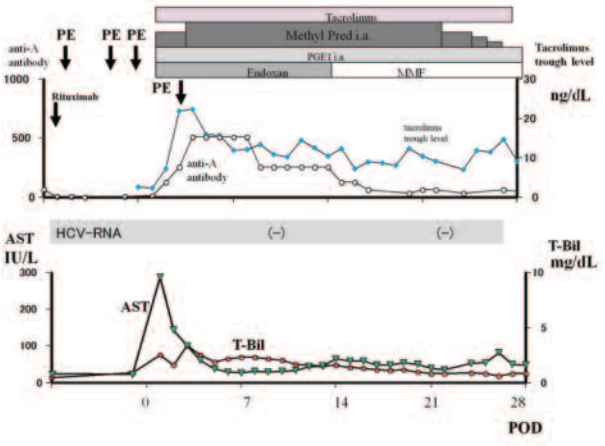
DOI: 10.6002/ect.2012.0158

20 IU/L; alanine aminotransferase, 26 IU/L; alkaline phosphatase, 250 U/L; gamma-glutamyl transpeptidase, 41 U/L; albumin, 4.2 g/dL; and prothrombin time, 12.5 seconds (90%). His viral profile was as follows: HBs antigen (-); HBs antibody (-); anti-HCV (+); and HCV-RNA (-). A needle liver biopsy was done, and the histologic findings showed only mild steatosis, no necrosis, no hepatitis, and no fibrosis. Despite the fact that the husband was anti-HCV-positive and ABO-I, we decided to proceed with an LDLT because her disease prognosis was poor and there was little chance of any other liver donor available. Furthermore, the donor was happy to donate his liver to his wife even though there is a risk to both the donor and the recipient with LDLT. Approval was obtained from the Ethics Committee of Kumamoto University Graduate School of Biomedical Sciences after an interview with the donor and the recipient.

We performed an LDLT using a left lobe graft without the caudate lobe. The surgical procedure for the donor and the recipient has been described elsewhere.[4] The donor's operative duration was 7 hours 32 minutes. The donor's operative blood loss was 470 mL, and no blood transfusion was performed. The total operative duration for the recipient was 10 hours 28 minutes. The actual graft weight was 470 grams, which was 1.04% of the recipient's body weight. The recipient's operative blood loss was 350 mL; thus, no transfusion was necessary.

Because of the ABO-I blood combination, the recipient was treated with an immunosuppression protocol consisting of preoperative rituximab, a plasma exchange, a triple immunosuppressive regimen, intra-arterial infusion therapy, and a splenectomy at surgery (Figure 1). She received 500 mg rituximab intravenously 2 weeks before the LDLT. Her anti-ABO IgM and IgG titers were ×512 and ×256 one week before the operation. Plasma exchange was performed 3 times within 1 week of the LDLT. Her anti-ABO IgM and IgG titers dropped to ×2 and ×4 just before the operation. For hepatic artery infusion, an intra-arterial catheter was placed during the operation, and continuous infusion of prostaglandin E1 (0.01 μg/kg/min on days 0 to 14) and methylprednisolone (125 mg/d on days 0 to 7, 50 mg/d on days 8 to 14; then we tapered the dosage and discontinued the drug on day 21). Endoxan (100 mg) was administered from postoperative days

Figure 1. Time Course After Living-Donor Liver Transplant



Abbreviations: IA, intra-arterial infusion; PE, plasma exchange; PGE1, prostaglandin E1; POD, postoperative day; T-Bil, total bilirubin

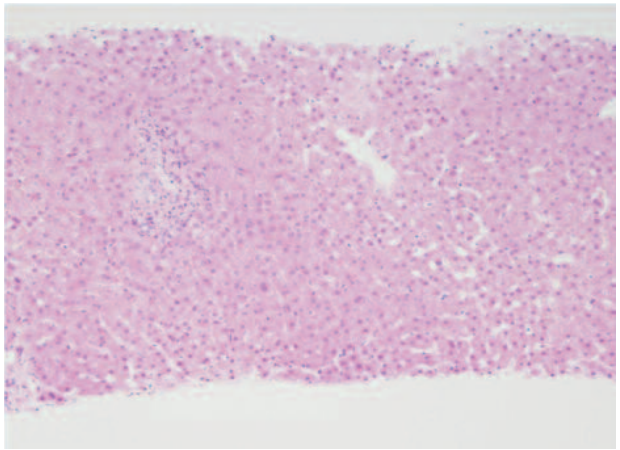
(POD) 1 to 14; this was followed by mycophenolate mofetil 500 mg twice a day from POD 15 onward.

Posttransplant immunosuppression consisted of tacrolimus and steroids. The trough level of tacrolimus was maintained between 10 and 15 ng/mL during the first 2 weeks. Because the anti-ABO IgM and IgG titers rose markedly from the day after transplant, we performed a plasma exchange on POD 3. Although the titers did not decrease immediately, the patient's liver function recovered well. The quantity of steroids in the hepatic artery infusion was increased and the titer gradually decreased. The patient had prolific nausea after transplant probably because of the original disease, but her liver function results recovered to normal on POD 21. Her renal functions were normal before and after the transplant. Hepatitis C virus RNA was not detectable by polymerase chain reaction after the transplant. The hepatic artery catheter was removed on POD 31, and she was discharged from hospital with excellent graft condition 50 days after the operation.

At the time of this writing it has been 6 years after the transplant, and the patient has been well, with excellent graft function, unremarkable liver biochemistry, and has been HCV-RNA negative. Figure 2 shows a liver biopsy 6 years after the transplant, with no evidence of cellular rejection or fibrosis. Progression of FAP is controlled and she has an excellent quality of life.

The postoperative course of the donor also was uneventful. Although serum aspartate aminotransferase increased to 225 IU/L on POD 3, it returned to normal by POD 7. The maximum total

Figure 2. Graft Liver Biopsy 6 Years After Living-Donor Liver Transplant



There was no evidence of fibrosis, hepatitis, or cellular rejection.

bilirubin level was 2.5 mg/dL on POD3. He left hospital on POD 17. He returned to work 3 months after the operation. At the time of this writing, after 6 years, his liver function test results are normal, and HCV-RNA is negative.

Discussion

Liver transplant is the only effective treatment for FAP. More than 65 patients in Japan with FAP have undergone a liver transplant, with living donors consisting of parents, siblings, or husbands; there has been 1 deceased donor.[6] In Japan, organs from deceased donors remain scarce, so that living-related liver transplant is more common. Because FAP is an autosomal dominant inherited disease, potential living donors are restricted. In the present case, there were potentially serious problems for the donor and recipient, such as a risk of flare-up of the HCV infection in the donor, and HCV transmission under strong immunosuppression due to ABO-I matching in the recipient.

ABO-I living-related liver transplant increasingly has been performed in Japan to overcome the shortage of donor organs. Initially, the outcome was poor because of antibody-mediated rejection; however, it has dramatically improved with the use of local steroid infusion and rituximab prophylaxis.[7] In the present case, the patient had no antibody-mediated rejection after receiving a living-related liver transplant.

Several single-center studies have shown no significant differences in survival among HCV-positive recipients transplanted with anti-HCV-positive grafts compared with recipients transplanted with anti-HCV-negative donor organs.[8-10] Saab and associates reported that the use of HCV-positive grafts in recipients with HCV infection does not appear to affect patient survival, graft survival, or recurrence of HCV infection when compared with using anti-HCV-negative grafts.[11] There are several reports of HCV flare-up after chemotherapy and bone marrow transplant in patients with anti-HCV-positive/HCV-RNA-positive grafts.[12-14] The persistence of HCV in patients with previously cleared HCV remains controversial. However, we could not find and research reporting on the use of anti-HCV-positive/HCV-RNA-negative allografts in non-HCV recipients.

In kidney transplant, Nicot and associates have reported the persistence of HCV in immunocompromised transplant patients who were cleared of the virus while on dialysis, but there was no relapse of HCV infection after long-term follow-up despite intensive immunosuppressive therapy.[15] In the current study, although we were concerned about a transmission of HCV virus and de novo HCV hepatitis in the recipient under strong immunosuppression, the patient had a successful posttransplant outcome, with normal liver biochemistry and undetectable HCV in the allograft and serum at 6 years' follow-up.

Conversely, living donor safety is mandatory. In the current case, we also were concerned about an HCV flare-up in the donor after surgery because of the stress of the invasive surgery and liver regeneration, but we could find no reports of an HCV flare-up after hepatectomy. Six years after surgery, the results of the donor's liver function tests are normal and his HCV-RNA remained negative. Although this is a special case of using a marginal donor, an anti-HCV-positive patient with an HCV-RNA negative donor can be taken into consideration for a donor candidate in a special occasion.

In conclusion, we describe the successful transplant of an FAP patient who underwent ABO-I LDLT using a graft from an anti-HCV-positive donor. When the donor is anti-HCV-positive and HCV-RNA-negative with normal liver histology, transplant may be considered in some situations. Long-term follow-up is required for donor and recipient.

References

1. Ikeda S, Hanyu N, Hongo M, et al. Hereditary generalized amyloidosis with polyneuropathy. Clinicopathological study of 65 Japanese patients. *Brain*. 1987;110 (Pt 2):315-337.
2. Takei Y, Ikeda S, Ikegami T, et al. Ten years of experience with liver transplantation for familial amyloid polyneuropathy in Japan: outcomes of living donor liver transplantations. *Intern Med*. 2005;44(11):1151-1156.
3. Ando Y. Liver transplantation and new therapeutic approaches for familial amyloidotic polyneuropathy (FAP). *Med Mol Morphol*. 2005;38(3):142-154.
4. Tanaka K, Uemoto S, Tokunaga Y, et al. Surgical techniques and innovations in living related liver transplantation. *Ann Surg*. 1993;217(1):82-91.
5. Inomata Y, Uemoto S, Asonuma K, Egawa H. Right lobe graft in living donor liver transplantation. *Transplantation*. 2000;69(2):258-264.
6. The Japanese Liver Transplantation Society. Liver Transplantation in Japan —Registry by the Japanese Liver Transplantation Society—. *Isyoku*. 2010;44:621-632.
7. Egawa H, Teramukai S, Haga H, Tanabe M, Fukushima M, Shimazu M. Present status of ABO-incompatible living donor liver transplantation in Japan. *Hepatology*. 2008;47(1):143-152.
8. Velidedeoglu E, Desai NM, Campos L, et al. The outcome of liver grafts procured from hepatitis C-positive donors. *Transplantation*. 2002;73(4):582-587.
9. Marroquin CE, Marino G, Kuo PC, et al. Transplantation of hepatitis C-positive livers in hepatitis C-positive patients is equivalent to transplanting hepatitis C-negative livers. *Liver Transpl*. 2001;7(9):762-768.
10. Busuttil RW, Tanaka K. The utility of marginal donors in liver transplantation. *Liver Transpl*. 2003;9(7):651-663.
11. Saab S, Ghobrial RM, Ibrahim AB, et al. Hepatitis C positive grafts may be used in orthotopic liver transplantation: a matched analysis. *Am J Transplant*. 2003;3(9):1167-1172.
12. Vento S, Cainelli F, Mirandola F, et al. Fulminant hepatitis on withdrawal of chemotherapy in carriers of hepatitis C virus. *Lancet*. 1996;347(8994):92-93.
13. Aksoy S, Abali H, Kilickap S, Erman M, Kars A. Accelerated hepatitis C virus replication with rituximab treatment in a non-Hodgkin's lymphoma patient. *Clin Lab Haematol*. 2006;28(3):211-214.
14. Zekri AR, Mohamed WS, Samra MA, Sherif GM, El-Shehaby AM, El-Sayed MH. Risk factors for cytomegalovirus, hepatitis B and C virus reactivation after bone marrow transplantation. *Transpl Immunol*. 2004;13(4):305-311.
15. Nicot F, Kamar N, Mariamé B, Rostaing L, Pasquier C, Izopet J. No evidence of occult hepatitis C virus (HCV) infection in serum of HCV antibody-positive HCV RNA-negative kidney-transplant patients. *Transpl Int*. 2010;23(6):594-601.