

OPEN

Assessment of 4 Cases of Kidney Transplantation from Hepatitis C Virus Antibody-Positive and RNA-Negative Donors to Antibody-Negative Recipients

Kohei Unagami, MD,¹ Hideki Ishida, MD, PhD,² Masayoshi Okumi, MD, PhD,² Toshihito Hirai, MD, PhD,² Daisuke Toki, MD, PhD,² Kazuya Omoto, MD, PhD,² Tomokazu Shimizu, MD, PhD,² Masashi Inui, MD, PhD,² Kosaku Nitta, MD, PhD,¹ and Kazunari Tanabe, MD, PhD²

Hepatitis C virus (HCV) infection is significantly more prevalent among hemodialysis patients than the general population,¹ and caution is required when evaluating these patients for kidney transplantation. It has been reported that HCV infection may develop in uninfected recipients receiving organs from HCV-infected donors² and that transplantation increases the risk of liver disease² and mortality.³ Therefore, at many institutions, kidneys from HCV antibody-positive donors are not allowed to be used for transplantation, regardless of the HCV RNA level.

Sustained virological response (SVR) rates in HCV have been increasing since the introduction of direct-acting antiviral agents. In renal transplant recipients, a series of successful HCV clearance using direct-acting antiviral agents was reported.^{4,5} Sustained virological response is associated with continuous HCV RNA conversion to negative status, alleviation of hepatitis,⁶ and suppression of liver disease progression.⁷

However, other risk factors of HCV transmission from kidney transplantation donors with HCV RNA-negative status are yet to be elucidated. Even if the donors have HCV, if their RNA is negative, the virions capable of multiplying or replicating are apparently absent, and HCV infection may

not develop; therefore, the risk of infection to the recipients may be relatively low. There have been only 3 reports of individual cases of transplantation from an HCV antibody-positive and RNA-negative donor to an HCV antibody-negative recipient⁸⁻¹⁰; moreover there have been no reports that have summarized a number of cases.

In this study, we assessed the possibility of indications for transplantation based on the cases of transplantation from HCV antibody-positive donors to HCV antibody-negative recipients in our institution.

CASE DESCRIPTION

We conducted a retrospective study of 6 transplantations from HCV antibody-positive donors to antibody-negative recipients performed between November 1, 1989, when it became possible to measure HCV antibodies, and November 30, 2014, at our institution. Before transplantation, details of transplantation and the risk of transmission were explained in detail to the patients, and all patients provided informed consent. In 2 old cases transplanted in 1992, HCV RNA testing had not been introduced at the time of transplantation, and the RNA status of the donors was unknown, therefore, they were excluded (total 4 included cases; Table 1). Patient clinical backgrounds and outcomes were recorded.

In all cases, donors were HCV antibody-positive, and RNA was undetectable at the time of transplantation.

Case 1

The donor had no history of IFN therapy and was HCV RNA-negative. Because this was a blood-type incompatible case, immunosuppression was induced with tacrolimus, mycophenolate mofetil, methylprednisolone, basiliximab, and rituximab 500 mg.

Case 2

The donor had no history of IFN therapy. Immunosuppression was induced with mycophenolate mofetil and methylprednisolone.

Case 3

The donor had a history of HCV infection. IFN therapy (details unknown) was performed before transplantation, and the donor was confirmed to be RNA-negative. SVR24 was achieved, the duration between treatment and transplantation was about 8 years. Because this was a donor-specific

Received 14 May 2016. Revision requested 30 June 2016.

Accepted 17 July 2016.

¹ Department of Medicine, Kidney Center, Tokyo Women's Medical University, Tokyo, Japan.

² Department of Urology, Kidney Center, Tokyo Women's Medical University, Tokyo, Japan.

The authors declare no funding or conflicts of interest.

K.U. performed research collected data and wrote the article. H.I. supervised this research and participated in article writing. M.O., D.T., K.O., T.S., and M.I. did the follow-up patients and collected data. K.N. and K.T. designed the study and participated in article writing.

Correspondence: Kohei Unagami, Department of Medicine, Kidney Center, Tokyo Women's Medical University, 8-1 Kawada-cho, Shinjuku-ku, 162-8666, Japan. (ko_umi@hotmail.com).

Copyright © 2016 The Authors. *Transplantation Direct*. Published by Wolters Kluwer Health, Inc. This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially.

ISSN: 2373-8731

Transplantation Direct 2016;2: e102; doi: 10.1097/TXD.0000000000000614.
Published online 26 August 2016.

TABLE 1.**Donor and recipient information**

Case	1	2	3	4
Year of transplantation	2006	2006	2008	2010
Period from transplantation (moths)	103	103	80	49
Living or deceased	Living	Living	Living	Living
Donor information				
Sex	Female	Female	Male	Female
HCV antibody	Positive ^a	Positive ^a	Positive ^a	Positive ^b
Antibody titer (cut off index)	1.2	1.5	18.8	31.9
Genotype	Unknown	Unknown	2a	2a
HCV RNA at time of transplantation	Undetectable ^c	Undetectable ^c	Undetectable ^d	Undetectable ^d
IFN therapy before transplantation	None	None	Done	Done
Recipient information				
Sex	Female	Female	Female	Female
Age at the transplanted time	27	31	20	51
Primary disease	Lupus nephritis	Interstitial nephritis	Renal hypoplasia	Chronic glomerulonephritis
ABO	Incompatible	Compatible	Minor mismatch	Incompatible
Induction	FK, MMF, MP, BASI, RIT	MMF, MP	FK, MMF, MP, BASI, RIT	FK, MMF, MP, BASI, RIT
Additional therapy	None	None	steroid pulse	steroid pulse
IFN therapy after transplantation	None	None	None	None
HCV antibody	Negative ^b	Negative ^b	Negative ^b	Negative ^b
Time between transplantation and HCV antibody testing (mo)	103	99	36	34
HCV RNA	Undetectable ^d	Undetectable ^d	Undetectable ^d	Undetectable ^d
Time between transplantation and HCV RNA testing (mo)	103	99	15	34

Data are expressed as means \pm SD. HCV RNA, result of virus PCR measurement; IFN therapy before transplantation, history of interferon therapy prior to transplantation; primary disease, cause of chronic kidney disease. IFN therapy after transplantation, interferon therapy after transplantation as prevention prescription.

^a HCV antibody was assessed by LumiPulsell Ortho HCV, Ortho Clinical Diagnostics, Tokyo (sensitivity, 100.0%; specificity, 99.54%).

^b HCV antibody was assessed by LumiPulse Presto Ortho HCV, Ortho Clinical Diagnostics, Tokyo (sensitivity 100.0%, specificity 99.71%).

^c HCV RNA was assessed by COBAS AmpliCore HCV v2.0, Roche Diagnostic, Tokyo. (The lower limits of detections for HCV RNA by PCR are 500 IU/mL.)

^d HCV RNA was assessed by COBAS, TaqMan HCV "auto" v1.0, Roche Diagnostic, Tokyo. (The lower limits of detections for HCV RNA by PCR are 15 IU/mL.)

ABO, ABO-compatible, incompatible, or minor mismatch for transplantation; DSA, donor-specific antibody in recipient; FK, tacrolimus; MMF, mycophenolate mofetil; MP, methyprednisolone; BASI, basiliximab; RIT, rituximab; DSG, deoxyspergualin.

antibody-positive case, immunosuppression was induced with rituximab 200 mg, γ -globulin, and plasmapheresis in addition to tacrolimus, mycophenolate mofetil, methylprednisolone, and basiliximab. A rejection reaction occurred postoperatively that improved with steroid pulse therapy.

Case 4

The donor had a history of HCV infection and had received IFN therapy (peg-IFN α 2 alone, without ribavirin) which helped in achieving a SVR24. The duration between treatment and transplantation was about 5 years. Because this was a blood type incompatible and donor-specific antibody-positive case, immunosuppression was induced with tacrolimus, mycophenolate mofetil, methylprednisolone, basiliximab, rituximab 200 mg, and plasmapheresis. Antibody-mediated rejection was noted postoperatively which improved with deoxyspergualin treatment.

The grafted kidney continues to function in all cases. In cases 3 and 4, the donors had a history of HCV hepatitis and had undergone IFN therapy prior to transplantation. Interferon therapy had not been performed in cases 1 and 2, and as antibody titers were low and RNA testing was negative, it appeared that the donors had either previously cleared the infection or test results had been false-positives. Rituximab was used in 3 cases as an immunosuppressive agent.

To date, patients have been followed up for a mean duration of 83.8 ± 25.6 months since transplantation with no detection of liver enzyme elevation or any abnormal findings in ultrasonography and/or CT images. Moreover, with a mean follow-up time of 66.5 ± 36.4 months postoperatively, all HCV antibody tests were found to be negative with no evidence of HCV infection in any of the recipients.

DISCUSSION

Screening for HCV infection is usually performed by testing for HCV antibodies. When results are HCV-antibody-positive, it is always necessary to check HCV infection status by quantitatively determining HCV RNA levels. Moreover, the HCV antibody test has a window period, infections are occasionally missed,¹¹ and previously immunosuppressed patients are occasionally later found to be RNA-positive despite originally being tested as HCV antibody-negative. Regular postoperative measurement of recipient HCV antibody and RNA levels are advisable in such cases. Furthermore, a previous report described cases of HCV transmission due to the window period of HCV RNA testing despite the use of HCV RNA-negative donors (HCV RNA status converted to positive postoperatively).¹¹ Thus, clinicians should consider the limitations of RNA measurements.¹²

Hepatitis C virus transmission by organ transplantation has been confirmed by previous studies, and transplantation of antibody-positive donor kidneys to antibody-negative recipients is associated with severe acute hepatitis, chronic hepatitis, and a lower survival rate posttransplantation. Therefore, it has been proposed that such transplantations should not be performed. However, when a sustained conversion to a HCV RNA-negative status has previously been achieved in donors, virions capable of multiplying or replicating are apparently absent and HCV infection may not develop when kidney transplantation is performed using such donor organs. In this study, despite a mean postoperative follow-up period of 83.8 ± 25.6 months, no evidence of HCV infection has been

observed in any of the 4 patients included in this study. In the pre-HCV RNA-testing era, we performed 2 kidney transplantations from donors who were HCV Ab-positive with unknown RNA status. In these 2 cases, the recipients also had no evidence of HCV infection, with no detection of HCV Ab or RNA measurement; about 20 years have passed since these transplantations.

The Kidney Disease: Improving Global Outcomes Guidelines state that there are no particular restrictions regarding the use of immunosuppressive agents other than tacrolimus, which can cause the development of new-onset diabetes mellitus after transplantation.¹³ However, despite being considered contraindicated in HCV infection patients, rituximab was used to treat 3 cases with no onset of symptoms observed. Nicot et al¹⁴ performed immunosuppressive therapy (including rabbit antithymocyte globulin in 59% and an anti-IL2 receptor blocker in 32% of recipients) in kidney transplantation recipients whose status was HCV antibody-positive and RNA-negative as a result of HCV treatment before transplantation and reported no evidence of HCV infection relapse based on serum, peripheral blood mononuclear cell (PBMC), and liver RNA measurements over a mean follow-up period of 10.5 years. Thus, even where donors are HCV antibody-positive and RNA-negative, the organ grafts are not absolutely ineligible for kidney transplantation, and there may be few restrictions for the use of immunosuppressive agents in recipients.

Nevertheless, even when blood testing for HCV RNA is negative, because there is a possibility of an occult HCV state where RNA may be extracted from the liver or PBMCs, decisions regarding indications for transplantation should be taken with caution. There have been many reports of reactivation of occult HCV in association with the use of immunosuppressive agents, use of chemotherapy, and immunocompromised states,¹⁵⁻²⁰ and should be particularly considered as cases have been reported where SVR has previously been achieved. Currently, there have been very few reports of the transmission of occult HCV to recipients after liver transplantation, and the possibility of transmission by kidney transplantation is considered to be relatively low. However, occult HCV is regarded as being potentially infective,²¹ and sufficient caution is necessary. Furthermore, because the sensitivity of RNA measurements is lower than ideally desired, a proportion of HCV antibody-positive and RNA-negative patients exhibit low-level viremia.²² Therefore, it is impossible to rule out the possibility of infection transmission, and repeated testing and concomitant measurements of liver function in donors and recipients appear to be advisable.

The use of HCV Ab-positive and RNA-negative grafts seems to be safe for graft and patient survival, but some issues remain regarding the progression of liver disease.²³ In our criteria, if other appropriate donor candidates are not available, and if the donor's HCV infectious status is adequately controlled, with HCV RNA negativity and SVR achieved, transplantation can proceed under fully informed consent.

This study has several limitations. This was a retrospective study with a small number of patients. Although there is currently no evidence of HCV infection in any of the 4 recipients, it is not possible to entirely rule out the possibility of future infection resulting from the transplantation of organs from HCV antibody-positive and RNA-negative donors. Moreover, even when blood testing for HCV RNA is negative,

because there is a possibility of an occult HCV state where RNA may be extracted from the liver or PBMCs, decisions regarding indications for transplantation should be taken with caution. The HCV antibody tests in cases 1 to 3 were second generation, as opposed to third generation in case 4, and there was a difference in the assay methods used. However, because there are no differences in cutoff values or titers between second-generation and third-generation assays they were treated as equivalent.

The outcome of this study indicates that kidney transplantation can be performed with minimal risk of recipient HCV infection when potential donors are HCV antibody-positive and RNA-negative.

REFERENCES

1. Kidney Disease: Improving Global Outcomes (KDIGO). KDIGO clinical practice guidelines for the prevention, diagnosis, evaluation, and treatment of hepatitis C in chronic kidney disease. *Kidney Int Suppl.* 2008; 109: S1–99.
2. Pereira BJ, Milford EL, Kirkman RL, et al. Transmission of hepatitis C virus by organ transplantation. *N Engl J Med.* 1991;325:454–460.
3. Bucci JR, Matsumoto CS, Swanson SJ, et al. Donor hepatitis C seropositivity: clinical correlates and effect on early graft and patient survival in adult cadaveric kidney transplantation. *J Am Soc Nephrol.* 2002;13: 2974–2982.
4. Sawinski D, Kaur N, Ajeti A, et al. Successful treatment of hepatitis C in renal transplant recipients with direct-acting antiviral agents. *Am J Transplant.* 2016;16:1588–1595.
5. Saxena V, Terrault NA. Treatment of hepatitis C infection in renal transplant recipients: the long wait is over. *Am J Transplant.* 2016;16:1345–7.
6. Hagiwara H, Hayashi N, Mita E, et al. Detection of hepatitis C virus RNA in serum of patients with chronic hepatitis C treated with interferon-alpha. *Hepatology.* 1992;15:37–41.
7. Cardoso AC, Moucari R, Figueiredo-Mendes C, et al. Impact of peginterferon and ribavirin therapy on hepatocellular carcinoma: incidence and survival in hepatitis C patients with advanced fibrosis. *J Hepatol.* 2010;52:652–657.
8. Cruzado JM, Gil-Vernet S, Castellote J, et al. Successful treatment of chronic HCV infection should not preclude kidney donation to an HCV negative recipient. *Am J Transplant.* 2013;13:2013.
9. Watanabe T, Koyama I, Shinozuka N, et al. A case of renal transplantation received from a living donor with second-generation anti-hepatitis C virus antibody positive into an anti-hepatitis C virus antibody negative recipient. *Transplant Proc.* 2000;32:1593–1594.
10. Bouatou Y, Negro F, Hadaya K. ABO incompatible kidney transplantation from an anti-hepatitis C virus antibody-positive RNA-negative donor into an anti-hepatitis C virus antibody-negative recipient. *Transpl Int.* 2014; 28:127–128.
11. Suryaprasad A, Basavaraju SV, Hocesvar SN, et al. Transmission of hepatitis C virus from organ donors despite nucleic acid test screening. *Am J Transplant.* 2015;15:1827–1835.
12. Ison MG. Nucleic acid testing of organ donors: is the glass half empty or half full? *Am J Transplant.* 2015;15:1743–1745.
13. KDIGO clinical practice guideline for the care of kidney transplant recipients. Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group. *Am J Transplant.* 2009; 9 (Suppl 3): S1–155.
14. Nicot F, Kamar N, Mariamé B, et al. No evidence of occult hepatitis C virus (HCV) infection in serum of HCV antibody-positive HCV RNA-negative kidney-transplant patients. *Transpl Int.* 2010;23:594–601.
15. Vento S, Cainelli F, Longhi MS. Reactivation of replication of hepatitis B and C viruses after immunosuppressive therapy: an unresolved issue. *Lancet Oncol.* 2002;3:333–340.
16. Melisko ME, Fox R, Venook A. Reactivation of hepatitis C virus after chemotherapy for colon cancer. *Clin Oncol (R Coll Radiol).* 2004;16: 204–205.
17. Zekri AR, Mohamed WS, Samra MA, et al. Risk factors for cytomegalovirus, hepatitis B and C virus reactivation after bone marrow transplantation. *Transpl Immunol.* 2004;13:305–311.
18. Melon S, Galarraga MC, Villar M, et al. Hepatitis C virus reactivation in anti-hepatitis C virus-positive renal transplant recipients. *Transplant Proc.* 2005;37:2083–2085.
19. Lee WM, Polson JE, Carney DS, et al. Reemergence of hepatitis C virus after 8.5 years in a patient with hypogammaglobulinemia: evidence for an occult viral reservoir. *J Infect Dis.* 2005;192:1088–1092.
20. Lin A, Thadareddy A, Goldstein MJ, et al. Immune suppression leading to hepatitis C virus re-emergence after sustained virological response. *J Med Virol.* 2008;80:1720–1722.
21. Carreño V. Seronegative occult hepatitis C virus infection: Clinical implications. *J Clin Virol.* 2014;61:315–320.
22. Ghany MG, Strader DB, Thomas DL, et al. Diagnosis, management, and treatment of hepatitis C: an update. *Hepatology.* 2009;49:1335–1374.
23. Coilly A, Samuel D. Pros and cons: usage of organs from donors infected with hepatitis C virus—revision in the direct-acting antiviral era. *J Hepatol.* 2016;64:226–231.