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Cardiac transplantation from non-viremic hepatitis C donors

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BACKGROUND: Hepatitis C (HCV) donors are rarely used for cardiac transplantation due to historically poor outcomes. In 2015, nucleic acid testing (NAT) for viral load was added to the routine work-up of organ donors, allowing for the distinction between subjects who remain viremic (HCV Ab^+/NAT^+) and those who have cleared HCV and are no longer viremic (HCV Ab^+/NAT^-). The American Society of Transplantation recently recommended that HCV Ab^+/NAT^- donors be considered non-infectious and safe for transplantation. We present our initial experience with such donors.

METHODS: All patients were counseled regarding donor HCV antibody (Ab) and NAT. Transplant recipients were tested post-transplant at 1 week and at 1, 3, and 6 months for HCV seropositivity and viremia. We also analyzed the UNOS database to determine the potential impact of widespread acceptance of HCV Ab^+/NAT^- organs.

RESULTS: Fourteen HCV Ab^- subjects received hearts from HCV Ab^+/NAT^- donors in 2017. Over a median follow-up of 256 (192 to 377) days, 3 patients developed a reactive HCV Ab, yet none had a detectable HCV viral load during prospective monitoring at any time. Analysis of the UNOS database for the calendar year 2016 revealed that only 7 (3%) of 220 HCV Ab^+/NAT^- donors were accepted for heart transplantation.

CONCLUSIONS: We have demonstrated the feasibility of utilizing HCV Ab^+/NAT^- donors for cardiac transplantation without recipient infection. A small percentage of recipients developed HCV Ab without evidence of viremia, possibly consistent with a biological false reactive test, as has been seen in other settings. Large-scale validation of our data may have a significant impact on transplantation rates.
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One hundred eighty-five million people worldwide and 3.6 million in the United States are infected with the hepatitis C virus (HCV).[1,2] HCV has a parenteral route of transmission and is highly infective, as exemplified by a nearly

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100% rate of transmission from blood transfusions.[3] Therefore, in the case of organ transplantation from an HCV-infected donor to an HCV-negative recipient, viral transmission is expected. In the early 2000s, due to severe organ shortage, cardiac transplantation from HCV-positive donors was explored. The experience from this era revealed an increased risk of mortality and accelerated coronary allograft vasculopathy (CAV) and, until more recently, HCV-positive donors have largely been declined.[4,5]

Exposure to HCV causes reliable production of a non-neutralizing anti-HCV antibody (Ab). Recently, rapid testing for HCV viral load via nucleic acid testing (NAT) has become available and is now routinely used in donor screening.[6] It is well documented that approximately 25% of individuals clear HCV spontaneously and NAT allows for the important distinction between those donors who remain viremic and those who are no longer viremic.[7] Unlike other viruses, such as hepatitis B, HCV is not thought to have a latent form and therefore it is reasonable to presume that donors with positive Ab but undetectable viral load (HCV Ab^+/NAT^-) have cleared the infection and are not at risk of transmitting the disease.[8] In fact, there has been a recent call to action for the use of HCV Ab^+/NAT^- donors, as they are considered non-infectious, a position also supported by the American Society of Transplantation.[9,10]

Based on these circumstances, in January 2017 we convened a meeting of our heart transplant team, infectious disease experts, and hepatologists. The members universally agreed that the current state of knowledge supported that the risk benefit/ratio of cardiac transplantation using HCV Ab^+/NAT^- donors was not materially different from that using donors who met standard Public Health Services (PHS) increased risk criteria.[6] Consequently, we decided to change our donor selection criteria to accept such donors with recipient consent similar to that in PHS increased risk donors.

In the current analysis, we present our initial experience with cardiac transplantation using recipients of HCV Ab^+/NAT^- hearts. In addition, we examined the United Network for Organ Sharing (UNOS) database to estimate the potential increased donor supply if such a strategy could be proven safe and universally adopted.

Methods

Patients

Effective March 1, 2017, we amended our donor selection criteria to include HCV Ab^+/NAT^- donors within a category equivalent to PHS increased risk. HCV Ab^+/NAT^- donors were only considered if they did not have a history of treatment for HCV (i.e., spontaneous vs treated clearance). Donors with treated HCV were excluded due to the possibility that coronary artery endothelial dysfunction may have developed over an unknown viremic period before treatment and viral clearance. In contrast, it is presumed that spontaneous clearance occurs within 6 months of viral transmission.[11–14] All subjects, active on the waiting list, were informed of the protocol change and were given the option to consider such donors. If and when an appropriate match was found with an HCV Ab^+/NAT^- organ, the recipient was once again counseled and we proceeded only after informed consent. As part of the protocol, all recipients are tested at or about 1 week and then 1, 3, 6, and 12 months after transplant for HCV seropositivity and viremia. The institutional review board at the Montefiore Medical Center approved analysis of the data yielded from this clinical protocol.

Assessment of hepatitis C

As per UNOS guidelines, all donors are required to have assessment of HCV Ab and NAT status. HCV Ab and NAT of donors is performed at a central lab specified by the local organ procurement organization. At our institution, HCV is assessed via a chemiluminescent immunoassay (Abbott), where a signal-to-cut-off (S/C) ratio of <0.8 is consider non-reactive, 0.8 to 1.0 is equivocal, and >1.0 is reactive. HCV viral load (quantitative viral RNA) is assessed by HCV testing (COBAS AmpliPrep/COBAS TaqMan HCV Test, v2.0; Roche Diagnostics), which utilizes a real-time polymerase chain reaction with a lower limit of detection of 15 IU/ml.

Estimation of potential suitable hepatitis C NAT^- donors

We analyzed the nationwide Organ Procurement and Transplant Network database, managed by UNOS, to determine the number of donors who were made available from January 1, 2016 to December 31, 2016. These donors were then stratified according to HCV status, that is, HCV Ab and NAT positive or negative. All HCV Ab^+/NAT^- donors were compared with HCV Ab^-/NAT^- donors for characteristics and subsequently analyzed for cause of non-recovery. No separate informed consent was required given that the UNOS data are de-identified, publicly available, and used in compliance with the UNOS data user agreement.

Statistical analysis

Due to non-normal distributions, continuous variables are expressed as median and range and categorical variables are expressed as number of patients (% of total). Continuous variables were compared using the Wilcoxon rank sum test and categorical variables were compared using the chi-square test. Heart utilization rates for HCV Ab^+/NAT^- and HCV Ab^-/NAT^- were also compared using the chi-square test.

Results

Between March 1 and November 1, 2017, 14 recipients underwent heart transplantation from an HCV Ab^+/NAT^- donor. The median cohort age was 49 (19 to 71) years, 36% were female, 71% were bridged from a left ventricular assist device (LVAD), and 71% were UNOS listing Status 1A at time of transplant. The median total wait time for transplantation was 164 (9 to 1,666) days; however, after changing consent to agree to a HCV Ab^+/NAT^- donor, the median wait time was 63 (4 to 150) days. Eighty-six percent were from local donors (Region 9). Before transplant, all patients had a negative HCV viral load. Two of the 14 patients, both with LVAD, at one point had a HCV Ab that