Transplantation of Hepatitis C-Infected Kidneys into Uninfected Recipients: A Review of the Literature

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INTRODUCTION

There is a severe shortage of available deceased donor kidneys for transplantation. In 2018, kidney transplants totaled 22,393, of a national waiting list of 78,675. Only 58% of patients removed from the waitlist were done so for transplant; the remaining 42% were removed due to death or because they became too ill for transplant.[1] Annual waitlist mortality is 5–7% annually, and increases with age and comorbidities such as diabetes. As our population ages and the average age on the waitlist increases, this mismatch of kidney supply and demand continues to grow. One rising source of deceased donor kidneys is from donors with overdose- related death. The opioid crisis in the United States is associated with both increasing rates of hepatitis C as well as overdose-related deaths. Overdose-related death accounted for only 1.1% of all donors in 2000 but 13.4% in 2017, and tended to be younger, and more likely to be infected with hepatitis C virus (HCV).[2] A recent advisory from the Centers for Disease Control and Prevention Health Alert Network revealed an accelerated increase in opioid overdose deaths during the COVID-19 pandemic.[3]

In the United States, patients on dialysis have a mortality rate that exceeds 20% during the first year of dialysis and 50% after 5 years. The prevalence of chronic kidney disease has steadily risen from 2000-2018.[4] Following kidney transplantation, most patients receive a doubling in their life expectancy.[5] Given the rise in opioid-related deaths, the prevalence of hepatitis C and the shortage of kidneys in the donor pool, a critical assessment of the criteria for transplantation is necessary. In the last ten years, there have been a few noteworthy changes that affect our understanding of high-risk organs. First, the use of nucleic acid amplification testing to detect viral load, and second, the development of direct-acting antiviral medications targeted against hepatitis C.

NUCLEIC ACID AMPLIFICATION TESTING

In 2015, the US Organ Procurement and Transplant Network (OPTN) mandated routine qualitative HCV nucleic acid testing (NAT) in all organ donors.[6] Nucleic acid amplification testing can be used to reveal viremia in a serologically negative patient, and is routinely performed for HIV-1 and HCV in blood donors in the United States.[7] Standard serology testing for HCV becomes positive ~70 days following infection, ~40 days with enhanced serology testing, and in 3–5 days with nucleic acid testing. This testing has allowed the creation of a new category of HCV donors, based on combined Ab and NAT results.[6] Both HCV Ab+/NAT+ and HCV Ab-/NAT+ donors are considered HCV positive. Donors who are HCV Ab–/NAT– are usually deemed negative.

There are a few conditions in which a person may be HCV Ab+/NAT– including a false positive HCV antibody test, testing during the window period, donors with previous HCV infection who are in the process of clearing the virus while on therapy or have cleared the virus. The most common condition for HCV Ab+/NAT– appears to be prior HCV infection with spontaneous immunologic viral clearance.[8] The incidence of spontaneous immunologic clearance is estimated to be around 25% based on a 2006 systematic literature review.[9]

There is a window period which may occur if a donor dies of an intravenous drug overdose and the serologic testing is done a few days after the exposure, for example. In this case the Ab may be positive from prior exposure but NAT may not yet be positive from this exposure, leading to HCV Ab+/NAT–. Or if the donor was never previously exposed, they may be HCV Ab–/NAT–. Alternatively, if there was no prior exposure, and testing was after the 3-5 day period, the donor would be HCV Ab-/NAT+.

In a retrospective review published in the American Journal of Transplantation in 2019, short-term outcomes of adult deceased donor kidney transplants of HCV uninfected recipients were compared with either HCV Ab+/NAT- or HCV Ab+/NAT+. In this study, data was analyzed from the OPTN STAR files from the United Network of Organ Sharing (UNOS), which includes data submitted by members on all donors, waitlisted candidates and transplanted recipients. Patients were included from January 2015 to June 2018, were over the age of 18, and underwent deceased donor kidney transplantation (DDKT). Patients receiving simultaneous kidney-pancreas or other multiorgan transplants were excluded. The primary outcomes were length of stay, delayed graft function, rejection rate, serum creatinine at 6

months post transplant. Delayed graft function was defined as requiring dialysis in the first week post transplant. Secondary outcomes included overall graft and patient survival at 12 months. There were 42,240 DDKT recipients studied, with 33,934 DDKT from HCV-uninfected donors to HCV-uninfected recipients, 352 from HCV Ab+/NAT– donors to uninfected recipients and 196 HCV Ab+/NAT+ donors to uninfected recipients. There was no statistical difference in overall graft survival among the three groups. For HCV Ab+/NAT-, there was no difference in length of stay, rejection rate or serum creatinine. Finally, there was no statistically significant difference in overall graft survival at 12 months post transplant. For HCV Ab+/NAT+ donors to uninfected recipients, there was actually a lower proportion of delayed graft function and decreased serum creatinine at 6 months. There was no difference in graft survival. When compared to the reference group (HCV uninfected donors), uninfected recipients of HCV viremic donors had a shorter time on the transplant waitlist and dialysis and a lower KDPI (kidney donor profile index) score. Lower KDPI score reflects an overall better quality donor kidney. These findings are profoundly clinically relevant, in demonstrating non-inferior outcomes with HCV positive organs. A major limitation of the study was that the use of a direct acting antiviral was not included.[10]

Many single center studies have evaluated the rate of transmission of HCV from HCV Ab+/NAT– to an HCV Ab- recipient, with almost all studies reporting a zero rate of transmission. The largest of this type of study comes from the University of Cincinnati published in 2019, which analyzed the incidence of HCV transmissions and clinical outcomes in HCV-naive kidney transplant recipients who received allografts from HCV Ab+/NAT- donors. The primary outcome was incidence of HCV transmission at 3-months post transplant. For recipients who developed HCV viremia post-kidney transplant, direct-acting antiviral therapy was initiated. Secondary outcomes included post-kidney transplant graft function, graft survival, and patient survival at time of follow-up. During the study period of July 2016 to February 2018, 163 deceased donor kidney transplants occurred with 52 kidneys (32%) from HCV Ab+/NAT– donors to HCV negative recipients. There was a single potential transmission identified. In this one case, the donor was tested at day 2 and found to be NAT- and was transplanted. The recipient returned with HCV RNA positivity, so samples from the donor taken from hospital day 4 were sent for NAT and found to be positive. In this case, the donor likely became infected shortly before his death, which put him just before the capability for NAT detection, in the window period. This would indicate a 1.69% transmission incidence.[6]

Interestingly, national surveys conducted by Kucirka and colleagues found that providers were more likely to consider a high-risk organ if NAT was performed. When HCV NAT was performed, there was a 2.69 fold higher odds of utilizing high- risk donors. It could be concluded that performing this test may influence provider bias about high-risk organs.[11]

DIRECT-ACTING ANTIVIRAL THERAPY

The advent of HCV direct-acting antivirals (DAAs) has allowed for new protocols to be studied in HCV recipients. These allow for treatment of both patients with ESRD and those post transplant. There are currently several choices, and they are frequently used in combination. There are many trials using different agents, administered at different timing, and for varied duration of treatment. Detailed below are a few representative trials with very promising results.

Elbasvir/grazoprevir was studied in genotype 1 infected patients in the C-SURER trial and the pangenotypic combination of glecaprevir/pibrentasvir in the EXPEDITION 4 trial. Both demonstrated excellent safety and efficacy in those with ESRD, including those on dialysis. Elbasvir/grazoprevir for 12 weeks resulted in a sustained viral response of 99%, and a response of 100% seen with glecaprevir/pibrentasvir for 12 weeks.[8]

The THINKER clinical trial at the University of Pennsylvania demonstrated excellent allograft function and cure of HCV infection in 10 HCV negative patients who received kidney transplants infected with genotype 1 HCV. All recipients had detectable HCV RNA on post-operative day 3, had elbasvir/grazoprevir initiated, and by 12 weeks had sustained viral response.[12] Twelve-month follow-up of 20 such patients demonstrated HCV cure and comparable allograft function to matched HCV-negative recipient controls for all recipients.[13]

A clinical trial at Johns Hopkins University evaluated the transplantation of HCV+ donors into negative recipients in combination with direct-acting antivirals as both pre- and post-transplant prophylaxis. Each recipient received grazoprevir/elbasvir prior to transplantation and continued with daily therapy for 12 weeks. Three patients also took sofosbuvir due to their strain of HCV. In 7 out of 10 recipients, HCV RNA was undetectable at all times. No participant had virologic or clinical evidence of chronic HCV infection with a follow-up period of 12 weeks after the discontinuation of DAA and there were no adverse events related to treatment.[14]

Furthermore, there is an ongoing trial now evaluating the safety of HCV+ organ donation with DAA therapy with a shortened course. Thirty HCV negative patients were enrolled in the trial and received HCV Ab+/NAT+ lung, kidney, heart, or kidney-pancreas transplants. All recipients received a single dose of ezetimibe and glecaprevir/pibrentasvir before transplant and once a day for 7 days after surgery. While low-level viremia was transiently detected in 21 of 30 patients, all 30 transplant recipients had undetectable HCV RNA at 12 weeks post transplant.[15]

ADDITIONAL CONSIDERATIONS

The cost of treatment with DAA therapy versus waiting for a HCV Ab- donor was analyzed by Gupta and colleagues in 2018. The group compared renal transplantation from an HCV+ donor into an HCV recipient followed by immediate DAA therapy versus HCV recipients continuing dialysis and waiting for renal transplantation from an HCV donor, over a 5-year time frame. Estimates of cost were determined by Medicare reimbursements or kidney transplant Diagnosis-Related Groups and corresponding provider costs. Their model estimated that patients receiving HCV+ organs and undergoing DAA therapy resulted an estimated $190,000 less cost compared to continuing hemodialysis.[16]

The discussion of HCV+ kidney offers with potential transplant recipients continues to evolve. As we have more data about donor and recipient status, as well as growing prior experience, we can be more specific in approach and counseling. Transplantation of HCV+ into HCV- recipients is currently only performed under research protocols, and very clear informed consent is obtained for participation. As this practice may transition from clinical trials to standard clinical practice, this discussion will need to become part of the routine transplant consent process, as transplant outcomes using HCV+ kidneys in the current DAA era are comparable.

FURTHER DISCUSSION

Outcomes from hepatitis C antibody positive donors, either viremic or not, appear to be as good as hepatitis C negative organs in terms of length of stay, rate of rejection, serum creatinine and 12-month rates of graft survival. Additionally, the rate of transmission from a NAT-donor remains exceedingly low with a single case report of transmission. In patients that do seroconvert from hepatitis C negative to positive, there are multiple drug therapies that exist that create sustained virologic response and are well tolerated in this patient population.

With this promising data, many questions remain, including the timing of administration of direct-acting antiviral medications – pre-exposure, post-exposure, or even delayed. Additional factors, including insurance coverage of direct-acting antiviral therapy are an important consideration. Perhaps in the future, hepatitis C organ donation may become the accepted standard practice in renal transplantation and for other organs as well.

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