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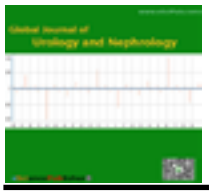

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Hepatitis C positive donor kidney transplants to decrease wait time for kidney recipients: Review of data and recent trials

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ABSTRACT

A kidney transplant is superior to dialysis for patients with end-stage renal disease. The increasing number of end-stage renal disease patients and limited number of available donor kidneys have led to long waiting times to receive a life-saving kidney transplant. Approximately, 14% of the patients wait for more than five years to receive a kidney transplant. The risk of death and becoming too sick to receive a transplant while on the waitlist poses another healthcare challenge. About 21% of the patients are removed from the waitlist every year without receiving a kidney transplant. Over time many strategies are being proposed and used to eliminate the shortage of kidney organs. The advent of the novel therapy for HCV infection and the increasing number of HCV infected donor kidneys due to the unfortunate opioid epidemic has provided new opportunities for kidney recipients. More than 500 high-quality HCV positive donor kidneys are discarded every year. The recent trials of HCV positive donor kidney transplants to HCV negative recipients followed by successful HCV treatment are very motivating. The studies have illustrated that the quality of HCV positive donor kidneys are very similar or even better than HCV negative donor kidneys. HCV positive donor kidney transplants will shorten wait-time for kidney transplant recipients and save lives.

Keywords: HCV infected kidney transplant, HCV positive kidney transplant, Underutilized HCV positive donor kidneys.

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Introduction:

Kidney transplant is a life-saving option for patients with end-stage renal disease (ESRD). When comparing to dialysis, kidney transplant is a superior option that increases longevity, provides a better quality of life, and reduces health care costs. Unfortunately, wait time for a kidney transplant has been increasing where about 14% listed patients wait for more than five years. At the same time, more than 500 high-quality kidneys from HCV positive donors are being discarded every year. The advent of Direct-Acting Antivirals (DAAs) has revolutionized HCV therapy with a cure rate of >95%. Recent trials where transplant centers have successfully transplanted HCV positive donor kidneys to HCV negative recipients are encouraging. Increasing the use of HCV positive donor kidneys can provide opportunities to recipients with longer wait-times. This paper will review transplant data, availability of HCV positive donor kidneys, curative therapy for HCV infection, recent trials and outcomes, risks, benefits, and future directions while utilizing HCV positive donor kidneys for HCV negative recipients.

Kidney transplant and HCV positive donors:

Based on the data review from Organ Procurement & Transplantation Network (OPTN) as of August 2019, more than 124,000 patients are waiting for an organ transplant. Out of these patients, 103,000 (83%) are waiting for kidney transplants and 1,700 (1.4%) patients waiting for combined kidney and pancreas transplant [1] (Table 1).

On average, 15,000 (14%) patients wait for kidney transplants for more than 5 years and another 18,000 (18%) wait for 3 to 5 years. The majority of the patients (21,000; 21%) wait for 1-2 years to obtain a life-saving kidney transplant. About 41,000 patients were removed from the kidney transplant list in 2018. Fortunately, the majority of them were removed for a good cause after a kidney transplant such as 14,000 after deceased donor kidney transplant and 6,400 after a living donor kidney transplant [1] (Table 2). However, 4,100 (10%) patients died in 2018 while waiting for a kidney transplant and another 4,500 (11%) patients became too sick to transplant and were taken off the list. Per OPTN data, for every 1,000 persons who received a kidney transplant, 328 eligible persons died while waiting for a transplant. On average 11 to 13 people die each day while waiting for a life-saving kidney transplant [1] (Table 3).

Similar to 2018, around 14,000 persons received a deceased donor kidney transplant in 2017. In 2017, there were 775 HCV positive donor kidneys available for transplant. Since 1995, 3,562 HCV infected kidneys have been discarded in the United States reaching a discard rate of 53.6% compared to 22.4% for HCV negative donor kidneys. Annually, up to 500 high-quality kidneys are discarded from HCV positive donors. However, only 29% of HCV positive recipients receive kidney procured from HCV positive donors [2].

Increasing number of HCV positive donors:

The opioid epidemic has led to a three-fold increase in deaths related to drug overdose that has further increased the number of HCV positive donors. According to all admissions reported to the Treatment Episode Data Set (TEDS) from 2004 to 2014, admissions due to an IV drug use increased to 76%, heroin injection increased to 85%, and prescription opioid analgesic (POA) injection increased to 258%. In the United States from 2004 to 2014, there were 12,953 acute HCV infection cases reported to the National Notifiable Disease Surveillance System showing an overall 133% rate increase [3]. According to Li et al., HCV positive donors increased from 3% in 2000 to 7% in 2016. However, HCV positive organs procured per donor rate (2.28) and transplant per donor (1.61) remained lower than HCV negative organs with a procured per donor rate of 3.64 and transplant per donor rate of 3.16[4].

In 2017 out of all 775 HCV positive kidneys, 474 kidneys were HCV antibody (HCV Ab) positive and Nucleic acid test (NAT) positive, 272 were HCV Ab positive and NAT negative, and 29 were

HCV Ab negative and NAT positive. According to OPTN/UNOS, about 67% of HCV Ab positive donors are also NAT positive [1].

Cure of HCV:

The advent of Direct-Acting Antivirals (DAAs) has reformed HCV therapy with a cure rate of more than 95%. DAA drugs target specific nonstructural proteins of the virus and lead to disruption of viral replication and infection. There are 4 classes of DAA defined based on their mechanism of action and therapeutic targets. The Protease inhibitors (Telaprevir, boceprevir) and NS5A nucleoside polymerase inhibitors (Daclatasvir and Ledipasir) target RNA translation and poly-protein processing. Whereas, non-nucleoside protease inhibitors (Deleobuvir, Filibuvir) and NS5B polymerase inhibitors (Sofosbuvir and Mericitabine) target RNA replication [5].

Table 1: Organ transplant waitlist based on the data retrieved from OPTN on August 1, 2019.

All Organs	Kidney	Liver	Pancreas	Kidney/Pancreas	Heart	Lung	Heart/Lung
124,544	103,608	13,384	836	1,704	3,810	1,444	45

Table 2: Wait- time for kidney transplant, data retrieved from OPTN on August 1, 2019.

Times	All Organs	Kidney
< 30 Days	4,995	3,429
30 to < 90 Days	8,603	6,212
90 Days to < 6 Months	11,649	8,849
6 Months to < 1 Year	18,421	14,694
1 Year to < 2 Years	25,493	21,283 (21%)
2 Years to < 3 Years	17,293	15,135
3 Years to < 5 Years	20,820	18,602 (18%)
5 or More Years	17,270	14,864 (14%)

Table 3: The reason for patient removal from the kidney transplant wait-list, data retrieved from OPTN on August 1, 2019.

KIDNEY	2019	2018
All Removal Reasons	20,970	40,787
Deceased Donor Txp	7,993	14,725
Living Donor Txp	3,381	6,434
Txp in another country	37	60
Died	1,710	4,132
Too Sick to Txp	2,155	4,480

Recent Trials and outcomes:

The treatment of HCV positive recipient and outcomes are very promising based on the reported data from recent trials such as Transplanting Hepatitis C Kidneys Into Negative KidnEy Recipients (THINKER), Exploring Renal Transplants Using Hepatitis C Infected Donors for HCV Negative Recipients (EXPANDER) and THINKER 2 trial.

In the THINKER trial, Reese et al transplanted 10 HCV negative recipients with HCV positive kidneys using only HCV genotype-1 kidneys. The recipients were treated when they experienced seroconversion. They achieved a 100% sustained virological response (SVR) with 12 weeks of Direct-Acting Antiviral (DAA) therapy [6]. Similarly, in EXPANDER trial Durand et al, transplanted 10 HCV positive kidneys into HCV negative recipients using HCV genotype 1 and 3 kidneys and achieved 100% SVR with DDA therapy [7].

In the THINKER2 trial Reese et al. transplanted an additional 10 HCV positive kidneys using their prior protocol. In this study, they evaluated the estimated glomerular filtration rate (eGFR) at six and twelve months and physical and mental scores as a measure of life quality. When compared eGFR with matched allocation KDPI kidney transplants, the results were very similar or better at 6 months (Trial patients 67.5 ml/min/1.73 m^2 vs 56.6 ml/min/1.73m^2 for matched KDPI comparators) and 12 months (Trial patients 72.8 ml/min/1.73 m^2 vs 57.7 ml/min/1.73m^2 for matched KDPI comparators) [8].

They further assumed these donors as non-HCV and recalculated their KDPI and compared with matched optimal KDPI comparators and found similar results at 6 months (Trial patients 67.5 ml/min/1.73 m^2 vs 66.2 ml/min/1.73m^2 for matched optimal KDPI comparators) and 12 months (Trial patients 67.5 ml/min/1.73 m^2 vs 67.2 ml/min/1.73m^2 for matched optimal KDPI comparators). The trial patients experienced a decrease in mean PCS (RAND-36 Physical Component Summary) and MCS (Mental Component Summary) quality of life scores at 4 weeks interval but overtime increased to above Pre-Transplant values by 12 months [8].

Underutilization of HCV positive Donor Kidneys:

Despite promising results from these studies and revolutionized HCV therapy, transplant from HCV positive donors to negative recipient is going down. When compared pre-DAA era (before 2014) with the post-DAA era (after-2014), kidney transplant rate from HCV-positive donor to HCV-negative recipient decreased from 4.67 to 2.89 [4].

The reason for underutilization appears to be multifactorial. The transplant centers might be reluctant to use HCV kidneys due to historical poorer outcomes from HCV therapy (interferon) and lower graft quality. However, a recent study showed similar grafts survival of HCV Ab (+)/NAT(+) kidney transplants when compared with KDPI-matched Ab (-)/NAT(-) controls [8]. The centers might speculate that HCV-positive kidneys are procured from older individuals and not deemed suitable for transplant. However, as previously described the average age of HCV positive donors declined to as low as 35 years in 2016 [3]. One may be concerned that HCV donors who die from a drug overdose and might have experienced prolonged anoxic making donor kidneys less viable. On the contrary, many of the US centers are now using PHS high-risk kidneys but this needs further investigation. The concern of concomitant risk for other blood-borne pathogens like HIV and hepatitis B virus is also valid because these are treatable but not curable. In general, donors are tested for a battery of infectious diseases but HIV, HBV, and HCV pose challenges due to their window period and risk of falsely negative results.

Window Period and Risk of infection transmission:

The window period for HIV is 17-22 days with standard serology, 7-16 days with enhanced serology, and 5-6 days with nucleic acid testing (NAT). For HCV, the window period is around 70

days with standard serology, 40-50 days with enhanced serology, and 3 - 5 days with NAT. HBV window period is 35-44 days with standard serology and 20-22 days with NAT testing. The estimated risk of window period infection for HCV is 3% with a standard serology and 0.32% with NAT from IV drug users, 0.33% with a standard serology and 0.04% with NAT from men who have sex with men (MSM), 1.2% with a standard serology and 0.1% with NAT from sex workers, and 0.07% with standard serology and 0.01% with NAT from incarcerated donors [9].

According to Pereira et al, with transplants from HCV Ab positive and NAT positive to HCV negative recipient, 14-100% recipients tested positive for HCV antibodies and 57-96% tested positive for HCV RNA by PCR [10]. As per Bixler et al., from 2014- 2017, there was no HIV transmission from Organ transplants, 20 cases of HCV transmission from donors with negative NAT (8 kidney recipients), and 7 cases of HBV transmission (one kidney recipient) [11].

Benefits of HCV positive donor kidney transplants:

The donor age is an important factor for graft survival. As noted with opiate endemic the increased number of HCV positive donor kidneys are available from younger individuals with a median age of 35 years for viremic donors [3]. Therefore, HCV positive donor kidneys are expected to have better graft survival but pending long term data. The recipients who elect to accept HCV positive kidneys will be transplanted faster than otherwise waiting for a long time on the waitlist and avoiding the risk of death while waiting for a life-saving kidney transplant.

The cost-effective analysis by Gupta et al is encouraging. In their 5-yrs cost-effective analysis, HCV Donor positive and recipient negative kidney transplant followed by treatment resulted in an expected 4.8 years of life with the cost of approximately $138,000 compared to an expected 4.7 years of life with a cost of $329,000 for HCV donor negative and recipient negative transplant [12].

Challenges and Future Directions:

The biggest obstacle is financial reimbursement for DAA therapy. The majority of the Center doing HCV positive donor kidney transplants are either pooling costs from research or funds from the hospital. Similarly, long-term data is needed to provide directions for treatment timing (preemptive or after seroconversion).

Incorporation of HCV positivity in the current KDPI calculation provides a speculation of inferior kidneys to transplant; whereas, in contrast, these kidneys come from younger individuals with better graft survival. Based on kidney qualities and current data of DAA outcomes, KDPI calculation will likely require a revision.

Conclusion:

Kidney transplant provides a better quality of life and longevity to the end-stage renal disease patients. However, due to the scarcity of kidney organs, either the patients wait for many years or taken off the list due to death or sickness where they become ineligible for a kidney transplant. Approximately, 21% of the patients are removed from the waitlist every year without receiving a kidney transplant. Many strategies are being proposed and used to eliminate the shortage of kidney organs including HCV positive donor kidney transplants to HCV negative recipients. This became possible with the help of novel curative therapy for HCV infection and the increasing number of HCV infected donor kidneys due to the unfortunate opioid epidemic. The recent trials of HCV positive donor kidney transplants to HCV negative recipients followed by successful HCV treatment are very encouraging. Based on recent study findings, quality of HCV positive donor kidneys are very similar or even better than HCV negative donor kidneys. HCV positive donor kidney transplants will shorten wait-time for recipients and save lives but we need more guidelines on treatment timing and upfront insurance approvals for direct-acting antiviral therapy in this patient population.

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References:

1. Organ Procurement and Transplant Network, OPTN Data, August 2019. Optn.tranplant.hrsa.gov/data.
2. Kucirka LM, Singer Al, Ros RL et al. Underutilization of hepatitis C-positive kidneys for hepatitis C-positive recipeints. Am J Transplant. 2010;10:1238-46.
3. Zibbell JE, Asher AK, Patel RC et al. Increases in acute hepatitis C virus infection related to a growing opioid epidemic and associated injection drug use, US, 2004 to 2014. Am J Public Health. 2018;108:175-81,
4. Li AA, Cholankeril G, Cheng XS et al. Underutilization of Hepatitis C virus seropositive donor kidneys in the United States in the current opioid epidemic and Direct-Acting Antiviral Era. Disease. 2018,6,62;doi:10.3390.
5. Pockros PJ et al. Clin Pharmacol Ther. 2014; 95:98.
6. Reese PP, Abt PL, Blumber EA et al. Transplanting hepatitis C-positive kidneys. N Engl J Med. 2015; 373: 303-305.
7. Durand CM, Bowring MG, Bair N, et al. Direct-acting ativiral prophylaxis in kidney transplantation from hepatitis C virus-infected donors to non-infected recipients: an open label non-randomized trial. Ann Intern Med. 2018;168:533-40.
8. Reese PP, Abt PL, Blumber EA, et al. Twelve-month outcomes after transplant of hepatitis C-infected kidneys into uninfected recipients. A single group trial. Ann Inern Med. 2018:169:273-81.
9. OPTN/UNOS Ad Hoc Disease Transmission Advisory Committee, briefing paper on guidance on explaining the risk related to the use of PHS increased risk donor organs when considering organ offers. June 2017.
10. Pereira BJ, Wright TL, Schmid CH, et al. A controlled study of hepatitis C transmission by organ transplantation. The New England Organ Bank Hepatitis C study group. Lancet. 1995;345:484-7.
11. Bixler D, Annambholta P, Abara WE, et al. hepatitis B and C virus infections transmitted through organ transplantation investigated by CDC, United States, 2014-2017. Am J Transplant. 2019; 19(9): 2570–2582.
12. Gupta G, Zhang Y, Carroll N, et al. Cost-effectiveness of hepatitis C-positive donor kidney transplantation for hepatitis C-negative recipients with concomitant direct-acting antiviral therapy. Am J Tranplant. 2018:18:2496-2505.