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Balancing the risk and rewards of utilizing organs from Hepatitis C viremic donors

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Abstract

Purpose of review: Because of long waitlist times and high waitlist morbidity and mortality, strategies to increase utilization of Hepatitis C viremic deceased donor organs are under investigation in kidney, liver, heart and lung transplantation.

Recent findings: Direct-acting antiviral medications for Hepatitis C virus infection have high cure rates and are well tolerated. Small, single-center trials in kidney and heart transplant recipients have demonstrated that with early post-transplant direct-acting antiviral therapy, 100% of uninfected recipients of Hepatitis C viremic organs have been cured of infection after transplantation.

Summary: In this manuscript, we review the risks and rewards of utilizing Hepatitis C viremic organs for transplantation.

Keywords

Hepatitis C virus; Kidney transplantation; Direct-acting antivirals; Organ allocation

Introduction

According to the Organ Procurement and Transplantation Network (OPTN), hundreds of thousands of patients in the United States with end-stage organ failure waited for an organ transplant in 2018, with expected annual mortality rates up to 15%, depending on the type of organ failure (Table 1). Despite the fact that the prevalence of end stage heart failure, liver disease, kidney disease, and lung disease continues to soar, the number of annual transplants has remained relatively fixed over the last decade[1]. Due to the shortage of viable transplant organs in the U.S., and in accordance with the OPTN Final Rule, it is paramount that available resources are handled efficiently; and that all potentially transplantable organs are

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utilized to their maximum potential. Quality of life and survival benefit for patients with end stage organ failure who receive a well-functioning transplant is well established[2–4]. High morbidity and mortality among patients waiting for solid organ transplantation have sparked interest in strategies that will decrease unnecessary discard of potentially viable donors to increase organ allocation.

Despite over twenty years of experience transplanting HCV-infected donor liver or kidneys to HCV-infected recipients, HCV-infected donor organs are still discarded at high rates. In a survey of kidney donations between 1995 and 2009, 50% of 93,825 HCV-seropositive deceased donors were discarded[5]. The American Society of Transplantation Consensus Conference on the Use of HCV Donors in Solid Organ Transplantation has highlighted the urgent need for prospective investigation of the risks and benefits of using organs from hepatitis C-infected donors[6]. There is also tremendous interest in increasing utilization of HCV-seropositive donors without active HCV infection; these potential donors, who have a positive HCV antibody test, but no detectable plasma HCV RNA, have an extremely low risk of transmitting HCV infection. This review, however, will be based on balancing the risks and rewards of using HCV viremic donors, focusing only those with detectable plasma HCV RNA.

Effects of the Opioid Crisis on the Characteristic of Hepatitis C viremic donors

The dramatic rise in HCV-infected donors over the last five years in the United States has been largely driven by the increase in injection drug use (IDU). As the opioid epidemic sweeps the United States, the number of deceased donors attributed to drug intoxication has sharply risen[7]. Recent analyses show that HCV-infected kidneys typically come from younger donors with less comorbidities[7]. Because very few injection drug users (IDUs) are linked to care, most remain viremic despite the availability of curative DAA therapies. Thus, it is estimated that the HCV epidemic will continue to spread amongst young IDUs for the foreseeable future. HCV-positive donor organs, by virtue of their young age, may be among the most viable in the donor pool.

Risks of Hepatitis C viremic donors in the era of interferon-ribavirin based therapies

Traditional anti-HCV therapy has until recently depended on interferon-alpha, which was poorly tolerated and correlated with an increased risk of serious systemic side-effects[8–10]. Interferon therapy has also been associated with allograft rejection, which often necessitates treatment with an increase in net immunosuppression that can ultimately promote viral replication, setting off a vicious cycle. This concern over graft rejection has been one of the most formidable arguments against interferon use in the immediate post-transplant setting. Compounding their intolerability, interferon therapy also produced underwhelming sustained virologic response (SVR) rates[8].

HCV infection among liver transplant recipients was common, since end stage liver disease due to chronic hepatitis C was for many years the leading indication for liver transplantation. For liver transplant recipients treated with interferon-based regimens, SVR rates were disappointing, successful in less than half of patients, and periodically contributed to the development of chronic rejection[11–14]. Recurrence of cirrhosis in the allograft occurred in up to 20% of liver transplant recipients with HCV infection five years post-transplant[15].

Because of the high prevalence of infection in patients with end-stage renal disease (between 8–10% in the United States); HCV is also common after kidney transplantation, affecting between 5–15% of kidney transplant recipients in the developed world[16–18]. In kidney transplant recipients, the use of interferon-based therapies for HCV are associated with acute cellular rejection[8]. Moreover, HCV infection is associated with worse graft and patient survival in kidney transplantation[19–21].

Unfortunately, there are limited studies comparing outcomes in lung or heart transplant recipients with either pre-existing or *de novo* HCV infection. However, conclusions drawn from the era of interferon-based therapy suggested that HCV infection after heart or lung transplantation was associated with poorer allograft outcomes and an increased risk of graft rejection[22–29]. These early findings led to guidelines recommending that otherwise acceptable heart and lung donors be excluded on the basis of HCV infection[30].

Hepatitis C post-transplantation in the era of direct-acting antiviral therapies

Direct-acting antiviral therapies (DAAs) have revolutionized the management of HCV infection. DAAs target viral proteins essential for viral replication and do not rely on the host's immune response. Clinical trials and real-world data have demonstrated excellent cure rates in solid organ transplant recipients, indicating that immunosuppression does not compromise the effectiveness of DAAs. Pangenotypic combination regimens that effectively function against the six major HCV genotypes have been approved by the FDA[31, 32].

Clinical trials using DAAs in liver transplant and kidney transplant recipients have demonstrated excellent cure rates. The SOLAR-1 and SOLAR-2 trials included over 400 liver transplant recipients who were treated with sofosbuvir/ledipasvir and weight-based ribavirin; the HCV cure rates were 93–96%.[33, 34] Colombo *et al.* randomized 114 adult patients who were at least 6 months post kidney transplant with eGFR ≥40mL/min/1.73m^2 to receive either 12 or 24 weeks of sofosbuvir-ledipasvir 400mg/90mg combination therapy; all patients were cured[35]. In the MAGELLAN-2 trial, 80 liver transplant recipients and 20 kidney transplant recipients with genotype 1–6 HCV received glecaprevir-pibrentasvir and all but two liver transplant recipients (98%) were cured.[36] In 2018, Agarwal and colleagues used sofosbuvir combined with velpatasvir to treat 79 patients post-liver transplant with genotype 1, 2, 3, or 4 HCV; 96% achieved SVR12.[37] Additionally, many retrospective studies with sofosbuvir-based DAA regimens after kidney transplant have confirmed excellent "real-world" treatment success rates of approximately 95%[38, 39]. DAAs are well tolerated, and medication discontinuation rates have been low. In view of these high success rates for post-transplant treatment, a transplant waitlist patient who is HCV-infected and is

awaiting a deceased donor transplant should be offered the opportunity to accept an HCV-infected donor liver or kidney provided that will shorten their waitlist time; recent estimates suggest that approximately 6% of the kidney transplant waitlist is HCV infected[40].

Because the need for heart or lung transplant in HCV-infected adults is less common, results of large clinical trials in these populations are not available. However, there have been promising small case series of patients treated with DAAs following heart or lung transplantation, demonstrating that therapy was extremely well tolerated and led to excellent SVR rates[41–45].

Use of Hepatitis C viremic donors in uninfected recipients

The ability to cure HCV with DAAs has opened the door to clinical trials that investigate whether transplantation from actively viremic HCV-infected donors to HCV naïve recipients, managed with preemptive or post-transplant treatment with DAAs, can lead to viable patient and allograft outcomes. Because HCV is a non-retroviral RNA virus without a stable DNA intermediate or latent phase, a sustained virologic response is tantamount to permanent clearance of virus. Thus, the strategy of acceptance of an HCV-infected donor organ coupled with immediate DAA therapy may be a defensible strategy for persons interested in shortening their time on the waitlist.

Two published studies exist that have explored this strategy in HCV-uninfected kidney transplant patients. The THINKER-1 and 2 trials showed that HCV virus could be eradicated with a 12 week course of DAAs begun shortly after transplant (early reactive approach) of HCV RNA positive organs into recipients who do not have HCV infection[46]. Twenty patients without HCV were transplanted with kidneys from HCV genotype 1-infected donors and began elbasvir-grazoprevir at day 3 post-transplant. All patients had a negative HCV RNA by day 30 of therapy and 100% achieved SVR. Elbasvir-grazoprevir was well tolerated in the immediate post-transplant period. One patient developed focal segmental glomerulosclerosis (FSGS) in the transplanted kidney that was deemed possibly related to DAA therapy. The authors reported excellent one-year graft function[47, 48]. The EXPANDER-1 trial has reported successful cure of 10 HCV-infected kidney transplant recipients with preemptive HCV treatment beginning at the time of transplantation from a HCV-infected donor[49]. In this study, all genotypes were included and sofosbuvir was added to elbasvir and grazoprevir if the donor had genotypes 2, 3, 5, or 6.

Besides a few successful, single patient case reports and small series, there are no published large trials regarding the use of HCV viremic donors of livers, hearts or lungs for HCV uninfected recipients[50–54] Nevertheless, there are numerous current ongoing studies evaluating utilization of HCV-infected donors for these organs (Table 2)[55].

Utilizing a pan-genotypic DAA regimen to prevent HCV infection during transplantation

HCV genotyping can require extra time and logistical challenges during the time-pressured process of organ allocation. Using a pan-genotypic regimen streamlines this process and

maximizes the likelihood that all HCV-infected organs are effectively utilized. The daily, fixed-dose combination of co-formulated sofosbuvir (400 mg)/velapatasvir (100 mg) is similarly effective to its predecessor sofosbuvir/ledispasvir but can treat all genotypes of HCV. It is currently recommended as first-line therapy for treatment-naïve, noncirrhotic HCV infection for genotypes 1–6. Reported cure rates in the non-transplant setting range from 98 to 100%. Glecaprevir (300mg)/pibrentasvir (120mg) was more recently approved by the FDA in 2017. Reported cure rates are comparable to sofosbuvir/velpatasvir (in the 99% range in ENDURANCE-1). Glecaprevir/pibrentasvir, which is cleared hepatically, is the only pan-genotypic DAA regimen that is has been approved for patients with advanced kidney failure or on dialysis.[56] This is relevant in kidney transplantation (where a substantial proportion of deceased donor transplant recipients have delayed graft function)[57].

Since their initial approval, there has been a decline in the cost of DAAs, with pan-genotypic regimens now having wholesale cost of $26,000 – $50,000 for an 8-week course, a significant decrease from the initial $70,000 – $100,000 price. However, the cost of DAA therapy in the United States remains high, which is a challenge to insuring payers will cover post-transplant.

Choosing the right recipients and educating them on risks

Recipients should be selected according to likelihood of benefit due to shortened waitlist time and ability to strictly comply with DAA therapy; conversely, recipients with increased risk of early post-operative complications or disease recurrence that may interfere with DAA administration should be excluded. Educating HCV-uninfected patients and their family members about HCV infection and the risks of accepting an HCV viremic donor is extremely important. Organ specific considerations for regimen and patient selection are shown in Table 2.

Interactions with immunosuppression

Retrospective analysis of kidney transplant recipients receiving DAAs for HCV noted that nearly one-third needed adjustment in calcineurin inhibitor dose during or shortly after stopping DAA therapy, suggesting that close monitoring of calcineurin inhibitor levels is needed, particularly if treatment is occurring in the early post-transplant period[58–69]. Interactions between common immunosuppression and DAAs have been reviewed, however, little is known about the interaction between DAAs and novel or second-line immunosuppressive agents, such as belatacept, mammalian target of rapamycin inhibitors, rituximab, or the effect of plasmapheresis on DAA levels.

Risks related to acquisition of HCV infection through transplant

A summary of the risks that should be discussed with any potential recipient of an HCV-viremic kidney is shown in Table 3. It is necessary that treatment with DAAs begin early after transplant to prevent potential early complications of acute HCV, including the development of fibrosing cholestatic hepatitis, a rare but life-threatening form of HCV

hepatitis. Successful clearance of HCV with DAAs administered at the time of transplant has the highest likelihood of eliminating the risk of chronic HCV-infection.

The efficacy, safety and tolerability of DAAs has been reviewed above; however, it is important to note that the use of DAAs after transplantation, particularly after heart or lung transplantation, has not yet been extensively studied. It is theoretically possible that taking immunosuppressant medications at the time of transmission of HCV with organ transplantation may alter the efficacy of DAAs. However, this seems unlikely given the many reports of preserved SVR rates in immunocompromised populations, including recipients of solid organ transplants.

There is also the possibility that virologic failure could lead to drug-resistant HCV. Reassuringly, recent data support that effective “salvage regimens” can successfully treat patients who have failed first-line DAA therapy with excellent SVR rates[70]. Collaboration with hepatologists knowledgeable about first and second-line DAA therapies is extremely important. As mentioned, the most important consideration is access to DAA therapy within the first week post-transplant. There is often uncertainty as to whether DAAs will be approved in a timely manner by insurance companies; of note, the safety of delays in starting treatment after transplant that exceed the first three days after transplant (as was done in the THINKER trial) is unknown. Data is needed to determine if it is safe to delay beyond this. In this regard, a recent report of a recipient of an HCV-viremic liver transplant who developed dialysis-dependent HCV-associated membranous nephropathy on post-operative day 18 due to a delay in DAA therapy raises concern[71]. A compelling case can be made for immediate DAA treatment in HCV uninfected recipients of HCV infected organs.

Conclusion

The advent of DAAs, which are well-tolerated, efficacious, and appear to be safe post-transplant, has sparked interest into transplanting HCV-viremic organs into HCV-uninfected recipients. Protocols that utilize DAAs post-transplant have the potential to play an important role in curtailing the current discard rates for HCV-viremic donor organs. Even with cure rates of 98% in the general population, it is postulated that HCV cure rates might be even higher in transplantation of other non-HCV reservoir organs, such as kidneys, lung, and hearts. This has the potential to result in a large increase *in the number and quality* of organs available in the United States. Future research is necessary to determine whether longer-term transplant outcomes are the same; it is reassuring that one-year outcomes were favorable in THINKER recipients[48]. Studies that examine the potential cost-saving of increasing access to transplantation are needed to further support these strategies. The determination of the minimal adequate duration of early, preemptive DAA therapy should also be an important area of further investigation.

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Key points:

1. Heart, lung, kidney, and liver transplantation waiting lists are long, with substantial morbidity and mortality incurred by patients on the waitlist.
2. Because direct acting antiviral therapies are safe and efficacious at curing HCV infection, many are interested in using HCV viremic donors for transplantation into HCV uninfected recipients
3. Trials that transplant HCV-viremic kidneys into uninfected recipients have been performed successfully; there are ongoing trials evaluating use of HCV viremic donors in HCV-uninfected patients waiting for heart, lung, kidney and liver transplants.
4. Transplantation teams that utilize HCV infected donors need to adequately educate patients on risks of the procedure and enlist specialists knowledgeable about first and second line direct-acting antiviral therapies.
5. Ensuring access to direct acting antiviral therapy in the first week post-transplant is an extremely important safety consideration.

Table 1.

Numbers waiting for transplantation, annual waitlist mortality, and donor discard by organ type

	Heart	Lung	Kidney	Liver
# waiting for organs	3,807	1,425	94,805	13,442
Annual mortality on waitlist, 2018	8.2%	15%	3.9%	8.5%
Donor procurement rates (i.e., percent of donors from whom the organ is harvested	30%	15%	88%	55%

Data from OPTN accessed on 2/18/2019.

Table 2.

Organ-specific concerns and direct-acting antiviral regimen selection

	Heart	**Lung**	**Kidney**	**Liver**
Organ-specific concerns	Accelerated coronary allograft vasculopathy associated with HCV;	Prolonged intubation post-transplant is common, and may require DAA pill crushing and administration via OG/NG tube which may alter bioavailability	Diseases with early recurrence (such as primary FSGS) may require intensification of immunosuppression	Fibrosing cholestatic hepatitis
	Highly sensitized patients that may require intensification of immunosupression with therapies not previously studied with DAAs (PLEX, RTX, etc)			
DAA-specific concerns	Amiodarone is contraindicated with sofosbuvir-based regimens	Prolonged periods of NPO after transplant require pill-crushing	Delayed graft function and dependence on dialysis may favor use of G/P, a pangenotypic DAA approved in ESRD	Early allograft dysfunction may preclude safe use of DAAs containing protease inhibitors, which accumulate in hepatic impairment.
			G/P restriction with CsA (not to dose >100/day per package insert) can limit CNI options	G/P restriction with CsA (not to dose >100/day per package insert) can limit CNI options

Abbreviations: DAAs = direct-acting antivirals, PLEX = plasma exchange, RTX = rituximab, OG/NG = orogastric/nasogastric, FSGS = focal segmental glomerulosclerosis, NPO = nothing per os, G/P = glecaprevir pibrentasvir, ESRD = end-stage renal disease, CsA = cyclosporine A, CNI = calcineurin inhibitor

Table 3.

Overview of risks of accepting an HCV viremic donor

Acute HCV infection risk
Acute hepatitis
Fibrosing cholestatic hepatitis
Chronic HCV infection
Chronic liver disease
Cirrhosis/End-stage liver disease, liver cancer, death
Extrahepatic manifestations - mixed cryoglobulinemia, glomerulonephritis, neurocognitive changes, lichen planus
Risk of DAA failure
Virologic failure, development of resistance, second-line treatment options
Incorrect genotyping test *
Risk of HCV transmission to household or sexual partners **
Side effects of particularly DAA regimen selected

* Only relevant if a pan-genotypic DAA regimen was used

** This is extremely low; however, we recommend avoiding blood contact and using barrier protection for sexual encounters until sustained virologic response 12 weeks after treatment. Abbreviations: HCV = hepatitis C virus, DAAs = direct-acting antivirals