Hepatitis C Virus Treatment and Solid Organ Transplantation

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Abstract: Hepatitis C virus (HCV) infection is a common indication for liver transplantation. If the patient's HCV is untreated prior to liver transplant, infection of the allograft is nearly universal and can lead to graft failure. The demand for deceased-donor organ transplantation continues to surpass the available supply of donor organs. Waitlist mortality remains an important concern, and several strategies have been enacted to increase organ supply, such as using high-risk donors, including those who are HCV positive. The development of safe and highly effective HCV therapy with direct-acting antiviral agents has revolutionized the management of liver transplant candidates and transplant recipients. Moreover, the newer antiviral therapies have paved the road for use of HCV-viremic organs, effectively expanding the donor pool and changing the landscape of solid organ transplantation. This article reviews the data on HCV treatment prior to and after organ transplantation.

Keywords
Chronic hepatitis C virus, direct-acting antiviral, liver transplantation, solid organ transplantation, hepatitis C virus–positive donor

Hepatitis C virus (HCV) infection affects approximately 130 million to 150 million people worldwide.[1] End-stage liver disease from HCV infection is one of the leading causes of liver disease and leading indications for liver transplantation.[2] However, the demand for organs continues to outpace the supply of organ donation, resulting in considerable waitlist mortality.[3,4] The availability of HCV-positive organs continues to increase, representing 9.7% of deceased-donor livers in 2019.[2] Historically, organs from deceased donors infected with HCV were discarded because of high transmission risk during reperfusion and risk of significant posttransplant morbidity and mortality.[5-7] Several strategies to expand the donor pool have been implemented, including donation after cardiac death, use of living donors, and increased utilization of high-risk donors to mitigate the global shortage. Organs categorized as high risk by the public health service are those associated with an increased risk for the transmission of blood-borne viruses, including HIV, hepatitis B virus, and HCV.

Notably, the landscape of HCV changed with the emergence of direct-acting antiviral (DAA) therapy. The high success rate and manageable side effects of DAA therapy, coupled with a dearth of organ

supply, have led to greater utilization of HCV-positive livers, increasing from 7% to 17% between 2010 and 2015.[8] Meanwhile, the rising national opioid epidemic has resulted in an increase in HCV transmission. The number of acute HCV infections more than doubled from 24,700 to 57,500 between 2012 and 2019, and the number of overdose-death donors increased from 1.1% to 13.7% between 2000 and 2017.[9,10] Opioid-related deaths more frequently occur in young donors, who are generally healthier and have fewer comorbidities than older donors, and therefore their HCV-viremic donor organs are often of relatively high quality.[11,12] These liver allografts have been associated with lower rates of biliary complications and improved rejection rates, graft survival, and overall survival.[13-15]

There have been significant advancements in the science of HCV therapy and in the use of HCV-positive organs, thereby substantially increasing the number of organ transplants and decreasing waitlist mortality. This article reviews the data on HCV treatment prior to and after organ transplantation.

Hepatitis C Virus Infection and Direct-Acting Antiviral Therapy

Over the past several years, a succession of pangenotypic DAA therapies for the treatment of chronic HCV infection has been introduced, with cure rates defined as sustained virologic response 12 weeks after treatment (SVR12) of greater than 98%.[16] Nonstructural protein 5B inhibitor sofosbuvir (SOF; Sovaldi, Gilead) has been approved for HCV treatment in combination with a nonstructural protein 5A (NS5A) inhibitor, nonstructural protein 3/4A (NS3/4A) protease inhibitor, and ribavirin. The combination of potent NS5A inhibitor ledipasvir (LDV) and SOF (LDV/SOF, 90 mg/400 mg; Harvoni, Gilead), administered once daily, is well tolerated and produces high SVR12 rates in HCV genotype (GT) 1, 4, 5, and 6 infection.[17] The combination of SOF and NS5A inhibitor velpatasvir (SOF/VEL; Epclusa, Gilead), administered once daily, provides SVR12 rates of greater than 95% across all GTs and has a favorable safety profile.[18-20] The combination of NS3/4A protease inhibitor glecaprevir and NS5A inhibitor pibrentasvir (GLE/PIB; Mavyret, AbbVie) was first approved in 2017 for the treatment of HCV infection without cirrhosis or with mild cirrhosis.[21] GLE/PIB is well tolerated and results in SVR12 rates greater than 97% across all GTs.[22-25]

The availability of safe and highly effective therapy has led to the delicate consideration of treating HCV infection prior to transplant or deferring therapy until after transplant. DAA therapy has been shown to improve liver function in patients with decompensated cirrhosis, some to the extent of no longer requiring liver transplant.[26] Furthermore, pretransplant DAA therapy reduces the risk of reinfection of the allograft.[27] However, not all patients with end-stage liver disease from HCV infection will benefit from treatment prior to liver transplantation. Clinical features associated with meaningful improvement in liver function from pretransplant therapy include low baseline Model for End-Stage Liver Disease score (<16), low baseline Child-Pugh score, and the absence of portal hypertension complications.[28,29] Patients with advanced liver disease are unlikely to improve with DAA therapy and those with Child-Pugh class C cirrhosis have lower SVR12 rates; therefore, deferring treatment in such situations may be preferred.[30,31] Lastly, the more recent practice of utilizing HCV-viremic donors has changed overall access to transplant and should be taken into consideration when deciding optimal timing of HCV treatment.

Direct-Acting Antiviral Therapy and Liver Transplantation

Persistence of HCV infection after liver transplant results in a variable clinical course ranging from mild fibrosis to severe graft damage. Progressive centrilobular ballooning degeneration, bridging fibrosis, and cholestasis are seen in 20% to 40% of posttransplant patients whose HCV infection has not been cured.[6] Advanced fibrosis can occur in up to 45% of posttransplant patients, and graft cirrhosis can develop within as little as 5 years posttransplant.[32,33] Five percent to 10% of posttransplant patients will develop severe progressive cholestatic hepatitis leading to liver failure.[34,35] With the increasing use of DAA therapy, significant HCV-related progression of liver disease posttransplant is now uncommon.

Use of DAA therapy following liver transplant has demonstrated excellent outcomes. Recipients who achieve SVR12 posttransplant have lower rates of liver fibrosis progression (20.5% vs 65.5%; $P<.001$) and lower mortality ($chi^2=6.9$; $P<.01$) rates compared with patients who do not receive or fail treatment.[36,37] In a multicenter phase 2 study, 17 patients with chronic HCV GT1 who received an HCV-negative liver followed by treatment with single-dose LDV/SOF for 4 weeks achieved SVR12.[38] In a study of 79 patients with chronic HCV GT1 to GT4 infection of whom 59% were treatment-experienced, use of SOF/VEL following liver transplant resulted in an SVR12 rate of 96%.[39] Two patients experienced virologic relapse, and 1 patient discontinued treatment because of hyperglycemia. No serious or severe adverse events were deemed SOF/VEL-related, and no liver transplant rejection episodes or deaths occurred during the study period.

Table 1. Interpretation of HCV Diagnostic Testing Results

HCV Antibody	HCV NAT	Clinical Interpretation	Transmission Risk
+	+	Active HCV infection	High
–	+	Acute HCV infection in antibody window period or false-positive NAT	High
+	–	No active HCV infection, cleared or treated HCV infection, or false-positive antibody	Low
–	–	No HCV infection	None

HCV, hepatitis C virus; NAT, nucleic acid testing.

Treatment of HCV infection in patients who undergo simultaneous liver-kidney transplant is both safe and efficacious. The HCV-TARGET trial used the Hepatitis C Therapeutic Registry and Research Network database to evaluate liver transplant and dual liver-kidney transplant recipients with HCV infection treated with LDV/SOF, ombitasvir/paritaprevir/ritonavir plus dasabuvir (Viekira Pak, AbbVie), or SOF plus daclatasvir (SOF/DAC; Darvoni, Beacon).[40] SVR12 rates among liver transplant and dual liver-kidney transplant recipients were 96.6% and 90.9%, respectively. Four episodes of acute rejection occurred in the liver transplant group. Successful outcomes from the real-world data of the large HCV-TARGET cohort provided confidence in treating liver transplant patients with a ribavirin-free regimen.

The use of a pangenotypic, ribavirin-free regimen in posttransplant patients without cirrhosis has demonstrated similar overall success. The MAGELLAN-2 study was a phase 3 open-label trial that confirmed the safety and efficacy of GLE/PIB once daily for 12 weeks in patients with treatment-naive HCV GT1 to GT6 infection or treatment-experienced HCV GT1, GT2, or GT4 to GT6 who had received a liver or kidney transplant.[41] Treatment with GLE/PIB for 3 months or longer posttransplant in 80 liver transplant and 20 kidney transplant patients resulted in an SVR12 rate of 98% (95% CI, 95.3%-100%). No patients discontinued therapy because of treatment-related adverse events. Only 1 patient experienced virologic failure, and 1 patient discontinued GLE/PIB because of an adverse event unrelated to treatment.

In transplant recipients who have compensated cirrhosis, DAA therapy following transplant is safe and efficacious. Treatment with SOF/VEL for 12 weeks in 14 liver transplant recipients with HCV GT1 to GT4 infection and cirrhosis resulted in an SVR12 rate of 93%.[39] SOLAR-1 and SOLAR-2 were 2 large trials that evaluated LDV/SOF plus ribavirin in liver transplant recipients with HCV GT1 to GT4 infection and liver disease.[30,31] In SOLAR-1, SVR12 was achieved in 96% to 98% of transplant recipients without cirrhosis or with compensated cirrhosis. Of the entire cohort, 13 patients (4%) discontinued treatment prematurely because of adverse events and 10 patients died, mainly from complications related to hepatic decompensation.[30] SOLAR-2, a multicenter open-label study that included HCV GT1 liver transplant recipients who had no cirrhosis, Child-Turcotte-Pugh (CTP)-A, CTP-B, or CTP-C cirrhosis, or fibrosing cholestatic hepatitis and were treated with 12 or 24 weeks of LDV/SOF plus ribavirin daily, demonstrated SVR12 rates of 100% (90% CI, 91%-100%), 96% (90% CI, 84%-100%), 95% (90% CI, 78%-100%), and 100% (90% CI, 86%-100%) in CTP-A patients with 12 weeks of treatment, CTP-A patients with 24 weeks of treatment, CTP-B patients with 12 weeks of treatment, and CTP-B patients with 24 weeks of treatment, respectively.[31] All recipients with fibrosing cholestatic hepatitis (n=5) achieved SVR12 (100%; 90% CI, 55%-100%). In posttransplant patients with HCV GT4 infection, SVR12 was achieved by 78% of patients who received 12 weeks of treatment (90% CI, 56%-92%) and 94% of patients who received 24 weeks of treatment (90% CI, 75%-100%). In the entire cohort studied (n=333), 7 patients (2%) discontinued LDV/SOF prematurely because of adverse events and 17 patients (5%) died, mainly from complications of hepatic decompensation.

Although historical data demonstrate that HCV infection has a negative long-term impact on both patient and graft survival, promising data on the safety and efficacy of DAA therapy for the treatment of HCV infection posttransplant led to a paradigm shift. Major strides in HCV eradication paved the way for use of HCV-positive organs, first in HCV-viremic recipients and now in HCV-negative recipients.

Defining Hepatitis C Virus–Positive Donors

HCV-positive donors encompass any stage of HCV infection. Serologic tests such as chemiluminescence assays

Table 2. Hepatitis C Virus–Viremic Liver Transplantation in Nonviremic Recipients

Organ Type(s)	Trial Name or Reference	Year	Cohort Size	Antiviral Therapy	Therapy Duration	SVR12
Liver, kidney, liver + kidney	HCV-TARGET[40]	2017	LT=347 KT=60 LT+KT=36	LDV/SOF, ombitasvir/paritaprevir/ritonavir + dasabuvir, or SOF/DAC	12-24 weeks	LT=312/324 (96.3%) KT=52/55 (94.5%) LT+KT=30/33 (90.9%)
Liver	Kwong et al[56]	2019	10	SOF/VEL, LDV/SOF, or SOF/DAC	12-24 weeks	10/10 (100%)
Liver	Bethea et al[57]	2020	14	GLE/PIB	12 weeks	10/10 (100%)
Liver	Bohorquez et al[58]	2021	51	SOF/VEL or GLE/PIB	12 weeks	51/51 (100%)
Liver, kidney	Terrault et al[59]	2021	13	SOF/VEL	12 weeks	13/13 (100%)
Liver	Aqel et al[60]	2021	20	GLE/PIB	12 weeks	20/20 (100%)

GLE/PIB, glecaprevir/pibrentasvir; KT, kidney transplant; LDV/SOF, ledipasvir/sofosbuvir; LT, liver transplant; SOF/DAC, sofosbuvir/daclatasvir; SOF/VEL, sofosbuvir/velpatasvir; SVR12, sustained virologic response 12 weeks after treatment.

and enzyme immunoassays detect antibodies within 2 to 6 months after exposure, but nucleic acid testing (NAT) detects RNA 5 to 7 days after exposure and provides a more accurate assessment of transmission risk.[42-44] HCV NAT has a sensitivity of 85% to 100% and a specificity of 99% to 100%.[45,46] It is important to distinguish between a seropositive and viremic donor when discussing organ transplant from an HCV-positive donor, as the risks of disease transmission vastly differ. Donors identified as HCV positive by serologic testing but NAT negative (nonviremic) are considered to have undergone spontaneous clearance or successful treatment of infection, or have a false-positive antibody result, and these donors have not been documented to transmit HCV infection.[47] An HCV-seropositive donor that is NAT positive (viremic) is considered to have an active infection and poses a high risk for disease transmission. An HCV-negative donor that is NAT positive (viremic) is considered to have an acute infection and poses a high risk for disease transmission (Table 1). Despite improvements in testing, risk of HCV transmission remains during the 1-week eclipse period between viral exposure and positive NAT results, particularly in persons who inject drugs.[42,43,48]

Hepatitis C Virus–Positive Donor Transplantation in Hepatitis C Virus–Negative Recipients

Before the availability of DAA therapy, transplantation of organs from HCV-positive donors into uninfected recipients was not routinely considered owing to low efficacy, high rates of HCV transmission, decreased patient and graft survival, and complications associated with interferon-based therapy in the posttransplant setting.[49-51] The lack of effective and well-tolerated treatments for HCV had curtailed utilization of HCV-infected organs in transplant recipients. However, the rapidly evolving treatments for HCV have improved outcomes, and perioperative use of DAA therapy has increased the utilization of HCV-viremic donor organs.

Early data have demonstrated favorable long-term graft outcomes in patients transplanted with HCV-seropositive donors. In a study published in 1998, 22 patients with HCV received HCV-seropositive grafts and had excellent 4-year patient and graft survival, 83.9% and 71.9%, respectively, vs 79.1% and 76.2%, respectively, with HCV-seronegative donor grafts (*P*=not significant [NS]).[52] In a larger study that included 2923 transplant recipients with HCV, 96 and 2827 received HCV-positive and -negative organs, respectively, and had comparable 2-year survival rates (90% vs 77%; *P*=.01).[53]

Liver Transplantation

Two large retrospective studies evaluated HCV-viremic donors in nonviremic liver transplant recipients and demonstrated no differences in patient or graft survival when compared with nonviremic donors.[54,55] Data from 2015 to 2017 from the Organ Procurement and Transplantation Network (OPTN) showed that 30 HCV-naive patients received HCV-viremic livers and had similar 1-year patient survival rates when compared with HCV-seropositive but NAT-negative and nonviremic livers (92% vs 92% vs 92%; *P*=NS). In a later study using 2016 to 2020 data from OPTN, comparable 2-year graft survival rates were seen in 568 liver transplant recipients with and without HCV infection (n=753 and n=87, respectively) who received HCV-viremic organs (90% vs 86%, respectively; *P*=NS).[54] The promising outcomes

laid the foundation for use of HCV-viremic livers in HCV-negative patients (Table 2).

The first prospective study included 10 HCV-negative patients who received HCV-viremic livers, 7 of which had been cured of HCV infection prior to transplant.[56] All 10 recipients developed viremia and received SOF/VEL-based, LDV/SOF-based, or SOF/DAC-based therapy and achieved SVR12. Adverse events included medication-related side effects requiring hospitalization with discontinuation of ribavirin but continuation of DAA therapy (n=1), biopsy-proven acute cellular rejection (n=1), and antibody-mediated rejection complicated by renal failure (n=1). Despite the small sample size, this early study demonstrated that HCV treatment within 3 months of transplantation increases the probability of successful graft function and reduces waitlist mortality.

GLE/PIB has been used successfully in HCV-naive patients who receive HCV-viremic livers. In a trial of 14 patients who received HCV-viremic livers, 9 patients developed viremia with SVR12 and 46-week survival rates of 100% and 100%, respectively.[57] There were no treatment-related or HCV-attributable adverse events and no GLE/PIB drug reactions or interactions that necessitated discontinuation of any posttransplant medications. Immediate treatment with GLE/PIB for HCV-viremic liver transplant into uninfected recipients is both safe and efficacious. A later study demonstrated that initiation of DAA therapy within 90 days of transplant, rather than preemptively or immediately following transplant, has also demonstrated favorable outcomes. The administration of SOF/VEL or GLE/PIB once daily for 12 weeks in HCV-naive patients who received viremic livers (n=51) produced similar 1-year patient and graft survival when compared with HCV-naive patients who received non-viremic livers (n=231), at 93.4% vs 93.9% (*P*=.89) and 91.8% vs 90.9% (*P*=.81), respectively.[58] A preemptive antiviral strategy using SOF/VEL is also successful in achieving SVR12. In a multicenter study evaluating the kinetics of early HCV infection, SOF/VEL once daily for 12 weeks when viremia was confirmed resulted in SVR12 in all patients (13 liver, 11 kidney).[59] However, serious adverse events in this study included biliary sclerosis, cardiomyopathy, and graft-vs-host disease, the last of which led to multiorgan failure and death, suggesting that close monitoring for adverse immunologic events is necessary. HCV-related acute membranous nephropathy resulting in end-stage kidney disease despite achieving SVR12 was reported in a prospective multicenter study evaluating outcomes in HCV-naive liver transplant and dual liver-kidney transplant.[60] Although all HCV-viremic organ recipients (n=20) achieved SVR12, the development of HCV-related complications suggests that careful and longer-term follow-up is still warranted.

Renal Transplantation

The prevalence of HCV among end-stage renal disease patients is 0.2% to 6%, and HCV infection traditionally has been a common complication after renal transplant.[61] Outcomes for untreated HCV infection in HCV-seropositive renal recipients are significantly worse than in their HCV-negative counterparts.[62,63] HCV seropositivity is associated with higher all-cause mortality (adjusted relative risk [aRR], 1.85; 95% CI, 1.49-2.31; *P*<.0001) and higher all-cause graft loss (aRR, 1.76; 95% CI, 1.46-2.11; *P*<.0001).[64]

Historically, kidneys from HCV-infected donors have been underutilized. However, studies in the past decade have demonstrated promising long-term outcomes of HCV-seropositive recipients transplanted with kidneys from HCV-positive donors. In a study of 545 kidney transplants performed in HCV-positive recipients, 5- and 10-year patient survival was 84.8% and 72.7%, respectively, for HCV-positive graft recipients compared with 86.6% and 76.5%, respectively (*P*=.25), for HCV-negative graft recipients.[65] Furthermore, the availability of DAA therapy and its administration around the time of transplant minimizes the risk of chronic HCV infection in the transplant recipient and thus has led to the recent growth of transplant of kidneys from HCV-infected donors into HCV-naive recipients.

Only a few prospective trials have evaluated the use of DAA therapy in renal transplant recipients with HCV infection. In 2017, the THINKER trial was the first open-label, single-group pilot study that sought to determine the safety and efficacy of the transplant of kidneys from HCV GT1–viremic donors into HCV-negative recipients (donor positive, recipient negative [D+/R-]) followed by treatment with elbasvir/grazoprevir (EBR/GZR; Zepatier, Merck) for 12 weeks (n=10).[66] All recipients had detectable HCV RNA, and all attained SVR12. In the THINKER-2 trial (n=20), which included THINKER participants, HCV-negative recipients of HCV-viremic kidneys experienced HCV cure and excellent renal allograft function with estimated glomerular filtration rates (eGFRs) not significantly different from those of matched recipients of HCV-negative kidneys at 6 months (median, 67.5 vs 66.2 mL/min/1.73 m^2; 95% CI, -4.2 to 7.5) and 12 months (median, 72.8 vs 67.2 mL/min/1.73 m^2; 95% CI, -7.2 to 9.8).[67]

The EXPANDER trial was an open-label single-center study (n=10) that examined the tolerability and feasibility of DAA prophylaxis before and after renal transplant in HCV-naive patients (n=10) who received HCV-viremic kidneys (GT1-GT3).[68] In this study, all recipients received a dose of EBR/GZR immediately before transplant, and recipients of kidneys from donors with GT1 infection continued receiving EBR/GZR for

12 weeks after transplant; those receiving organs from donors with GT2 or GT3 infection received SOF along with EBR/GZR for 12 weeks of triple therapy. Preemptive use of EBR/GZR for 12 weeks in HCV-naive recipients who received HCV-infected kidneys (n=8) led to SVR12 with no study-related adverse events.[69]

SOF-based regimens are safe and effective in HCV-naive recipients undergoing HCV-viremic kidney transplant. In a study of 7 HCV-naive kidney recipients receiving HCV GT1– and HCV GT3–viremic kidneys, antiviral treatment with LDV/SOF (n=4) and SOF/VEL (n=3) for 8 to 12 weeks resulted in SVR12 and stable renal allograft function.[70] In a subsequent, larger, single-center, observational study, use of SOF/VEL or LDV/SOF resulted in SVR12 rates of 100% and stable allograft function in 53 HCV-naive recipients who received SOF/VEL or LDV/SOF for 8 to 12 weeks following HCV-viremic kidney transplant.[71] Four recipients developed acute rejection.

GLE/PIB once daily for 12 weeks has been shown to be well tolerated in patients with chronic HCV GT1 to GT6 infection who have undergone kidney transplantation.[41] In the MYTHIC trial, 30 HCV-naive patients received HCV-viremic kidneys across 7 transplant centers.[72] All 30 recipients achieved SVR12, and no severe adverse events related to HCV infection or GLE/PIB were noted in any patient. Although all recipients had good allograft function, adverse events included acute cellular rejection (n=3) and polyomavirus (BK) viremia (n=3). In a large, prospective, real-world study, 64 HCV-naive patients underwent HCV-viremic kidney transplant followed by posttransplant NAT to determine the need for treatment[73]; 61 patients developed viremia, of which 41 patients achieved SVR12, 10 reached undetectable viral loads, and 7 remained on treatment. There was 1 nonresponder owing to NS5A resistance. At a median 8-month follow-up, patient and graft survival were both 98%.

Shorter-course DAA regimens have also been evaluated with promising results. In a study of 10 HCV D+/R- kidney transplants, 4-week GLE/PIB prophylaxis resulted in undetectable HCV RNA after day 7 and stable allograft function with eGFR of 54.5 mL/min/1.73 m^2 (range, 30-79 mL/min/1.73 m^2).[74] The DAPPER trial treated patients with a single pretransplant dose of SOF/VEL followed by 1 or 3 posttransplant doses.[75] The 4-day strategy reduced viral transmission to 7.5% (3/40; 95% CI, 1.8%-20.5%) but did result in detectable viremia in 17 of 50 (34%) patients by posttransplant day 14, of which only 6 of 50 (12%) required treatment; the remaining 11 recipients had self-limited, low-level viremia. Of the 6 patients who required treatment, 5 patients achieved SVR12, with 1 patient requiring the addition of ribavirin owing to resistance and 2 patients requiring retreatment with second-line DAA agents owing to relapse.[63]

Thoracic Transplantation

Among heart transplant recipients, the reported prevalence of HCV infection is as high as 12%.[76] Early studies demonstrated reduced survival in recipients with HCV infection, regardless of acquisition of HCV pre– or post–heart transplant.[77,78] The transplantation of HCV-infected hearts was nearly abandoned in the era of interferon-based HCV treatment regimens because of concerns about virally mediated coronary vasculopathy and development of severe and rapidly progressive liver disease. Donor HCV seropositivity was reported to be an independent risk factor for increased mortality when matched with controls (2.8-fold greater; 95% CI, 1.3-5.7; *P*=.006) and for the development of accelerated allograft vasculopathy when compared with matched controls, with a hazard ratio of 9.4 (97% CI, 3.3-26.6; *P*≤.0001) vs 3.08 (95% CI, 1.52-6.20; *P*=.001), respectively.[77]

The first prospective study utilizing HCV-viremic hearts included 11 HCV-naive recipients, 9 of whom developed HCV viremia after transplant and 8 of whom achieved SVR12 through treatment with either LDV/SOF (GT1) or SOF/VEL (GT3).[79] One patient died during week 7 of treatment owing to pulmonary embolism, but DAA therapy was well tolerated in all treated patients.[79] Preemptive administration of GLE/PIB in HCV-viremic cardiac transplant into HCV-naive recipients (n=20) has demonstrated rapid HCV suppression (median time to clearance, 3-5 days; interquartile range, 0.0-8.3), prevention of chronic HCV infection (SVR12 rate of 100%), and excellent early allograft function (100% at a median follow-up of 10.7 months) in patients receiving HCV-viremic donor hearts.[80] In the USHER trial, HCV GT1–viremic hearts were transplanted into HCV-naive recipients (n=10) followed by 12-week treatment with EBR/GZR and demonstrated SVR12 rates of 90%, although 1 NAT-negative recipient died because of antibody-mediated rejection. There were no serious adverse events from HCV transmission or treatment.[81]

In the largest-to-date prospective single-center study of 80 patients who underwent heart transplant with HCV-positive donors (70 NAT-positive, GT1-GT3 donors and 10 antibody-positive, NAT-negative donors), 67 of 70 (96%) recipients developed viremia following transplant and started treatment with LDV/SOF, SOF/VEL, or GLE/PIB for 12 weeks.[82] Of those who started DAA treatment (n=55), 37 achieved SVR12 with 17 recipients pending, and 1 recipient died prior to achieving SVR12. Although there were higher rates of severe primary graft dysfunction (13.7% vs 3.1%;

Table 3. Hepatitis C Virus–Viremic, Nonhepatic Solid Organ Transplantation in Nonviremic Recipients

Organ Type(s)	Trial Name or Reference	Year	Cohort Size	Antiviral Therapy	Therapy Duration	SVR12
Kidney	THINKER[66]	2017	10	EBR/GZR	12 weeks	10/10 (100%)
Kidney	THINKER-2[67]	2018	20	EBR/GZR	12 weeks	20/20 (100%)
Kidney	EXPANDER[68]	2018	10	EBR/GZR ± sofosbuvir	12 weeks	10/10 (100%)
Kidney	Friebus-Kardash et al[70]	2019	7	SOF/VEL or LDV/SOF	8-12 weeks	7/7 (100%)
Kidney	Molnar et al[71]	2019	53	GLE/PIB, SOF/VEL, or LDV/SOF	12 weeks	53/53 (100%)
Kidney	Sise et al[69]	2020	8	EBR/GZR	12 weeks	8/8 (100%)
Kidney	DAPPER[75]	2020	50	SOF/VEL	4 days	49/50 (98%)
Kidney	MYTHIC[72]	2020	30	GLE/PIB	8 weeks	30/30 (100%)
Kidney, liver	Terrault et al[59]	2021	Kidney=11	SOF/VEL	12 weeks	11/11 (100%)
Kidney	REHANNA[74]	2021	10	GLE/PIB	4 weeks	10/10 (100%)
Heart	Schlendorf et al[79]	2018	9	LDV/SOF or SOF/VEL	12-24 weeks	8/9 (89%)[a]
Heart	USHER[81]	2019	10	EBR/GZR	12 weeks	9/10 (90%)[a]
Heart	Bethea et al[80]	2019	20	GLE/PIB	8 weeks	20/20 (100%)
Heart	Schlendorf et al[82]	2020	80	LDV/SOF, SOF/VEL, or GLE/PIB	12 weeks	37/50 (74%)[b]
Heart	Reyentovich et al[83]	2020	22	GLE/PIB	8 weeks	22/22 (100%)
Heart, lung	DONATE HCV[85]	2019	Heart=8 Lung=36	SOF/VEL	4 weeks	Heart=7/7 (100%) Lung=28/28 (100%)[c]
Heart, lung	Smith et al[86]	2021	Heart=22 Lung=16	GLE/PIB	8 weeks	Heart=22/22 (100%) Lung=16/16 (100%)
Lung	Cypel et al[84]	2020	22	SOF/VEL	12 weeks	18/20 (90%)[d]
Pancreas	Lonze et al[87]	2021	8	SOF/VEL or GLE/PIB	12 weeks	8/8 (100%)

EBR/GZR, elbasvir/grazoprevir; GLE/PIB, glecaprevir/pibrentasvir; LDV/SOF, ledipasvir/sofosbuvir; SOF/VEL, sofosbuvir/velpatasvir; SVR12, sustained virologic response 12 weeks after treatment.
[a]1 patient died. [b]Study ongoing. [c]Some patients lost to follow-up. [d]2 patients did not develop viremia.

P=.002) among patients who received HCV-viremic heart transplant, there was no difference regarding the hospital length of stay (15% vs 15.5%; *P*=.53), rejection requiring treatment (16.3% vs 27%; *P*=.06), survival at 30 days (93.7% vs 96.2%; *P*=.39), or 1-year patient survival (90.7% vs 90.5%; *P*=0.88) compared with patients who received transplants from HCV-negative donors during the same period.[82]

Shorter duration of DAA treatment with GLE/PIB for 8 weeks following cardiac transplant was evaluated in 22 HCV-naive patients who received HCV-viremic organs.[83] All patients developed detectable viremia, and

all achieved SVR12. There was no difference in 1-year survival (95% vs 100%; *P*=NS) or moderate or severe acute cellular rejection (18% vs 27%; *P*=NS).[83]

Only a few studies have evaluated the safety of using lungs from HCV-viremic donors for transplantation. In a single-center prospective study of 22 HCV-naive recipients of HCV-viremic lungs treated with 12 weeks of SOF/VEL, 6-month HCV-free survival was 86%.[84] Six-month survival after transplant of HCV-viremic and -nonviremic donors was 95% vs 94%, respectively. In the HCV-viremic group, the most common adverse events were respiratory complications and infections, at 23% (n=5) and 18% (n=4), respectively. Serious adverse events requiring admission to the hospital occurred in 45% (n=10) of recipients. Two patients developed HCV relapse and required retreatment.

The DONATE-HCV trial was a single-center pilot study that evaluated transplanting HCV-viremic organs into 8 cardiac and 36 lung HCV-naive recipients who preemptively received treatment with SOF/VEL for a total of 4 weeks.[85] HCV viremia developed in 95% of recipients immediately after transplant, and of the first 35 patients enrolled who had completed 6 months of follow-up, 100% (95% CI, 90%-100%) achieved SVR12 with excellent graft function. Similar outcomes were reported in a cohort of HCV-naive patients (16 lung recipients and 22 heart recipients) who received HCV-viremic donor organs followed by DAA therapy with GLE/PIB for 8 weeks.[86] Of the 16 lung recipients, 11 developed viremia posttransplant and all achieved SVR12. At 6 months posttransplant, there was no difference between HCV-viremic and HCV-negative recipients when comparing mortality (6.3% vs 3.9%; *P*=1), primary graft dysfunction (0.0% vs 11.5%; *P*=.275), clinically significant rejection requiring treatment (31.8% vs 37%; *P*=.769), or acute cellular rejection (90.9% vs 100%; *P*=.196).[86]

Pancreas Transplantation

The data on utilizing HCV-viremic organs in pancreas transplantation are limited. In 2021, the first reported series included 8 HCV-naive patients who received either deceased donor simultaneous pancreas-kidney transplant or pancreas transplant after living donor kidney transplant.[87] All patients developed viremia and were treated with either GLE/PIB or SOF/VEL and all achieved SVR12. All recipients had excellent pancreas graft function and rates of rejection (0 vs 0; *P*=NS). Length of stay (16 days vs 10 days; *P*=.06) was similar between those who received HCV-viremic organs and those who did not, respectively. These preliminary findings suggest that HCV-viremic pancreas transplant may be safely used for potential pancreas recipients; however, further study regarding morbidity and mortality of pancreas transplantation with HCV-positive donors is needed.

Much of the available data for utilization of HCV-viremic organs in naive recipients are from clinical trials (Table 3), and thus there is minimal real-world experience with treatment delays, failures, and relapse. Short-term outcomes for solid organ transplantation appear to be comparable for HCV-viremic and -nonviremic donors, based on the previously discussed preliminary data. Promising data are most robust in kidney followed by liver transplant but offer limited results past 1 year.

Conclusion

Organ transplantation in the United States is negatively impacted by long waitlist times and high waitlist mortality owing to organ shortages. Transplantation of HCV-viremic organs into HCV-naive recipients followed by the use of DAA agents provides excellent patient and allograft survival. In carefully selected patients, the use of HCV-viremic grafts appears to be efficacious and well tolerated. This practice has demonstrated acceptable short-term outcomes and has the potential to significantly close waitlist gaps and decrease morbidity and mortality. However, securing DAA therapy posttransplant is essential and patients should be fully informed of the associated risks, including the potential of HCV treatment failure. It remains unclear whether HCV infection in posttransplant patients may lead to lasting changes to the immune system or inadvertent interactions with immunosuppressive therapy. Understanding long-term outcomes of HCV-viremic organ utilization remains on the near horizon.

Disclosures

The authors have no relevant conflicts of interest to disclose.

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