Update on the Management of Hepatitis C Virus Infection in the Setting of Chronic Kidney Disease and Kidney Transplantation

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Abstract: Hepatitis C virus (HCV) infection is one of the major global health burdens. Chronic HCV infection can increase the risks of proteinuria and chronic kidney disease (CKD), as well as cause various types of glomerulonephritides. This article provides an update on the management of patients with HCV infection with CKD and a kidney transplantation. Newer direct-acting antiviral (DAA) agents are safe and effective in eliminating HCV infection in patients with CKD and in kidney transplant recipients. Society guidelines recommend elbasvir/grazoprevir and glecaprevir/pibrentasvir for HCV-infected patients with CKD stage 4 or 5, including patients on hemodialysis. Patients with CKD stages 1 to 3 with HCV infection can be treated with various sofosbuvir-based regimens. Major clinical trials have demonstrated the safety, efficacy, and feasibility of the use of DAA agents in treating HCV-uninfected kidney transplant recipients of HCV-infected donors. The utilization of HCV-infected kidney donors may decrease kidney transplant waiting list mortality and reduce the donated kidney discard rate.

Hepatitis C virus (HCV) infection is one of the major global health burdens. The World Health Organization estimated that 71 million people worldwide were living with HCV infection in 2015, accounting for 1% of the population.[1] In 2016, 42 states reported a total of 2967 new cases of acute HCV infection to the Centers for Disease Control and Prevention.[2] That same year, the overall incidence rate of HCV infection was 1 case per 100,000 population, which is an increase from 2015 (0.8 cases/100,000 population).[2] The surge of new HCV infection cases is largely secondary to the current opioid epidemic and improper needle-sharing practices among intravenous drug users.[3,4] The prevalence of chronic HCV infection in the United States is estimated to be 3.5 million people.[5] In the United States, American Indian and Alaskan Natives have the

highest HCV-related mortality rates compared with other races due to the disparity in health care resources and funding.[6] This article provides an update on the management of patients with HCV infection with chronic kidney disease (CKD) and a kidney transplantation.

Hepatitis C Virus Infection and Chronic Kidney Disease

Chronic HCV infection primarily affects the liver; however, it can also affect other organs and systems such as the kidneys, skin, joints, and the immune system. Additionally, chronic HCV infection can cause both tubulointerstitial and glomerular diseases of the kidneys.[7,8] A 2015 meta-analysis demonstrated that patients with chronic HCV infection had a 51% increased risk of proteinuria and a 43% increased risk of CKD.[9] Cryoglobulinemic, membranoproliferative, and membranous glomerulonephritis are among the most common renal manifestations of chronic HCV infection.[10]

Patients with end-stage renal disease on hemodialysis are at risk of acquiring HCV infection via hemodialysis access. The worldwide prevalence of HCV infection in patients on hemodialysis varies greatly due to different hemodialysis practices, such as contact precaution techniques, number of blood transfusions, and length of time on hemodialysis. Regardless of regional differences, the 2 most common factors that increase the prevalence of HCV infection in hemodialysis patients are the number of blood transfusions and patient age.[11,12] In the United States, patients on hemodialysis are routinely screened for HCV infection. In addition to infection-control precautions and decreased requirements of packed red blood cell transfusion (owing to replacement of human erythropoietin), routine screening has led to a decline in the prevalence of HCV infection in this patient setting. However, the prevalence of HCV infection among these patients is still higher than the prevalence that is reported among the nonhemodialysis population.[13,14] Therefore, it is essential to routinely screen patients on hemodialysis for HCV infection.

Treatment for Hepatitis C Virus Infection

HCV infection treatment has evolved from lengthy regimens of interferon injection and ribavirin to shorter-duration regimens with all-oral, direct-acting antiviral (DAA) agents. First-generation DAA agents (ie, telaprevir and boceprevir) with pegylated interferon and ribavirin therapy were approved by the US Food and Drug Administration (FDA) in 2011 and had a sustained virologic response (SVR) rate as high as 75%.[15,16] The era of second-generation DAA agents began in 2013, when sofosbuvir (Sovaldi, Gilead), a nucleotide analog that blocks the HCV viral nonstructural (NS) 5B protein, was approved by the FDA to treat HCV infection with a reported SVR rate of more than 90%.[17] Newer DAA agents provide dramatically increased rates of SVR with much shorter durations of therapy. Several of these DAA agents have since been approved by the FDA to treat various genotypes of HCV infection, with a greater impact on SVR. Most newer DAA agent regimens do not require interferon or ribavirin therapy.

Although the majority of second-generation DAA therapies for HCV infection have been found to be safe and effective among patients with CKD, their safety and efficacy in patients with an estimated glomerular filtration rate (eGFR) of less than 30 mL/min have not been established. However, there is increasing evidence of safety of sofosbuvir-based regimens in patients with an eGFR of less than 30 mL/min.[18,19]

Treatment Recommendations for Patients With Chronic Kidney Disease Stage 4 or 5 and End-Stage Renal Disease on Hemodialysis

Currently, 2 DAA regimens have been approved by the FDA to treat HCV infection in patients with CKD stage 4 or 5 and end-stage renal disease on hemodialysis: elbasvir/grazoprevir (Zepatier, Merck) and glecaprevir/pibrentasvir (Mavyret, AbbVie).

Elbasvir/Grazoprevir

In 2015, the C-SURFER (Hepatitis C: Study to Understand Renal Failure's Effect on Responses) trial demonstrated the safety and efficacy of the combination therapy elbasvir/grazoprevir for the treatment of HCV genotype 1 infection in patients with CKD stage 4 or 5 and end-stage renal disease on renal replacement therapy.[20] In the United States, the combination therapy has also been shown to be cost-effective in treatment-naive and -experienced patients with HCV genotype 1 infection and CKD.[21] Although patients with HCV genotype 4 infection were not evaluated in the C-SURFER trial, elbasvir/grazoprevir is expected to be highly effective in the treatment of this patient population with CKD stage 4 or 5 as well as in patients on hemodialysis. Elbasvir/grazoprevir was the first DAA combination therapy to be approved by the FDA to treat HCV-infected patients with end-stage renal disease on hemodialysis.

Glecaprevir/Pibrentasvir

Glecaprevir is a pangenotypic NS3/4 protease inhibitor, and pibrentasvir is a pangenotypic NS5A inhibitor. The safety and efficacy of the combination therapy

Table 1. Recommended DAA Regimens for Patients With CKD[24]

CKD Stage	HCV Genotype	DAA Regimens	Treatment Duration
Stage 4 or 5 (eGFR, <30 mL/min or hemodialysis)	• 1a, 1b, 4 • All (1-6)	• Elbasvir/grazoprevir • Glecaprevir/pibrentasvir	• 12 weeks • 8-16 weeks
Stages 1-3 (eGFR, 31-90 mL/min)	No specific genotype	• Glecaprevir/pibrentasvir • Ledipasvir/sofosbuvir • Sofosbuvir/velpatasvir • Sofosbuvir/velpatasvir/voxilaprevir • Daclatasvir All regimens can be used without the requirement of dose adjustment.	Treatment durations vary based on the specific HCV genotype and fibrosis/cirrhosis status.

CKD, chronic kidney disease; DAA, direct-acting antiviral; eGFR, estimated glomerular filtration rate; HCV, hepatitis C virus.

glecaprevir/pibrentasvir for 12 weeks in patients with HCV genotypes 1 through 6 infection have been demonstrated in the EXPEDITION-4 (Efficacy and Safety of ABT-493/ABT-530 in Renally Impaired Adults With Chronic Hepatitis C Virus Genotype 1-6 Infection) trial, which also included patients with CKD and end-stage renal disease.[22] The reported intention-to-treat and modified intention-to-treat SVR12 rates were 98% and 100%, respectively.[22] No virologic failure was observed in this trial.

Treatment Recommendations for Patients With Chronic Kidney Disease Stage 1, 2, or 3

The HCV-TARGET (Hepatitis C Therapeutic Registry and Research Network) study demonstrated that sofosbuvir-based DAA regimens (ie, ledipasvir/sofosbuvir [Harvoni, Gilead], sofosbuvir/velpatasvir [Epclusa, Gilead], and sofosbuvir/velpatasvir/voxilaprevir [Vosevi, Gilead]) can be used safely and effectively for the treatment of HCV-infected patients with CKD stages 1 through 3 without the requirement of dose adjustment.[23] The rates of SVR in patients with CKD who were treated with sofosbuvir-based regimens were comparable to those in patients without renal impairment. Table 1 summarizes DAA regimens that are recommended for patients with CKD by guidance from the American Association for the Study of Liver Diseases and the Infectious Diseases Society of America.[24]

Treatment Recommendations for Kidney Transplant Recipients

Public Health Service Increased Risk Donors

In the United States, the median waiting time for a deceased donor kidney transplantation can be 3 to 5 years at most centers, and even longer in some parts of the country. Despite the long wait time for kidney transplantation, more than 500 high-quality kidney grafts from HCV-infected deceased donors are discarded every year.[25-27] In 2013, the US Public Health Service (PHS) published new guidelines for reducing HIV, hepatitis B virus (HBV), and HCV transmission through solid organ transplantation. The Organ Procurement and Transplantation Network/United Network for Organ Sharing (UNOS) Ad-Hoc Disease Transmission Advisory Committee, in collaboration with the Joint Society Steering Committee, developed a guidance document to help transplant clinicians to consider the risk of undetected HIV, HBV, and HCV infections in the donor during the time of organ offers.[24] A potential organ donor may be labeled as PHS Increased Risk (PHS IR) for several reasons (Table 2). The intention of the PHS IR donor declaration is to identify donors who are at high risk of having a recent infection with HIV, HBV, or HCV. Prior to organ procurement, organ donors are tested for antibody via enzyme-linked immunosorbent assay (ELISA) and undergo nucleic acid testing (NAT; Table 3). NAT is performed to reduce the risk of the serologic eclipse, or window, period infection by 10 times for most exposures. The window period is defined as time to detection of infection by a specific testing method. The estimated window period for HCV ELISA is 40 to 50 days, whereas HCV NAT has a window period of 3 to 5 days.[28] Table 4 demonstrates the estimated risk of window period–infections per 10,000 donors.[28]

PHS IR donor classification has no significance on the donor organ quality. In general, the risk of HCV transmission from donor to recipient via the window period is extremely small if a risky behavior occurred more than 2 to 3 weeks prior to NAT. The risk of HCV transmission may vary broadly among PHS IR donors. For example, donors with a history of intravenous drug use have a greater risk than do donors with a history of incarceration or men who have sex with men. The risk of HCV transmission from a NAT-negative donor organ is

Table 2. Potential Organ Donors Labeled as Having Public Health Service Increased Risk

Potential Organ Donors of All Ages	Potential Organ Donors of Pediatric Age	Laboratory Findings
• People who have had sex with a person known or suspected to have HIV, HPV, or HCV infection in the preceding 12 months • Men who have had sex with men in the preceding 12 months • Women who have had sex with a man who has had sex with men in the preceding 12 months • People who have had sex in exchange for money or drugs in the preceding 12 months • People who have had sex with a person who had sex in exchange for money or drugs in the preceding 12 months • People who have had sex with a person who has injected drugs by an IV, IM, or SQ route for nonmedical reasons in the preceding 12 months • People who have injected drugs by an IV, IM, or SQ route for nonmedical reasons in the preceding 12 months • People who have been in jail, prison, or a juvenile correctional facility for ≥72 hours in the preceding 12 months • People who have been newly diagnosed with, or have been treated for, syphilis, gonorrhea, chlamydia, or genital ulcers in the preceding 12 months • People who have been on hemodialysis in the preceding 12 months (risk for HCV only)	• A child who is ≤18 months of age and born to a mother known to be infected with, or at increased risk for, HIV, HBV, or HCV infection • A child who has been breastfed within the preceding 12 months by a mother known to be infected with, or at increased risk for, HIV	• Any evidence of hemodilution • National Organ Transplant Act precludes the use of HIV-infected donors; this restriction now waived for research due to the HOPE Act

HBV, hepatitis B virus; HCV, hepatitis C virus; HOPE, HIV Organ Policy Equity; HPV, human papillomavirus; IM, intramuscular; IV, intravenous; SQ, subcutaneous.

Table 3. Definitions and Status of HCV Infection in HCV-Infected Kidney Donors

HCV Antibody–Positive, NAT-Positive
• Indicates active infection and high risk for disease transmission
HCV Antibody–Negative, NAT-Positive
• Indicates acute infection (within 2 months) and high risk for disease transmission
HCV Antibody–Positive, NAT-Negative
• Spontaneous clearance of the virus • Successful use of antiviral therapy (cured) • Reinfection, window phase • False positive • Originally no risk of transmission; now documented transmission

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

Table 4. Estimated Risk of Window Period–Infections Per 10,000 Donors

Risk	HCV ELISA	HCV NAT
IV drug user	300.6 (3.0%)	32.4 (0.32%)
Commercial sex worker	114.9 (1.2%)	12.3 (0.12%)
Men who have sex with men	32.5 (0.33%)	3.5 (<0.1%)
Sex with a partner who is an IV drug user, a commercial sex worker, or a man who has sex with men	114.9 (1.2%)	12.3 (0.12%)
Incarceration	7.2 (<0.1%)	0.8 (<0.1%)
Blood product exposure	4.0 (<0.1%)	0.4 (<0.1%)

ELISA, enzyme-linked immunosorbent assay; HCV, hepatitis C virus; IV, intravenous; NAT, nucleic acid testing.

less than 1%. By comparison, the lifetime risk of dying from a motor-vehicle accident is higher than the risk of HCV transmission from a PHS IR donor (0.9% vs 0.4%).[28] Therefore, declining PHS IR donors has been associated with an increased waiting list mortality and morbidity among kidney transplant candidates who are on hemodialysis.[28]

de Vera and colleagues conducted a retrospective review of HCV-uninfected patients who received kidney allografts from donors who were HCV antibody–positive

and NAT-negative.[29] All patients were HCV antibody–negative prior to transplantation. HCV antibody and HCV RNA status were checked at 1, 3, 6, and 12 months. In patients whose donors were labeled PHS IR, HBV and HIV testing were performed at the same time points. Overall, 32 HCV-uninfected patients received kidney allografts from 25 donors who were HCV antibody–positive and NAT-negative. Twelve donors (48%) met PHS IR status. Mean follow-up after transplantation was 10 months (±3 months). Patient and graft survival rates were 100% and 97%, respectively. Fourteen patients (44%) seroconverted and became HCV antibody–positive; however, none of the 32 patients became viremic (ie, their HCV RNA was undetectable). The results of this study demonstrated that transplanting HCV-uninfected patients with HCV antibody–positive, NAT-negative donor organs triggers HCV antibody seroconversion without necessarily causing HCV infection.[29]

Hepatitis C Virus–Infected Kidney Donors

Transplantation experts and the transplantation community have advocated for the utilization of HCV-infected kidney donors in HCV-uninfected kidney recipients to increase the donor pool, particularly with the advancement of newer DAA regimens and their excellent SVR rates.

THINKER Trial The THINKER (Transplanting Hepatitis C Kidneys Into Negative Kidney Recipients) trial was an open-label, nonrandomized, pilot trial at the University of Pennsylvania in which researchers sought to determine the safety and efficacy of transplantation of kidney grafts from HCV genotype 1–viremic donors followed by administration of elbasvir/grazoprevir treatment.[30] The primary outcome of the trial was HCV cure or SVR. Exploratory outcomes included RAND-36 Physical Component Summary (PCS) and Mental Component Summary (MCS) quality-of-life scores at enrollment and after transplant, and posttransplant kidney graft function. Twenty HCV-uninfected kidney transplant candidates received HCV genotype 1–infected kidneys. The treatment of HCV genotype 1 infection with elbasvir/grazoprevir was started on posttransplant day 3. The mean age of trial participants was 56.3 years, and 70% were male. All 20 participants achieved SVR with the combination therapy. Renal and hepatic complications were transient or were successfully managed. Quality-of-life scores were comparable between matched-sample HCV-uninfected kidney graft recipients. Mean PCS and MCS quality-of-life scores decreased at 4 weeks posttransplant; PCS scores then increased above pretransplant values, and MCS scores returned to baseline values. Posttransplant kidney function was similar between HCV-viremic donor graft recipients and HCV-uninfected donor graft recipients at 6 and 12 months.[31]

EXPANDER-1 Trial The EXPANDER-1 (Exploring Renal Transplants Using Hepatitis C Infected Donors for HCV-Negative Recipients) trial was an open-label, nonrandomized, pilot trial conducted at the Johns Hopkins University School of Medicine.[32] In this trial, the researchers aimed to use DAA agents as prophylaxis before and after kidney transplantation from HCV-infected (both HCV NAT- and HCV antibody–positive) donors to HCV-uninfected recipients. Ten recipients older than 50 years of age with no available living donor options were included in the trial. All of the participants received a dose of elbasvir/grazoprevir immediately before transplantation. HCV-uninfected kidney transplant recipients from donors with HCV genotype 1 infection continued the combination therapy for 12 weeks, whereas HCV-uninfected kidney transplant recipients from donors with HCV genotype 2 or 3 infection received sofosbuvir plus elbasvir/grazoprevir for 12 weeks of triple therapy. No treatment-related adverse events occurred during the peri- or posttransplant period. HCV RNA was not detected in all 10 HCV-uninfected kidney transplant recipients from HCV-viremic donors. The researchers concluded that pre- and posttransplant HCV infection treatment was safe and prevented chronic HCV infection in HCV donor–infected/recipient-uninfected kidney transplant recipients. Additionally, they suggested that this strategy could markedly expand organ options and help decrease mortality and morbidity of kidney transplant candidates.[32]

Although the transmission of HCV infection from HCV-viremic donors to HCV-uninfected recipients was evident in almost all cases, the transmission risk from HCV antibody–positive, NAT-negative donors to HCV-uninfected recipients was unknown. Researchers from the University of Cincinnati conducted a study to estimate the incidence of HCV transmission from HCV antibody–positive, NAT-negative liver donors to HCV-uninfected liver transplant recipients.[33] Twenty-five HCV-uninfected liver transplant recipients receiving HCV antibody–positive, NAT-negative donor livers were prospectively followed. HCV transmission was considered to have occurred if recipients exhibited a positive HCV polymerase chain reaction test by 3 months following transplantation. The incidence of HCV transmission from HCV antibody–positive, NAT-negative liver donors to HCV-uninfected recipients was 16%, with the highest risk conferred by donors who died of drug overdose.[33] The researchers urged the transplant community to consider utilizing such organs to expand the donor pool due to the safe and highly effective antiviral therapies available with DAA agents.[33] The incidence of HCV transmission

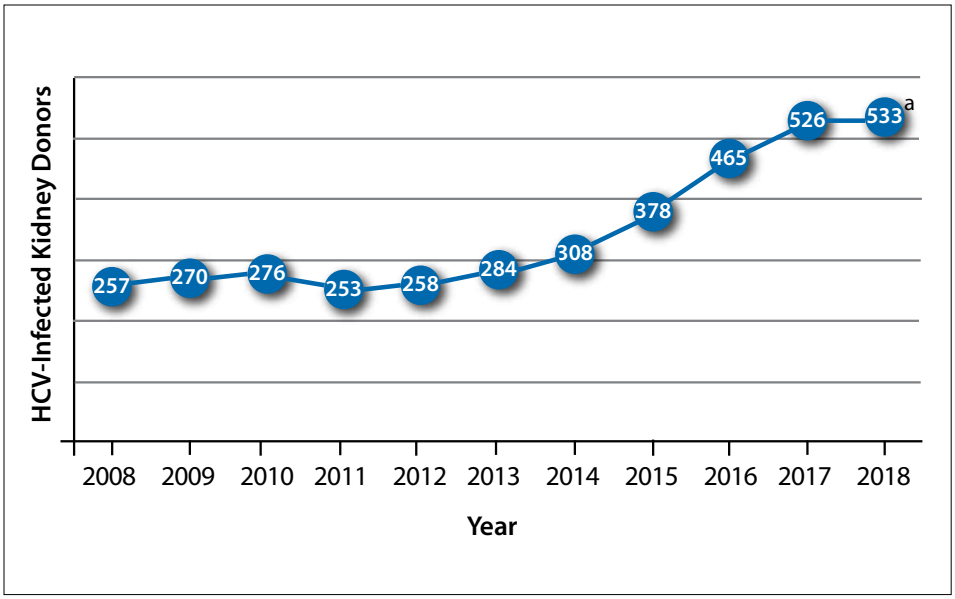

Figure 1. UNOS data trends of increasing HCV-infected kidney donors.

[a]Donors recovered up to September 30, 2018.

HCV, hepatitis C virus; UNOS, United Network for Organ Sharing.

from HCV antibody–positive, NAT-negative liver donors to HCV-uninfected liver transplant recipients could be extrapolated for kidney transplantation. Eighty-four percent of HCV-uninfected recipients are not likely to contract HCV infection from their donors.[33]

Hepatitis C Virus Infection and Kidney Transplantation

The treatment strategy for kidney transplant recipients can be divided into 2 categories: pre- and postkidney transplantation. Kiberd and colleagues used a theoretical Markov medical decision analysis model to examine the outcomes of treating HCV-infected patients on the kidney transplant waiting list before or after transplantation.[34] The delayed HCV infection treatment group (ie, treatment after transplant) was modeled to be transplanted 1 year earlier, with a higher cumulative transplant incidence of 54% at 5 years after being placed on the waiting list, compared to 45% in the immediate treatment group (ie, treatment prior to transplant). In the model, HCV infection treatment prior to kidney transplantation offered 0.43 (95% CI, 0.38-0.49) more life-years than did HCV infection treatment after transplantation. However, HCV infection treatment after transplantation was preferred for regions with much greater access to HCV-infected donors or in patients with very low HCV-associated mortality. The researchers concluded that the best option from an individual patient's perspective would differ by region and candidate.[34] In the United States, HCV-infected organ donation rates have increased dramatically in recent years, likely due to the opioid epidemic. UNOS data trends show that although only 258 HCV-infected kidneys were donated in 2012, the number of HCV-infected donated kidneys trended up to 526 in 2017, out of 15,218 total donated kidneys (Figure 1).[35] This number has continued to rise in 2018. By October 2018, 533 HCV-infected donated kidneys out of 12,088 total had been utilized.[35] Therefore, based on the Markov model demonstrated by Kiberd and colleagues,[34] HCV infection treatment after transplantation should be the preferred practice in order to increase the overall utilization of donated kidneys and to decrease kidney transplant waiting list mortality.

In a Markov state-transition decision model study, Eckman and colleagues aimed to examine whether it is more cost-effective to transplant HCV-infected or -uninfected kidneys into HCV-infected patients.[36] The state-transition decision model compared transplantation of an HCV-infected kidney followed by HCV infection treatment vs transplantation of an HCV-uninfected kidney followed by HCV infection treatment. The results of a base-case analysis demonstrated that transplantation of an HCV-infected kidney followed by HCV infection treatment was more effective and less costly than the other method. The model estimated that a typical 58-year-old patient on hemodialysis would benefit an average of 0.50 quality-adjusted life-years at a lifetime cost savings of $41,591 (2017 US dollars value). This trend of transplanting an HCV-infected kidney followed by treatment was also preferred in a sensitivity analysis of many model parameters. The investigators concluded that transplanting HCV-infected kidneys into HCV-infected recipients would increase quality-adjusted life-years and reduce costs compared with transplanting HCV-uninfected kidneys into HCV-infected recipients.[36]

Given the high mortality and morbidity rate in kidney transplant waiting list patients with end-stage renal disease on hemodialysis, HCV antibody–positive and either NAT-negative or NAT-positive kidney transplant donors should be considered to increase the survival of waitlisted kidney transplant candidates.

Kidney Transplant Recipients

In the pre–DAA agent era, use of interferon and ribavirin to treat HCV infection in kidney transplant recipients was limited due to the risk of allograft rejection and intolerance. Newer DAA agents have been well studied in terms of their safety, efficacy, and drug-drug interactions with immunosuppressive agents, such as calcineurin inhibitors, in liver transplant recipients with recurrent HCV infection. The safety profiles and outcomes of these DAA agents can be extrapolated to kidney transplant recipients. There are also several clinical trials that directly studied the safety and efficacy of the DAA agents in kidney transplant recipients.

Patients With Hepatitis C Virus Genotype 1 or 4 Infection In a randomized, open-label, phase 2, clinical trial, treatment-naive or -experienced kidney transplant recipients (N=114) with HCV genotype 1 or 4 infection with or without compensated cirrhosis and with an eGFR of more than 40 mL/min were treated with ledipasvir/sofosbuvir for 12 or 24 weeks.[37] All patients achieved SVR regardless of treatment duration. The most frequent adverse effects were headache (n=22; 19%), asthenia (n=16; 14%), and fatigue (n=11; 10%). Eleven percent of patients developed more serious adverse effects, such as elevation in creatinine, pulmonary embolism, and syncope. Overall, treatment with ledipasvir/sofosbuvir was well tolerated with an acceptable safety profile and excellent treatment outcome.[37]

In a small study in which 20 kidney transplant recipients were treated with interferon-free, sofosbuvir-based DAA regimens for HCV infection, all patients achieved SVR after completion of DAA therapy.[38] Eighty-eight percent of patients had HCV genotype 1 infection, 50% had biopsy-proven advanced hepatic fibrosis (F3 or F4), and 60% had a history of treatment failure with interferon-based therapy.[38] Another small study of 25 kidney transplant recipients with chronic HCV infection assessed treatment with various sofosbuvir-based regimens, and found that all patients achieved SVR after completion of therapy.[39] The tolerance to DAA agents was excellent, and no serious adverse effects were reported. A significant reduction in calcineurin inhibitor trough levels was observed after HCV clearance.[39]

The HCV-TARGET trial assessed 443 liver and kidney transplant recipients (liver transplant, n=347; kidney transplant, n=60; simultaneous liver and kidney transplant, n=36) in a multicenter, prospective, observational cohort.[40] Transplant recipients were treated with various DAA regimens, such as ledipasvir/sofosbuvir, sofosbuvir/daclatasvir, and ombitasvir/paritaprevir/ritonavir (Technivie, AbbVie) with and without ribavirin. Forty-two percent of patients had cirrhosis, and 54% had a history of treatment failure. The SVR rate was 95% in kidney transplant recipients and 91% in simultaneous liver and kidney recipients. Ribavirin did not influence SVR rates, and graft rejection was rare.[40]

Patients With Hepatitis C Virus Genotype 2, 3, 5, or 6 Infection The MAGELLAN-2 (A Single-Arm, Open-Label, Multicenter Study to Evaluate the Safety and Efficacy of ABT-493/ABT-530 in Adult Post-Liver or Post-Renal Transplant Recipients With Chronic Hepatitis C Virus Genotype 1–6 Infection) trial was a phase 3, open-label, single-arm, clinical trial that evaluated a 12-week course of the pangenotypic, ribavirin-free regimen of glecaprevir/pibrentasvir in 80 liver transplant recipients and 20 kidney transplant recipients with HCV genotypes 1 through 6 infection.[41] Most patients had no or minimal fibrosis (F0 or F1). The overall SVR rate was 98%. Adverse effects were mostly mild in severity, and laboratory abnormalities were uncommon. The researchers concluded that a once-daily, 12-week course of glecaprevir/pibrentasvir was well-tolerated and efficacious as a ribavirin-free treatment for liver and/or kidney transplant recipients with HCV genotypes 1 through 6 infection.[41]

Based on the HCV-TARGET real-world study as well as the MAGELLAN-2 trial, patients with HCV genotype 2, 3, 5, or 6 infection who are receiving a kidney transplant can be treated with either glecaprevir/pibrentasvir or sofosbuvir/daclatasvir.[40,41] Sofosbuvir-based pangenotypic regimens, such as sofosbuvir/velpatasvir and sofosbuvir/velpatasvir/voxilaprevir, can also be considered; however, there is a paucity of evidence demonstrating the efficacy of these regimens in kidney transplant recipients. Figure 2 displays the proposed management algorithm and guideline for kidney transplant recipients who receive HCV antibody–positive, NAT-negative or -positive kidneys.

Summary

The emergence of the second-generation DAA agents has revolutionized the treatment of HCV infection in patients with CKD. Prior to DAA agents, safe and effective HCV infection therapy was not available for this patient population. Many oral DAA regimens have been proven to be highly effective in the treatment of HCV infection in patients with CKD stages 3 to 5, including patients on hemodialysis. These regimens can provide SVR rates

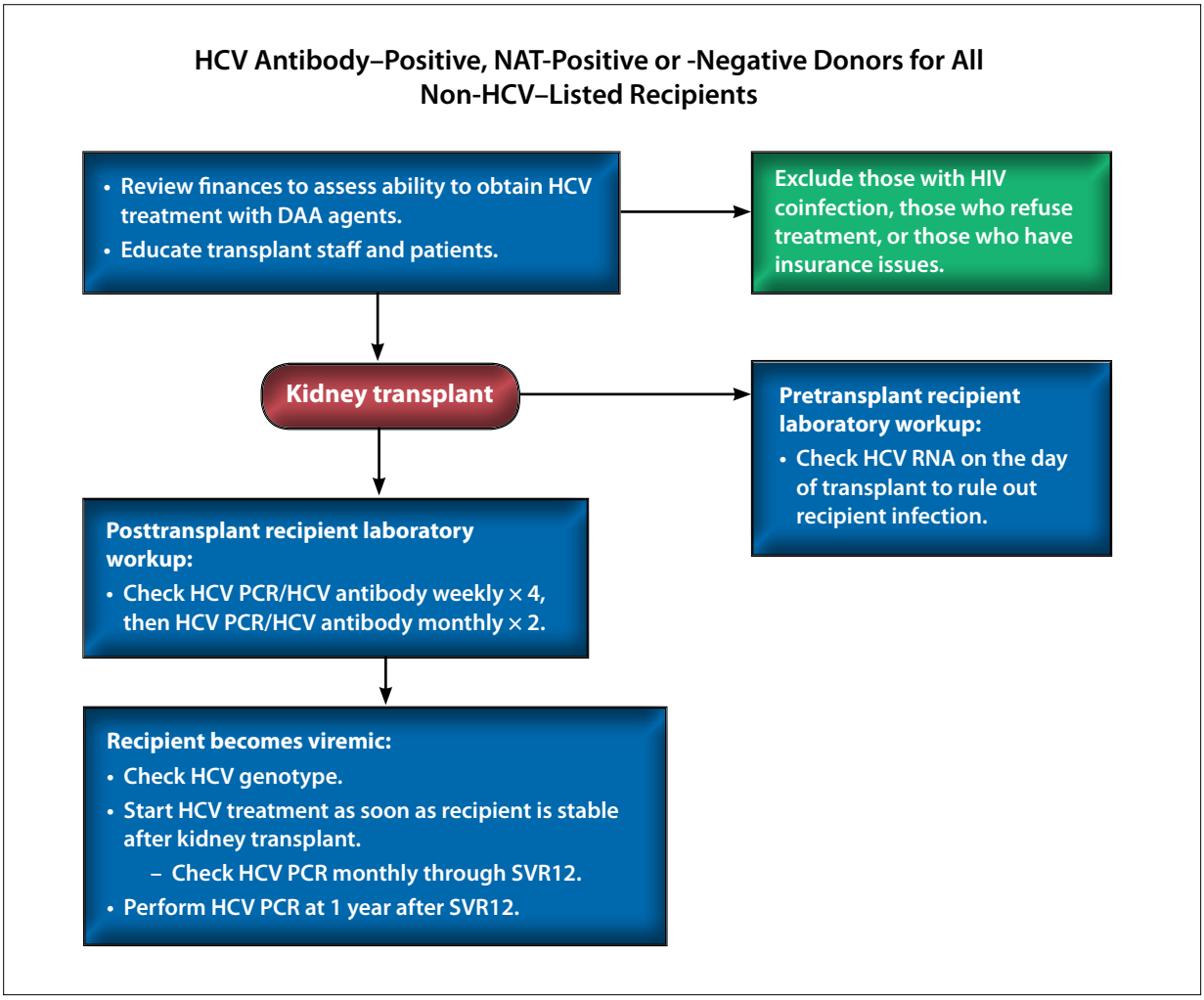

Figure 2. Proposed management guidelines for kidney transplant recipients who receive kidneys from HCV antibody–positive, NAT-positive or -negative donors.

DAA, direct-acting antiviral; HCV, hepatitis C virus; NAT, nucleic acid testing; PCR, polymerase chain reaction; SVR, sustained virologic response.

Algorithm adopted from the Ochsner Multi-Organ Transplant Institute.

above 90% with a shorter duration of therapy (8-16 weeks) based on HCV treatment experience and cirrhosis status. Kidney transplant candidates on the waiting list are also encouraged to accept HCV antibody–positive, NAT-positive donors, as HCV infection treatment after kidney transplantation is safe and effective. Not accepting HCV-infected donors may increase the rates of kidney transplant waiting list mortality and morbidity.

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